Global prevalence and risk factors of fatigue and post-infectious fatigue among patients with dengue: a systematic review and meta-analysis

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Summary

Background Fatigue during the acute phase of dengue infection can persist as post-infectious fatigue (PIF), potentially impacting quality of life. We aimed to determine the prevalence and risk factors of fatigue and PIF among dengue patients.

Methods This systematic review and meta-analysis was registered in the PROSPERO (CRD42024543058). We searched PubMed, Ovid MEDLINE, Web of Science, Embase, and CINAHL from their inception to June 22, 2024. Observational studies reporting the prevalence of fatigue or PIF among dengue patients were included. We excluded case studies, review articles, conference abstracts, protocols, duplicate publications, and studies without full text. Quality assessment was performed using Hoy's risk of bias tool. Data were analyzed using R software version 4.3.3. A random-effects model pooled prevalence with 95% confidence intervals (CIs). Risk factors were identified using odd ratios (ORs) and 95% CIs or *p* values. Heterogeneity, moderator analysis, sensitivity analysis, and publication bias were also assessed.

Findings From 715 identified studies, 40 were included for review. Of these, 37 studies were included in the meta-analysis for fatigue prevalence and nine studies for PIF prevalence, respectively involving 37,790 and 5045 dengue patients. The pooled prevalence of fatigue was 59.0% (95% CI 0.47–0.70), and that of PIF was 20.0% (95% CI 0.10–0.36), with significant heterogeneity but no significant moderators. Sensitivity analysis confirmed the robustness of this meta-analysis. Female sex (pooled OR = 1.65, 95% CI 1.27–2.14), dengue hemorrhagic fever (pooled OR = 1.80, 95% CI 1.02–3.16), and preexisting comorbidities (pooled OR = 2.14, 95% CI 1.36–3.38) were significant risk factors for PIF.

Interpretation This meta-analysis highlights the high prevalence of fatigue and PIF among dengue patients, with several risk factors identified. Although the study has its limitations, these results can inform future studies to more standardized study designs, improved definitions, and systematic assessment methods for fatigue, PIF, and potential moderators. These are essential to better understand the mechanisms of fatigue in dengue patients and explore potential interventions.

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Keywords: Dengue; Fatigue; Meta-analysis; Post-infectious fatigue (PIF); Prevalence; Risk factors; Systematic review

Introduction

Dengue, a mosquito-borne acute febrile illness, is a significant public health problem in tropical and subtropical regions globally.[1] In 2024, over 7.6 million cases were reported, including 3.4 million confirmed cases, more than 16,000 severe cases, and over 3000 deaths.[1] Dengue transmission is currently active in 90 countries.[1] Symptomatic dengue typically manifests as mild

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Research in context

Evidence before this study

Fatigue is a subjective feeling of tiredness that can range from mild to severe and impair daily functioning. Post-infectious fatigue (PIF), however, refers to persistent fatigue that lasts for weeks or months after the acute phase of an infection. PIF has been observed in infections such as Q fever, Epstein–Barr virus, Ebolavirus, SARS-CoV-2, and chikungunya, with prevalence ranging from 10% to 50%, depending on the infection. Although fatigue is recognized as a common symptom in dengue, its global prevalence and factors contributing to it in dengue patients have not been systematically studied.

Added value of this study

To the best of our knowledge, this is the first systematic review and meta-analysis to estimate the global prevalence and risk factors of fatigue and PIF following dengue. By including 40 studies across multiple countries, our study provides a comprehensive analysis of these symptoms. The findings emphasize the importance of recognizing fatigue, as almost 60% of dengue patients experience this symptom, and 20% suffer from PIF.

Implications of all the available evidence

The high prevalence of fatigue and PIF among dengue patients emphasizes the need for healthcare professionals to recognize and address fatigue during the acute phase of infection and monitor patients in the convalescent phase. Future research should focus on understanding the mechanisms behind fatigue and PIF in dengue patients and explore potential interventions to prevent the worsening of these conditions and improve patient outcomes.

to moderate acute febrile illness lasting from 2 to 7 days,[1] with treatment focusing solely on supportive care.[2]

Diagnosing dengue virus infection involves both clinical assessments and laboratory tests, as the infection presents with a wide range of non-specific symptoms.[3] It is crucial to consider the stage of infection at which the patient seeks medical attention,[4] as dengue progresses through three distinct phases: febrile (acute), critical, and convalescent phases.[5] Clinical symptoms such as sudden onset of fever, nausea, and body aches and pains typically lead to suspicion of dengue during the acute phase, but these are not specific to dengue and may overlap with other febrile illnesses.[6] Therefore, a definitive diagnosis of acute dengue should be confirmed through laboratory tests, including viral isolation, detection of viral RNA via a nucleic acid amplification test (NAAT), or detection of viral antigens by an enzyme-linked immunosorbent assay (ELISA) or rapid diagnostic test.[3,6]

Fatigue, which is defined as a subjective and unpleasant symptom ranging from tiredness to complete exhaustion and impacting individuals' normal functioning,[7,8] is commonly experienced during the acute phase alongside high fever and other signs of infection.[9–15] Fatigue is not unique to dengue; it is also a common symptom in other acute viral infections, such as Q fever, Epstein–Barr virus, Ebola virus, SARS-CoV-2, and chikungunya virus.[16–18] In some cases, fatigue can persist beyond the acute phase of infection and potentially develop into chronic or post-infectious fatigue (PIF) syndrome. Terms like PIF syndrome and post-viral fatigue syndrome are sometimes used to describe fatigue that occurs after infections, including dengue, where the infectious agent plays a significant role in its persistence.[19] However, there is no clear consensus on distinctions between these terms.[19] Various viral infections are potential causes of post-viral fatigue syndrome or chronic fatigue syndrome.[20,21] The proposed mechanisms for post-viral fatigue syndrome or chronic fatigue syndrome include viral persistence, autoimmunity, immune dysfunction, and autonomic dysregulation,[18,22] although the exact mechanisms remain unclear.

In the context of dengue, fatigue can persist into the convalescent phase after the acute phase has passed. While the majority of dengue patients recover from the acute phase with no complications, a minority can experience various post-acute symptoms, such as myalgia, weakness, headaches, and fatigue.[23] Fatigue that persists beyond the acute phase can progress to PIF, lasting from 2 weeks to 6 months or longer, depending on the severity of the infection and the patient's overall health.[14,23–28] Unlike acute fatigue, PIF can result in decreased productivity, challenges in working, and difficulties with daily activities.[23,27] Dengue patients with persistent symptoms experienced a 45% reduction in work productivity and a 13% increase in the economic burden due to productivity loss.[29]

Some strategies that have been explored to manage post-viral fatigue in other infections include the use of Chinese medicine, supportive therapies, self-management, educational programs, nutritional supplements, and rehabilitation approaches.[30–33] However, evidence for effective interventions to reduce fatigue following dengue infection remains limited, possibly due to the lack of a synthesis of its prevalence and contributing factors. Additionally, the assessment of fatigue in dengue patients is often inadequate, indicating that this symptom is underrecognized in clinical practice.[26]

Since fatigue among dengue patients can persist over time and have a significant economic burden, it is crucial to assess its symptoms. However, to date, few studies have systematically examined them. Therefore,

in this study, we aimed to determine the global prevalence and risk factors of fatigue and PIF among dengue patients, in order to provide essential information for future research to explore interventions for managing fatigue and PIF among dengue patients.

Methods

Data sources and search strategy

This systematic review and meta-analysis was reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement.[34] The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD4202 4543058.

A systematic search was conducted across five databases of PubMed, Ovid MEDLINE, Web of Science, Embase, and CINAHL to identify relevant studies from database inception to June 22, 2024. Search terms included both free-text words and Medical Subject Headings (MeSH) terms, combined with Boolean operators: (dengue OR dengue fever OR dengue infection) AND (fatigue OR postviral fatigue OR post-infection fatigue OR post-dengue fatigue syndrome OR post-infectious fatigue syndrome) (Supplementary Table S1). There were no restrictions on language or publication year. In addition, reference lists of included studies were manually searched for additional articles. Two authors independently performed the search. Any discrepancies were resolved through discussion with the third author, when needed.

The studies included in this systematic-review and meta-analysis had to meet the following criteria: (1) studies reporting the prevalence of fatigue or PIF (fatigue that persisted after the acute phase) among dengue patients; and (2) studies were observational studies (cross-sectional, prospective, and retrospective). Case studies, review articles, conference abstracts, protocols, duplicate publications, and studies with no full-text available were excluded. After pooling all articles in Endnote version 20 and removing duplicates, two authors independently screened the titles and abstracts. Furthermore, they comprehensively reviewed the full-text articles for eligibility.

Definitions of fatigue and PIF

In this study, fatigue was defined as a sense of tiredness or weakness that impacts the ability to perform usual activities,[8] experienced during the acute phase of dengue, typically lasting 2–7 days. We included each study that reported the number of fatigue occurrences during the acute phase of dengue infection, either as described by patients, observed by healthcare professionals using clinical symptoms, or assessed through validated questionnaires completed by patients to capture their experience of fatigue. PIF was defined as fatigue that persisted beyond the acute phase of dengue,[14] lasting from 2 weeks to 6 months or longer.[23–28]

Data extraction and risk of bias assessment

Two authors independently extracted data from each included study using a table that contained author (year), country, study design, sample size of dengue patients, mean age, percentage of females, methods used to assess fatigue (fatigue measures, such as clinical symptoms reported by patients or healthcare professionals, or validated fatigue questionnaires completed by patients), and the prevalence of fatigue or PIF. Any disagreements were resolved through discussion with a third author, when needed. The first author contacted the corresponding authors of the included studies to request missing data on key variables, such as the percentage of female participants and mean age. If no response was received, a reminder email was sent. In cases where no response was obtained, the studies were included in the pooled prevalence analysis but excluded from the moderator analysis for those particular variables.

Regarding the risk of bias assessment of included studies, two authors independently evaluated the quality of each study using Hoy's risk of bias tool.[35] This assessment tool, which comprises 10 items plus a summary assessment, was specifically designed to evaluate the quality of prevalence or incidence studies. Items 1–4 focus on the external validity, while items 5–10 focus on the internal validity.[35] Each item was rated as either "yes" (1) or "no" (0), and total scores were grouped into the following three categories: low risk (8–10), moderate risk (5–7), or high risk (0–4).[36,37]

Statistical analysis

Data were analyzed with the meta and metafor packages of R version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria). A random-effects model was used to pool prevalence estimates for both fatigue and PIF, with corresponding 95% confidence intervals (CIs), as the study characteristics of the included studies were not homogenous. An arcsine square-root transformation was applied for fatigue prevalence due to non-normality.

Cochran's Q statistics and I^2 were used to assess heterogeneity among the included studies, with p less than 0.10 for Cochran's Q or $I^2 \geq 25\%$ indicating substantial heterogeneity.[38] When heterogeneity was observed, subgroup analysis and meta-regression were performed to identify potential sources of heterogeneity. Subgroup analyses were conducted for categorical variables such as continent (Asia vs. others), study design (cross-sectional vs. others), and fatigue measures (clinical symptom vs. fatigue questionnaire). Mixed-effects meta-regression models were performed, with the prevalence of fatigue and PIF as the response variables.

Predictors in the meta-regression included the percentage of female patients and mean age, both of which were treated as continuous variables. A linear link function was used, with the restricted maximum-likelihood (REML) estimator for between-study variance (Tau^2), and the Hartung-Knapp (HKSJ) adjustment applied for robust confidence intervals. To assess linearity of the predictors, scatterplots were visually inspected, which indicated an approximately linear relationship between predictors and response variables.

To identify risk factors for fatigue and PIF, we used odd ratios (ORs) and associated 95% CIs from the included articles. Since the number of studies providing risk factor information was limited, we provided pooled ORs only when at least two studies contributed data; if only a single study reported on a specific risk factor, no pooled OR was calculated. There were inconsistencies in the reporting of ORs across studies: some provided adjusted ORs, others reported unadjusted ORs, and some did not calculate ORs but provided events and sample sizes from which unadjusted ORs could be derived. For studies without calculated ORs, we calculated unadjusted ORs by entering the events and sample sizes for the particular risk factor. When a risk factor included both adjusted ORs and unadjusted ORs, we pooled the most commonly reported OR type and excluded studies without comparable ORs.

Sensitivity analysis was performed by excluding studies with a high risk of bias and removing studies with a sample size of less than 50 to ensure the robustness of the study findings. Publication bias was assessed by visually inspecting the funnel plot, with asymmetry indicating the presence of publication bias.[39] Additionally, we used Egger's linear regression test to statistically identify publication bias, considering p less than 0.10 as significant publication bias.[39] In cases where publication bias was detected, the trim-and-fill method was performed to adjust the bias.[40]

Role of the funding source

There was no funding source for this study.

Results

Study selection

The initial search from five databases identified 715 studies. After removing 172 duplicates, 543 studies were screened based on their titles and abstracts. In total, 465 studies were excluded due to not discussing fatigue among dengue patients. Subsequently, two authors independently evaluated the full texts of 77 articles for eligibility. Thirty-nine studies were excluded due to irrelevant study designs, not reporting prevalence, or being duplicate publications. Additionally, two studies from the manual search were eligible for inclusion. In total, 40 studies were included in the review.[9–15,24–26,41–70] From the 40 studies, 37 were included for fatigue prevalence, nine for PIF prevalence,[11,12,14,15,24–26,41,67] two for fatigue risk factor,[47,58] and four for PIF risk factor meta-analysis (Fig. 1).[14,25,26,41]

Descriptive characteristics of included studies

In total, 40 included studies involved 38,406 dengue patients, of whom 48.2% were female, with a mean age (SD) of 40.9 (18.5) years. Most studies were conducted in Asian countries (n = 25, 62.5%), followed by South America (n = 7, 17.5%), Africa (n = 4, 10.0%), Europe (n = 3, 7.5%), and North America (n = 1, 2.5%). In terms of study design, 16 studies (40.0%) were prospective cohort, 13 studies (32.5%) were retrospective cohort, eight studies (20.0%) were cross-sectional, two studies (5.0%) were case-control, and one study (2.5%) was a time series. Regarding fatigue measures, most studies assessed fatigue using clinical symptoms (n = 35, 87.5%), while five studies used fatigue questionnaire (n = 5, 12.5%) (Table 1).

Among the 37 studies included for fatigue prevalence, 37,790 dengue patients were analyzed, with 48.3% of them being female and a mean age (SD) of 41.1 (18.5) years. Most studies were conducted in Asian countries (n = 22, 59.5%), followed by South America (n = 7, 18.9%), Africa (n = 4, 10.8%), Europe (n = 3, 8.1%), and North America (n = 1, 2.7%). In terms of study design, 13 studies (35.1%) were prospective cohort, 13 studies (35.1%) were retrospective cohort, eight studies (21.6%) were cross-sectional, two studies (5.4%) were case-control, and one study (2.7%) was a time series. Most studies assessed fatigue using clinical symptoms (n = 35, 94.6%), while only two studies (5.4%) used a validated fatigue questionnaire.

For the nine studies analyzing the PIF prevalence, 5045 dengue patients were included, with 50.8% of them being female and a mean age (SD) of 29.5 (13.7) years. Most studies were conducted in Asia (n = 6, 66.7%), followed by South America (n = 3, 33.3%). Asian countries included Sri Lanka and Singapore, while South America countries included Brazil, Colombia, and Peru. In terms of study design, eight studies (88.9%) were prospective cohort and one study (11.1%) was cross-sectional. Regarding fatigue measures, four studies (44.4%) assessed fatigue using clinical symptoms, while five studies (55.6%) used a validated fatigue questionnaire. Furthermore, two studies were included in the meta-analysis for fatigue risk factors (conducted in Brazil and Vietnam), and four studies were included for PIF risk factors (conducted in Singapore and Sri Lanka).

Risk of bias assessment

Two authors independently evaluated the risk of bias of the included studies. Any discrepancies in evaluating the risk of bias were discussed face-to-face. The authors then re-reviewed the articles together and reached a consensus on scoring each study. Among the 40

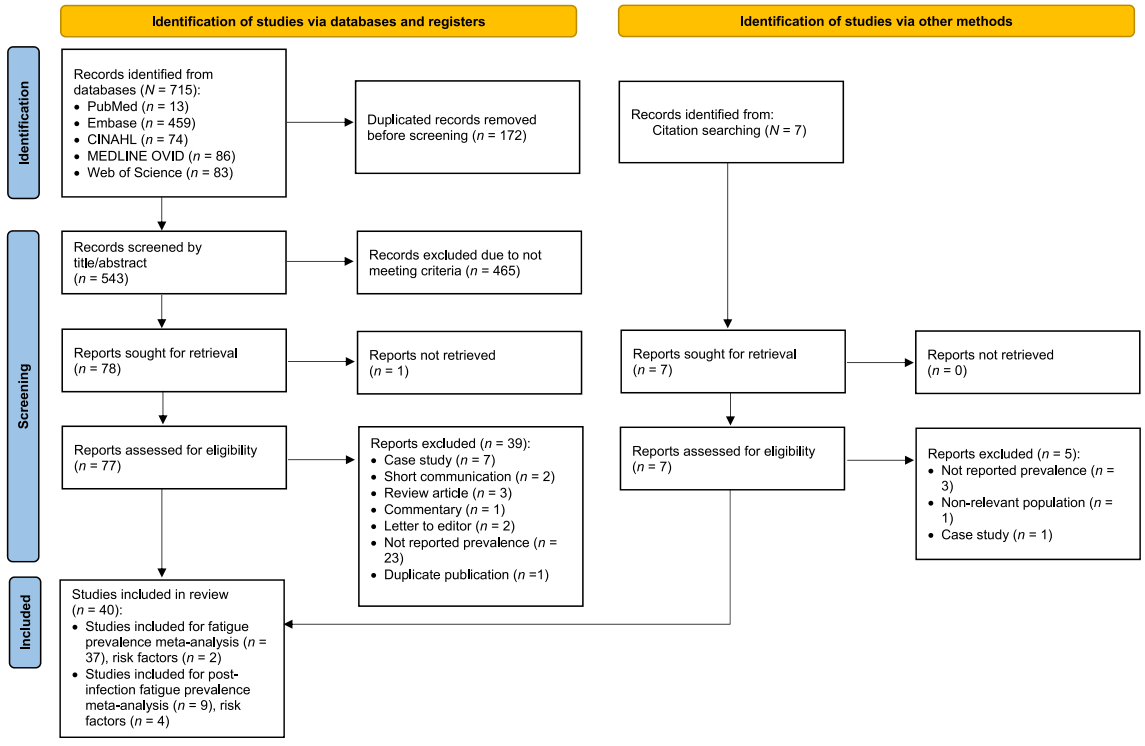

Fig. 1: PRISMA 2020 flow diagram.

included studies, three studies had a low risk of bias (7.5%), 28 had a moderate risk (70.0%), and nine studies had a high risk (22.5%) (Supplementary Table S2). The studies were assessed as high risk because the study's target population was not a close representation of the national population, random sampling selection was not used, or the fatigue definition and its measurement were not clearly defined.[9,44,45,47,49,50,63,64,70]

Pooled prevalence and risk factors of fatigue and PIF

The pooled prevalence of fatigue was 59.0% (95% CI 0.47–0.70), with significant heterogeneity ($Q = 32026.88$, $p < 0.0001$, $I^2 = 99.90\%$) (Fig. 2). Moderator analysis was performed to identify possible reasons for this heterogeneity, but no significant moderators were found (Supplementary Table S3). The pooled prevalence of PIF was 20.0% (95% CI 0.10–0.36), and significant heterogeneity was observed ($Q = 649.05$, $p < 0.0001$, $I^2 = 98.77\%$) (Fig. 3). Study design ($Q = 8.11$, $p = 0.0044$) and mean age ($\beta = 0.24$, 95% CI 0.01–0.48, $p = 0.043$) were identified as significant moderators for PIF (Supplementary Table S3). Cross-sectional studies reported a higher prevalence of PIF (39.7%) compared to other study designs (18.2%), and studies with older participants tended to report a higher prevalence of PIF. However, due to the limited number of studies included in these moderator analyses, the results should be interpreted with caution.

Regarding risk factors, two studies reported the risk factor for fatigue (Table 2).[47,58] Patients with dengue hemorrhagic fever (DHF) were more likely to have fatigue, although these associations were not statistically significant (pooled OR = 1.29, 95% CI 0.43–3.88). Moreover, four studies provided data on risk factors for PIF (Table 2).[14,25,26,41] Six risk factors (older age, female sex, post-discharge myalgia, post-discharge headaches, DHF, and preexisting comorbidities) were reported in more than one article, and thus the ORs were pooled. The remaining risk factors were only reported by single studies, so pooled OR could not be determined.

Dengue patients who were female (pooled OR = 1.65, 95% CI 1.27–2.14), had DHF (pooled OR = 1.80, 95% CI 1.02–3.16), or had preexisting comorbidities (pooled OR = 2.14, 95% CI 1.36–3.38) had higher odds of experiencing PIF compared to their counterparts (Table 2).

Sensitivity analysis

In terms of the sensitivity analysis, we used two different sensitivity analysis methods for fatigue studies. First, we excluded nine studies with a high risk of bias.[9,44,45,47,49,50,63,64,70] The findings showed that the estimated pooled prevalence of fatigue among dengue patients was 58.0% (95% CI 0.43–0.71) (Supplementary Fig. S1a). Second, after we removed nine studies with a sample size of less than 50,[12,24,48,52,57,59,60,63,69] the estimated pooled fatigue prevalence was 61.0% (95% CI

No.	Study name	*n* (fatigue)	*n* (PIF)	Sample size dengue	Country	Continent	Study design	Outcome measurement	No of female	Percentage of female (%)	Mean age (year)	SD age (year)
1.	Abeysena et al., 2019	251	188	473	Sri Lanka	Asia	Cross-sectional	Clinical symptoms	243	51.4	36.6	13.0
2.	Ahmad et al., 2020	462	–	799	Pakistan	Asia	Prospective cohort	Clinical symptoms	NI	NI	N/A[d]	N/A[d]
3.	Ali et al., 2013	122	–	319	Pakistan	Asia	Cross-sectional	Clinical symptoms	50	15.7	N/A[d]	N/A[d]
4.	Berberian et al., 2022	50	–	239	Argentina	South America	Time-series	Clinical symptoms	101	42.3	11.0[a]	8.5–13.0[b]
5.	Bodinayake et al., 2021	883	–	1064	Sri Lanka	Asia	Prospective cohort	Clinical symptoms	360	33.8	32.7[a]	24.3–45.7[b]
6.	Bodinayake et al., 2018	307	–	388	Sri Lanka	Asia	Prospective cohort	Clinical symptoms	138	35.6	34.0[a]	25.0–45.0[c]
7.	Borim et al., 2022	17	–	24	Brazil	South America	Cross-sectional	Clinical symptoms	19	79.2	37.0[a]	18.0–68.0[c]
8.	Chuang et al., 2008	50	–	126	Hong Kong	Asia	Retrospective cohort	Clinical symptoms	57	45.2	38.4	5.0–72.0[c]
9.	Farag et al., 2022	16	–	166	Qatar	Asia	Retrospective cohort	Clinical symptoms	40	24.0	32.9	12.0
10.	Feng et al., 2020	73	–	96	China	Asia	Retrospective cohort	Clinical symptoms	49	51.0	50.6	8.0–96.0[c]
11.	Ferreira et al., 2018	259	–	419	Brazil	South America	Retrospective cohort	Clinical symptoms	197	47.0	8.3	0.1–16.0[c]
12.	Ghweil et al., 2019	100	–	100	Egypt	Africa	Prospective cohort	Clinical symptoms	49	49.0	40.3	15.7
13.	Halsey et al., 2014	3575	98	3659	Peru	South America	Prospective cohort	Clinical symptoms	1919	52.5	28.1	14.0
14.	Jia et al., 2021	14	–	18	China	Asia	Case-control	Clinical symptoms	18	100.0	27.9	5.3
15.	Joubert et al., 2021	49	–	61	France	Europe	Retrospective cohort	Clinical symptoms	30	49.2	42.0	13.4
16.	Kalimuddin et al., 2022	38	4	48	Singapore	Asia	Prospective cohort	Clinical symptoms	18	37.5	37.0[a]	21.0–68.0[c]
17.	Laferl et al., 2006	24	–	93	Austria	Europe	Retrospective cohort	Clinical symptoms	43	46.2	32.5[a]	17.0–68.0[c]
18.	Lim et al., 2021	53	–	119	Gabon	Africa	Prospective cohort	Clinical symptoms	49	41.2	9.0	6.6
19.	Lim et al., 2020	269	–	295	Kenya	Africa	Prospective cohort	Clinical symptoms	117	39.7	23.4	9.2
20.	Luengas et al., 2015	11	11	32	Colombia	South America	Prospective cohort	Fatigue questionnaire (FQ)	19	59.4	35.0	10.8
21.	Ly et al., 2022	2	–	44	Belize	North America	Prospective cohort	Clinical symptoms	22	50.0	21.0[a]	22.0[b]
22.	Mushtaq et al., 2023	197	–	580	Pakistan	Asia	Cross-sectional	Clinical symptoms	120	20.7	32.5	9.0
23.	Mutricy et al., 2020	34	–	90	French Guiana	Europe	Case-control	Clinical symptoms	34	37.8	34.0[a]	22.0–49.0[b]
24.	Padmaprakash et al., 2020	68	–	751	India	Asia	Cross-sectional	Clinical symptoms	196	26.1	30.7	10.5
25.	Passos et al., 2008	280	–	453	Brazil	South America	Cross-sectional	Clinical symptoms	258	57.0	35.7	15.5
26.	Proesmans et al., 2019	11	–	19	Congo	Africa	Cross-sectional	Clinical symptoms	11	57.9	N/A[d]	N/A[d]
27.	Recker et al., 2024	1125	–	1593	Vietnam	Asia	Retrospective cohort	Clinical symptoms	792	49.7	38.7	13.0–91.0[c]
28.	Ren et al., 2018	433	–	529	China	Asia	Retrospective cohort	Clinical symptoms	253	47.8	42.0	1.0–96.0[c]
29.	Sahak 2020	1	–	15	Afghanistan	Asia	Retrospective cohort	Clinical symptoms	4	26.7	34.3	12.3
30.	Seet et al., 2007	102	31	127	Singapore	Asia	Prospective cohort	Fatigue questionnaire (FQ)	56	44.1	36.1	13.7
31.	Sinha et al., 2023	12	–	23	India	Asia	Cross-sectional	Clinical symptoms	8	34.8	24.0	12.9
32.	Tissera et al., 2022	48	–	55	Sri Lanka	Asia	Prospective cohort	Clinical symptoms	NI	NI	N/A[d]	N/A[d]

(Table 1 continues on next page)

No.	Study name	n (fatigue)	n (PIF)	Sample size dengue	Country	Continent	Study design	Outcome measurement	No of female	Percentage of female (%)	Mean age (year)	SD age (year)
(Continued from previous page)												
33.	Tristão-Sá et al., 2012	83	18	90	Brazil	South America	Prospective cohort	Clinical symptoms	47	52.2	35.8	12.7
34.	Wang et al., 2021	519	–	718	China	Asia	Retrospective cohort	Clinical symptoms	394	54.9	N/A[d]	N/A[d]
35.	Yeh et al., 2017	798	–	22,777	Taiwan	Asia	Retrospective cohort	Clinical symptoms	11,469	50.4	45.6	21.2
36.	Yoshimura et al., 2015	39	–	46	Japan	Asia	Retrospective cohort	Clinical symptoms	13	28.3	42.0	16.0
37.	Zhang et al., 2007	1049	–	1342	China	Asia	Retrospective cohort	Clinical symptoms	655	48.8	34.7	13.2
38.	Sigera et al., 2021	–	51	158	Sri Lanka	Asia	Prospective cohort	Fatigue questionnaire (FQ)	70	44.3	28.0[a]	NI
39.	Umakanth, 2018	–	9	52	Sri Lanka	Asia	Prospective cohort	Fatigue questionnaire (FQ)	31	59.6	N/A[d]	12.0–69.0[c]
40.	Perera et al., 2023	–	142	406	Sri Lanka	Asia	Prospective cohort	Fatigue questionnaire (FQ)	162	39.9	30.8	11.5

N/A = Not applicable; NI = No information; PIF = post-infectious fatigue. [a]Data reported as Median. [b]Data reported as IQR. [c]Data reported as range. [d]Age reported in ranges with participants percentages, not mean or median.

Table 1: **Characteristics of the included studies (*n* = 40).**

0.48–0.74) (Supplementary Fig. S1b). Both methods revealed that the estimated pooled prevalence consistently fell within the 95% CI of the pooled fatigue prevalence before removing the studies (95% CI 0.47–0.70), reflecting the robustness of the current meta-analysis. Furthermore, for PIF studies, we removed two studies with a sample size of less than 50[12,24] and used the leave-one-study-out method for sensitivity analysis. The estimated pooled prevalence of PIF for the first method was 21.0% (95% CI 0.09–0.41) (Supplementary Fig. S2a). In addition, estimated pooled PIF prevalence for the second method ranged from 18.0% (95% CI 0.08–0.35) to 27.0% (95% CI 0.18–0.37) (Supplementary Fig. S2b). Both results consistently fell within the 95% CI of the pooled PIF prevalence before removing the studies (95% CI 0.10–0.36), demonstrating the robustness of the current meta-analysis.

Publication bias

Funnel plots of fatigue studies visually illustrated asymmetric proportions (Supplementary Fig. S3). Egger's linear regression test revealed no significant publication bias for fatigue studies ($z = -0.39$, $p = 0.69$). Regarding publication bias of PIF studies, funnel plots indicated an asymmetric distribution (Supplementary Fig. S4). However, no publication bias was found for PIF studies according to Egger's test ($t = 0.06$, $p = 0.95$).

Discussion

To the best of our knowledge, this systematic review and meta-analysis is the first to specifically address the global prevalence and risk factors for fatigue and PIF among dengue patients. Fatigue and PIF are significant issues in dengue patients; our findings highlighted that 59% of dengue patients experience fatigue during the acute phase, while 20% suffer from PIF. While no significant risk factors were identified for fatigue, female sex, preexisting comorbidities, and DHF were identified as risk factors for developing PIF.

The pooled global prevalence of fatigue among dengue patients indicates that it is common during the acute phase. However, limited studies used validated questionnaires to measure fatigue,[14,24] with most relying on clinical symptoms. This could have affected the objectivity of fatigue measurements[71] and the internal validity of the results. Although the subgroup analysis showed similar prevalence of fatigue between those measured by clinical symptoms and fatigue questionnaires, the findings should be interpreted with caution.

In our meta-analysis, the prevalence of PIF following dengue was 20.0%, which is similar to the prevalence of chronic fatigue following Q-fever infections reported in a systematic review by Morroy et al.[72] However, this prevalence was lower compared to fatigue within the first 6 months after SARS-CoV-2 infection, which ranged 41.0%–46.6%.[73–76] These studies also lacked a uniform definition of fatigue and PIF, as well as standardized instruments for their assessment and measurement. Although our subgroup analysis did not show statistically significant differences between PIF prevalence estimates using different fatigue measurement methods, clinical symptoms identified PIF in only 12.6% of cases, while validated fatigue questionnaires detected PIF in 29.5% of dengue patients. Similar findings were reported in the meta-analysis of post-COVID-19 fatigue, where standardized questionnaires identified more cases of fatigue (47.5%) than did simple

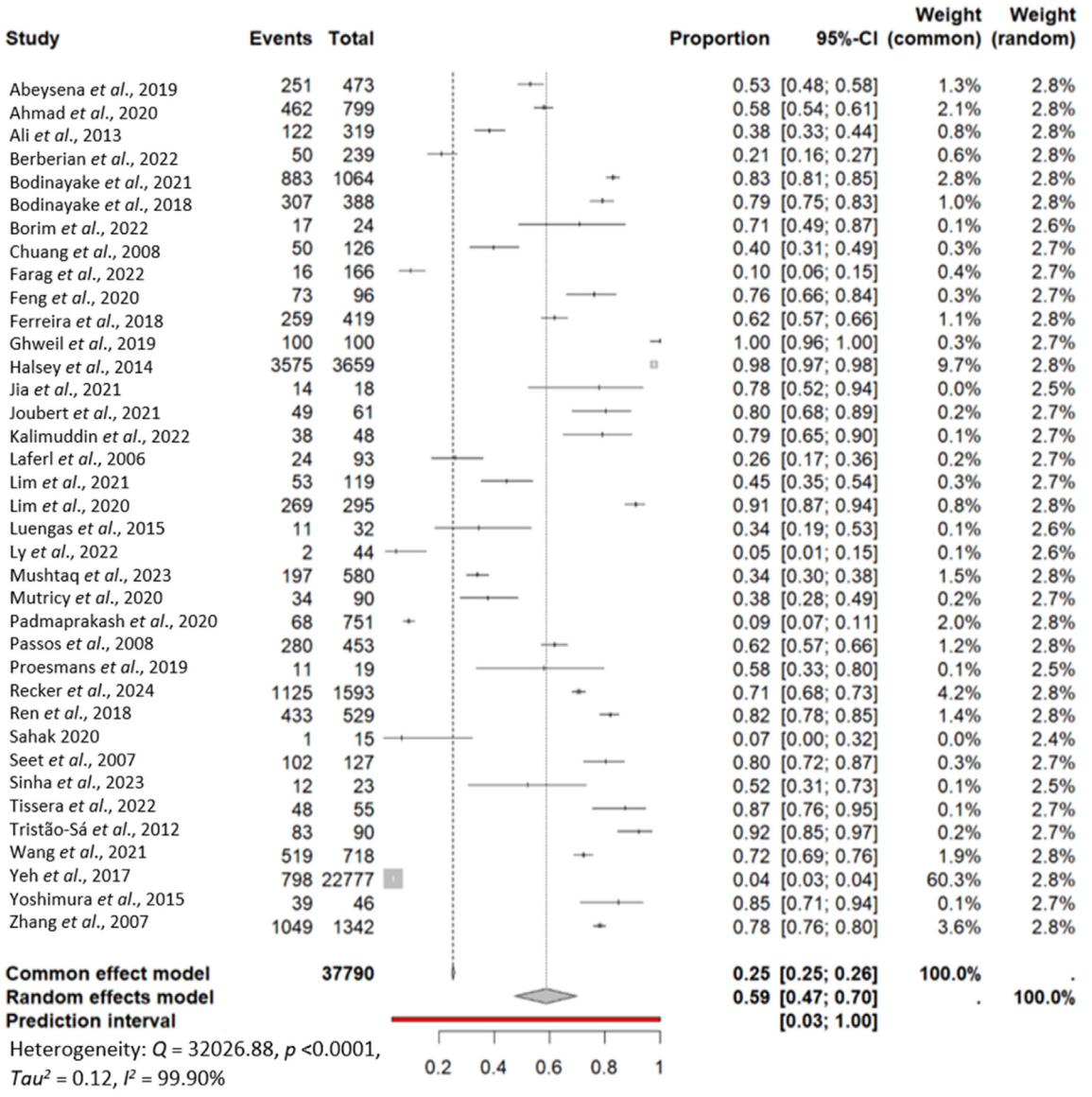

Fig. 2: Forest plots of the global prevalence of fatigue among patients with dengue (n = 37).

checklists (43.2%).[73] This suggests that using standardized questionnaires is advisable to accurately identify fatigue symptoms; otherwise, the prevalence of fatigue may be underestimated.

Although there was significant heterogeneity in the prevalence of fatigue and PIF among the studies, our moderator analysis identified no significant variables that could explain the heterogeneity of fatigue prevalence. This may be due to the limited number of studies included for each moderator variable. However, study design and mean age were identified as significant moderators that could explain the heterogeneity of PIF prevalence. It is difficult to interpret the findings on study design because only one cross-sectional study was included, compared to eight studies with other designs. Nevertheless, the estimated PIF prevalence was 39.7% in the cross-sectional study, and it was 18.2% in studies with other designs. Furthermore, our meta-regression analysis suggested that mean age could be a factor contributing to the heterogeneity in PIF prevalence across studies. The positive coefficient for mean age indicated that studies with older patients tended to report a higher prevalence of PIF. However, since only six studies were included in this meta-regression, these findings should be interpreted with caution. Future research should explore other potential moderators to better understand factors influencing heterogeneity and consider updating the meta-analysis in the next decade to gather more data on fatigue and PIF.

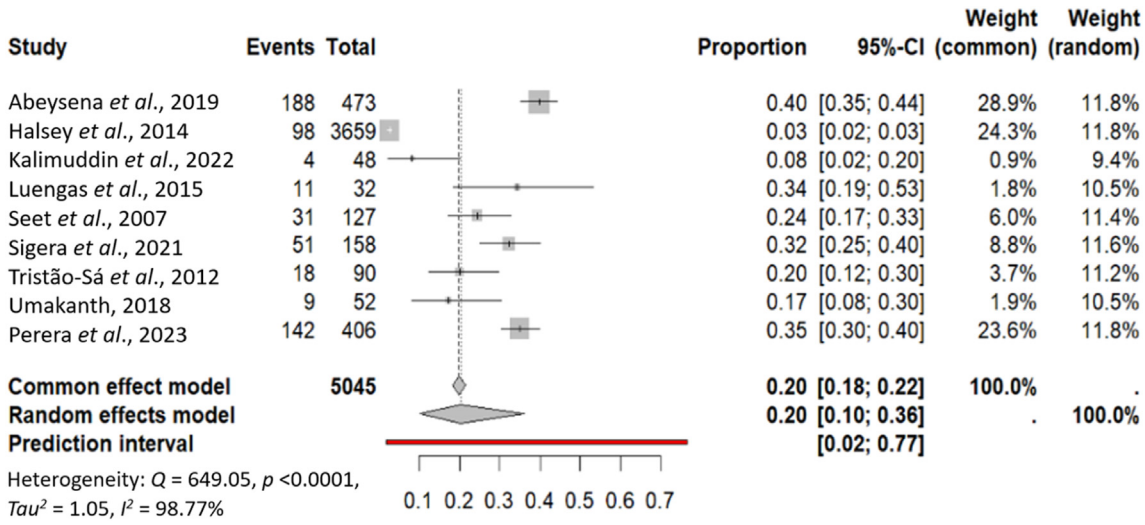

Fig. 3: Forest plot of the global prevalence of post-infectious fatigue among dengue patients (n = 9).

Our findings identified female sex, DHF, and pre-existing comorbidities as significant risk factors for developing PIF among dengue patients. Previous studies did not explore the mechanisms behind these associations.[14,26,28] However, the condition of PIF may be linked to the complex immune response between the virus and host,[77] which is influenced by factors such as genetics, gender, dengue severity, comorbidities, and autoimmune responses.[14,26,28,77] Females tend to have stronger immune responses than males, producing more antibodies and higher levels of immune cells like cluster of differentiation 4 (CD4) cells.[78] In addition, estrogens stimulate B cell activation and antibody production, which can lead to a prolonged immune response and increase the likelihood of autoimmune reactions.[78] These autoimmune reactions, where the immune system mistakenly attacks healthy cells, may contribute to persistent fatigue.[77] However, this proposed mechanism requires further confirmation. For DHF patients, the severity of dengue infection results in intense inflammation and plasma leakage, which can extend the recovery time and contribute to persistent symptoms such as fatigue.[77] In addition, PIF was also more prevalent among dengue patients with preexisting comorbidities. This could be associated with complex immunological responses involving cytokines and interactions with the neuroendocrine, musculoskeletal, and immune systems.[12,26] Patients with underlying diseases, such as diabetes, chronic renal disease, and heart disease, had higher relative odds of progressing to severe dengue,[79] which can further delay recovery and worsen fatigue.

Our study had several limitations. First, the methods used to measure fatigue varied across studies, with some using validated questionnaires and others relying

Risk factors	*n* studies	Statistics			Heterogeneity		
		OR	95% CI	*p*	*Q*	*p*	I^2
Fatigue							
Having DHF	2	1.29*	0.43–3.88	0.65	15.41	<0.0001	93.51
Ferreira et al., 2018[47]		2.31*	1.40–3.80				
Recker et al., 2024[58]		0.75*	0.58–0.97				
Post-infectious fatigue							
Older age	2	2.03	0.58–7.14	0.27	13.36	0.00030	92.51
Seet et al., 2007[14]		1.12	1.03–1.21				
Perera et al., 2023[25]		4.05	2.04–8.04				
Female sex	3	1.65*	1.27–2.14	0.00020	0.50	0.78	0.00
Seet et al., 2007[14]		9.69*	0.78–4.01				
Perera et al., 2023[25]		1.82*	1.20–2.75				
Abeysena et al., 2019[41]		1.50*	1.03–2.17				
Having myalgia post-discharge	3	1.82	0.66–5.05	0.24	10.52	0.0052	81.00
Seet et al., 2007[14]		1.90	0.32–11.24				
Sigera et al., 2021[26]		0.85	0.42–1.73				
Perera et al., 2023[25]		3.63	2.16–6.11				
Having headache post-discharge	3	1.16	0.41–3.31	0.78	11.12	0.0039	82.00
Seet et al., 2007[14]		0.39	0.06–2.50				
Sigera et al., 2021[26]		0.82	0.46–1.45				
Perera et al., 2023[25]		2.69	1.60–4.53				
Having DHF	2	1.80*	1.02–3.16	0.042	1.22	0.27	18.00
Sigera et al., 2021[26]		3.43*	0.92–12.76				
Perera et al., 2023[25]		1.58*	1.04–2.40				
Having pre-existing comorbidities	2	2.14*	1.36–3.38	0.0010	0.19	0.66	0.00
Sigera et al., 2021[26]		1.73*	0.61–4.95				
Perera et al., 2023[25]		2.25*	1.36–3.73				

DHF: dengue hemorrhagic fever; Hb: hemoglobin; *OR: unadjusted OR.

Table 2: **Risk factors for fatigue and post-infectious fatigue among dengue patients.**

on clinical symptoms reported by patients or observed by healthcare professionals. This lack of standardization made it difficult to compare results across studies and might not have accurately identified fatigue. Future research should aim to use standardized and validated tools to assess fatigue. Second, the number of variables available for the moderator analysis was limited, which made it difficult to explain the heterogeneity of fatigue prevalence estimates. However, we thoroughly explored and included all possible variables for the moderator analysis. Third, some studies had small sample sizes, potentially introducing sparse-data bias with wide confidence intervals. To address this, we performed sensitivity analysis by excluding studies with small sample sizes, and the results were reliable despite this limitation. Fourth, we did not apply inverse probability weighting (IPW) due to a lack of population data, which may have impacted the accuracy of the pooled prevalence estimates. Future studies should consider employing IPW to better address population differences across studies. Lastly, since most articles indicated a moderate risk of bias, the results should be interpreted with caution.

This systematic review and meta-analysis concluded that almost 60% of dengue patients experience fatigue, and one-fifth suffer from PIF. Healthcare professionals can use these results to advise dengue patients on recognizing fatigue, as it can persist beyond the acute phase of infection. Despite PIF potentially reducing productivity and extending the recovery period,[23] there is insufficient evidence on its management in dengue patients. Future research should explore interventions to alleviate fatigue in dengue patients. Risk factors for PIF include female sex, DHF, and preexisting comorbidities. Subsequent studies should focus on understanding the mechanisms behind PIF in these high-risk groups. Healthcare professionals should also educate dengue patients about these risk factors so that they can be more attentive to their fatigue and seek timely management.

Contributors

NSH: conceptualization, methodology, data curation, formal analysis, writing–original draft, writing–review & editing, visualization. TVN: conceptualization, methodology, data curation, writing–review & editing. Y-HC: conceptualization, methodology, writing–review & editing, supervision. All authors accessed and verified the data and had final responsibility for the decision to submit for publication.

Data sharing statement

Data extracted from the included articles and used in our analysis will be made available upon reasonable request to the corresponding author.

Declaration of interests

We declare no competing interests.

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None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.103041.

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