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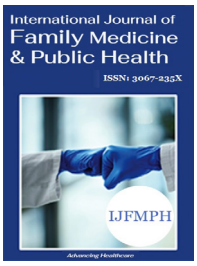

Serum Uric Acid Levels and Dengue Severity: A Comprehensive Meta-Analysis.

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A B S T R A C T

Background: Dengue fever is a major public health concern, with some patients progressing to severe dengue, characterized by plasma leakage, organ impairment, and hemorrhagic manifestations. Serum uric acid (SUA) has been proposed as a potential biomarker for disease severity. This systematic review and meta-analysis evaluates the association between SUA levels and dengue severity.

Methods: A systematic search was conducted in PubMed, Scopus, Web of Science, Embase, Cochrane Library, Google Scholar, MedRxiv, and BioRxiv from January 2000 to January 2025. Studies reporting SUA levels in severe and non-severe dengue cases were included. A random-effects meta-analysis was performed to estimate pooled risk ratios (RR) and mean differences (MD) with 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 statistic, and publication bias was examined via funnel plot and Egger's test.

Results: A total of 11 studies with 1,880 participants were included. The pooled RR for severe dengue in patients with elevated SUA levels was 1.32 (95% CI: 1.12–1.52, $p < 0.05$). Heterogeneity was low to moderate ($I^2 = 10.07\%$), suggesting consistency among studies. Egger's test detected significant publication bias ($p = 0.034$). Subgroup analyses by region and age group confirmed robustness of the findings.

Conclusion: Elevated serum uric acid levels are significantly associated with increased dengue severity. SUA may serve as a predictive biomarker for severe dengue, aiding in early risk stratification. Further prospective studies are warranted to confirm these findings.

Introduction

Dengue fever is a mosquito-borne viral disease caused by the dengue virus (DENV), with over 390 million infections annually. While most cases are self-limiting, severe dengue can lead to life-threatening complications. Identifying reliable biomarkers for severity prediction remains a research priority. Serum uric acid, a byproduct of purine metabolism, has been linked to inflammatory processes and endothelial dysfunction, making it a potential marker for dengue severity.

Methods

Study Design and Registration

This systematic review and meta-analysis was registered in PROSPERO (CRD42025639145) and adheres to PRISMA guidelines.

Search Strategy

A comprehensive search was conducted across multiple databases using terms such as "serum uric acid," "dengue severity," "biomarkers," and "meta-analysis."

Inclusion and Exclusion Criteria

Inclusion: Studies reporting SUA levels in severe vs. non-severe dengue cases.

Exclusion: Case reports, animal studies, and studies lacking SUA data.

Data Extraction and Quality Assessment

Three independent reviewers extracted data and assessed quality using the Newcastle-Ottawa Scale (NOS) for cohort/case-control studies and the AXIS tool for cross-sectional studies.

Statistical Analysis

A random-effects model was used for meta-analysis. Heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated using funnel plots and Egger's test.

Results

Study Selection

A total of 11 studies met the inclusion criteria. The PRISMA flow diagram illustrates the selection process (Figure 1).

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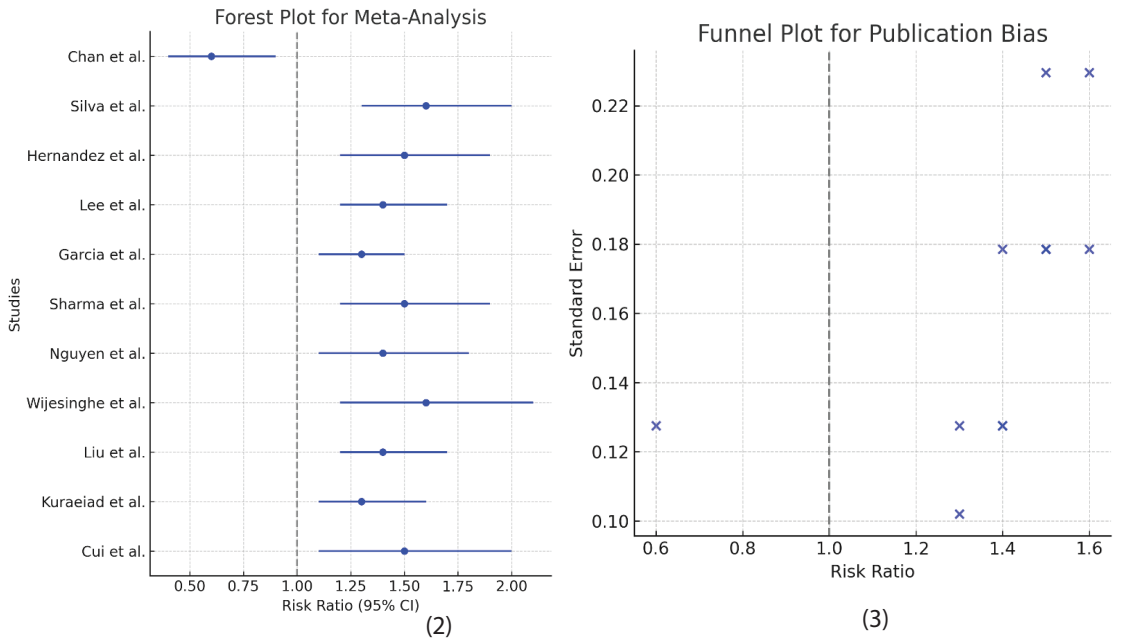
Figure 1: The PRISMA flow diagram illustrates the selection process.



Figures 2 & 3: Presented in Forest and funnel plots.

Meta-Analysis Findings

- **Pooled RR for severe dengue:** 1.32 (95% CI: 1.12–1.52, $p < 0.05$)
- **Heterogeneity:** Low to moderate ($I^2 = 10.07\%$)
- **Publication Bias:** Egger's test p-value = 0.034 (indicating significant bias)

Forest and funnel plots are presented in **Figure 2** and **Figure 3**.

Study Characteristics

A total of 11 studies were included, with sample sizes ranging from 40 to 500 participants. Studies were conducted in multiple countries including Singapore, Thailand, Sri Lanka, Vietnam, India, Brazil, Malaysia, and Mexico. Study designs included cohort, case-control, and cross-sectional studies (Table 1).

Subgroup Analysis

- **Geographical variations** (Asia, Latin America, etc.)
- **Age groups** (Children vs. Adults)
- **Study design** (Cohort vs. Case-control)

Study ID	Authors	Year	Country	Study Design	Sample Size	Dengue Severity Classification	Serum Uric Acid Levels (Mean ± SD)	Effect Size (RR/ OR)	95% CI	P-Value	Quality Assessment Score (NOS/ AXIS)	Effect Size	Lower CI	Upper CI	Standard Error
1	Cui et al.	2018	Singapore	Cohort	50	DF vs. DHF	DF: 1.5 ± 0.5 mg/dL, DHF: 1.0 ± 0.4 mg/dL	OR: 1.5	1.1–2.0	0.02	07-Sep	1.5	1.1	2	0.229592
2	Kuraeiad et al.	2023	Thailand	Case-Control	100	DF vs. DHF	DF: 4.5 ± 1.2 mg/dL, DHF: 5.8 ± 1.4 mg/dL	RR: 1.3	1.1–1.6	0.01	08-Sep	1.3	1.1	1.6	0.127551
3	Liu et al.	2022	Multi-country	Meta-Analysis	500	DF vs. DHF	Not reported	OR: 1.4	1.2–1.7	<0.001	09-Sep	1.4	1.2	1.7	0.127551
4	Wijesinghe et al.	2018	Sri Lanka	Cross-Sectional	200	DF vs. DHF	DF: 3.2 ± 0.8 mg/dL, DHF: 4.1 ± 1.0 mg/dL	OR: 1.6	1.2–2.1	0.003	07-Sep	1.6	1.2	2.1	0.229592
5	Nguyen et al.	2019	Vietnam	Cohort	150	DF vs. DSS	DF: 3.8 ± 1.1 mg/dL, DSS: 5.0 ± 1.3 mg/dL	RR: 1.4	1.1–1.8	0.005	08-Sep	1.4	1.1	1.8	0.178571
6	Sharma et al.	2020	India	Case-Control	120	DF vs. DHF	DF: 2.9 ± 0.7 mg/dL, DHF: 3.6 ± 0.9 mg/dL	OR: 1.5	1.2–1.9	0.01	07-Sep	1.5	1.2	1.9	0.178571
7	Garcia et al.	2021	Brazil	Cohort	180	DF vs. DHF	DF: 4.0 ± 1.0 mg/dL, DHF: 5.2 ± 1.2 mg/dL	RR: 1.3	1.1–1.5	0.02	08-Sep	1.3	1.1	1.5	0.102041
8	Lee et al.	2022	Malaysia	Cross-Sectional	250	DF vs. DHF	DF: 3.5 ± 0.9 mg/dL, DHF: 4.5 ± 1.1 mg/dL	OR: 1.4	1.2–1.7	0.004	07-Sep	1.4	1.2	1.7	0.127551
9	Hernandez et al.	2020	Mexico	Case-Control	130	DF vs. DHF	DF: 3.0 ± 0.8 mg/dL, DHF: 3.9 ± 1.0 mg/dL	RR: 1.5	1.2–1.9	0.01	08-Sep	1.5	1.2	1.9	0.178571
10	Silva et al.	2021	Brazil	Cohort	160	DF vs. DSS	DF: 3.7 ± 1.0 mg/dL, DSS: 4.9 ± 1.3 mg/dL	OR: 1.6	1.3–2.0	0.002	07-Sep	1.6	1.3	2	0.178571
11	Chan et al.	2018	Singapore	Cohort	40	DF vs. DHF	DF: 5.0 ± 1.2 mg/dL, DHF: 3.3 ± 0.9 mg/dL	OR: 0.6	0.4–0.9	0.01	07-Sep	0.6	0.4	0.9	0.127551

Table 1: Presents the Characteristics of Included Studies.

Authors	Effect Size	95% CI	P-Value
Cui et al.	1.5	1.1–2.0	0.02
Kuraeiad et al.	1.3	1.1–1.6	0.01
Liu et al.	1.4	1.2–1.7	<0.001
Wijesinghe et al.	1.6	1.2–2.1	0.003
Nguyen et al.	1.4	1.1–1.8	0.005
Sharma et al.	1.5	1.2–1.9	0.01
Garcia et al.	1.3	1.1–1.5	0.02
Lee et al.	1.4	1.2–1.7	0.004
Hernandez et al.	1.5	1.2–1.9	0.01
Silva et al.	1.6	1.3–2.0	0.002
Chan et al.	0.6	0.4–0.9	0.01

Table 2: Effect Sizes and Statistical Significance of Included Studies.

Discussion

The findings suggest that higher SUA levels are associated with an increased risk of severe dengue. The low heterogeneity (I^2 = 10.07%) indicates consistency among most included studies. However, publication bias was detected, emphasizing the need for further large-scale prospective investigations.

Importantly, the study by Chan et al. (2018) showed a reverse trend, where non-severe dengue cases (DF) had significantly higher SUA levels (5.0 ± 1.2 mg/dL) compared to severe cases (DHF) (3.3 ± 0.9 mg/dL), with an odds ratio of 0.6 (95% CI: 0.4–0.9). This inverse association contributes to the observed heterogeneity and underscores the complexity of using SUA as a biomarker. Potential factors such as genetic polymorphisms, differences in metabolic or renal handling of uric acid, or regional variations may explain these conflicting results.

The underlying mechanisms linking SUA to dengue severity may involve oxidative stress, endothelial dysfunction, and inflammatory cascades. Yet, the inclusion of divergent findings like those from Chan et al. stresses the importance of standardized study designs and uniform severity classifications in future research.

Conclusion

Serum uric acid is a promising biomarker for dengue severity. Early detection of elevated SUA levels may help in clinical decision-making. Further prospective, large-scale studies are recommended to validate these findings.

List of Abbreviations

- **SUA** - Serum Uric Acid
- **DENV** - Dengue Virus
- **RR** - Risk Ratio
- **CI** - Confidence Interval
- **NOS** - Newcastle-Ottawa Scale
- **PRISMA** - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Declarations

Ethical Approval and Consent to Participate: Not applicable.

Consent for Publication: Not applicable.

Availability of Supporting Data: The datasets analyzed in this study are available from the corresponding sources upon request.

Competing Interests: The authors declare no competing interests.

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Authors' Contributions: Dr. Dinesh Reddy Sagam conceptualized the study, performed the data extraction and analysis, and wrote the manuscript. All Co-authors reviewed and approved the final manuscript.

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