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Research Article

SEVERE DENGUE IN CHILDREN: CLINICAL SPECTRUM, NEUROLOGICAL COMPLICATIONS, AND CONTEMPORARY MANAGEMENT - A SYSTEMATIC REVIEW

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Abstract

Background: Dengue can progress rapidly in children to severe plasma leakage, bleeding, organ dysfunction, or disabling neurological disease. **Objective**: To synthesize evidence on the clinical spectrum, neurological complications, prognostic features, and contemporary management of severe pediatric dengue. **Methods**: PubMed/MEDLINE and Europe PMC were searched from January 1, 2010, through August 25, 2026, for pediatric severe dengue, neurological disease, critical care, organ dysfunction, prognosis, and outcomes. Studies involving patients aged 0–18 years or reporting separable pediatric data were eligible. One reviewer performed screening, extraction, and design-specific risk-of-bias assessment. Heterogeneous findings were synthesized narratively. **Results**: The searches identified 2,798 records; 1,324 duplicates were removed, 1,474 records were screened, and 495 full-text reports were assessed. After 414 exclusions, 81 studies were included: 74 addressing severe dengue or critical care and seven focused on neurological disease. Twenty-eight had high risk of bias and 53 had some concerns. Severe disease involved plasma leakage, shock, bleeding, and hepatic, cardiac, respiratory, renal, or multiorgan dysfunction. Serial perfusion, hematocrit, urine-output, respiratory, fluid-balance, and organ-function trends were more informative than isolated measurements. Neurological presentations included encephalopathy, encephalitis, seizures, acute necrotizing encephalopathy, demyelination, stroke or hemorrhage, and neuromuscular syndromes. Management remained supportive and phase-directed, emphasizing titrated isotonic crystalloid, reassessment, recognition of bleeding and organ dysfunction, avoidance of unnecessary fluid and prophylactic platelet transfusion, and targeted intensive care. Evidence supporting dengue-specific antivirals or routine immunomodulation was insufficient. **Conclusions**: Severe pediatric dengue is a time-sensitive multisystem disorder. Early recognition of the critical phase, serial hemodynamic assessment, judicious fluid therapy, and prompt treatment of bleeding and organ failure remain central. Altered consciousness or seizures require simultaneous evaluation for systemic encephalopathy and direct or immune-mediated neurological disease, followed by structured neurological and developmental surveillance when major involvement occurs.

Keywords: Dengue, Severe dengue, Children, Dengue shock syndrome, Neurological complications, Encephalitis, Fluid therapy, Critical care.

INTRODUCTION

Dengue is caused by four antigenically distinct dengue virus serotypes and is transmitted principally by Aedes aegypti. Its global burden has increased markedly, with the World Health Organization (WHO) reporting 14.6 million cases in 2024. Most infections are asymptomatic or self-limited, but a minority progress to severe plasma leakage, shock, severe bleeding, or organ impairment [1,2,8]. Children may deteriorate rapidly during defervescence because a relatively modest absolute fluid loss can produce major hemodynamic consequences, while compensated shock may initially preserve blood pressure. The 2009 WHO classification organizes symptomatic infection as dengue without warning signs, dengue with warning signs, and severe dengue [1]. In pediatric cohorts, the revised classification improves sensitivity for identifying clinically severe illness, although specificity is lower than that of the earlier dengue hemorrhagic fever/dengue shock syndrome framework [3]. The practical value of classification lies in directing observation and treatment rather than replacing clinical judgment. Neurological involvement has become increasingly recognized. Altered consciousness in dengue may reflect shock, hepatic failure, electrolyte disturbance, hypoglycemia, hypoxemia, intracranial bleeding, or drug effects; however, direct neuroinvasion and postinfectious immune-mediated syndromes also occur.

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Distinguishing encephalopathy from encephalitis and immune-mediated disease matters because diagnostic testing, prognostic counseling, rehabilitation, and selected adjunctive treatments differ [4–7]. Management remains principally supportive. The central therapeutic challenge is to restore perfusion during active leakage without producing avoidable fluid overload as vascular integrity returns. Contemporary bedside assessment therefore emphasizes illness phase, perfusion, hematocrit trajectory, urine output, respiratory status, and response to each intervention [1,2,8]. This review integrates recent pediatric evidence with established guidance and gives particular attention to neurological syndromes and critical-care decisions.

METHODS

Review design and reporting

This systematic review and clinical update was developed with reference to PRISMA 2020 [9]. No protocol was registered prospectively; this is acknowledged as a limitation. The review question was: among children and adolescents with dengue, what clinical manifestations, neurological complications, prognostic features, management strategies, and outcomes characterize severe infection?

Information sources and search strategy

PubMed/MEDLINE and Europe PMC were searched from January 1, 2010, to August 25, 2026. Search concepts

combined dengue and pediatric terms with severe disease, neurological complications, prognostic features, critical-care management, organ dysfunction, and clinical outcomes. The complete PubMed strategy was:

(dengue[Title/Abstract]) AND (child*[Title/Abstract] OR pediatric*[Title/Abstract] OR paediatric*[Title/Abstract] OR adolescen*[Title/Abstract] OR infant*[Title/Abstract]) AND ("severe dengue"[Title/Abstract] OR "dengue shock"[Title/Abstract] OR neurolog*[Title/Abstract] OR encephal*[Title/Abstract] OR mening*[Title/Abstract] OR myelit*[Title/Abstract] OR "Guillain-Barre"[Title/Abstract] OR seizure*[Title/Abstract] OR "critical care"[Title/Abstract] OR "intensive care"[Title/Abstract] OR "organ failure"[Title/Abstract] OR "organ dysfunction"[Title/Abstract] OR hemorrhag*[Title/Abstract] OR haemorrhag*[Title/Abstract] OR bleed*[Title/Abstract] OR "plasma leakage"[Title/Abstract] OR "capillary leak"[Title/Abstract] OR "capillary leakage"[Title/Abstract] OR myocard*[Title/Abstract] OR "liver failure"[Title/Abstract] OR "hepatic failure"[Title/Abstract] OR "acute kidney injury"[Title/Abstract] OR "renal failure"[Title/Abstract] OR "mechanical ventilation"[Title/Abstract] OR mortality[Title/Abstract] OR prognos*[Title/Abstract] OR outcome*[Title/Abstract]) AND (2010/01/01:2026/08/25[Date - Publication]).

An equivalent title/abstract query was used in Europe PMC. Reference lists of major guidelines and systematic reviews were searched for additional clinically relevant studies. LILACS was planned because of the importance of Latin American evidence, but automated access was blocked during the review; this limitation may have reduced retrieval of regional reports.

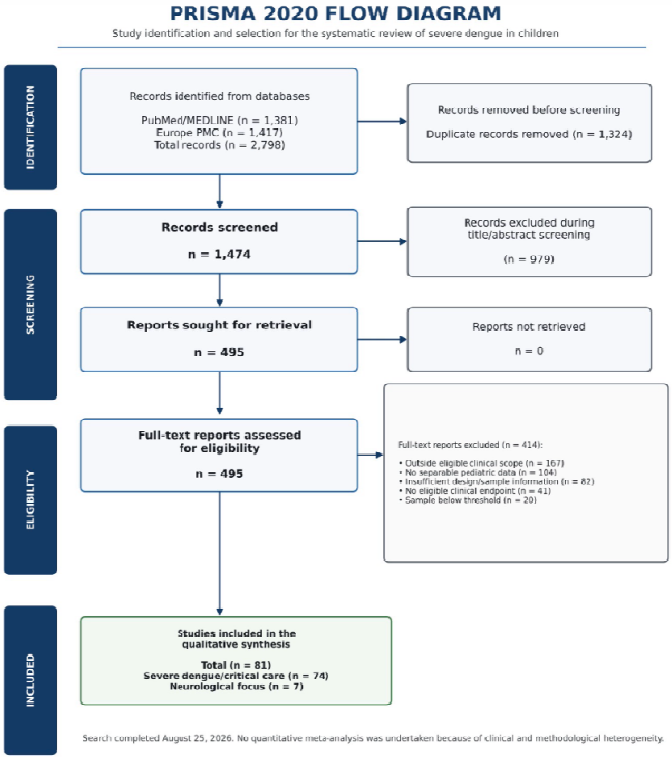
Eligibility criteria

Original studies were eligible when they: (1) included patients aged 0–18 years or reported separable pediatric data; (2) evaluated laboratory-confirmed or clinically classified dengue; and (3) described severe dengue, dengue shock syndrome, neurological disease, critical-care management, organ dysfunction, prognosis, or relevant clinical outcomes. Cohort, case-control, cross-sectional, diagnostic-accuracy, clinical prediction-model, registry, and interventional studies were eligible. Biomarker and prediction studies were retained only when they evaluated a clinically relevant pediatric endpoint, such as severe dengue, shock, mechanical ventilation, organ failure, or mortality. Neurological series required at least five patients; other clinical studies generally required at least 30 participants unless they evaluated a distinct intervention or uncommon severe phenotype. Excluded records comprised isolated case reports, narrative reviews, editorials, protocols without outcomes, vaccine-effectiveness or immunogenicity studies, vector or knowledge-attitude studies, purely mechanistic or genetic investigations without an eligible clinical management or outcome question, non-severe studies outside the stated review outcomes, and mixed-age or mixed-etiology reports without separable pediatric dengue data. Systematic reviews and guidelines were retained only for contextual synthesis.

Study selection, extraction, and appraisal

Records were deduplicated by PMID, DOI, and normalized title. One reviewer (VMMC) screened titles and abstracts, assessed potentially eligible reports, rechecked exclusions, and extracted data using prespecified criteria. Extracted variables included country, design, population, sample size, dengue definition, severity category, neurological syndrome, interventions, and outcomes. Both authors contributed to the clinical interpretation of the extracted evidence and critically reviewed the narrative synthesis. Risk of bias was assessed by VMMC using design-appropriate tools: Cochrane RoB 2 for randomized trials, QUADAS-2 for diagnostic-accuracy studies, PROBAST for clinical prediction-model studies, and the relevant Joanna Briggs Institute checklist for cohort, case-control, analytical cross-sectional, and case-series designs. Overall concern was derived from the applicable domains rather than a numerical quality score and was categorized as low, some concerns, or high. Studies were not excluded solely because of risk of bias; the judgments informed the strength and wording of the narrative synthesis. The study-level assessments are reported in Supplementary Table S2. Because the literature was heterogeneous and many studies were retrospective or single-center, no pooled effect estimate was calculated. Findings from uncontrolled intervention series were treated as hypothesis-generating.

RESULTS



Source: Authors' own elaboration in accordance with the PRISMA 2020 statement.

Figure 1. PRISMA 2020 flow diagram for study identification and selection

Figure legend: The PRISMA 2020 flow diagram summarizes study identification, screening, retrieval, eligibility assessment, and inclusion. The searches identified 2,798 records, of which 1,324 duplicates were removed. Among 1,474 unique records screened, 979 were excluded during title and abstract screening. All 495 reports sought for retrieval were obtained and assessed for eligibility. After full-text assessment, 414 reports were excluded because they were outside the core clinical, neurological, or management scope or did not address an eligible severe or neurological outcome (n = 167), involved mixed populations without separable pediatric dengue data (n = 104), provided insufficient design or sample information (n = 82), were mechanistic, genetic, or otherwise lacked an eligible clinical endpoint (n = 41), or had samples below the prespecified threshold (n = 20). Eighty-one primary studies were included in the qualitative synthesis: 74 addressing severe dengue or critical care and seven with a neurological focus. No quantitative meta-analysis was performed because of clinical and methodological heterogeneity.

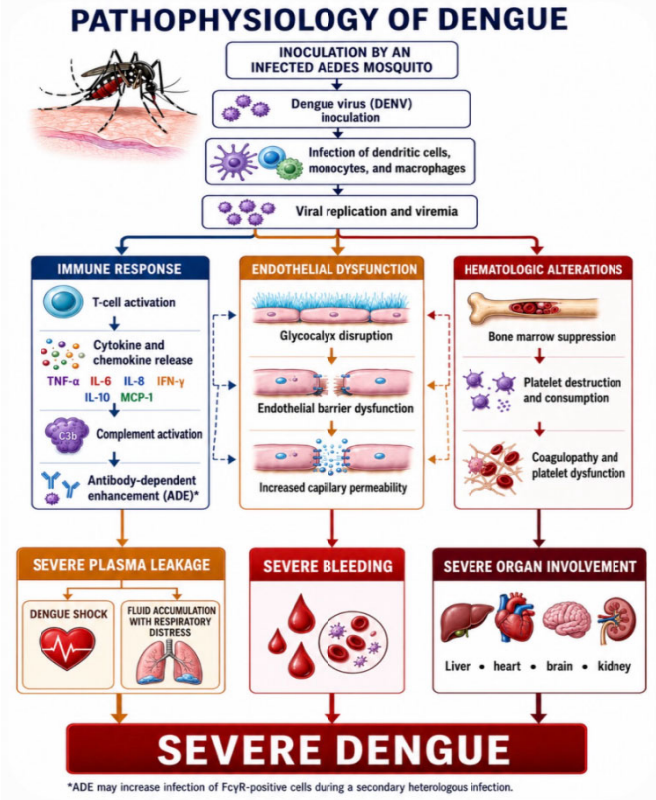
The detailed search strings and audit counts are provided in Supplementary Appendix S1.

Study selection and evidence characteristics

The expanded searches identified 2,798 records: 1,381 from PubMed/MEDLINE and 1,417 from Europe PMC. After removal of 1,324 duplicates, 1,474 unique records were screened; 979 were excluded during title and abstract screening. All 495 reports sought for retrieval were obtained and assessed for eligibility. Of these, 414 were excluded for the reasons detailed in Figure 1, leaving 81 primary clinical studies in the qualitative synthesis. Seventy-four addressed severe dengue, shock, organ dysfunction, prognostic features, critical care, or management, and seven focused primarily on neurological complications. Most were hospital-based observational studies from South or Southeast Asia and Latin America. Definitions of severity, timing of measurements, admission thresholds, and access to intensive care varied substantially, precluding a defensible meta-analysis. Risk-of-bias appraisal identified high concern in 28 studies and some concerns in 53; no study was judged free of important methodological concerns across all applicable domains. Recurrent limitations included retrospective design, referral bias toward severe disease, incomplete control of confounding, inconsistent virological confirmation, mixed WHO 1997 and 2009 classifications, small neurological samples, model overfitting or absent external validation, and limited long-term follow-up. Randomized evidence for specific resuscitation fluids or disease-directed adjunctive therapy was sparse. Study-level judgments are provided in Supplementary Table S2. Representative pediatric studies addressing neurological complications, hemodynamic assessment, prognostic factors, and selected therapeutic interventions are summarized in Table 3.

Clinical phases and spectrum of severe disease

The clinical course of symptomatic dengue is commonly described in three phases febrile, critical, and recovery although not every child progresses through all three. The febrile phase typically lasts 2–7 days and may include high fever, headache, retro-orbital pain, myalgia, nausea, vomiting, rash, leukopenia, and thrombocytopenia. The critical phase generally begins around defervescence and usually lasts 24–48 hours. During this interval, a transient increase in vascular permeability may develop even as fever subsides and the child appears initially to improve. Warning signs include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy or restlessness, hepatomegaly, and an increase in hematocrit accompanied by a rapid fall in platelet count [1,2,8]. Warning signs identify children who require closer observation, but their absence does not exclude subsequent severe disease. During recovery, endothelial-barrier function improves and extravasated fluid is reabsorbed. Appetite, urine output, and hemodynamic status generally improve, while hematocrit returns toward baseline and the platelet count begins to recover. Intravenous fluid that remains appropriate during active leakage may cause pulmonary edema or other manifestations of fluid overload once reabsorption begins; fluid prescriptions must therefore be reassessed and reduced promptly as the clinical phase changes [1,2]. The interacting viral, immunological, endothelial, and hematological mechanisms underlying progression to severe dengue are summarized in Figure 2.



Source: Authors' own elaboration.

Figure 2. Pathophysiology of dengue and progression to severe dengue

Figure legend: Dengue virus infection engages interacting viral, immunological, endothelial, and hematological pathways. Viral replication and the host response including cytokine and chemokine release and complement activation can produce predominantly functional and transient disruption of the endothelial barrier. Antibody-dependent enhancement may amplify viral infection and immune activation in some secondary heterologous infections, but it is neither necessary nor sufficient to explain every case of severe dengue. Increased vascular permeability may cause hemoconcentration, serous effusions, intravascular volume depletion, shock, and respiratory compromise. Concurrent bone marrow suppression, platelet destruction or consumption, platelet dysfunction, coagulation abnormalities, hepatic injury, and shock can interact to increase bleeding risk. Severe hepatic, cardiac, neurological, renal, or other organ involvement may coexist with plasma leakage or occur as the predominant manifestation. The figure is a conceptual synthesis; the relative contribution of each pathway varies among patients and across phases of illness.

Under the WHO classification, severe dengue is defined by one or more of three manifestations: severe plasma leakage leading to shock or fluid accumulation with respiratory distress; severe bleeding; or severe organ involvement [1,2,8]. Plasma leakage is central to many severe pediatric presentations, but it should not be presented as a universal prerequisite because major hemorrhage or organ dysfunction may predominate. In children, tachycardia, cool extremities, prolonged capillary refill, weak peripheral pulses, narrowing pulse pressure, oliguria, and altered mental status may precede hypotension. Because hypotension is a late sign, a child with apparently normal systolic blood pressure may already have compensated shock and require urgent phase-appropriate assessment and treatment [1,2].

Across pediatric cohorts, ascites, pleural effusion, hemoconcentration, hepatomegaly, hypoalbuminemia, persistent vomiting, and marked thrombocytopenia have been associated with severe disease [10–14]. However, their predictive value depends on illness day, case definition, referral setting, baseline values, and the prevalence of severe

disease. These findings may support risk stratification and serial reassessment, but individual variables or study-derived cutoffs should not be used as universal treatment thresholds without external validation. Severe bleeding may occur with or without profound thrombocytopenia and is usually multifactorial, reflecting interactions among prolonged or recurrent shock, platelet dysfunction, coagulopathy, hepatic impairment, mucosal injury, and invasive procedures [1,2,15,16]. Hematocrit must therefore be interpreted dynamically against the child's baseline, clinical perfusion, bleeding, illness phase, and administered fluids. A rising hematocrit with worsening perfusion supports ongoing plasma leakage, whereas a falling hematocrit in an unstable child should raise concern for occult or overt hemorrhage rather than being assumed to indicate resolution of leakage [1,2,15]. Fatal pediatric series have consistently identified active bleeding, respiratory failure, recurrent shock, and hepatic, renal, or multiorgan dysfunction as features of the highest-risk phenotype [15,16].

Organ involvement

Hepatic involvement ranges from asymptomatic aminotransferase elevation to clinically apparent hepatitis, impaired synthetic function, coagulopathy, hyperammonemia, encephalopathy, and acute liver failure. A systematic review and meta-analysis found that dengue-associated acute liver failure was more frequent in children than in adults and was associated with substantial mortality once established [17]. Aminotransferase elevation should be interpreted cautiously because aspartate aminotransferase may also originate from injured skeletal or cardiac muscle, particularly when myositis or rhabdomyolysis is present [7,17]. Hypoglycemia, worsening lactate, prolongation of prothrombin time or international normalized ratio, encephalopathy, rising bilirubin, and progressive metabolic instability indicate a high-risk phenotype requiring intensive monitoring and consideration of early consultation with a liver or transplant center when available [15–17]. Cardiovascular involvement is heterogeneous and reflects the interaction of intravascular volume depletion, altered vascular tone, myocardial dysfunction, and, less commonly, clinically overt myocarditis. Transient systolic or diastolic abnormalities, arrhythmias, elevated troponin or natriuretic peptides, and echocardiographic evidence of myocardial impairment have been described in children with severe dengue [18–20]. Serial echocardiography in dengue shock syndrome suggests that reduced preload caused by plasma leakage is often the dominant hemodynamic abnormality, although reversible myocardial dysfunction may coexist [20]. This distinction is clinically important: persistent or recurrent shock should prompt reassessment for ongoing leakage, occult bleeding, myocardial dysfunction, vasoplegia, and increased intrathoracic or intra-abdominal pressure rather than automatic repetition of fluid boluses [1,2,20]. Respiratory compromise may result from large pleural effusions, pulmonary edema during active leakage or fluid reabsorption, acute respiratory distress syndrome, pulmonary hemorrhage, pneumonia, encephalopathy, or cumulative fluid overload. Respiratory failure and active bleeding have been strongly associated with fatal outcomes in pediatric severe dengue, while mechanically ventilated cohorts represent a particularly high-risk population [15,16,25]. Because respiratory deterioration may arise from both insufficient perfusion and excess intravascular or extravascular fluid, management should be guided by illness phase, hemodynamic findings, fluid balance, imaging, and response to prior therapy [1,2,15,20,25]. Acute kidney injury is usually multifactorial and may reflect renal hypoperfusion, prolonged or recurrent shock, rhabdomyolysis, hemolysis, nephrotoxic exposure, direct or immune-mediated renal injury, or multiorgan dysfunction. Its appearance should prompt reassessment of perfusion, cumulative fluid balance, medication exposure, urine output, and the severity of accompanying organ failure [7,15–17,25]. Hyperinflammatory presentations resembling secondary hemophagocytic lymphohistiocytosis have also been reported, but substantial clinical and laboratory overlap with severe dengue complicates diagnosis. Evidence supporting immunomodulatory treatment remains limited to uncontrolled experience and should not be generalized to routine dengue care [21].

Neurological complications

As summarized in Table 1, neurological manifestations can be organized into four mechanistic groups: systemic encephalopathy; direct neuroinvasive disease; immune-mediated complications; and neurological injury secondary to vascular, hematologic, muscular, or metabolic disturbances [4–7]. These categories can overlap. Encephalopathy is the most common neurological presentation and may accompany shock, hepatic failure, hypoglycemia, hyponatremia, hypoxemia, uremia, cerebral edema, intracranial bleeding, or medication exposure. The neurological examination must occur in parallel with immediate correction of life-threatening systemic abnormalities. Encephalitis is suggested by fever with altered mental status lasting at least 24 hours, seizures, focal deficits, inflammatory cerebrospinal fluid, compatible magnetic resonance imaging, or dengue RNA/IgM in cerebrospinal fluid after competing etiologies have been assessed. Normal cerebrospinal fluid does not exclude dengue-associated neurological disease. In a pediatric cohort with dengue RNA detected in cerebrospinal fluid, seizures, encephalitis, meningitis, focal signs, ataxia, and motor deficits were documented, and neurological recovery sometimes required months [5]. Acute necrotizing encephalopathy is a severe clinicoradiological phenotype characterized by rapid deterioration, seizures, and symmetric thalamic lesions, often with hemorrhage. A systematic review of 162 dengue-associated encephalitis-spectrum cases found acute necrotizing encephalopathy to be a major phenotype; mortality and disability were substantial [6].

Postinfectious and peripheral syndromes include acute disseminated encephalomyelitis, transverse myelitis, Guillain–Barré syndrome, brachial neuritis, myositis, rhabdomyolysis, and hypokalemic paralysis. Their timing may be para-infectious or delayed. A 2025 systematic review of neuromuscular reports found Guillain–Barré syndrome, myositis/myopathy, rhabdomyolysis, and hypokalemic paralysis most frequently represented, although publication bias toward unusual cases was unavoidable [7]. Neurological outcomes are not uniformly benign. In a cohort of 56 children with dengue-associated acute encephalitis syndrome, 39.3% had neurological sequelae, cognitive or behavioral impairment was common, six children had severe disability, and one died after discharge [4]. A 2026 multicenter registry of 47 Argentine children with atypical dengue found encephalitis in 60%, myositis in 38%, pediatric intensive-care admission in 32%, and residual weakness, seizures, or myocardial fibrosis in four patients, although no deaths occurred [22]. These findings

support planned neurological follow-up rather than discharge without reassessment.

Diagnostic approach

During the first week of illness, nucleic-acid amplification testing or detection of the nonstructural protein 1 (NS1) antigen is most useful because viremia and circulating antigen concentrations decline thereafter. Dengue-specific IgM generally becomes more informative later in the course, although its timing and magnitude may differ between primary and secondary infections [1,2]. Test interpretation should therefore incorporate the day of illness, previous dengue infection or vaccination, possible cross-reactivity with other flaviviruses, and local assay performance. A negative result obtained with a single method does not exclude dengue when sampling occurs outside that test's optimal diagnostic window; repeat testing or a complementary direct or serological assay may be necessary [1,2].

Baseline and serial assessment should include a complete blood count with hematocrit and platelet count, glucose, electrolytes, renal and hepatic indices, and a coagulation profile when severe disease, hepatic dysfunction, or clinically significant bleeding is suspected [1,2,15,17]. Lactate may assist in assessing tissue hypoperfusion and prognosis in shock, but it should be interpreted alongside serial clinical and hemodynamic findings rather than as an isolated threshold [26]. The frequency of repeat testing should be individualized according to illness phase, warning signs, hemodynamic status, organ involvement, and response to treatment [1,2]. Imaging should be performed to answer a defined clinical question. Ultrasonography can demonstrate ascites, pleural effusion, gallbladder-wall edema, or other evidence of plasma leakage, whereas chest imaging may help evaluate respiratory deterioration, pleural effusions, pulmonary edema, hemorrhage, or another pulmonary process [1,2]. Electrocardiography and echocardiography are appropriate when arrhythmia, persistent or recurrent shock, disproportionate tachycardia, elevated cardiac biomarkers, or myocardial dysfunction is suspected. Serial echocardiographic assessment may help distinguish reduced preload from coexisting myocardial impairment and thereby refine fluid and vasoactive management [18–20].

In children with altered consciousness, focal neurological deficits, or seizures, urgent assessment should include glucose, sodium, calcium, oxygenation, perfusion, blood pressure, and hepatic and renal function because shock, hypoglycemia, electrolyte disturbances, hypoxemia, hepatic failure, uremia, and intracranial bleeding may produce secondary encephalopathy [4–7]. The differential diagnosis should also include bacterial meningitis, herpesvirus encephalitis, malaria, Japanese encephalitis, chikungunya, Zika, scrub typhus, leptospirosis, and toxic or metabolic causes according to local epidemiology and individual exposure [4–7]. Lumbar puncture may support the diagnosis of meningitis or encephalitis but should be deferred when shock, severe coagulopathy, suspected intracranial hypertension, or cardiorespiratory instability makes the procedure unsafe. Normal routine cerebrospinal-fluid findings do not exclude dengue-associated neurological disease, and detection of DENV RNA or intrathecal IgM may provide supportive evidence in selected cases [4,5]. Magnetic resonance imaging is preferred when encephalitis, acute necrotizing encephalopathy, demyelination, myelitis, ischemic stroke, or intracranial hemorrhage is suspected; computed tomography remains useful when magnetic resonance imaging is unavailable or urgent detection of hemorrhage or mass effect is required [4–7].

Contemporary management

Triage and monitoring: Children without warning signs who can drink, urinate, and return promptly may be managed as outpatients with oral fluids, acetaminophen, and explicit return precautions. Aspirin and nonsteroidal anti-inflammatory drugs should be avoided. Admission is indicated for shock, significant bleeding, organ dysfunction, inability to maintain oral intake, concerning warning signs, major comorbidity, infancy with clinical concern, or unreliable follow-up [1,2]. Monitoring frequency should match the illness phase and severity. During evolving leakage, serial pulse pressure, capillary refill, extremity temperature, mental status, respiratory effort, urine output, hematocrit, and fluid balance are more useful than any single observation. Weight-based calculations are essential, but obese children may require an appropriate weight scalar and closer evaluation of response.

Fluid therapy and shock: Isotonic crystalloid is the initial resuscitation fluid for dengue shock. The volume and rate should reflect whether shock is compensated or hypotensive, the degree of respiratory compromise, and prior fluids. After each bolus or rate change, the child should be reassessed before further fluid is given. Improvement in perfusion with stable or falling respiratory burden supports de-escalation; persistent instability requires reassessment of hematocrit and alternative mechanisms. The practical interpretation of shock according to the hematocrit trajectory and the corresponding immediate clinical responses are summarized in Table 2. A high or rising hematocrit with shock suggests continuing leakage and possible need for additional carefully titrated fluid. A low or rapidly falling hematocrit with instability suggests occult bleeding and may require blood rather than more crystalloid. Persistent shock with an unchanged hematocrit should raise concern for myocardial dysfunction, vasoplegia, abdominal compartment physiology, or an incorrect diagnosis. In a 2025 cohort, greater resuscitation-fluid load and the balance between colloid and crystalloid were associated with outcomes, but confounding by severity limits causal inference [23]. Hyperosmolar sodium lactate reduced fluid accumulation in one small randomized trial, yet it is not established as routine therapy [24]. As leakage resolves, previously extravasated fluid returns to the circulation. Failure to reduce intravenous fluids can then cause pulmonary edema and other overload. Diuretics are generally inappropriate during active shock but may be considered after hemodynamic stability and clear evidence of reabsorption with fluid overload.

Blood products and critical care: Platelet count alone is not an indication for prophylactic platelet transfusion in a clinically stable child without significant bleeding. Transfusion decisions should be based on the presence and severity of bleeding, hemodynamic status, hematocrit trajectory, coagulation abnormalities, and the anticipated need for an invasive procedure rather than on an isolated platelet threshold [1,2]. Major hemorrhage should be recognized promptly and treated with appropriate blood components according to the estimated blood loss, clinical response, and local transfusion protocols. A falling hematocrit accompanied by persistent hemodynamic instability should raise concern for occult

bleeding rather than automatic resolution of plasma leakage [1,2,15]. Unnecessary invasive procedures should be minimized because thrombocytopenia, platelet dysfunction, coagulopathy, hepatic injury, and shock may act together to increase bleeding risk [1,2,15]. Vasoactive support is appropriate when shock persists after carefully assessed intravascular volume restoration or when myocardial dysfunction or vasoplegia is present. Before escalating vasoactive therapy, clinicians should reassess for ongoing plasma leakage, occult hemorrhage, inadequate intravascular replacement, myocardial dysfunction, and obstructive physiology [1,2,20]. Mechanical ventilation may be required for respiratory failure, severe encephalopathy, or other standard indications, but induction and positive-pressure ventilation can reduce venous return and worsen preload-dependent shock; hemodynamic preparation and close reassessment are therefore essential [1,2,20,25]. Renal replacement therapy, liver-center consultation or advanced liver support, and neurocritical care should be considered according to standard organ-failure indications and local resources [4–7,17,25].

Neurological treatment: Seizures should be treated promptly using standard pediatric protocols while hypoglycemia, electrolyte abnormalities, hypoxemia, impaired perfusion, and fever are identified and corrected [1,2,4–7]. Because altered consciousness and seizures in a child with suspected dengue may also reflect bacterial meningitis, herpesvirus encephalitis, malaria, or another treatable infection, empirical antimicrobials or acyclovir may be appropriate until these alternatives have been reasonably excluded, according to the clinical presentation and local epidemiology [4–7]. Suspected intracranial hypertension should be managed according to established pediatric neurocritical-care principles, with particular attention to avoiding hypotension, hypoxemia, fever, and unnecessary hypotonic fluid [4–6]. There is no proven dengue-specific antiviral or universally effective immunomodulatory treatment for dengue-associated neurological disease [1,2,4–7]. Corticosteroids, intravenous immunoglobulin, or plasma exchange may be considered only when the clinical, imaging, cerebrospinal-fluid, or electrophysiological findings support a defined immune-mediated syndrome, such as acute disseminated encephalomyelitis or Guillain–Barré syndrome; these therapies are not indicated routinely for uncomplicated dengue encephalopathy [6,7]. Evidence for anakinra in hyperinflammatory severe dengue remains limited to uncontrolled observational experience. Although a retrospective series reported possible benefit, it cannot establish efficacy or support routine use [21].

Prognosis and follow-up

With early recognition and appropriate care, mortality from severe dengue can be kept low, but delayed presentation, repeated shock, respiratory failure, major bleeding, acute liver failure, and multiorgan dysfunction markedly worsen prognosis [15–17,25]. Admission lactate and coagulopathy may help identify high-risk children, although proposed thresholds require external validation [26]. Before discharge, the child should be afebrile, hemodynamically stable, tolerating oral intake, producing adequate urine, free of respiratory distress, and showing a stable or improving hematocrit and platelet trend. Children with encephalitis, prolonged seizures, weakness, ataxia, behavioral change, school difficulties, or critical illness should receive planned neurological, developmental, psychological, and rehabilitation follow-up [4,5].

DISCUSSION

This review reinforces three clinically important conclusions. First, severe pediatric dengue is a dynamic vascular and multisystem syndrome rather than a static laboratory diagnosis. Deterioration frequently occurs around defervescence, when increasing capillary permeability may produce intravascular volume depletion despite an apparent improvement in fever. Consequently, serial assessment of perfusion, pulse pressure, hematocrit trajectory, urine output, respiratory status, fluid balance, and response to each intervention is more informative than any isolated clinical or laboratory measurement [1,2,10–14]. Thrombocytopenia is common, but platelet count alone neither reliably defines severity nor justifies prophylactic platelet transfusion in a child without clinically significant bleeding [1,2,10,11]. Second, neurological disease in dengue extends well beyond nonspecific encephalopathy. Direct neuroinvasive, systemic or metabolic, immune-mediated, hemorrhagic, vascular, and neuromuscular mechanisms may coexist and produce overlapping presentations [4–7]. Immediate correction of shock, hypoxemia, hypoglycemia, electrolyte disturbances, hepatic dysfunction, and other systemic causes should therefore proceed in parallel with targeted evaluation for encephalitis, acute necrotizing encephalopathy, demyelination, stroke, intracranial hemorrhage, myelitis, Guillain–Barré syndrome, myositis, and rhabdomyolysis [4–7,22]. Recent pediatric cohorts documenting persistent cognitive, behavioral, seizure, and motor abnormalities support structured neurological, developmental, psychological, and rehabilitation follow-up after encephalitis or other major neurological involvement [4,5,22]. Third, contemporary management remains centered on phase-directed supportive care. Point-of-care ultrasonography and echocardiography can refine assessment of plasma leakage, preload, myocardial function, and alternative causes of persistent shock, while lactate and selected laboratory markers may assist with risk stratification [20,23,26]. Nevertheless, these tools supplement rather than replace repeated bedside evaluation. Candidate prognostic markers, clinical risk factors, obesity-associated risk estimates, machine-learning models, and severity scores remain promising but require external validation across populations and levels of care before routine implementation [26–30]. Likewise, hyperosmolar sodium lactate and immunomodulatory approaches such as anakinra cannot be recommended routinely on the basis of small trials or uncontrolled observational experience [21,24].

This review has several limitations. Only PubMed/MEDLINE and Europe PMC were reproducibly searched; the inability to search LILACS may have reduced retrieval of Latin American and non-English-language evidence. Screening, extraction, and risk-of-bias assessment were performed by one reviewer, increasing the possibility of selection, extraction, and appraisal errors despite prespecified criteria and internal consistency checks. The protocol was not prospectively registered, and deviations from an a priori plan cannot therefore be independently assessed. Many included studies were retrospective, single-center investigations conducted in referral hospitals, creating referral and severity bias and limiting generalizability.

Table 1. Mechanistic classification of neurological complications in pediatric dengue

Mechanism	Representative syndromes	Diagnostic clues	Management priorities
Systemic or secondary encephalopathy	Shock-related, hepatic, hypoglycemic, electrolyte-related, hypoxemic, uremic, or drug-related encephalopathy	Global altered consciousness; systemic derangement; CSF may be normal	Restore perfusion and oxygenation; correct glucose and electrolyte abnormalities; treat organ failure
Direct neuroinvasive disease	Encephalitis, meningitis, meningoencephalitis	Fever, altered mental status, seizures, or focal signs; CSF inflammation or DENV RNA/IgM may support the diagnosis	Exclude treatable infections; control seizures; provide neurocritical supportive care
Para- or postinfectious immune-mediated disease	ADEM, transverse myelitis, Guillain–Barré syndrome, brachial neuritis	Delayed or biphasic course; characteristic MRI, CSF, or electrophysiological findings	Provide syndrome-specific neurological care; consider corticosteroids, IVIG, or plasma exchange only when indicated
Vascular, hematologic, muscular, or metabolic injury	Intracranial hemorrhage, ischemic stroke, myositis, rhabdomyolysis, hypokalemic paralysis	Focal deficit, severe headache, muscle pain or weakness, elevated creatine kinase, or potassium abnormality	Stabilize dengue; obtain targeted imaging; manage bleeding, rhabdomyolysis, electrolyte disturbances, or stroke

Abbreviations: ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; DENV, dengue virus; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging.
Source: Authors' own elaboration.

Table 2. Practical interpretation of shock according to the hematocrit trajectory

Clinical state	Hematocrit pattern	Leading concern	Immediate response
Poor perfusion during the critical phase	High or rising	Ongoing plasma leakage with intravascular depletion	Administer carefully titrated isotonic crystalloid and reassess after each intervention
Persistent shock	Low or rapidly falling	Occult or overt bleeding	Search for hemorrhage and prepare appropriate blood replacement
Persistent shock	Little change	Inadequate resuscitation, myocardial dysfunction, vasoplegia, obstructive physiology, or an alternative diagnosis	Perform bedside reassessment; consider ultrasonography or echocardiography and vasoactive support
Respiratory distress after stabilization	Falling toward baseline with a positive fluid balance	Reabsorption phase and fluid overload	Reduce or stop intravenous fluid; provide oxygen or ventilatory support; consider diuresis only after hemodynamic stabilization

Note: Hematocrit must be interpreted in relation to the child's baseline value, illness phase, bleeding status, and administered fluids; it should never be used in isolation.
Source: Authors' own elaboration.

Table 3. Representative pediatric studies informing the synthesis

Study	Design and population	Principal finding	Interpretation
Srivastava et al., 2025 [4]	Follow-up study of 56 children with dengue-associated acute encephalitis syndrome	Neurological sequelae occurred in 39.3%; cognitive and behavioral impairment was common	Supports structured postdischarge follow-up
Bentes et al., 2021 [5]	Prospective follow-up of 56 children with DENV detected in CSF	Neurological recovery sometimes required months; CSF could be noninflammatory	Normal routine CSF findings do not exclude neurological disease
López et al., 2026 [22]	Ten-center registry of 47 children with atypical manifestations	Encephalitis occurred in 60%, myositis in 38%, and PICU admission in 32%	Atypical neurological and organ involvement is clinically important
Chanh et al., 2026 [20]	Prospective serial echocardiographic study of 90 children with DSS	Recurrent shock was mainly preload-limited; transient myocardial impairment coexisted	Hemodynamic reassessment can refine fluid-management decisions
Laoprasopwattana et al., 2014 [15]	Retrospective cohort of 238 children with severe dengue	Respiratory failure, bleeding, repeated shock, and liver and kidney failure clustered among deaths	Multiorgan dysfunction identifies the highest-risk patients
Luan et al., 2025 [23]	Cohort of children with DSS	Resuscitation-fluid exposure was associated with clinical outcomes	Both under-resuscitation and cumulative fluid overload should be avoided
Somasetia et al., 2014 [24]	Randomized trial involving 50 children with DSS	Hyperosmolar sodium lactate reduced fluid accumulation without a clear survival advantage	Evidence is insufficient to support routine use
Bhat et al., 2025 [21]	Retrospective uncontrolled series of children with severe dengue	Improvement after anakinra was reported in a hyperinflammatory phenotype	Findings are hypothesis-generating and do not establish efficacy

Abbreviations: CSF, cerebrospinal fluid; DENV, dengue virus; DSS, dengue shock syndrome; PICU, pediatric intensive care unit.
Source: Authors' own elaboration.

Twenty-eight studies were judged at high risk of bias and the remaining 53 had some concerns, particularly because of residual confounding, selective referral, small samples, incomplete follow-up, or absent external validation of prediction models. Definitions of severe dengue, neurological involvement, organ dysfunction, and clinical outcomes varied across studies and over time. Neurological evidence was additionally vulnerable to small samples, selective reporting of unusual phenotypes, inconsistent virological confirmation, and limited long-term follow-up [4–7]. Accordingly, cohort-specific frequencies should not be interpreted as population incidence estimates, and causal conclusions cannot be drawn from uncontrolled treatment series.

Future research should prioritize multicenter prospective pediatric cohorts using standardized WHO definitions, illness-day-specific sampling, uniform measures of plasma leakage and organ dysfunction, consistent neurological phenotyping, and long-term functional outcomes. Pragmatic trials are needed to refine fluid-resuscitation and de-escalation strategies, transfusion thresholds, hemodynamic monitoring, and treatment of dengue-associated acute liver failure and hyperinflammatory phenotypes [17,20,21,23,24]. Neurological studies should incorporate standardized cerebrospinal-fluid analysis, neuroimaging, electroencephalography, functional disability, cognition, behavior, sleep, and school-performance

measures, together with sufficiently long follow-up to characterize recovery and persistent morbidity [4–7,22].

Conclusion

Severe dengue in children is a rapidly evolving, multisystem disorder defined by severe plasma leakage, severe bleeding, or severe organ involvement. Hepatic injury, myocardial dysfunction, respiratory failure, acute kidney injury, and neurological complications may occur alone or in combination. Early recognition of warning signs and the critical phase, together with frequent reassessment of perfusion, hematocrit trajectory, urine output, respiratory status, fluid balance, and organ function, is essential to reduce avoidable deterioration.
Management remains supportive and phase-directed. Isotonic crystalloid should be carefully titrated to the child's hemodynamic status and response, with prompt evaluation for ongoing plasma leakage, occult hemorrhage, myocardial dysfunction, or alternative causes when shock persists. Intravenous fluid should be reduced as vascular permeability recovers to minimize fluid overload. Platelet count alone should not prompt prophylactic platelet transfusion in the absence of clinically significant bleeding. Neurological presentations require immediate correction of systemic derangements alongside targeted evaluation for encephalopathy, encephalitis, acute necrotizing encephalopathy, immune-mediated disorders, stroke, intracranial hemorrhage, and neuromuscular complications. No biomarker, prediction model, antiviral agent, or immunomodulatory therapy currently replaces repeated clinical assessment and appropriate supportive care. Children surviving dengue-associated encephalitis, critical illness, or another major neurological syndrome should receive structured neurological, developmental, psychological, and rehabilitation follow-up addressing seizures, motor function, cognition, behavior, sleep, and school reintegration.

Declarations

Author contributions: Vicente Manuel Martínez Cárdenas: Conceptualization, methodology, investigation, data curation, formal analysis, visualization, writing original draft, writing review and editing, and project administration. Vivian Rosario Mena Miranda: Conceptualization, clinical interpretation, validation, writing review and editing, and supervision. Both authors approved the final version of the manuscript and agreed to be accountable for the work.

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Conflicts of interest: The authors declare no conflicts of interest.

Ethics statement: Ethics approval was not required because this study synthesized previously published data and did not involve identifiable participants.

Data availability: Search strategies, screening counts, and the evidence map are included in the article and its supplementary appendix. No new participant-level dataset was generated.

Protocol registration: The review protocol was not prospectively registered.

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Supplementary Appendix S1. Search and screening audit

Search date: August 25, 2026. Date limits: January 1, 2010–August 25, 2026. PubMed/MEDLINE records exported: 1,381. Europe PMC records exported: 1,417. Total records identified: 2,798. Duplicates removed: 1,324. Unique records screened: 1,474. Records excluded at title/abstract screening: 979. Reports sought and retrieved: 495. Full-text reports excluded: 414. Primary studies included in the evidence map: 81 (74 severe-dengue/critical-care studies and seven neurologically focused studies).

Full-text exclusions comprised reports outside the eligible severe-dengue, neurological, critical-care, management, or clinical-outcome scope (n = 167); mixed populations without separable pediatric dengue data (n = 104); insufficient design or sample information (n = 82); mechanistic, genetic, or other reports without an eligible clinical endpoint (n = 41); and samples below the prespecified threshold (n = 20). The categories were mutually exclusive and sum to 414.

The complete PubMed/MEDLINE strategy is reported in Section 2.2. The Europe PMC title/abstract strategy was:

TITLE_ABS:dengue AND (TITLE_ABS:child* OR TITLE_ABS:pediatric* OR TITLE_ABS:paediatric* OR TITLE_ABS:adolescen* OR TITLE_ABS:infant*) AND (TITLE_ABS:"severe dengue" OR TITLE_ABS:"dengue shock" OR TITLE_ABS:neurolog* OR TITLE_ABS:encephal* OR TITLE_ABS:mening* OR TITLE_ABS:myelit* OR TITLE_ABS:"Guillain-Barre" OR TITLE_ABS:seizure* OR TITLE_ABS:"critical care" OR TITLE_ABS:"intensive care" OR TITLE_ABS:"organ failure" OR TITLE_ABS:"organ dysfunction" OR TITLE_ABS:hemorrhag* OR TITLE_ABS:haemorrhag* OR TITLE_ABS:bleed* OR TITLE_ABS:"plasma leakage" OR TITLE_ABS:"capillary leak" OR TITLE_ABS:"capillary leakage" OR TITLE_ABS:myocard* OR TITLE_ABS:"liver failure" OR TITLE_ABS:"hepatic failure" OR TITLE_ABS:"acute kidney injury" OR TITLE_ABS:"renal failure" OR TITLE_ABS:"mechanical ventilation" OR TITLE_ABS:mortality OR TITLE_ABS:prognos* OR TITLE_ABS:outcome*) AND FIRST_PDATE:[2010-01-01 TO 2026-08-25]

Record counts refer to the database exports generated on August 25, 2026. Because database indexing is dynamic, later execution of the same date-limited strategies may retrieve additional retrospectively indexed records. The original exports, deduplication log, screening decisions, full-text exclusion log, and extraction files should be retained by the authors as submission audit material.

Supplementary Table S1. Evidence map and complete citations of included primary studies

Year	Domain	Design	Reported n	Complete citation
2026	Neurological	Case series	47	López O, Tirao E, Juarez X, Piedra E, Ensinck G, Gaiano A, et al. Atypical manifestations of dengue in pediatric patients hospitalized during the 2023-2024 epidemic in Argentina: a multicenter registry. Eur J Pediatr. 2026;185(7):539. doi: 10.1007/s00431-026-07199-5.
2026	Severe dengue/critical care	Analytical cross-sectional study	346	Chowdhury AS, Parveen S, Ponir FH, Roy S, Hossain F. Clinical Spectrum and Predictors of Severe Dengue Among Hospitalized Children in a Tertiary Care Hospital in Bangladesh. Cureus. 2026;18(4). doi: 10.7759/cureus.107326.
2026	Neurological	Retrospective cohort study	176	Birne RO, Neri MA, Rossetti CA, Sena MO, Duarte LPR, Takenami LI, et al. Clinical features of dengue-associated myositis in children: a retrospective study. J Pediatr (Rio J). 2026;102(4):101549. doi: 10.1016/j.jped.2026.101549.
2026	Severe dengue/critical care	Retrospective cohort study	114	Swaroop S, Kumar R, Srivastava P, Mishra A, Tanti SK, Mukherjee B, et al. Hyperlactatemia, Coagulopathy, and Hepatic Injury as Prognostic Markers of Mortality in Pediatric Dengue: A Single-Center Retrospective Cohort Study. Cureus. 2026;18(1). doi: 10.7759/cureus.101498.
2026	Severe dengue/critical care	Observational cohort or comparative study	113	Le Phuoc T, Phung NTN. Serial Biomarker Monitoring Reveals Progressive Cardiac Injury in Pediatric Dengue Shock Syndrome. Pediatr Infect Dis J. 2026. doi: 10.1097/INF.0000000000005256.
2026	Severe dengue/critical care	Prospective cohort study	90	Chanh HQ, Trieu HT, Vuong NL, Tran KH, Huynh NTV, Phan TQ, et al. Serial bedside echocardiography identifies children at risk of recurrent Dengue shock: a prospective cohort study. BMC Emerg Med. 2026;26(1):131. doi: 10.1186/s12873-026-01546-3.
2025	Severe dengue/critical care	Diagnostic-accuracy study	250	Lyle NN, Chanh HQ, Nguyen Van H, Anibal J, Karolcik S, Ming D, et al. An artificial intelligence-based approach to identify volume status in patients with severe dengue using wearable PPG data. PLOS Digit Health. 2025;4(7). doi: 10.1371/journal.pdig.0000924.
2025	Severe dengue/critical care	Clinical prediction-model study	NR	Thanh NT, Luan VT. Comparison of serum lactate and lactate-derived ratios as prognostic biomarkers in pediatric dengue shock syndrome using supervised machine learning models. PLoS One. 2025;20(10). doi: 10.1371/journal.pone.0335022.
2025	Severe dengue/critical care	Retrospective cohort study	77	Chattopadhyay A, Singla S, Saigal K, Qureshi S, Saikia D. Distinguishing the overlapping features of severe multi-inflammatory syndrome in children from severe dengue, scrub typhus and other endemic tropical infections-a comparative study from a tertiary care pediatric intensive care unit. J Trop Pediatr. 2025;71(4). doi: 10.1093/tropej/fmaf022.
2025	Severe dengue/critical care	Observational cohort or comparative study	556	Setrkraising K, Kittitrakul C. Gastrointestinal Manifestations and Prognostic Factors for Severe Dengue in Thai Children. Am J Trop Med Hyg. 2025;112(3):642-647. doi: 10.4269/ajtmh.24-0434.
2025	Severe dengue/critical care	Retrospective cohort study	200	Vo LT, Do VC, Trinh TH, Nguyen TT. In-Hospital Mortality in Mechanically Ventilated Children With Severe Dengue Fever: Explanatory Factors in a Single-Center Retrospective Cohort From Vietnam, 2013-2022. Pediatr Crit Care Med. 2025;26(6). doi: 10.1097/PCC.0000000000003728.
2025	Severe dengue/critical care	Clinical prediction-model study	230	Nguyen RN, Lam HT, Phan HV, Bui NQ. Machine Learning Nomogram for Predicting Dengue Shock Syndrome in Pediatric Patients With Dengue Fever in Vietnam. Cureus. 2025;17(4). doi: 10.7759/cureus.81819.
2025	Neurological	Observational cohort or comparative study	56	Srivastava N, Mankal R, Beniwal R, Agarwal A, Alam U, Pandey AK, et al. Neurologic Sequelae After Encephalitis Associated With Dengue Virus in Children. Open Forum Infect Dis. 2025;12(10). doi: 10.1093/ofid/ofaf521.
2025	Severe dengue/critical care	Retrospective cohort study	120	Salombe LES, Nurnaningsih, Adhi S, Arguni E. Prognostic factors for mortality in children with severe dengue: a single-centre retrospective cohort study. Heliyon. 2025;11(9). doi: 10.1016/j.heliyon.2025.e43021.
2025	Severe dengue/critical care	Uncontrolled intervention cohort	49	Bhat C, Martin F, Chennakeshava D, Ramanan AV, Ramesh D, Viswanathan P, et al. Role of anakinra in the management of children with severe dengue. Arch Dis Child. 2025;110(12):977-982. doi: 10.1136/archdischild-2025-329078.
2025	Severe dengue/critical care	Analytical cross-sectional study	205 hospitalized; 10 severe cases	Sevilla ME, Bokser V, Miño L, Oks I, Amatto MB, Nicolau V, et al. Severe dengue in pediatrics: 10 cases in Buenos Aires, Argentina. Arch Argent Pediatr. 2025;123(4). doi: 10.5546/aap.2024-10568.eng.
2024	Severe dengue/critical care	Clinical prediction-model study	278	Thanh NT, Luan VT, Viet DC, Tung TH, Thien V. A machine learning-based risk score for prediction of mechanical ventilation in children with dengue shock syndrome: A retrospective cohort study. PLoS One. 2024;19(12). doi: 10.1371/journal.pone.0315281.
2024	Severe dengue/critical care	Clinical prediction-model study	4522	Tran PNT, Siranart N, Sukmark T, Limothai U, Tachaboon S, Tantawichien T, et al. A simple nomogram to predict dengue shock syndrome: A study of 4522 south east Asian children. J Med Virol. 2024;96(8). doi: 10.1002/jmv.29874.
2024	Severe dengue/critical care	Analytical cross-sectional study	NR	Silva ÁSAD, Carvalho FL, Pinto GA, Saad LSR, Curado MO, Dombroski TCD, et al. Analysis of signs and symptoms in confirmed cases of severe dengue among children aged 0 to 10 years old. Einstein (Sao Paulo). 2024;22. doi: 10.31744/einstein_journal/2024AO0546.
2024	Severe dengue/critical care	Observational cohort or comparative study	49	Avuthu OPR, Mishra A, Patil MG, Tandur BS, Salunkhe S, Kumar G, et al. Association of Liver Function Tests With the Severity and Outcome of Dengue Fever in Children. Cureus. 2024;16(8). doi: 10.7759/cureus.67700.
2024	Severe dengue/critical care	Retrospective cohort study	178	Mahajan V, Singh J, Guglani V. CLINICAL PROFILE OF EXPANDED DENGUE SYNDROME IN CHILDREN. Pediatr Infect Dis J. 2024. doi: 10.1097/INF.0000000000004421.
2024	Neurological	Case series	5	Gupta J, Choudhary R, Gupta A, Sharma P, Sehra RN, Devpura K, et al. Child Neurology: Acute Necrotizing Encephalopathy of Childhood Associated With Dengue: Good Neurologic Outcome Despite a Fulminant Presentation. Neurology. 2024;103(9). doi: 10.1212/WNL.0000000000209954.
2024	Severe	Prospective cohort	135	Nusrat N, Chowdhury K, Sinha S, Mehta M, Kumar S, Haque M. Clinical and

	dengue/critical care	study		Laboratory Features and Treatment Outcomes of Dengue Fever in Pediatric Cases. Cureus. 2024;16(12). doi: 10.7759/cureus.75840.
2024	Severe dengue/critical care	Case-control study	144	Aung MTT, Tangpukdee N, Limkittikul K, Keeratiwasin R, Sukharom R, Hattasingh W, et al. Early-phase factors associated with pediatric severe dengue in the Thai-Myanmar cross-border region. BMC Public Health. 2024;24(1):1957. doi: 10.1186/s12889-024-19492-9.
2024	Severe dengue/critical care	Prospective cohort study	16	Chanh HQ, Trieu HT, Tran Kim H, Huynh Ngoc Thien V, Huyen VNT, Moncada A, et al. Kinetics of cardiovascular and inflammatory biomarkers in paediatric dengue shock syndrome. Oxf Open Immunol. 2024;5(1). doi: 10.1093/oxfimm/iqae005.
2024	Severe dengue/critical care	Retrospective cohort study	NR	Vo LT, Nguyen DT, Tran TN, Tran HH, Đoan TT, Pham TN, et al. Pediatric Profound Dengue Shock Syndrome and Use of Point-of-Care Ultrasound During Mechanical Ventilation to Guide Treatment: Single-Center Retrospective Study, 2013-2021. Pediatr Crit Care Med. 2024;25(4). doi: 10.1097/PCC.0000000000003413.
2024	Severe dengue/critical care	Clinical prediction-model study	459	Nguyen TT, Ngo PT, Vo LT. Predicting the risk of mortality in children with dengue-induced hepatitis admitted to the paediatric intensive care unit. World J Crit Care Med. 2024;13(4):98862. doi: 10.5492/wjccm.v13.i4.98862.
2024	Severe dengue/critical care	Clinical prediction-model study	492	Nguyen Tat T, Vo Hoang-Thien N, Nguyen Tat D, Nguyen PH, Ho LT, Doan DH, et al. Prognostic values of serum lactate-to-bicarbonate ratio and lactate for predicting 28-day in-hospital mortality in children with dengue shock syndrome. Medicine (Baltimore). 2024;103(17). doi: 10.1097/MD.0000000000038000.
2024	Severe dengue/critical care	Analytical cross-sectional study	NR	Alam A, Andriyani FM, Peryoga SU. Severe COVID-19 multisystem inflammatory syndrome versus severe dengue in children from Indonesia: a cross-sectional study. Int J Emerg Med. 2024;17(1):85. doi: 10.1186/s12245-024-00658-6.
2024	Severe dengue/critical care	Analytical cross-sectional study	NR	Karyanti MR, Uiterwaal CSPM, Hadinegoro SR, Widyahening IS, Saldi SRF, Heesterbeek JAPH, et al. The Value of Warning Signs From the WHO 2009 Dengue Classification in Detecting Severe Dengue in Children. Pediatr Infect Dis J. 2024;43(7):630-634. doi: 10.1097/INF.0000000000004326.
2023	Severe dengue/critical care	Clinical prediction-model study	NR	Corzo-Gómez J, Guzmán-Aquino S, Vargas-De-León C, Megchún-Hernández M, Briones-Aranda A. Bayesian Analysis Used to Identify Clinical and Laboratory Variables Capable of Predicting Progression to Severe Dengue among Infected Pediatric Patients. Children (Basel). 2023;10(9):1508. doi: 10.3390/children10091508.
2023	Severe dengue/critical care	Analytical cross-sectional study	208	Yesmin S, Ahammad AM, Sarmin S, Rafi MA, Islam S, Hasan MJ. Clinical Profile of Pediatric Cases of Dengue during the 2019 Epidemic in Bangladesh: A Multicenter Cross-Sectional Study. Mymensingh Med J. 2023;32(2):502-509. PMID: 37002764.
2023	Severe dengue/critical care	Uncontrolled intervention cohort	34	Vo LT, Do VC, Trinh TH, Vu T, Nguyen TT. Combined Therapeutic Plasma Exchange and Continuous Renal Replacement Therapy in Children With Dengue-Associated Acute Liver Failure and Shock Syndrome: Single-Center Cohort From Vietnam. Pediatr Crit Care Med. 2023;24(10):818-828. doi: 10.1097/PCC.0000000000003304.
2023	Severe dengue/critical care	Retrospective cohort study	254	Idrus NL, Md Jamal S, Abu Bakar A, Embong H, Ahmad NS. Comparison of clinical and laboratory characteristics between severe and non-severe dengue in paediatrics. PLoS Negl Trop Dis. 2023;17(12). doi: 10.1371/journal.pntd.0011839.
2023	Severe dengue/critical care	Clinical prediction-model study	312	Gayathri V, Lakshmi SV, Murugan SS, Poovazhagi V, Kalpana S. Development and Validation of a Bedside Dengue Severity Score for Predicting Severe Dengue in Children. Indian Pediatr. 2023;60(5):359-363. doi: 10.1007/s13312-023-2880-7.
2023	Severe dengue/critical care	Retrospective cohort study	NR	Nguyen RN, Lam HT, Phan HV. Liver Impairment and Elevated Aminotransferase Levels Predict Severe Dengue in Vietnamese Children. Cureus. 2023;15(10). doi: 10.7759/cureus.47606.
2022	Severe dengue/critical care	Observational cohort or comparative study	31	Balasubramani S, Govindaraj V, Agarwal R, Pathania A, Vij A. COVID-19 Antibodies as Predictor of Severe Dengue among Hospitalized Children with Dengue Illness in the Post-third-wave Period of COVID-19 Infection in India. J Assoc Physicians India. 2022;70(9):11-12. doi: 10.5005/japi-11001-0092.
2022	Severe dengue/critical care	Retrospective analytical study	528	Juliansen A, Meliani F, Budiputri CL, Muljono MP, Heriyanto RS, Chandra S, et al. Clinical characteristics and laboratory parameters in differentiating pediatric dengue fever and dengue hemorrhagic fever. Infect Dis Trop Med. 2022;8. doi: 10.32113/idtm_20224_829.
2022	Severe dengue/critical care	Retrospective cohort study	50	Mutanabbi M, Shova SS, Kibtiar M, Mosleh T. Clinical Profile and Lab Findings of Dengue Fever in Children Admitted in a Tertiary Care Hospital. Mymensingh Med J. 2022;31(3):741-748. PMID: 35780359.
2022	Severe dengue/critical care	Retrospective cohort study	60	Preeprem N, Phumeetham S. Paediatric dengue shock syndrome and acute respiratory failure: a single-centre retrospective study. BMJ Paediatr Open. 2022;6(1). doi: 10.1136/bmjpo-2022-001578.
2022	Severe dengue/critical care	Observational cohort or comparative study	339	Lue AM, Richards-Dawson MEH, Gordon-Strachan GM, Kodilinye SM, Dunkley-Thompson JAT, James-Powell TD, et al. Severity and Outcomes of Dengue in Hospitalized Jamaican Children in 2018-2019 During an Epidemic Surge in the Americas. Front Med (Lausanne). 2022;9:889998. doi: 10.3389/fmed.2022.889998.
2021	Severe dengue/critical care	Analytical cross-sectional study	190	Khan MAS, Al Mosabbir A, Raheem E, Ahmed A, Rouf RR, Hasan M, et al. Clinical spectrum and predictors of severity of dengue among children in 2019 outbreak: a multicenter hospital-based study in Bangladesh. BMC Pediatr. 2021;21(1):478. doi: 10.1186/s12887-021-02947-y.
2021	Severe dengue/critical care	Prospective cohort study	172	Sachdev A, Pathak D, Gupta N, Simalti A, Gupta D, Gupta S, et al. Early Predictors of Mortality in Children with Severe Dengue Fever: A Prospective Study. Pediatr Infect Dis J. 2021;40(9):797-801. doi: 10.1097/INF.0000000000003179.
2021	Severe dengue/critical care	Retrospective cohort study	146	Armenda S, Rusmawatiningtyas D, Makrufardi F, Arguni E. Factors associated with clinical outcomes of pediatric dengue shock syndrome admitted to pediatric intensive care unit: A retrospective cohort study. Ann Med Surg (Lond). 2021;66:102472. doi: 10.1016/j.amsu.2021.102472.
2021	Severe dengue/critical care	Retrospective cohort study	402	Senavong P, Yamamoto E, Keomoungkhoune P, Prasith N, Somoulay V, Kariya T, et al. Factors associated with severe dengue in Savannakhet Province, Lao People's Democratic Republic. Nagoya J Med Sci. 2021;83(4):749-763. doi: 10.18999/nagjms.83.4.749.

2021	Neurological	Prospective cohort study	56	Bentes AA, Maia De Castro Romanelli R, Crispim APC, Marinho PES, Loutfi KS, Araujo ST, et al. Neurological manifestations due to dengue virus infection in children: clinical follow-up. Pathog Glob Health. 2021;115(7-8):476-482. doi: 10.1080/20477724.2021.1942680.
2021	Severe dengue/critical care	Observational cohort or comparative study	1064	Bodinayake CK, Nagahawatte AD, Devasiri V, Dahanayake NJ, Wijayaratne GB, Weerasinghe NP, et al. Outcomes among children and adults at risk of severe dengue in Sri Lanka: Opportunity for outpatient case management in countries with high disease burden. PLoS Negl Trop Dis. 2021;15(12). doi: 10.1371/journal.pntd.0010091.
2021	Severe dengue/critical care	Retrospective cohort study	93	Hussain W, Shaikh M, Hanif M, Ashfaq M, Ahmed H, Nisa BU. Pattern and Outcome of Dengue Fever in a Pediatric Tertiary Hospital: A Retrospective Report. Cureus. 2021;13(3). doi: 10.7759/cureus.14164.
2021	Severe dengue/critical care	Analytical cross-sectional study	170	Arora SK, Nandan D, Sharma A, Benerjee P, Singh DP. Predictors of severe dengue amongst children as per the revised WHO classification. J Vector Borne Dis. 2021;58(4):329-334. doi: 10.4103/0972-9062.318312.
2021	Severe dengue/critical care	Analytical cross-sectional study	811	Sondo AK, Diendéré EA, Meda BI, Diallo I, Zoungrana J, Poda A, et al. Severe dengue in adults and children, Ouagadougou (Burkina Faso), West Africa, October 2015-January 2017. IJID Reg. 2021;1:53-59. doi: 10.1016/j.ijregi.2021.09.010.
2021	Severe dengue/critical care	Analytical cross-sectional study	NR	Phung NTN, Vo DM, Le TN, Doan TT. Total serum cortisol level is low in children with severe dengue shock syndrome. Trop Biomed. 2021;38(3):396-402. doi: 10.47665/tb.38.3.076.
2020	Severe dengue/critical care	Prospective cohort study	61	Prasad D, Bhriguvanshi A. Clinical Profile, Liver Dysfunction and Outcome of Dengue Infection in Children: A Prospective Observational Study. Pediatr Infect Dis J. 2020;39(2):97-101. doi: 10.1097/INF.0000000000002519.
2020	Severe dengue/critical care	Retrospective cohort study	127	Rajan M, Geminiganesan S, Sankaranarayanan S, Padmanaban R, Selvam MP. Renal Manifestations in Children with Dengue Fever Hospitalized in Pediatric Intensive Care Unit. Indian J Pediatr. 2020;87(12):1014-1017. doi: 10.1007/s12098-020-03402-z.
2020	Severe dengue/critical care	Retrospective cohort study	NR	Hegazi MA, Bakarman MA, Alahmadi TS, Butt NS, Alqahtani AM, Aljedaani BS, et al. Risk Factors and Predictors of Severe Dengue in Saudi Population in Jeddah, Western Saudi Arabia: A Retrospective Study. Am J Trop Med Hyg. 2020;102(3):613-621. doi: 10.4269/ajtmh.19-0650.
2020	Severe dengue/critical care	Prospective cohort study	350	Sreenivasan P, Geetha S, Kumar AS. WHO 2009 Warning Signs as Predictors of Time Taken for Progression to Severe Dengue in Children. Indian Pediatr. 2020;57(10):899-903. PMID: 33089804.
2018	Severe dengue/critical care	Case-control study	NR	Wakimoto MD, Camacho LAB, Gonin ML, Brasil P. Clinical and Laboratory Factors Associated with Severe Dengue: A Case-Control Study of Hospitalized Children. J Trop Pediatr. 2018;64(5):373-381. doi: 10.1093/tropej/fmx078.
2018	Severe dengue/critical care	Clinical prediction-model study	359	Sreenivasan P, S G, K S. Development of a Prognostic Prediction Model to Determine Severe Dengue in Children. Indian J Pediatr. 2018;85(6):433-439. doi: 10.1007/s12098-017-2591-y.
2018	Severe dengue/critical care	Clinical prediction-model study	198	Phakhounthong K, Chaovalit P, Jittamala P, Blacksell SD, Carter MJ, Turner P, et al. Predicting the severity of dengue fever in children on admission based on clinical features and laboratory indicators: application of classification tree analysis. BMC Pediatr. 2018;18(1):109. doi: 10.1186/s12887-018-1078-y.
2018	Severe dengue/critical care	Uncontrolled intervention cohort	NR	Ranjit S, Ramanathan G, Ramakrishnan B, Kissoon N. Targeted Interventions in Critically Ill Children with Severe Dengue. Indian J Crit Care Med. 2018;22(3):154-161. doi: 10.4103/ijccm.IJCCM_413_17.
2018	Severe dengue/critical care	Diagnostic-accuracy study	372	Srivastava G, Chhavi N, Goel A. Validation of Serum Aminotransferases Levels to Define Severe Dengue Fever in Children. Pediatr Gastroenterol Hepatol Nutr. 2018;21(4):289-296. doi: 10.5223/pghn.2018.21.4.289.
2017	Severe dengue/critical care	Clinical prediction-model study	7563	Nguyen MT, Ho TN, Nguyen VV, Nguyen TH, Ha MT, Ta VT, et al. An Evidence-Based Algorithm for Early Prognosis of Severe Dengue in the Outpatient Setting. Clin Infect Dis. 2017;64(5):656-663. doi: 10.1093/cid/ciw863.
2017	Neurological	Observational cohort or comparative study	70 meningitis cases; 5 DENV-positive	de Oliveira DB, Candiani TM, Franco-Luiz APM, Almeida GMF, Abrahão JS, Rios M, et al. Etiological agents of viral meningitis in children from a dengue-endemic area, Southeast region of Brazil. J Neurol Sci. 2017;375:390-394. doi: 10.1016/j.jns.2017.02.025.
2017	Neurological	Analytical cross-sectional study	NR	Sil A, Biswas T, Samanta M, Konar MC, De AK, Chaudhuri J. Neurological manifestations in children with dengue fever: an Indian perspective. Trop Doct. 2017;47(2):145-149. doi: 10.1177/0049475516679788.
2017	Severe dengue/critical care	Observational cohort or comparative study	238	Laoprasopwattana K, Binsaai J, Pruekprasert P, Geater A. Prothrombin Time Prolongation was the Most Important Indicator of Severe Bleeding in Children with Severe Dengue Viral Infection. J Trop Pediatr. 2017;63(4):314-320. doi: 10.1093/tropej/fmw097.
2017	Severe dengue/critical care	Clinical prediction-model study	2301	Lam PK, Ngoc TV, Thu Thuy TT, Hong Van NT, Nhu Thuy TT, Hoai Tam DT, et al. The value of daily platelet counts for predicting dengue shock syndrome: Results from a prospective observational study of 2301 Vietnamese children with dengue. PLoS Negl Trop Dis. 2017;11(4). doi: 10.1371/journal.pntd.0005498.
2016	Severe dengue/critical care	Observational cohort or comparative study	471	Lovera D, Martinez de Cuellar C, Araya S, Amarilla S, Gonzalez N, Aguiar C, et al. Clinical Characteristics and Risk Factors of Dengue Shock Syndrome in Children. Pediatr Infect Dis J. 2016;35(12):1294-1299. doi: 10.1097/INF.0000000000001308.
2016	Severe dengue/critical care	Case series	33	Laoprasopwattana K, Jundee P, Pruekprasert P, Geater A. Outcome of Severe Dengue Viral Infection-caused Acute Liver Failure in Thai Children. J Trop Pediatr. 2016;62(3):200-5. doi: 10.1093/tropej/fmv099.
2015	Severe dengue/critical care	Clinical prediction-model study	1207	Lam PK, Tam DT, Dung NM, Tien NT, Kieu NT, Simmons C, et al. A Prognostic Model for Development of Profound Shock among Children Presenting with Dengue Shock Syndrome. PLoS One. 2015;10(5). doi: 10.1371/journal.pone.0126134.
2015	Severe dengue/critical care	Prospective cohort study	81	Sahana KS, Sujatha R. Clinical profile of dengue among children according to revised WHO classification: analysis of a 2012 outbreak from Southern India. Indian J Pediatr. 2015;82(2):109-13. doi: 10.1007/s12098-014-1523-3.

2015	Severe dengue/critical care	Prospective cohort study	115 confirmed cases	Kumar A, Gittens-St Hilair M, Jason V, Ugwuagu C, Krishnamurthy K. The clinical characteristics and outcome of children hospitalized with dengue in Barbados, an English Caribbean country. J Infect Dev Ctries. 2015;9(4):394-401. doi: 10.3855/jidc.5566.
2014	Severe dengue/critical care	Clinical prediction-model study	238	Laoprasopwattana K, Chaimongkol W, Pruekprasert P, Geater A. Acute respiratory failure and active bleeding are the important fatality predictive factors for severe dengue viral infection. PLoS One. 2014;9(12). doi: 10.1371/journal.pone.0114499.
2014	Severe dengue/critical care	Analytical cross-sectional study	796	Mena Lora AJ, Fernandez J, Morales A, Soto Y, Feris-Iglesias J, Brito MO. Disease severity and mortality caused by dengue in a Dominican pediatric population. Am J Trop Med Hyg. 2014;90(1):169-72. doi: 10.4269/ajtmh.13-0440.
2014	Severe dengue/critical care	Randomized controlled trial	50	Somasetia DH, Setiati TE, Sjahrodji AM, Idjradinata PS, Setiabudi D, Roth H, et al. Early resuscitation of dengue shock syndrome in children with hyperosmolar sodium-lactate: a randomized single-blind clinical trial of efficacy and safety. Crit Care. 2014;18(5):466. doi: 10.1186/s13054-014-0466-4.
2014	Severe dengue/critical care	Case-control study	77	Branco Mdos R, Luna EJ, Braga Júnior LL, Oliveira RV, Rios LT, Silva Mdo S, et al. Risk factors associated with death in Brazilian children with severe dengue: a case-control study. Clinics (Sao Paulo). 2014;69(1):55-60. doi: 10.6061/clinics/2014(01)08.
2014	Severe dengue/critical care	Diagnostic-accuracy study	267	Macedo GA, Gonin ML, Pone SM, Cruz OG, Nobre FF, Brasil P. Sensitivity and specificity of the World Health Organization dengue classification schemes for severe dengue assessment in children in Rio de Janeiro. PLoS One. 2014;9(4). doi: 10.1371/journal.pone.0096314.
2013	Severe dengue/critical care	Retrospective cohort study	273	Namvongsa V, Sirivichayakul C, Songsithichok S, Chanthavanich P, Chokejindachai W, Sitcharungsi R. Differences in clinical features between children and adults with dengue hemorrhagic fever/dengue shock syndrome. Southeast Asian J Trop Med Public Health. 2013;44(5):772-9. PMID: 24437312.
2013	Severe dengue/critical care	Prospective cohort study	67	Yadav DK, Choudhary S, Gupta PK, Beniwal MK, Agarwal S, Shukla U, et al. The Tei index and asymptomatic myocarditis in children with severe dengue. Pediatr Cardiol. 2013;34(6):1307-13. doi: 10.1007/s00246-013-0639-y.
2012	Severe dengue/critical care	Case series	8	Khositseth A, Tangnararatchakit K, Chuansumrit A, Wanitkun S, Kuptanon T, Chaiyaratana W, et al. Cardiovascular change in children with dengue shock syndrome. J Pediatr Intensive Care. 2012;1(3):153-160. doi: 10.3233/PIC-2012-025.
2011	Severe dengue/critical care	Observational cohort or comparative study	43	Michels M, Djamiatun K, Faradz SM, Koenders MM, de Mast Q, van der Ven AJ. High plasma mid-regional pro-adrenomedullin levels in children with severe dengue virus infections. J Clin Virol. 2011;50(1):8-12. doi: 10.1016/j.jcv.2010.09.008.
2011	Severe dengue/critical care	Retrospective cohort study	483	Gupta V, Yadav TP, Pandey RM, Singh A, Gupta M, Kanaujiya P, et al. Risk factors of dengue shock syndrome in children. J Trop Pediatr. 2011;57(6):451-6. doi: 10.1093/tropej/fmr020.
2010	Severe dengue/critical care	Observational cohort or comparative study	37	Oliveira GA, Machado RC, Horvat JV, Gomes LE, Guerra LR, Vandesteen L, et al. Transient reticular gallbladder wall thickening in severe dengue fever: a reliable sign of plasma leakage. Pediatr Radiol. 2010;40(5):720-4. doi: 10.1007/s00247-009-1489-x.

Abbreviations: DENV, dengue virus; NR, not reliably reported in the indexed record.
Note: Reported n denotes the principal analytic population relevant to the review; where a report described a smaller severe or neurological subgroup within a larger cohort, both values are shown when necessary.

Supplementary Table S2. Design-specific risk-of-bias appraisal of included primary studies

PMID/identifier	Study	Appraisal tool	Overall concern	Principal limitation
42371151	López O, 2026	JBI case-series checklist	High	Small or uncontrolled series; confounding and selection bias cannot be excluded
42181500	Chowdhury AS, 2026	JBI analytical cross-sectional checklist	Some concerns	Temporal ambiguity and potential referral or selection bias
42001987	Birne RO, 2026	JBI cohort checklist	Some concerns	Retrospective ascertainment and residual confounding
41694828	Swaroop S, 2026	JBI cohort checklist	Some concerns	Retrospective ascertainment and residual confounding
42056842	Le Phuoc T, 2026	JBI design-appropriate checklist	Some concerns	Incomplete reporting of design-specific bias domains
41882554	Chanh HQ, 2026	JBI cohort checklist	Some concerns	Mostly single-center cohorts with limited adjustment or follow-up
40680024	Lyle NN, 2025	QUADAS-2	Some concerns	Potential spectrum and reference-standard limitations
41144436	Thanh NT, 2025	PROBAST	High	No clearly independent external validation or potential overfitting
40514190	Chattopadhyay A, 2025	JBI cohort checklist	High	Retrospective design, limited sample, and incomplete control of confounding
39719114	Setrkraising K, 2025	JBI design-appropriate checklist	Some concerns	Incomplete reporting of design-specific bias domains
40105396	Vo LT, 2025	JBI cohort checklist	Some concerns	Retrospective ascertainment and residual confounding
40337565	Nguyen RN, 2025	PROBAST	High	No clearly independent external validation or potential overfitting
41035537	Srivastava N, 2025	JBI design-appropriate checklist	Some concerns	Incomplete reporting of design-specific bias domains
10.1016/j.heliyon.2025.e43021	Salombe LES, 2025	JBI cohort checklist	Some concerns	Single-center retrospective design and imprecise multivariable estimates
40830031	Bhat C, 2025	JBI cohort checklist	High	Small or uncontrolled series; confounding and selection bias cannot be excluded
40168496	Sevilla ME, 2025	JBI analytical cross-	Some concerns	Temporal ambiguity and potential

		sectional checklist		referral or selection bias
39642139	Thanh NT, 2024	PROBAST	High	No clearly independent external validation or potential overfitting
39165074	Tran PNT, 2024	PROBAST	High	No clearly independent external validation or potential overfitting
38695477	Silva ÁSAD, 2024	JBI analytical cross-sectional checklist	Some concerns	Temporal ambiguity and potential referral or selection bias
39318954	Avuthu OPR, 2024	JBI design-appropriate checklist	Some concerns	Incomplete reporting of design-specific bias domains
38900047	Mahajan V, 2024	JBI cohort checklist	Some concerns	Retrospective ascertainment and residual confounding
39374471	Gupta J, 2024	JBI case-series checklist	High	Small or uncontrolled series; confounding and selection bias cannot be excluded
39698191	Nusrat N, 2024	JBI cohort checklist	Some concerns	Mostly single-center cohorts with limited adjustment or follow-up
39039529	Aung MTT, 2024	JBI case-control checklist	Some concerns	Selection of controls and residual confounding
39193474	Chanh HQ, 2024	JBI cohort checklist	Some concerns	Mostly single-center cohorts with limited adjustment or follow-up
37966344	Vo LT, 2024	JBI cohort checklist	High	Retrospective design, limited sample, and incomplete control of confounding
39655306	Nguyen TT, 2024	PROBAST	High	No clearly independent external validation or potential overfitting
38669370	Nguyen Tat T, 2024	PROBAST	High	No clearly independent external validation or potential overfitting
38992604	Alam A, 2024	JBI analytical cross-sectional checklist	Some concerns	Temporal ambiguity and potential referral or selection bias
38652064	Karyanti MR, 2024	JBI analytical cross-sectional checklist	Some concerns	Temporal ambiguity and potential referral or selection bias
37761469	Corzo-Gómez J, 2023	PROBAST	High	No clearly independent external validation or potential overfitting
37002764	Yesmin S, 2023	JBI analytical cross-sectional checklist	Some concerns	Temporal ambiguity and potential referral or selection bias
37310173	Vo LT, 2023	JBI cohort checklist	High	Small or uncontrolled series; confounding and selection bias cannot be excluded
38113250	Idrus NL, 2023	JBI cohort checklist	Some concerns	Retrospective ascertainment and residual confounding
36757000	Gayathri V, 2023	PROBAST	High	No clearly independent external validation or potential overfitting
37886653	Nguyen RN, 2023	JBI cohort checklist	High	Retrospective design, limited sample, and incomplete control of confounding
36082886	Balasubramani S, 2022	JBI design-appropriate checklist	Some concerns	Incomplete reporting of design-specific bias domains
10.32113/idtm_20224_829	Juliansen A, 2022	JBI analytical cross-sectional checklist	Some concerns	Retrospective single-center analysis and residual confounding
35780359	Mutanabbi M, 2022	JBI cohort checklist	High	Retrospective design, limited sample, and incomplete control of confounding
36645744	Preeprem N, 2022	JBI cohort checklist	High	Retrospective design, limited sample, and incomplete control of confounding
35801209	Lue AM, 2022	JBI design-appropriate checklist	Some concerns	Incomplete reporting of design-specific bias domains
34715835	Khan MAS, 2021	JBI analytical cross-sectional checklist	Some concerns	Temporal ambiguity and potential referral or selection bias
34321449	Sachdev A, 2021	JBI cohort checklist	Some concerns	Mostly single-center cohorts with limited adjustment or follow-up
34150206	Armenda S, 2021	JBI cohort checklist	Some concerns	Retrospective ascertainment and residual confounding
34916719	Senavong P, 2021	JBI cohort checklist	Some concerns	Retrospective ascertainment and residual confounding
34223795	Bentes AA, 2021	JBI cohort checklist	Some concerns	Mostly single-center cohorts with limited adjustment or follow-up
34962920	Bodinayake CK, 2021	JBI design-appropriate checklist	Some concerns	Incomplete reporting of design-specific bias domains
33936876	Hussain W, 2021	JBI cohort checklist	High	Retrospective design, limited sample, and incomplete control of confounding
35381822	Arora SK, 2021	JBI analytical cross-sectional checklist	Some concerns	Temporal ambiguity and potential referral or selection bias
35757818	Sondo AK, 2021	JBI analytical cross-sectional checklist	Some concerns	Temporal ambiguity and potential referral or selection bias
34608113	Phung NTN, 2021	JBI analytical cross-sectional checklist	Some concerns	Temporal ambiguity and potential referral or selection bias
31815826	Prasad D, 2020	JBI cohort checklist	Some concerns	Mostly single-center cohorts with limited adjustment or follow-up
32557142	Rajan M, 2020	JBI cohort checklist	Some concerns	Retrospective ascertainment and residual confounding
31933467	Hegazi MA, 2020	JBI cohort checklist	High	Retrospective design, limited sample, and incomplete control of confounding

33089804	Sreenivasan P, 2020	JBI cohort checklist	Some concerns	Mostly single-center cohorts with limited adjustment or follow-up
29059411	Wakimoto MD, 2018	JBI case-control checklist	Some concerns	Selection of controls and residual confounding
29344875	Sreenivasan P, 2018	PROBAST	High	No clearly independent external validation or potential overfitting
29534694	Phakhounthong K, 2018	PROBAST	High	No clearly independent external validation or potential overfitting
29657372	Ranjit S, 2018	JBI cohort checklist	High	Small or uncontrolled series; confounding and selection bias cannot be excluded
30345242	Srivastava G, 2018	QUADAS-2	Some concerns	Potential spectrum and reference-standard limitations
28034883	Nguyen MT, 2017	PROBAST	High	No clearly independent external validation or potential overfitting
28320174	de Oliveira DB, 2017	JBI design-appropriate checklist	Some concerns	Incomplete reporting of design-specific bias domains
27913754	Sil A, 2017	JBI analytical cross-sectional checklist	Some concerns	Temporal ambiguity and potential referral or selection bias
28177091	Laoprasopwattana K, 2017	JBI design-appropriate checklist	Some concerns	Incomplete reporting of design-specific bias domains
28448490	Lam PK, 2017	PROBAST	High	No clearly independent external validation or potential overfitting
27455442	Lovera D, 2016	JBI design-appropriate checklist	Some concerns	Incomplete reporting of design-specific bias domains
26851434	Laoprasopwattana K, 2016	JBI case-series checklist	High	Small or uncontrolled series; confounding and selection bias cannot be excluded
25946113	Lam PK, 2015	PROBAST	High	No clearly independent external validation or potential overfitting
24986196	Sahana KS, 2015	JBI cohort checklist	Some concerns	Mostly single-center cohorts with limited adjustment or follow-up
25881529	Kumar A, 2015	JBI cohort checklist	Some concerns	Mostly single-center cohorts with limited adjustment or follow-up
25460594	Laoprasopwattana K, 2014	PROBAST	High	No clearly independent external validation or potential overfitting
24218410	Mena Lora AJ, 2014	JBI analytical cross-sectional checklist	Some concerns	Temporal ambiguity and potential referral or selection bias
25189175	Somasetia DH, 2014	RoB 2	Some concerns	Small single-blind trial with imprecision for clinical outcomes
24473560	Branco Mdos R, 2014	JBI case-control checklist	Some concerns	Selection of controls and residual confounding
24777054	Macedo GA, 2014	QUADAS-2	Some concerns	Potential spectrum and reference-standard limitations
24437312	Namvongsa V, 2013	JBI cohort checklist	Some concerns	Retrospective ascertainment and residual confounding
23397334	Yadav DK, 2013	JBI cohort checklist	Some concerns	Mostly single-center cohorts with limited adjustment or follow-up
31214401	Khositseth A, 2012	JBI case-series checklist	High	Small or uncontrolled series; confounding and selection bias cannot be excluded
20952250	Michels M, 2011	JBI design-appropriate checklist	Some concerns	Incomplete reporting of design-specific bias domains
21367851	Gupta V, 2011	JBI cohort checklist	Some concerns	Retrospective ascertainment and residual confounding
20012951	Oliveira GA, 2010	JBI design-appropriate checklist	Some concerns	Incomplete reporting of design-specific bias domains

Abbreviations: JBI, Joanna Briggs Institute; PROBAST, Prediction model Risk Of Bias ASsessment Tool; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies 2; RoB 2, Cochrane risk-of-bias tool for randomized trials.

Note: Overall concern was derived from design-appropriate domains rather than a numerical quality score. Studies were not excluded solely because of risk of bias; judgments informed the strength and wording of the narrative synthesis.

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