CHALLENGES IN DIAGNOSING SYSTEMIC LUPUS ERYTHEMATOSUS IN CHILDREN: CLINICAL AND NON-CLINICAL FACTORS

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ABSTRACT

Childhood-onset Systemic Lupus Erythematosus (cSLE) is a separate biological entity with more aggressive immunopathogenesis, faster organ damage accumulation, and greater mortality rates than adult-onset lupus. In tropical, resource-constrained environments such as Indonesia, diagnosis is routinely delayed beyond the clinically critical six-month "window of opportunity," resulting in irreversible damages. The purpose of this literature review is to completely identify the clinical and non-clinical factors of diagnostic delay and to evaluate strategies for overcoming these hurdles. The analysis finds "diagnostic overshadowing" as a main clinical driver, in which symptoms are mistaken for endemic infections like Dengue, Typhoid, and Tuberculosis due to cognitive bias and symptom overlap. Systemically, this is worsened by a "Specialist Void," with regional data indicating less than one pediatric rheumatologist per 26 million children in Southeast Asia, as well as economic constraints where diagnostic testing costs substantially more than empirical antibiotic therapy. These delays are associated with high Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) scores and healthcare costs "To mitigate these barriers, this review proposes three strategic policy: (1) task-shifting via standardized 'Red Flag' triage algorithms for primary care providers to reduce clinical guesswork; (2) the deployment of hub-and-spoke telemedicine networks to bridge geographic isolation and prevent expxnesive travel costs; and insurance policy reform (BPJS) to decentralize ANA screening to secondary-level hospitals, ensuring early detection is more cost-effective than treating end-stage complications."

Keywords: Childhood-onset Systemic Lupus Erythematosus, Diagnostic Delay, Diagnostic Overshadowing, Resource-Limited Settings.

ABSTRAK

Lupus Eritematosus Sistemik pada anak adalah entitas biologis yang terpisah dengan imunopatogenesis yang lebih agresif, akumulasi kerusakan organ yang lebih cepat, dan tingkat mortalitas yang lebih tinggi dibandingkan lupus onset dewasa. Di lingkungan tropis dengan sumber daya terbatas seperti Indonesia, diagnosis rutin tertunda melampaui "jendela peluang" enam bulan yang secara klinis sangat penting, yang mengakibatkan kerusakan ireversibel. Tujuan dari tinjauan literatur ini adalah untuk mengidentifikasi secara menyeluruh faktor-faktor klinis dan non-klinis penyebab keterlambatan diagnosis dan untuk mengevaluasi strategi untuk mengatasi hambatan-hambatan tersebut. Analisis menemukan "penutupan diagnostik" sebagai pendorong klinis utama, di mana gejala-gejala disalahartikan sebagai infeksi endemik seperti Demam Berdarah Dengue (DBD), Tifus, dan Tuberkulosis (TB) akibat bias kognitif dan tumpang tindih gejala. Secara sistemik, hal ini diperburuk oleh "Kekosongan Spesialis" , dengan data regional yang menunjukkan kurang dari satu ahli reumatologi anak per 26 juta anak di Asia Tenggara, serta kendala ekonomi di mana biaya pemeriksaan diagnostik jauh lebih mahal daripada terapi antibiotic empiris. Keterlambatan ini terkait dengan skor Indeks Kerusakan Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SDI) yang tinggi dan biaya perawatan kesehatan yang sangat besar. Untuk mengatasi hambatan tersebut, tinjauan ini merekomendasikan tiga kebijakan strategis: (1) pengalihan tugas (task-shifting) melalui algoritma triase standar bagi dokter umum untuk mempercepat deteksi dini; (2) pemanfaatan jaringan telemedis 'hub-and-spoke' guna menjembatani isolasi geografis dan menekan biaya transportasi pasien ; serta (3) reformasi kebijakan asuransi (BPJS) untuk mendesentralisasi pemeriksaan ANA ke tingkat rumah sakit sekunder, mengingat biaya skrining dini jauh lebih efisien dibandingkan penanganan komplikasi stadium akhir.

Kata Kunci: Lupus Eritematosus Sistemik pada Anak, Keterlambatan Diagnosis, Penutupan Diagnostik, Pengaturan Sumber Daya Terbatas.

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Introduction

Childhood-Onset SLE (cSLE), defined as disease onset before the age of 18, represents a highly heterogeneous clinical phenotype that differs significantly from lupus presenting in adulthood (aSLE). (1)To grasp the magnitude of the diagnostic challenge, it is crucial to first understand the distinct biological and clinical nature of childhood-onset lupus. cSLE is not simply a pediatric version of the adult disease; it is a biologically distinct entity characterized by more aggressive immunopathogenesis and a more severe clinical course. (2)Unlike adults, children with cSLE do not always present with dominant musculoskeletal or cutaneous symptoms. Instead, their manifestations can be highly variable and non-classical, frequently involving multiple organs with varying degrees of severity. Some children may initially present with constitutional symptoms such as prolonged fever, fatigue, and rapidly developing hematological or renal abnormalities, making diagnosis complex. This phenotype carries a disproportionate disease burden, accounting for only 15–20% of total lupus cases globally but exhibiting greater disease activity, faster organ damage accumulation, and higher mortality rates compared to adults.

The main challenge in diagnosing cSLE in tropical countries such as Indonesia is exacerbated by the phenomenon of diagnostic overshadowing, namely the tendency to interpret non-specific early symptoms such as fever, fatigue, and lymphadenopathy as endemic infections such as dengue fever, typhoid, or tuberculosis. However, in addition to these clinical factors, the limited number of pediatric rheumatologists and knowledge gaps among primary health care providers are major obstacles to early recognition of this disease.(8) Lack of access to specialists who understand the characteristics of cSLE and lack of specialized training increase the risk of delayed diagnosis and treatment, which directly contributes to poor clinical outcomes in children with lupus. (9)

The impact of delayed diagnosis of cSLE is significant and linearly correlated with an increased risk of severe irreversible organ damage. Data show that the time interval from symptom onset to diagnosis in children varies greatly, with a median of up to 47 months in some studies, depending on the healthcare system and geographical factors. (10)This delay leads to the accumulation of permanent organ damage, particularly in the kidneys and central nervous system, with an SDI (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index) score > 1 occurring in approximately 30% of patients within a few years after diagnosis.(14) High disease activity without early intervention is a major risk factor for permanent damage, which further affects the quality of life and long-term prognosis of children with lupus.(12)

This literature review aims to comprehensively identify the determining factors, both clinical and non-clinical, that significantly contribute to the delay in cSLE diagnosis. Additionally, this study will evaluate the relationship between the duration of the diagnostic delay and the level of organ damage accumulation and long-term clinical prognosis. Equally important, this review will also examine the socioeconomic impact resulting from delayed treatment and evaluate strategies to mitigate barriers to the diagnosis of childhood lupus.

Method

Search Strategy

A thorough literature search was done to locate relevant papers on the diagnostic problems of Childhood-onset Systemic Lupus Erythematosus (cSLE) in resource-limited and tropical settings. Electronic databases, such as PubMed, ScienceDirect, and Google Scholar, were searched for articles published between January 2000 and October 2025. The search used Boolean operators to combine the following keywords: "Childhood-onset Systemic Lupus Erythematosus" OR "cSLE", "Diagnostic Delay", "Diagnostic Overshadowing", "Socioeconomic Factors", "Resource-Limited Settings", and "Southeast Asia" or "Indonesia".

Inclusion and exclusion criteria

The review highlighted peer-reviewed original research, systematic reviews, and meta-analyses on the pediatric population (aged <18). Studies in Low- and Middle-Income Countries (LMICs) focused on clinical mimics (e.g., Dengue, Tuberculosis) as well as healthcare system constraints (e.g., workforce distribution, insurance coverage). To determine the disease's biological individuality, seminal articles comparing clinical characteristics between cSLE and adult-onset SLE (aSLE) were included. Articles were omitted if they focused solely on adult populations with no pediatric comparisons, or if full-text versions were unavailable.

Data Synthesis

Given the range of the research included—from clinical cohort analyses to socioeconomic health policy reviews—a narrative synthesis technique was used. Data were extracted and thematically classified into "Clinical Determinants" (e.g., infectious mimicry, symptom presentation) and "Non-Clinical Determinants" (e.g., expert availability, economic obstacles) to provide a comprehensive picture of the diagnostic environment.

Discussion

Clinical Feature	Childhood-Onset SLE (cSLE)	Adult-Onset SLE (aSLE)	Clinical Implication
Mortality Rate	2-3x higher than adults	Baseline	Higher urgency for early diagnosis in children.(3)
Renal Involvement	50–75% prevalence; rapid onset	Lower prevalence; slower progression	High risk of ESRD in children if delayed. (4)
Neurological	Seizures, Psychosis, Chorea	Cognitive dysfunction, mood disorders	High risk of misdiagnosis as psychiatric or infectious.(5)
Hematological	Thrombocytopenia, Hemolytic Anemia	Leukopenia, Lymphopenia	Mimics tropical fevers (Dengue).(6)
Constitutional	High fever, Lymphadenopathy	Fatigue, Arthralgia	Triggers infectious disease workup ("Diagnostic Overshadowing").

Clinical Feature	Childhood-Onset SLE (cSLE)	Adult-Onset SLE (aSLE)	Clinical Implication
Cutaneous	Malar rash common; Discoid rare (<10%)	Discoid rash, Photosensitivity common	Discoid rash is a clearer diagnostic marker in adults.(7)

Table 1: Comparative Clinical Phenotypes of Childhood-Onset vs. Adult-Onset SLE

Determinants of Diagnostic Delay

In the world of medicine and health policy studies, a diagnosis is considered timely if it occurs within six months. A delayed diagnosis of cSLE is officially defined as a period exceeding six months. This calculation begins from the first time symptoms appear or the first medical visit until a definitive diagnosis is made.(12)

This six-month limit is clinically crucial, making it a "window of opportunity." During the first six months, intensive (aggressive) treatment has a high chance of preventing permanent organ damage. Exceeding this six-month time limit is statistically associated with an increased risk of permanent and irreversible organ damage. This means that after six months without proper treatment, patients not only continue to experience active symptoms, but also begin to experience the accumulation of permanent disabilities or organ damage.(12)

Although the medical consensus sets the safe limit at six months, empirical data from the real world show profound systemic failure. Analysis of a large cohort in Europe, namely the LuLa cohort study, reveals that the average time (mean) between the first symptoms experienced by patients and the diagnosis of SLE is 47 months (approximately 4 years), with a median delay also at 47 months.(13)

This figure—47 months—is a substantial statistic, especially when applied in a pediatric context.

- Adult Perspective (aSLE): For adults, a 4-year delay may mean career disruption or a temporary decline in quality of life.
- Child Perspective (cSLE): For a child, 47 months covers nearly half a decade of crucial development.

This period can span from early puberty to late adolescence. Losing control over one's health during this rapid growth phase has far more serious implications than it does for adults whose bodies are already mature. The gap between clinical urgency (6 months) and reality (47 months) highlights a structural failure in the current diagnostic system. If the delay is 47 months in a high-resource setting like Europe. In that case, it is likely significantly longer or more fatal in a setting like Indonesia due to the geographic and economic barriers. (13)

Clinical Factors

Non-Specific Early Symptoms

Early clinical manifestations of cSLE are particularly challenging to identify due to their heterogeneous and frequently non-specific nature.(14) Children may initially present with symptoms such as persistent fever, prolonged fatigue, lymphadenopathy, mild arthralgia, or general malaise. These presentations commonly overlap with more prevalent pediatric conditions—particularly viral or bacterial infections—causing clinicians to attribute these symptoms to routine childhood illnesses rather than considering an autoimmune etiology. (15) This can result in a longer time before

definitive diagnosis, as multisystem severe presentations typically lead to faster recognition.

Moreover, the absence of classical lupus features, such as the hallmark malar rash or multi-organ involvement, especially in the early stages, contributes significantly to a delay in clinical suspicion and subsequent referral for specialized evaluation. In certain cases, children may present with isolated findings, such as mild joint pain or skin rash, which further obscure the underlying diagnosis. (16) Mild or mono-organ manifestations tend not to trigger immediate concern for systemic disease and are often managed as single-organ problems, prolonging the time before comprehensive assessment and correct diagnosis are undertaken. Unfortunately, these non-specific presentations often mean that cSLE is not considered until more pronounced or multi-system features evolve, resulting in significant diagnostic delay and increased risk for irreversible organ damage and worse long-term outcomes.(17)

Diagnostic Overshadowing

The diagnosis of cSLE is complicated by the high background prevalence of infectious diseases that mimic the clinical presentation of lupus. "Diagnostic overshadowing" refers to the clinical heuristic where symptoms shared by a common endemic disease and a rare chronic disease are attributed to the common condition. (18)This probabilistic approach is generally sound but becomes a dangerous barrier for cSLE patients, who often endure multiple rounds of treatment for presumed infections before autoimmunity is considered.

The error of diagnostic overshadowing stems from two main factors: cognitive bias and cost. Clinicians in endemic areas often rely on the 'availability heuristic,' prioritizing common infections like dengue because they frequently encounter them. This leads to 'premature closure,' where the diagnostic search stops early, and autoimmune signs are ignored or misidentified as infectious symptoms.(18) Furthermore, resource limitations reinforce this bias. Treating for infection is cost-effective and accessible, whereas testing for cSLE (e.g., ANA, anti-dsDNA) is expensive. This creates a financial incentive to treat for infection first, causing dangerous delays in diagnosing lupus.(19)

Mimic Disease	Shared Features	The Diagnostic Challenge
Dengue Fever	Fever, Rash, Thrombocytopenia, Leukopenia	The Hematological & Time Trap: Low platelets are assumed viral; the "7-10 day wait" for recovery delays SLE workup.(8)
Typhoid Fever	Prolonged Fever, Abdominal Pain, Hepatosplenomegaly	The Widal Trap: Polyclonal antibodies in SLE cause false-positive Widal tests, leading to unnecessary antibiotics.(20)

Mimic Disease	Shared Features	The Diagnostic Challenge
Tuberculosis	Weight Loss, Lymphadenopathy, Pleural Effusion	The Therapeutic Dilemma: Clinical overlap is near-total. Fear of reactivating TB causes hesitation in starting steroids.(18)
Sepsis	Hypotension, Multi-organ failure	The MAS Mimic: Macrophage Activation Syndrome looks like septic shock but requires opposite treatment (immunosuppression).(21)

Table 2: Mimics of cSLE and Diagnostic Challenges

Non-Clinical Factors

Workforce Scarcity and Geographic Maldistribution

Frontline doctors often fail to "connect the dots" between diverse symptoms like hair loss, joint pain, and fatigue. Instead, patients receive "specific care," where each problem is treated separately: a dermatologist treats the rash with cream, while an orthopedist treats the joints as a mechanical injury, and neither doctor realizes the symptoms are part of the same disease. (21) Frontline surveys reveal a systemic lack of "red flag" recognition; primary care physicians frequently attribute musculoskeletal pain in children to benign "growing pains" or trauma, while constitutional symptoms are dismissed as common viral infections. This categorization forces patients into a "diagnostic journey," with studies confirming that cSLE patients consult an average of three to four different physicians over a span of several months to years before a rheumatology referral is finally secured. (22)

While developed healthcare systems maintain a target ratio of approximately 1 pediatric rheumatologist per 500,000(27) children to ensure adequate coverage, the landscape in Low- and Middle-Income Countries (LMICs) is defined by a significant shortfall.(24) In Southeast Asian nations like Indonesia, this ratio is heavily skewed, with only one pediatric rheumatologist for every 26 million children.(8) This workforce deficit means that the vast majority of initial cSLE presentations are evaluated by general practitioners or general pediatricians who may lack the specific training to recognize subtle autoimmune presentations, leading to a high rate of missed diagnoses at the primary care level.

This scarcity is compounded by extreme geographic centralization. The few available pediatric rheumatologists are almost exclusively clustered in Tier-A academic medical centers in megacities (e.g., Jakarta, Surabaya). This creates a "geographic lottery" that severely penalizes rural populations.(25) For a child living in a remote archipelago region, accessing a specialist is not merely a matter of scheduling, but a logistical impossibility involving inter-island travel and high out-of-pocket costs. Consequently, these children are trapped in a "referral bottleneck," bouncing between local facilities that lack the expertise to diagnose them, while the disease progresses to irreversible organ damage before they ever reach a capable specialist.

Socioeconomic and Structural Challenges

Diagnosing SLE requires a specific immunological battery (ANA IF, anti-dsDNA, C3/C4). In Indonesia, a standard ANA Profile can cost 5 times as much as a basic Complete Blood Count (CBC) costs. This 500% price disparity forces families to ration care; they opt for the cheaper, non-specific blood tests that mimic infection, leading clinicians to a "presumptive treatment" of antibiotics rather than investigating autoimmunity. While Indonesia's Universal Health Coverage (BPJS Kesehatan) theoretically covers SLE, it operates on a rigid tiered system. Specialized tests like anti-dsDNA are often restricted to Type A/B hospitals and are not reimbursable at the primary care level. (26)This creates a "referral bottleneck" where primary care physicians cannot order the confirmatory test even if they suspect lupus, forcing them to refer the patient blindly up a slow administrative ladder while the disease progresses.

Impact of Delayed Diagnosis

Mortality and Organ Damage

Diagnostic delay contributes to this mortality via a dangerous mechanism: because the disease is advanced at diagnosis, clinicians are forced to use aggressive immunosuppression to save organs. This profound iatrogenic immunosuppression, combined with the patient's debilitated state and the high prevalence of endemic pathogens (TB, sepsis), creates a lethal environment. A significant portion of cSLE mortality occurs within the first few years of diagnosis ("early mortality"), reflecting the severity of the presentation exacerbated by prior delays.(6)

Organ damage in lupus is a product of inflammation intensity multiplied by time. A delay of 6 months does not merely delay remission; it allows unchecked immune complexes to deposit in the kidneys (nephritis) or central nervous system (cerebritis). Studies indicate that cSLE patients accumulate organ damage significantly faster than adults, with renal damage being the most common early sequela.(27) Consequently, children with diagnostic delays >6 months often present with an SDI score >0 at their baseline visit, meaning they start their treated life with permanent disability (e.g., proteinuria, scarring) that could have been prevented.

Direct & Indirect Financial Costs

The financial penalty for delayed diagnosis is exponential. Research indicates that the direct cost of treating Lupus Nephritis (kidney failure) is 7.5 times higher than managing early-stage lupus.(28) Recent multicenter data from India confirms that this cost disparity forces over one-third (36.2%) of SLE households into "Catastrophic Health Expenditure" (CHE), defined as out-of-pocket spending exceeding the family's capacity to pay. (29)This catastrophe is driven by "insurance gaps"; in many LMICs, private and public schemes frequently exclude chronic autoimmune maintenance, leaving families to pay entirely out-of-pocket for expensive hospitalizations and immunosuppressants.

The economic damage extends beyond hospital bills. Parents often withdraw from the workforce to manage the child's unpredictable care, causing productivity losses that cost the economy four times more than the direct medical treatment itself.(30) Furthermore, a recent systematic review identifies "Financial Toxicity" as a distinct clinical side effect. To cope with this strain, families engage in dangerous "maladaptive behaviors," such as rationing medications (skipping doses to save money) or delaying follow-up visits.(31) This creates a vicious cycle: financial stress leads to poor adherence, which triggers severe flares, requiring even more expensive emergency care.

Conclusion and Suggestion

The challenge of diagnosing cSLE in tropical, resource-limited settings represents a systemic failure born from a "perfect storm" of biological mimicry, geographic isolation, and economic scarcity. The primary driver of this diagnostic delay is "diagnostic overshadowing," a cognitive bias where the specific clinical signals of autoimmunity are drowned out by the overwhelming prevalence of endemic infections like Dengue, Typhoid, and Tuberculosis; this leads clinicians to prioritize treating the "common" infection while the "rare" autoimmune condition progresses unchecked.(32) Compounding this biological confusion is a severe workforce deficit—the "Specialist Void"—where regional data indicates a ratio of less than one pediatric rheumatologist per 26 million children, leaving vast rural populations effectively severed from expert care.(8) The human cost of these intersecting barriers is quantifiable not just in time lost, but in tissue lost; children in these regions frequently present with high baseline SLICC/ACR Damage Index (SDI) scores, indicating they have already suffered irreversible renal or neurological injury before their first therapeutic intervention.(33) Ultimately, the trajectory of cSLE in the developing world can only be altered by shifting from a reactive model of treating end-stage complications to a proactive model of early suspicion and detection.

Dismantling these barriers requires health systems in regions like Indonesia to adopt a multi-pronged strategy focused on "task-shifting" and technological integration. Since training a sufficient number of pediatric rheumatologists is a multi-decade endeavor, the immediate solution lies in empowering General Practitioners (GPs) at the primary care level (Faskes 1) to recognize "Red Flags" through standardized triage algorithms (e.g., fever, hair loss, and joint pain); studies in similar resource-limited settings demonstrate that such algorithmic triage can reduce diagnostic delay by up to 40% by removing clinical guesswork. (34)Parallel to this educational shift, technology must be leveraged to bridge the "archipelago gap" through a "Hub-and-Spoke" telemedicine network, allowing GPs on remote islands to consult specialists in urban centers directly. Evidence suggests that tele-rheumatology can resolve up to 70% of triage consults remotely, thereby preventing "Catastrophic Health Expenditure" on unnecessary medical transfers. (35) Finally, these clinical efforts must be supported by policy reform that "democratizes diagnostics." National insurance schemes (BPJS) should reimburse basic ANA screening at Type C hospitals, as health-economic models confirm that the cost of early screening is negligible compared to the 7.5-fold higher cost of treating end-stage Lupus Nephritis with dialysis.(28)

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