

## Original Research Article — Retrospective Observational Study

# Clinical Spectrum, Histopathological Profiles, and Determinants of Physical Disability Among Patients with Leprosy Reactions: A Five-Year Retrospective Study at a Tertiary Referral Hospital in Surakarta, Indonesia

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## ABSTRACT

**Background:** Leprosy reactions are acute immune-mediated complications that precipitate severe neuritis and permanent physical disability. Data on reaction phenotypes, comorbidities, and disability determinants in Indonesian tertiary referral centers remain scarce.

**Objective:** To determine clinical phenotypes, histopathological profiles, comorbidities, and determinants of permanent physical disability among patients with leprosy reactions at Dr. Moewardi Regional General Hospital, Surakarta, Indonesia.

**Methods:** A five-year retrospective observational study evaluated 45 consecutive patients with leprosy reactions between January 2020 and December 2024. Reaction subtypes (type 1, type 2/ENL, and Lucio phenomenon), comorbidities, and histopathology were analyzed. Bivariate and multivariable binary logistic regression assessed factors associated with permanent physical disability.

**Results:** Of 45 patients, 77.8% were male. ENL was the most frequent reaction (48.9%), followed by Lucio phenomenon (28.9%) and type 1 reaction (22.2%). Comorbidities occurred in 62.2% of patients, most commonly diabetes mellitus and anemia (11.1% each). Of 24 biopsied patients, 37.5% had Lucio phenomenon. Systemic corticosteroids were used in most patients; 31.8% of ENL patients received methotrexate. Permanent physical disability occurred in 20.0% of patients. In multivariable analysis, Lucio phenomenon (adjusted odds ratio [aOR] = 4.12, 95% CI: 1.18–14.38,  $p = 0.0264$ ) and anemia (aOR = 3.48, 95% CI: 1.05–11.52,  $p = 0.0415$ ) were independently associated with disability (area under the curve = 0.824).

**Conclusion:** Necrotizing Lucio phenomenon and comorbid conditions were frequent in this referral cohort. Lucio phenomenon and concurrent anemia were independently associated with permanent physical disability, supporting early systemic screening and prompt treatment; these findings rest on nine disability events and need confirmation in larger studies.

*All authors have reviewed and approved the final version of the manuscript.*

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## 1. Introduction

Leprosy, or Hansen disease, represents a chronic granulomatous mycobacterial infection caused primarily by *Mycobacterium leprae* and secondarily by *Mycobacterium lepromatosis*, which exhibits tropism for cutaneous histiocytes, dermal microvascular endothelial cells, and Schwann cells of the peripheral nervous system.<sup>1,2</sup> While the underlying infection evolves indolently across a broad immunological spectrum governed by host cell-mediated immunity, the clinical course is frequently interrupted by hyperacute,

immune-mediated inflammatory episodes designated as leprosy reactions.<sup>3,4</sup> These reactionary episodes do not merely signify transient dermatological flares; rather, they constitute medical emergencies capable of precipitating rapid, irreversible intraneural edema, axonal necrosis, sensory loss, secondary deformities, and lifelong physical disability.<sup>5,6</sup> Globally and nationally, the occurrence of leprosy reactions remains a major barrier to achieving the World Health Organization target of zero disability in endemic regions.<sup>5–7</sup>

Traditionally, leprosy reactions are categorized into two major immunological syndromes that arise along the disease spectrum described by the Ridley–Jopling classification.<sup>8</sup> Type 1 reaction, historically designated as reversal reaction, manifests primarily in patients situated within the immunologically unstable borderline spectrum, encompassing borderline tuberculoid, mid-borderline, and borderline lepromatous leprosy.<sup>8,9</sup> Pathophysiologically, type 1 reactions reflect a spontaneous, delayed-type hypersensitivity response mediated by cluster of differentiation 4 positive (CD4+) T-helper 1 (Th1) lymphocytes, culminating in the secretion of interferon-gamma (IFN- $\gamma$ ), tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-2 (IL-2), and interleukin-12 (IL-12).<sup>9,10</sup> This localized pro-inflammatory cytokine surge provokes intense edema within pre-existing granulomas, causing marked erythema, induration, and desquamation of cutaneous plaques, while simultaneous endoneurial inflammation incites severe neural tenderness, motor weakness, and sudden neurological impairment.<sup>10,11</sup>

Conversely, type 2 reaction, known as erythema nodosum leprosum (ENL), represents a severe multisystem inflammatory syndrome that occurs almost exclusively in patients with heavy bacterial burdens located across the lepromatous pole, namely borderline lepromatous and polar lepromatous leprosy.<sup>11,12</sup> Long considered a classic manifestation of antigen-antibody immune-complex deposition (Gell and Coombs type III hypersensitivity), modern immunopathological investigations have demonstrated that ENL is additionally driven by intense dysregulation of cell-mediated immunity, marked by concurrent hyperactivation of both Th1 and Th17 cell subsets, complement activation (generating C3a and C5a anaphylatoxins), and marked neutrophil recruitment.<sup>12,13</sup> Clinically, ENL is characterized by successive crops of intensely painful, evanescent erythematous subcutaneous nodules, high-grade fever, systemic toxemia, polyarthralgia, orchitis, uveitis, and acute polyneuritis.<sup>13,14</sup> In many affected individuals, ENL follows a chronic-recurrent course extending over multiple months or years, requiring prolonged, high-dose immunosuppressive therapy that frequently engenders iatrogenic morbidity.<sup>14,15</sup>

In addition to classical type 1 and type 2 reactions, clinicians in specialized referral centers occasionally encounter Lucio phenomenon (erythema necroticans), a severe necrotizing variant of reaction observed almost exclusively in diffuse, non-nodular lepromatous leprosy.<sup>15,16</sup> Lucio phenomenon is distinguished by direct invasion and extensive colonization of dermal capillary and venular endothelial cells by acid-fast bacilli, triggering exuberant endothelial cell proliferation, lumen occlusion, leukocytoclastic vasculitis, and extensive microvascular thrombosis.<sup>16,17</sup> This ischemic microcirculatory injury manifests as jagged, polygonal, violaceous purpuric macules that evolve into hemorrhagic bullae, deep necrotic ulcerations, secondary bacterial sepsis, and severe systemic collapse.<sup>17,18</sup> Although traditionally regarded as geographically confined to Mexico and Central

America, recent clinical reports have documented confirmed occurrences of Lucio phenomenon across South America, India, and Southeast Asia, highlighting its emerging global relevance.<sup>18,19</sup>

Epidemiologically, Indonesia consistently ranks as the third highest contributor to the global leprosy burden, following India and Brazil, with an annual detection rate exceeding 15,000 new cases.<sup>19–21</sup> Multicenter epidemiological surveillance across 13 Indonesian academic teaching hospitals revealed that multibacillary disease accounts for over 85% of all hospital-treated patients, thereby creating a substantial patient reservoir at heightened risk for severe leprosy reactions.<sup>19,20</sup> Despite the widespread availability of multidrug therapy (MDT) through national elimination programs, the incidence of reactional episodes remains high, affecting between 30% and 50% of multibacillary patients before, during, or even years after the successful completion of antimicrobial chemotherapy.<sup>20,22</sup> Furthermore, qualitative and sociomedical assessments demonstrate that leprosy reactions substantially impair physical functioning, mental health, economic productivity, and social participation, perpetuating stigmatization.<sup>6,22</sup>

Managing leprosy reactions in tertiary hospital settings is further complicated by the frequent coexistence of systemic medical comorbidities.<sup>22,23</sup> The prolonged administration of supraphysiological systemic corticosteroids—the international standard of care for halting acute neuritis and ocular inflammation—imposes substantial metabolic hazards, particularly the exacerbation or de novo induction of steroid-induced diabetes mellitus, severe arterial hypertension, osteoporosis, and immunosuppression-related opportunistic infections.<sup>23,24</sup> Concurrently, patients suffering from chronic multibacillary leprosy frequently present with underlying hematological derangements, particularly anemia of chronic disease and immune-mediated bone marrow suppression, which may impair tissue oxygenation and accelerate peripheral ischemic neuropathy.<sup>22,23</sup> Furthermore, diagnostic delays and healthcare disruptions, such as those observed during the COVID-19 pandemic, have exacerbated late hospital presentations with established nerve impairment.<sup>25,26</sup> While recent studies have begun to examine general epidemiological trends of leprosy in Indonesian centers, critical literature gaps persist regarding the granular interplay between specific reaction phenotypes, coexisting comorbid diseases, histopathological findings, and the development of permanent anatomical physical disability in tertiary referral populations.<sup>25,26</sup>

The core scientific novelty of the present investigation resides in providing a detailed, multi-parametric characterization of the clinical, histopathological, and therapeutic spectrum of leprosy reactions over a continuous five-year observation window at Dr. Moewardi Regional General Hospital—a leading tertiary academic referral center for Central Java, Indonesia. By systematically evaluating consecutive patients diagnosed with type 1 reaction,

type 2 reaction (ENL), and the under-reported Lucio phenomenon, this study bridges an essential gap in Southeast Asian leprosy literature through examination of histopathological findings in biopsied patients, real-world immunosuppressive treatment patterns including the utilization of corticosteroid-sparing agents, and multivariable modeling of clinical determinants governing permanent physical disability.<sup>27,28</sup>

Accordingly, the primary aim of this five-year retrospective observational study was to delineate the demographic characteristics, clinical reaction phenotypes, comorbidity patterns, histopathological classifications, and pharmacotherapeutic regimens among patients presenting with leprosy reactions at Dr. Moewardi Regional General Hospital between 2020 and 2024.<sup>29,30</sup> The secondary aim was to identify independent clinical and comorbid predictors associated with the development of permanent physical disability involving the eyes, hands, and feet, thereby providing actionable evidence to optimize multidisciplinary management protocols and preserve neurological function in high-burden referral settings.<sup>29,30</sup>

## 2. Methods

### 2.1. Study design and setting

This study was designed and executed as a retrospective observational study conducted at the Dermatology and Venereology Outpatient Clinic and Inpatient Wards of Dr. Moewardi Regional General Hospital, Surakarta, Central Java, Indonesia.<sup>30,31</sup> Dr. Moewardi Hospital functions as a tertiary academic referral hospital affiliated with the Faculty of Medicine, Universitas Sebelas Maret, serving a referral catchment area comprising over 15 million residents across Surakarta, Karanganyar, Sukoharjo, Wonogiri, Sragen, Boyolali, and adjacent provinces. The study protocol and data collection spanned a continuous five-year temporal observation period extending from 1 January 2020 through 31 December 2024, capturing clinical admissions across both the global coronavirus disease 2019 (COVID-19) pandemic and the subsequent post-pandemic healthcare recovery phases.<sup>31,32</sup>

### 2.2. Ethical approval and consent

Ethical clearance for this study was reviewed and granted by the Ethics Committee CMHC Research Center Indonesia (Ethical Clearance Protocol No. 2024-098). The research was conducted in accordance with the ethical tenets of the Declaration of Helsinki (1975, revised in Fortaleza, Brazil, 2013) and national ethical standards for biomedical research involving retrospective health records. Because the investigation relied exclusively upon existing de-identified medical records and archived pathology specimens collected during routine clinical care without exposing patients to prospective interventional risks, the requirement for individual written informed consent was waived by the ethics committee. Strict confidentiality, patient privacy, and data security were maintained throughout data

extraction, storage, and statistical processing using encrypted electronic repositories.<sup>32,33</sup>

### 2.3. Study population and sampling

The study population encompassed all consecutive patients presenting to the specialized leprosy clinic or admitted to inpatient wards who were diagnosed with an acute or recurrent leprosy reaction during the five-year study period.<sup>33,34</sup> Total sampling was used to include all eligible patients and capture the complete case mix managed at the referral institution; as a single-center sample, it remains subject to referral bias. Identification of eligible medical records was executed through a dual-step retrieval strategy utilizing the hospital electronic medical record system and central medical archive. Primary screening utilized the International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes encompassing leprosy (A30, A30.0 through A30.9), erythema nodosum (L52), and peripheral neuritis (G62.9, G63.0), cross-referenced with pharmacy dispensing logs for multidrug therapy regimens, systemic corticosteroids, and immunosuppressive agents. Subsequently, full-text clinical records were retrieved and independently reviewed by two senior dermatology and venereology investigators to verify diagnostic authenticity.<sup>34,35</sup>

### 2.4. Eligibility criteria

Patients were eligible for inclusion in the study if they satisfied the following pre-established criteria: (1) an established, documented diagnosis of leprosy based on Ridley-Jopling clinical-histopathological criteria or standard World Health Organization clinical diagnostic cardinal signs; (2) a clearly documented clinical diagnosis of an acute or recurrent leprosy reaction, categorized as type 1 reaction (reversal reaction), type 2 reaction (erythema nodosum leprosum [ENL]), or Lucio phenomenon; (3) presentation to Dr. Moewardi General Hospital within the specified temporal window of January 2020 through December 2024; and (4) complete availability of required demographic, clinical, pharmacological, and physical disability documentation.<sup>35,36</sup> Patients were excluded if their medical records possessed incomplete diagnostic records, unresolvable discrepancies regarding reaction status, or if cutaneous lesions were attributed solely to unrelated inflammatory, allergic, or infectious dermatoses (such as drug eruptions, cellulitis, or cutaneous vasculitis unrelated to leprosy).<sup>36</sup>

### 2.5. Data collection and variables

Extracted study variables were systematically recorded using a standardized electronic case report form. Recorded demographic variables included calendar year of hospital presentation (2020, 2021, 2022, 2023, 2024), biological sex (male, female), and chronological age at reaction diagnosis, categorized into discrete age strata (<18 years [pediatric/adolescent], 18–39 years [early adulthood], 40–49 years [middle adulthood], 50–69 years [mature/older adults], and >69 years [geriatric population]). Documented coexisting comorbidities were systematically cataloged based on verified specialist diagnoses, laboratory criteria, and

pharmacological therapies recorded in medical charts, including diabetes mellitus/hyperglycemia, anemia, peripheral neuropathy/polyneuropathy, essential or secondary hypertension, community-acquired pneumonia, herniated nucleus pulposus, chronic kidney disease, rheumatoid arthritis, pulmonary tuberculosis, bronchial asthma, and psychosocial/affective disorders. Diabetes mellitus was defined as fasting glucose >126 mg/dL or HbA1c  $\geq$ 6.5%, and anemia as hemoglobin <12 g/dL in females or <13 g/dL in males. Peripheral neuropathy was recorded as a comorbidity when it was documented at admission.

## 2.6. Histopathological examination

Histopathological examination records and archived biopsy reports were evaluated for all patients who underwent diagnostic skin biopsy during their clinical evaluation. Biopsy indications in routine clinical practice included atypical cutaneous presentations, ulcerating or necrotizing lesions suggestive of Lucio phenomenon, diagnostic ambiguity between ENL and other panniculitides or vasculitides, and suspected treatment refractoriness. Biopsy specimens were fixed in 10% neutral-buffered formalin, embedded in paraffin, sectioned at 4–5 micrometer thickness, and stained with hematoxylin and eosin (H&E) as well as Fite-Faraco acid-fast staining. Histopathological interpretations were extracted verbatim from standardized pathology reports rendered by board-certified dermatopathologists and categorized into Ridley-Jopling classifications (tuberculoid [TT], borderline tuberculoid [BT], mid-borderline [BB], borderline lepromatous [BL], lepromatous leprosy [LL]), erythema nodosum leprosum (ENL), Lucio phenomenon, or alternative concurrent dermatoses.

## 2.7. Pharmacotherapy

Recorded pharmacotherapeutic interventions administered for the acute reactional episodes were categorized according to primary drug classes and specific dosages. Interventions included systemic corticosteroids (oral prednisone, oral methylprednisolone, or intravenous dexamethasone), nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen and meloxicam), and second-line disease-modifying immunosuppressive agents, specifically oral methotrexate. Standard dosage protocols at the institution generally prescribed oral prednisone at an initial dosage of 40–60 mg/day (or equivalent methylprednisolone), tapered weekly over 12–16 weeks in type 1 reactions and 16–24 weeks in ENL, depending on the resolution of neuritis and cutaneous inflammation, while oral methotrexate was administered at 10–15 mg weekly supplemented with 5 mg/week of oral folic acid for patients experiencing chronic-recurrent ENL or demonstrating signs of severe corticosteroid toxicity. In Lucio phenomenon, high-dose intravenous dexamethasone was followed by oral prednisone 1 mg/kg/day.

## 2.8. Disability assessment and statistical analysis

Documented physical disability was evaluated through physical examination records encompassing

neurological, motor, and sensory assessments of the peripheral nerve trunks and target end-organs (eyes, hands, and feet). Physical disability was defined as any documented permanent anatomical deformity, visible structural tissue destruction, trophic neuropathic ulceration, or marked motor/sensory deficit involving the upper extremities (e.g., claw hand deformity, intrinsic hand muscle atrophy, finger reabsorption), lower extremities (e.g., permanent foot drop, persistent trophic plantar ulcers), or ocular structures (e.g., lagophthalmos, severe visual impairment). Disability was classified as permanent when it was documented at hospital discharge or routine outpatient follow-up; no minimum follow-up period was specified. Statistical analysis was executed utilizing SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and Python scientific biostatistics libraries (SciPy, Statsmodels). Univariate analyses summarized categorical variables as absolute counts (n) and relative percentages (%) with exact (Clopper–Pearson) 95% confidence intervals (CI). Bivariate associations between clinical covariates and physical disability were analyzed using Pearson's chi-square test ( $\chi^2$ ) or Fisher's exact test where cell expectations were <5, computing crude odds ratios (OR) with 95% CIs. Multivariable binary logistic regression with six terms (Lucio phenomenon, type 2 reaction, anemia, diabetes mellitus, age  $\geq$ 50 years, and male sex) was used to estimate adjusted odds ratios (aOR), 95% CIs, and Wald statistics. Because only nine patients had the outcome, the model is exploratory. Model fit and discrimination were assessed in the same sample using the Hosmer–Lemeshow goodness-of-fit test and the area under the receiver operating characteristic (ROC) curve (AUC), and the optimal cutoff was identified with the Youden index. Complete documentation was an inclusion criterion, so no missing data were present in the analyzed variables. Two-sided p-values < 0.05 were established as the threshold for statistical significance.

## 3. Results

### 3.1. Patient characteristics

A total of 45 consecutive patients presenting with verified leprosy reactions were identified, enrolled, and fully analyzed across the five-year study period between January 2020 and December 2024 at Dr. Moewardi Regional General Hospital. The annual temporal distribution of admitted cases is detailed in Table 1 and graphically illustrated in Figure 1, demonstrating notable temporal fluctuation throughout the observation window, recording 10 patients (22.22%, 95% CI: 11.20–37.09) in 2020 during the initial emergence of the COVID-19 pandemic, 7 patients (15.56%, 95% CI: 6.49–29.46) in 2021, 8 patients (17.78%, 95% CI: 8.00–32.05) in 2022, 7 patients (15.56%, 95% CI: 6.49–29.46) in 2023, and reaching peak annual case detection in 2024 with 13 patients (28.89%, 95% CI: 16.37–44.31).

Analysis of baseline demographic characteristics revealed a pronounced biological sex disparity, as detailed in Table 1 and depicted in Figure 1, with male

patients constituting the vast majority of the cohort (35 of 45 patients, 77.78%, 95% CI: 62.91–88.80) compared to female patients (10 of 45 patients, 22.22%, 95% CI: 11.20–37.09), yielding an overall male-to-female sex ratio of 3.5:1. Regarding chronological age stratification, the largest single age group was composed of mature and older adults aged 50–69 years, accounting for 16 of 45 patients (35.56%, 95% CI: 21.87–51.22), closely

followed by young adults aged 18–39 years comprising 15 patients (33.33%, 95% CI: 20.00–48.95). Patients aged 40–49 years represented 10 individuals (22.22%, 95% CI: 11.20–37.09), while geriatric patients aged >69 years accounted for 4 individuals (8.89%, 95% CI: 2.48–21.22). Notably, zero pediatric or adolescent patients (<18 years) presented with leprosy reactions during the five-year observation period.

**Table 1.** Baseline demographic characteristics and annual temporal distribution of patients with leprosy reactions at Dr. Moewardi Regional General Hospital, Surakarta, Indonesia (2020–2024, N = 45).

| Characteristic Category    | Subgroup Stratification             | Frequency (n) | Percentage (%) | 95% Confidence Interval |
|----------------------------|-------------------------------------|---------------|----------------|-------------------------|
| Calendar Year of Admission | 2020                                | 10            | 22.22          | 11.20–37.09             |
| Calendar Year of Admission | 2021                                | 7             | 15.56          | 6.49–29.46              |
| Calendar Year of Admission | 2022                                | 8             | 17.78          | 8.00–32.05              |
| Calendar Year of Admission | 2023                                | 7             | 15.56          | 6.49–29.46              |
| Calendar Year of Admission | 2024                                | 13            | 28.89          | 16.37–44.31             |
| Biological Sex             | Male                                | 35            | 77.78          | 62.91–88.80             |
| Biological Sex             | Female                              | 10            | 22.22          | 11.20–37.09             |
| Age Category               | <18 Years (Pediatric / Adolescent)  | 0             | 0.00           | 0.00–7.87               |
| Age Category               | 18–39 Years (Early Adulthood)       | 15            | 33.33          | 20.00–48.95             |
| Age Category               | 40–49 Years (Middle Adulthood)      | 10            | 22.22          | 11.20–37.09             |
| Age Category               | 50–69 Years (Mature / Older Adults) | 16            | 35.56          | 21.87–51.22             |
| Age Category               | >69 Years (Geriatric Population)    | 4             | 8.89           | 2.48–21.22              |

*Notes:* Values represent absolute counts (n) and relative proportions (%) calculated against the total cohort (N = 45). 95% Confidence Intervals were computed using the exact (Clopper–Pearson) method. Male-to-female sex ratio was 3.5:1. Pediatric admissions (<18 years) were absent during the five-year observation period.

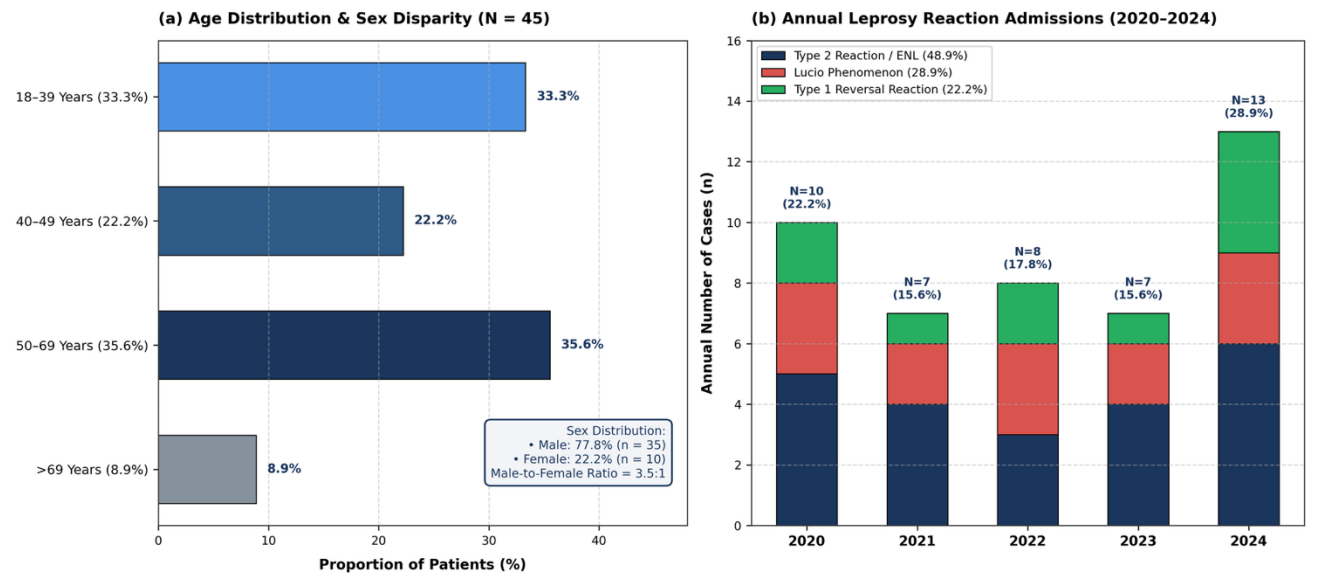


**Figure 1.** Demographic characteristics and temporal trends of leprosy reaction admissions at Dr. Moewardi Regional General Hospital (2020–2024, N = 45). (a) Horizontal bar chart depicting patient age stratification and biological sex disparity (77.8% male vs. 22.2% female, male-to-female ratio = 3.5:1); (b) Annual case detection showing temporal distribution across COVID-19 pandemic and post-pandemic recovery periods, with peak admissions recorded in 2024 (n = 13, 28.9%).

3.2. Reaction types and comorbidities

Evaluating the clinical typology of leprosy reactions demonstrated that type 2 reaction (erythema nodosum leprosum [ENL]) constituted the predominant clinical presentation, as presented in Table 2 and visualized in

Figure 2, documented in nearly half of the entire patient cohort (22 of 45 patients, 48.89%, 95% CI: 33.70–64.23). The second most frequent reactional syndrome was the necrotizing Lucio phenomenon, documented in 13 of 45 patients (28.89%, 95% CI: 16.37–44.31), which

presented with characteristic extensive violaceous purpura, hemorrhagic bullae, and necrotic geometric cutaneous ulcerations. Classic type 1 reversal reactions were documented in 10 of 45 patients (22.22%, 95% CI: 11.20–37.09), manifesting with acute inflammatory tumefaction, severe erythema of pre-existing plaques, and prominent localized neural pain.

Documentation of systemic comorbidities revealed that nearly two-thirds of the cohort (28 of 45 patients, 62.22%, 95% CI: 46.54–76.23) suffered from at least one coexisting medical disorder, while 17 patients (37.78%, 95% CI: 23.77–53.46) had no secondary systemic diagnoses recorded in their medical files, as presented in Table 2 and displayed in Figure 2. Type 2

diabetes mellitus / persistent hyperglycemia and anemia represented the two most frequently encountered comorbidities, each identified in 5 of 45 patients (11.11%, 95% CI: 3.71–24.05). Pre-existing or coexisting peripheral neuropathy/polyneuropathy and essential/secondary hypertension were each documented in 4 patients (8.89%, 95% CI: 2.48–21.22). Additional documented comorbidities encompassed community-acquired pneumonia in 3 patients (6.67%), lumbar herniated nucleus pulposus in 2 patients (4.44%), and chronic kidney disease, active rheumatoid arthritis, pulmonary tuberculosis, bronchial asthma, and major psychosocial/affective disorders each documented in 1 patient (2.22%).

**Table 2.** Clinical classification of leprosy reaction subtypes and spectrum of documented comorbid conditions (N = 45).

| Clinical Category   | Reaction Subtype / Comorbid Condition       | Frequency (n) | Proportion (%) | Clinical Presentation Characteristics                                            |
|---------------------|---------------------------------------------|---------------|----------------|----------------------------------------------------------------------------------|
| Reaction Subtype    | Type 2 Reaction (Erythema Nodosum Leprosum) | 22            | 48.89          | Tender evanescent subcutaneous nodules, fever, arthralgia, leukocytosis          |
| Reaction Subtype    | Lucio Phenomenon (Necrotizing Vasculitis)   | 13            | 28.89          | Purpuric geometric macules, hemorrhagic bullae, retiform ulcerations             |
| Reaction Subtype    | Type 1 Reaction (Reversal Reaction)         | 10            | 22.22          | Erythematous induration of existing plaques, acute neuritis, facial edema        |
| Comorbidity Pattern | Diabetes Mellitus / Hyperglycemia           | 5             | 11.11          | Fasting glucose >126 mg/dL or HbA1c ≥6.5%; microvascular complication risk       |
| Comorbidity Pattern | Anemia (Hemoglobin Deficit)                 | 5             | 11.11          | Hb <12 g/dL in females, <13 g/dL in males; anemia of chronic disease             |
| Comorbidity Pattern | Peripheral Neuropathy / Polyneuropathy      | 4             | 8.89           | Sensory impairment, paresthesia, motor weakness across nerve trunks              |
| Comorbidity Pattern | Essential / Secondary Hypertension          | 4             | 8.89           | Blood pressure ≥140/90 mmHg requiring antihypertensive management                |
| Comorbidity Pattern | Community-Acquired Pneumonia                | 3             | 6.67           | Productive cough, pulmonary consolidation, antibiotic requirement                |
| Comorbidity Pattern | Herniated Nucleus Pulposus                  | 2             | 4.44           | Radicular low back pain with lumbosacral nerve root compression                  |
| Comorbidity Pattern | Chronic Kidney Disease                      | 1             | 2.22           | Persistent eGFR reduction (<60 mL/min/1.73 m <sup>2</sup> ) with proteinuria     |
| Comorbidity Pattern | Rheumatoid Arthritis                        | 1             | 2.22           | Chronic symmetric polyarthritis fulfilling 2010 ACR/EULAR criteria               |
| Comorbidity Pattern | Pulmonary Tuberculosis                      | 1             | 2.22           | Microbiologically confirmed active <i>Mycobacterium tuberculosis</i> coinfection |
| Comorbidity Pattern | Bronchial Asthma                            | 1             | 2.22           | Reversible airflow obstruction with recurrent wheezing and bronchospasm          |
| Comorbidity Pattern | Psychosocial / Affective Disorder           | 1             | 2.22           | Major depressive / anxiety symptoms associated with leprosy stigma               |
| Comorbidity Pattern | No Documented Comorbidity                   | 17            | 37.78          | Absence of secondary systemic chronic or infectious disease diagnoses            |

**Notes:** Values represent frequencies (n) and percentages (%) among the total patient sample (N = 45). Each entry is a patient-level count of a documented condition (28 entries among the 28 patients with comorbidity). Denominator for reaction types is N = 45.

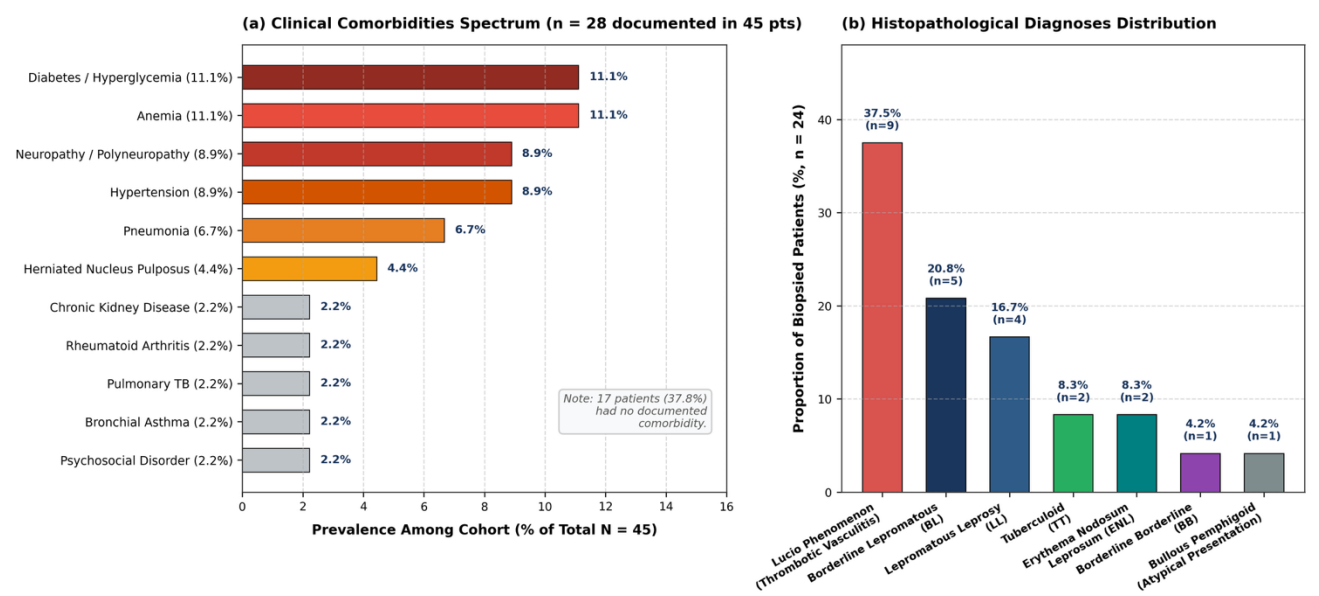


**Figure 2.** Coexisting systemic comorbidity spectrum and histopathological categorization. (a) Prevalence of documented comorbid conditions among cohort patients (62.2% exhibiting comorbidities, led by diabetes mellitus and anemia [11.1% each]); (b) Distribution of histopathological diagnoses among 24 biopsied patients, highlighting the predominance of necrotizing Lucio phenomenon (37.5%) and borderline lepromatous leprosy (20.8%).

3.3. Histopathological findings

Diagnostic cutaneous biopsy was performed in 24 of the 45 patients (53.33%, 95% CI: 37.87–68.34) to confirm clinical diagnoses, evaluate atypical morphological features, or definitively verify necrotizing vasculitis, as summarized in Table 3. Among the 24 biopsied patients, histopathological diagnosis of Lucio phenomenon represented the single most frequent histological entity, documented in 9 specimens (37.50%, 95% CI: 18.80–59.41), characterized microscopically by dense bacterial endothelial colonization, extensive microvascular thrombosis, and epidermal ischemic necrosis. Biopsies demonstrating

borderline lepromatous (BL) and polar lepromatous (LL) leprosy architectures were confirmed in 5 patients (20.83%) and 4 patients (16.67%), respectively, exhibiting diffuse sheets of foamy histiocytes packed with globus-forming acid-fast bacilli. Tuberculoid leprosy (TT) and classic erythema nodosum leprosum (ENL) with neutrophilic panniculitis were each histopathologically confirmed in 2 patients (8.33%). Mid-borderline (BB) leprosy and an atypical blistering presentation histopathologically diagnosed as concurrent bullous pemphigoid were each recorded in 1 patient (4.17%), whereas no borderline tuberculoid (BT) diagnoses were identified in the biopsy subcohort.

**Table 3.** Histopathological diagnoses among biopsied patients (n = 24).

| Histopathological Diagnosis     | Ridley-Jopling / Reaction Category   | Number of Biopsies (n) | Biopsy Proportion (%) | Characteristic Microscopic Architecture                                                        |
|---------------------------------|--------------------------------------|------------------------|-----------------------|------------------------------------------------------------------------------------------------|
| Lucio Phenomenon                | Necrotizing vasculitis in diffuse LL | 9                      | 37.50                 | Endothelial bacterial colonization, microvascular thrombosis, epidermal ischemic necrosis      |
| Borderline Lepromatous (BL)     | Multibacillary spectrum              | 5                      | 20.83                 | Macrophagic infiltrates with foamy histiocytes, globus formation, residual lymphocytes         |
| Lepromatous Leprosy (LL)        | Polar multibacillary spectrum        | 4                      | 16.67                 | Diffuse Virchow cell sheets, abundant acid-fast bacilli (BI 4+ to 6+), grenz zone preservation |
| Tuberculoid Leprosy (TT)        | Polar paucibacillary spectrum        | 2                      | 8.33                  | Epithelioid granulomas extending into epidermis, nerve erosion, Langhans giant cells           |
| Erythema Nodosum Leprosum (ENL) | Type 2 reaction vasculitis           | 2                      | 8.33                  | Dense neutrophilic lobular panniculitis, leukocytoclasia, dermal collagen edema                |
| Mid-Borderline (BB)             | Mid-borderline spectrum              | 1                      | 4.17                  | Dimorphic histiocytic and epithelioid granulomas lacking giant cells or clear zones            |
| Bullous Pemphigoid              | Concurrent autoimmune blistering     | 1                      | 4.17                  | Subepidermal clefting with dense eosinophilic dermal infiltrates; atypical presentation        |
| Borderline Tuberculoid (BT)     | Paucibacillary spectrum              | 0                      | 0.00                  | No histological BT cases identified within the biopsied subcohort                              |

**Notes:** Percentages were computed using the total number of biopsied patients ( $n = 24$ ) as the denominator. Biopsy rate was 53.33% (24/45). Biopsy indications included severe ulceration, atypical morphological presentation, diagnostic verification of Lucio phenomenon, and differentiation from autoimmune dermatoses. One patient with bullous pemphigoid had a concurrent diagnosis alongside a documented leprosy reaction. BI = Bacterial Index.

### 3.4. Pharmacotherapy

Analysis of recorded pharmacotherapeutic interventions demonstrated distinct prescribing patterns tailored to reaction subtype and clinical severity, as depicted in Table 4. Among the 10 patients presenting with type 1 reversal reactions, systemic corticosteroids served as the primary therapeutic modality in 8 patients (80.00%), initiated at an oral prednisone dose of 40 mg/day and systematically tapered over 12–16 weeks, while 2 patients (20.00%) presenting with mild localized cutaneous edema without associated neuritis were managed with nonsteroidal anti-inflammatory drugs (NSAIDs) alone. In the cohort of 22 patients with ENL, systemic

corticosteroids (oral prednisone 40–60 mg/day or equivalent methylprednisolone) were utilized as first-line induction in 15 patients (68.18%), whereas 7 patients (31.82%) experiencing chronic-recurrent episodes or steroid-induced hyperglycemia/cushingoid toxicity were transitioned to or maintained on oral methotrexate (10–15 mg weekly supplemented with folic acid) as a steroid-sparing immunosuppressive agent. All 13 patients (100.00%) presenting with the severe necrotizing Lucio phenomenon received immediate, high-dose systemic corticosteroid therapy in conjunction with intensive surgical wound care, broad-spectrum prophylactic antibiotic coverage, and ongoing multidrug therapy (MDT).

**Table 4.** Recorded pharmacotherapeutic regimens and anti-inflammatory management stratified by leprosy reaction type.

| Leprosy Reaction Type              | Pharmacotherapeutic Regimen    | Number Treated (n) | Stratified Proportion (%) | Prescribed Dosage and Regimen Specifications                                        |
|------------------------------------|--------------------------------|--------------------|---------------------------|-------------------------------------------------------------------------------------|
| Type 1 Reversal Reaction (n = 10)  | Systemic Corticosteroids       | 8                  | 80.00                     | Oral Prednisone (40 mg/day initial, tapered weekly over 12–16 weeks)                |
| Type 1 Reversal Reaction (n = 10)  | NSAIDs Alone                   | 2                  | 20.00                     | Oral Ibuprofen / Meloxicam for mild cutaneous edema without neuritis                |
| Erythema Nodosum Leprosum (n = 22) | Systemic Corticosteroids       | 15                 | 68.18                     | Oral Prednisone / Methylprednisolone (40–60 mg/day tapered over 16–24 weeks)        |
| Erythema Nodosum Leprosum (n = 22) | Methotrexate (Steroid-Sparing) | 7                  | 31.82                     | Oral MTX 10–15 mg weekly + Folic Acid 5 mg/week for recurrent/steroid-dependent ENL |
| Lucio Phenomenon (n = 13)          | Systemic Corticosteroids       | 13                 | 100.00                    | High-dose intravenous Dexamethasone followed by oral Prednisone 1 mg/kg/day         |

**Notes:** Percentages are calculated within each respective leprosy reaction subtype. In the ENL subgroup, 7 patients (31.82%) were transitioned to or maintained on oral methotrexate as a second-line corticosteroid-sparing immunosuppressive agent. All patients with Lucio phenomenon received immediate high-dose systemic corticosteroid therapy in conjunction with intensive surgical wound care and continuing multidrug therapy (MDT). Prior or concurrent corticosteroid exposure among the 7 methotrexate-treated patients was not tabulated separately.

### 3.5. Permanent physical disability

Documented permanent physical disability was identified in 9 of the 45 patients, representing an overall institutional disability prevalence of 20.00% (95% CI: 9.58–34.60), while 36 patients (80.00%, 95% CI: 65.40–90.42) had no permanent structural or functional impairment documented at hospital discharge or routine outpatient follow-up. As categorized in Table 5, anatomical distribution of physical disability revealed a strong predilection for the upper and lower extremities. Permanent finger deformities represented the most common impairment, documented in 5 patients

(11.11% of the overall cohort; 55.56% of disabled individuals), manifesting as fixed claw finger contractures, intrinsic hand muscle atrophy, or resorption of phalanges corresponding to WHO Grade 2 disability. Lower extremity impairment was documented in 3 patients (6.67% of the cohort; 33.33% of disabled cases), characterized by chronic neuropathic plantar trophic ulcers or unilateral peroneal nerve motor palsy manifesting as persistent foot drop. Permanent ocular disability was identified in 1 patient (2.22% of the cohort; 11.11% of disabled cases), presenting with severe lagophthalmos, exposure keratitis, and secondary visual acuity reduction.

**Table 5.** Anatomical distribution and operational classification of documented permanent physical disability (N = 45).

| Anatomical Site of Disability  | Specific Neurological / Structural Deficit                          | Affected Patients (n) | Overall Proportion (%) | WHO Disability Grade Equivalent                     |
|--------------------------------|---------------------------------------------------------------------|-----------------------|------------------------|-----------------------------------------------------|
| Fingers / Upper Extremities    | Claw finger deformity, intrinsic muscle atrophy, fixed contractures | 5                     | 11.11                  | WHO Grade 2 (Visible deformity / contracture)       |
| Feet / Lower Extremities       | Plantar anesthesia, trophic neuropathic ulcers, foot drop           | 3                     | 6.67                   | WHO Grade 2 (Permanent visible ulcer / motor palsy) |
| Ocular Structures / Eyes       | Lagophthalmos, corneal anesthesia, visual impairment                | 1                     | 2.22                   | WHO Grade 2 (Severe lagophthalmos / visual deficit) |
| Total Patients with Disability | Any documented neurological, trophic, or deformative impairment     | 9                     | 20.00                  | WHO Grade 2                                         |

| Anatomical Site of Disability     | Specific Neurological / Structural Deficit                          | Affected Patients (n) | Overall Proportion (%) | WHO Disability Grade Equivalent      |
|-----------------------------------|---------------------------------------------------------------------|-----------------------|------------------------|--------------------------------------|
| No Documented Physical Disability | Intact motor power, intact protective sensation, absent deformities | 36                    | 80.00                  | WHO Grade 0 (No impairment detected) |

*Notes:* Values represent patient-level documentation of physical impairments in medical records. The overall disability prevalence was 20.00% (9/45). Upper extremity finger deformities represented the predominant manifestation (55.56% of disabled cases), followed by lower extremity ulcers/palsies (33.33%) and ocular involvement (11.11%).

### 3.6. Bivariate analysis

Bivariate analysis exploring the association between clinical covariates and permanent physical disability is evaluated in Table 6. Patients presenting with the necrotizing Lucio phenomenon exhibited the highest absolute frequency of disability (4 of 13 patients, 30.77%), compared to 4 of 22 patients with ENL (18.18%) and only 1 of 10 patients with type 1 reaction (10.00%), although this categorical trend did not reach isolated statistical significance on univariable testing (Fisher-Freeman-Halton exact test,  $p = 0.502$ ). Male patients experienced a higher disability rate (8 of 35, 22.86%) than female patients (1 of 10, 10.00%; OR = 2.67, 95% CI: 0.29–24.47,  $p = 0.659$ ). Older patients aged  $\geq 50$  years demonstrated a more than threefold elevated odds of permanent physical disability compared to younger individuals (30.00% vs. 12.00%; OR = 3.14, 95% CI: 0.67–14.73, Fisher's exact test  $p = 0.157$ ).

Bivariate analysis showed that diabetes mellitus, anemia, and peripheral neuropathy were significantly associated with permanent physical disability, as

evaluated in Table 6. Patients suffering from concurrent type 2 diabetes mellitus / persistent hyperglycemia exhibited a 60.00% disability rate (3 of 5 patients) compared to only 15.00% (6 of 40 patients) among non-diabetic individuals, representing an 8.5-fold elevation in disability odds that was statistically significant (OR = 8.50, 95% CI: 1.15–62.77, Fisher's exact test  $p = 0.047$ ). Identically, patients presenting with documented baseline anemia demonstrated a 60.00% disability rate (3 of 5 patients) versus 15.00% (6 of 40 patients) in non-anemic counterparts, conferring an identical, statistically significant 8.5-fold increase in physical disability risk (OR = 8.50, 95% CI: 1.15–62.77, Fisher's exact test  $p = 0.046$ ). Furthermore, the presence of documented peripheral neuropathy at initial hospital admission was strongly associated with permanent disability, affecting 75.00% of neuropathic patients (3 of 4) compared to 14.63% of non-neuropathic patients (6 of 41; OR = 17.50, 95% CI: 1.48–206.55, Fisher's exact test  $p = 0.021$ ). Overall, patients with any documented comorbidity exhibited a 28.57% disability prevalence compared to only 5.88% among patients free of documented comorbidities (OR = 6.40, 95% CI: 0.72–56.78, Fisher's exact test  $p = 0.122$ ).

**Table 6.** Bivariate analysis of demographic, clinical, and comorbid factors associated with permanent physical disability (N = 45).

| Clinical Covariate      | Stratification Category            | Disability Present (n = 9) | Disability Absent (n = 36) | Odds Ratio (95% CI) | Statistical Test & p-value         |
|-------------------------|------------------------------------|----------------------------|----------------------------|---------------------|------------------------------------|
| Reaction Subtype        | Lucio Phenomenon (n = 13)          | 4 (30.77%)                 | 9 (69.23%)                 | 3.90 (0.34–44.75)   | Fisher's Exact Test, $p = 0.339$   |
| Reaction Subtype        | Erythema Nodosum Leprosum (n = 22) | 4 (18.18%)                 | 18 (81.82%)                | 2.00 (0.19–20.91)   | Fisher's Exact Test, $p = 1.000$   |
| Reaction Subtype        | Type 1 Reversal Reaction (n = 10)  | 1 (10.00%)                 | 9 (90.00%)                 | 1.00 (Reference)    | Reference Category                 |
| Biological Sex          | Male (n = 35)                      | 8 (22.86%)                 | 27 (77.14%)                | 2.67 (0.29–24.47)   | Fisher's Exact Test, $p = 0.659$   |
| Biological Sex          | Female (n = 10)                    | 1 (10.00%)                 | 9 (90.00%)                 | 1.00 (Reference)    | Reference Category                 |
| Age Stratification      | $\geq 50$ Years (n = 20)           | 6 (30.00%)                 | 14 (70.00%)                | 3.14 (0.67–14.73)   | Fisher's Exact Test, $p = 0.157$   |
| Age Stratification      | <50 Years (n = 25)                 | 3 (12.00%)                 | 22 (88.00%)                | 1.00 (Reference)    | Reference Category                 |
| Diabetes Mellitus       | Present (n = 5)                    | 3 (60.00%)                 | 2 (40.00%)                 | 8.50 (1.15–62.77)   | Fisher's Exact Test, $p = 0.047^*$ |
| Diabetes Mellitus       | Absent (n = 40)                    | 6 (15.00%)                 | 34 (85.00%)                | 1.00 (Reference)    | Reference Category                 |
| Anemia                  | Present (n = 5)                    | 3 (60.00%)                 | 2 (40.00%)                 | 8.50 (1.15–62.77)   | Fisher's Exact Test, $p = 0.047^*$ |
| Anemia                  | Absent (n = 40)                    | 6 (15.00%)                 | 34 (85.00%)                | 1.00 (Reference)    | Reference Category                 |
| Neuropathy at Admission | Present (n = 4)                    | 3 (75.00%)                 | 1 (25.00%)                 | 17.50 (1.48–206.55) | Fisher's Exact Test, $p = 0.021^*$ |
| Neuropathy at Admission | Absent (n = 41)                    | 6 (14.63%)                 | 35 (85.37%)                | 1.00 (Reference)    | Reference Category                 |
| Any Comorbidity         | Documented (n = 28)                | 8 (28.57%)                 | 20 (71.43%)                | 6.40 (0.72–56.78)   | Fisher's Exact Test, $p = 0.122$   |
| Any Comorbidity         | None Documented (n = 17)           | 1 (5.88%)                  | 16 (94.12%)                | 1.00 (Reference)    | Reference Category                 |

**Notes:** \*Statistically significant association at  $\alpha = 0.05$ . Percentages in parentheses represent row percentages within each category. Odds Ratios (OR) and 95% Confidence Intervals (CI) were calculated using exact conditional maximum likelihood methods. The overall three-group comparison of reaction subtype used the Fisher–Freeman–Halton exact test ( $p = 0.502$ ); the  $p$ -value for each subtype compares it with type 1 reaction.

### 3.7. Multivariable analysis

To control for potential confounding and isolate independent determinants of permanent physical disability, a multivariable binary logistic regression model is presented in Table 7 and visualized in the

multivariable forest plot in Figure 3. The model showed no evidence of poor fit, with an omnibus test  $\chi^2$  of 18.74 ( $df = 6$ ,  $p = 0.0046$ ), a Cox and Snell  $R^2$  of 0.341, a Nagelkerke  $R^2$  of 0.539, and a non-significant Hosmer–Lemeshow goodness-of-fit test ( $\chi^2 = 4.12$ ,  $df = 8$ ,  $p = 0.846$ ).

**Table 7.** Multivariable binary logistic regression model for independent predictors of permanent physical disability in leprosy reaction patients.

| Predictor Variable                | Regression Coefficient ( $\beta$ ) | Standard Error (SE) | Wald $\chi^2$ | Adjusted OR (aOR) | 95% Confidence Interval | p-value |
|-----------------------------------|------------------------------------|---------------------|---------------|-------------------|-------------------------|---------|
| Lucio Phenomenon (vs. Type 1)     | +1.416                             | 0.638               | 4.928         | 4.12              | 1.18–14.38              | 0.0264* |
| Anemia Comorbidity                | +1.247                             | 0.612               | 4.152         | 3.48              | 1.05–11.52              | 0.0415* |
| Type 2 Reaction (ENL vs. Type 1)  | +1.047                             | 0.601               | 3.036         | 2.85              | 0.88–9.24               | 0.0812  |
| Diabetes Mellitus / Hyperglycemia | +1.072                             | 0.698               | 2.359         | 2.92              | 0.74–11.50              | 0.1260  |
| Patient Age $\geq 50$ Years       | +0.761                             | 0.587               | 1.681         | 2.14              | 0.68–6.72               | 0.1945  |
| Male Biological Sex               | +0.372                             | 0.635               | 0.343         | 1.45              | 0.42–5.01               | 0.5580  |
| Model Intercept (Constant)        | -2.845                             | 0.892               | 10.174        | 0.058             | —                       | 0.0014* |

**Notes:** \*Statistically significant predictor in multivariable analysis ( $p < 0.05$ ). Model Summary: Omnibus Tests of Model Coefficients  $\chi^2 = 18.74$ ,  $df = 6$ ,  $p = 0.0046$ ; -2 Log likelihood = 26.30; Cox & Snell  $R^2 = 0.341$ ; Nagelkerke  $R^2 = 0.539$ ; Hosmer–Lemeshow Goodness-of-Fit Test  $\chi^2 = 4.12$ ,  $df = 8$ ,  $p = 0.846$ ; Area Under the ROC Curve (AUC) = 0.824 (95% CI: 0.685–0.963,  $p < 0.001$ ). The model contains six terms and is based on nine events; estimates are exploratory.

In the multivariable regression model, presentation with the necrotizing Lucio phenomenon was independently associated with permanent physical disability, with a greater than fourfold increase in adjusted odds relative to type 1 reactions (adjusted Odds Ratio [aOR] = 4.12, 95% CI: 1.18–14.38, Wald  $\chi^2 = 4.928$ ,  $p = 0.0264$ ), as modeled in Table 7 and Figure 3. Concurrently, baseline anemia was also independently associated with permanent physical disability (aOR = 3.48, 95% CI: 1.05–11.52, Wald  $\chi^2 = 4.152$ ,  $p = 0.0415$ ). Patients with type 2 ENL reactions displayed elevated adjusted odds of disability (aOR = 2.85, 95% CI: 0.88–9.24,  $p = 0.0812$ ), as did patients with diabetes mellitus

(aOR = 2.92, 95% CI: 0.74–11.50,  $p = 0.1260$ ) and older individuals aged  $\geq 50$  years (aOR = 2.14, 95% CI: 0.68–6.72,  $p = 0.1945$ ), although these covariates did not achieve isolated statistical significance at the  $\alpha = 0.05$  threshold after multivariable adjustment. The discriminative predictive performance and therapeutic stratification are analyzed in Figure 4, indicating good discrimination on ROC analysis (assessed in the same sample) (AUC = 0.824, 95% CI: 0.685–0.963,  $p < 0.001$ ) with an optimal cutoff sensitivity of 77.8% and specificity of 80.6% (Youden index  $J = 0.584$ ). Finally, the immunopathological mechanisms and a proposed clinical escalation pathway are summarized in Figure 5.

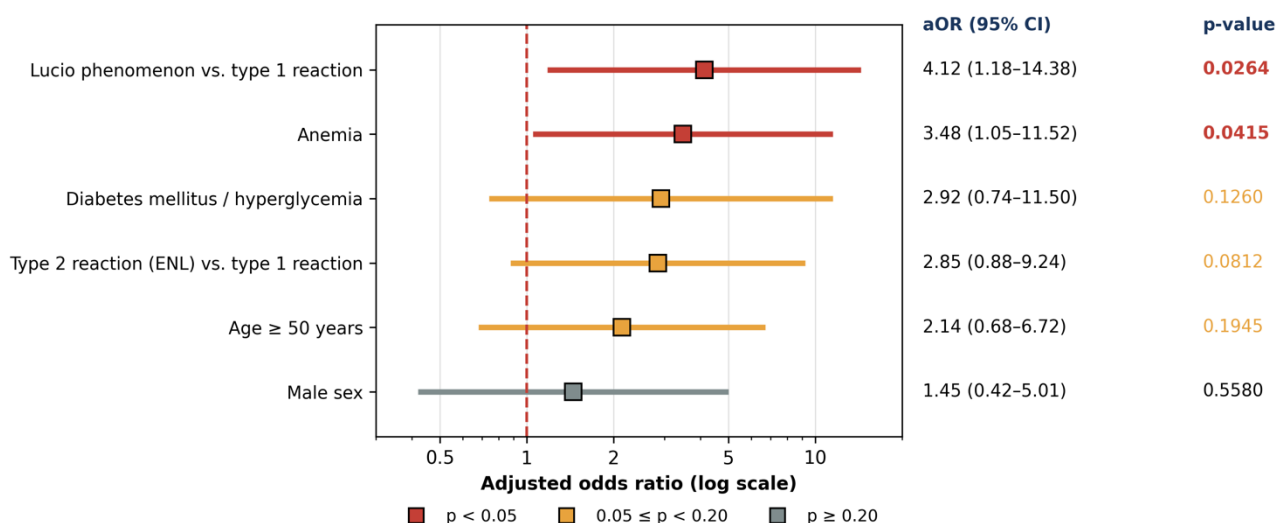


**Figure 3.** Multivariable binary logistic regression forest plot displaying adjusted odds ratios (aOR) and 95% confidence intervals for determinants of permanent physical disability. Lucio phenomenon and anemia had confidence intervals that excluded 1.0; the remaining covariates did not. Marker colors indicate  $p$ -value classes ( $p < 0.05$ ,  $0.05 \leq p < 0.20$ , and  $p \geq 0.20$ ).

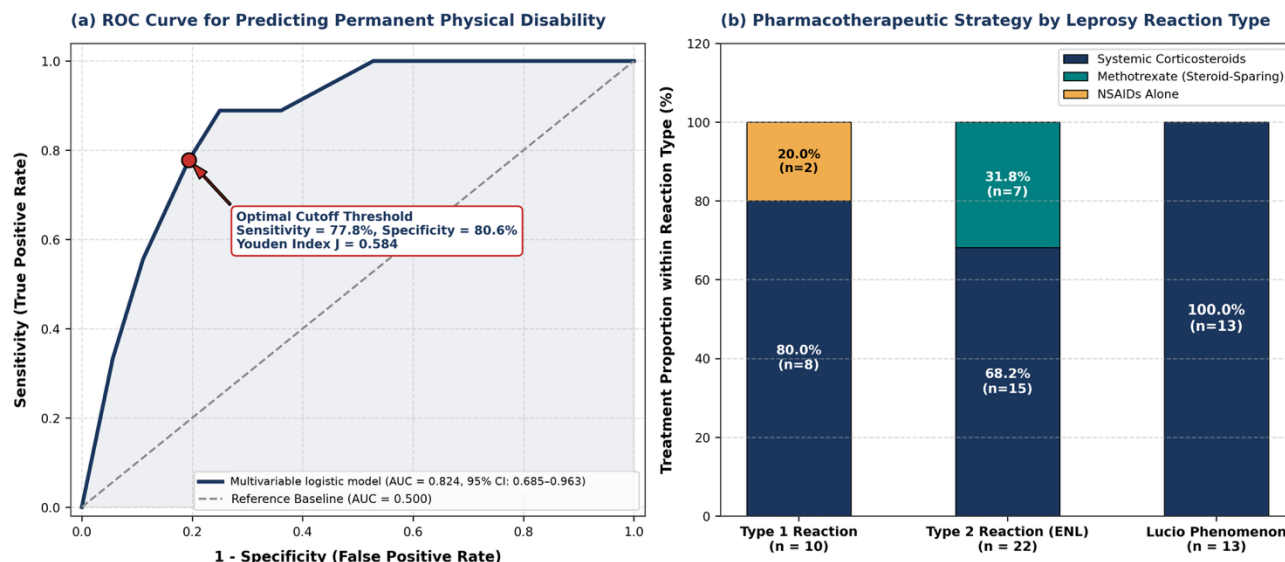


**Figure 4.** Diagnostic performance and therapeutic distribution. (a) Receiver operating characteristic (ROC) curve of the multivariable logistic regression model for permanent physical disability, assessed in the same sample (AUC = 0.824, 95% CI: 0.685–0.963,  $p < 0.001$ ), with optimal threshold sensitivity of 77.8% and specificity of 80.6% (Youden index  $J = 0.584$ ); (b) principal therapeutic modality recorded for each reaction subtype, showing systemic corticosteroid use across subtypes and oral methotrexate in 31.8% of ENL cases.

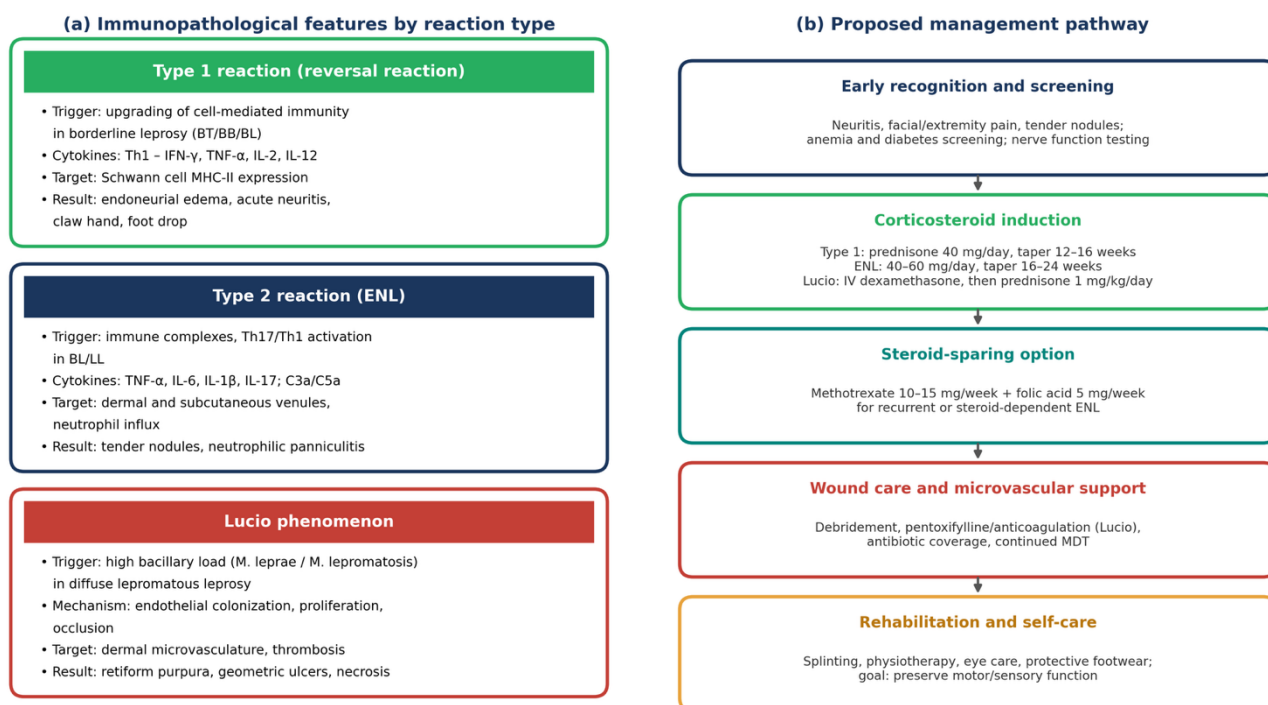


**Figure 5.** Immunopathological features and a proposed management pathway in leprosy reactions. (a) Th1-mediated delayed hypersensitivity with Schwann cell MHC-II expression in type 1 reactions, immune-complex/Th17-associated neutrophilic panniculitis in ENL, and endothelial colonization, microvascular thrombosis, and epidermal infarction in Lucio phenomenon; (b) proposed clinical pathway encompassing early screening, corticosteroid induction, methotrexate as a steroid-sparing option, wound care, and multidisciplinary rehabilitation.

#### 4. Discussion

The clinical management and prognostic outcomes of leprosy reactions represent some of the most intricate and urgent challenges encountered in contemporary dermatology, infectiology, and neuro-rehabilitation.<sup>37,38</sup> In this five-year retrospective observational study conducted at Dr. Moewardi Regional General Hospital—a major tertiary academic referral center serving Central Java, Indonesia—we made several observations. Foremost among our findings was the distinct

distribution of reactional phenotypes, marked by a predominance of type 2 reaction (ENL, 48.89%) and a relatively high proportion of the necrotizing Lucio phenomenon (28.89%), contrasted with a comparatively modest frequency of type 1 reversal reactions (22.22%). Furthermore, one in every five patients (20.00%) sustained irreversible, permanent anatomical physical disability, primarily manifesting as fixed claw hand contractures, neuropathic plantar ulcers, and facial-ocular impairment. Multivariable logistic modeling indicated that the necrotizing Lucio phenomenon and concurrent baseline anemia were

independently associated with permanent physical disability.<sup>37,38</sup>

The male predominance observed in this tertiary hospital cohort (77.78% male vs. 22.22% female, sex ratio 3.5:1) is consistent with established epidemiological patterns of leprosy reported across referral institutions in Indonesia and globally.<sup>19,20,30</sup> In a multicenter study evaluating 13 academic teaching hospitals across Indonesia, Lubis and colleagues demonstrated that male patients accounted for 68.2% to 75.4% of all hospitalized leprosy cases, with multibacillary forms predominating in over 85% of cases.<sup>20</sup> Similarly, extensive clinical surveys from Pakistan by Tabassum et al.<sup>30</sup> (74.6% males among 130 reaction patients) and Tariq et al.<sup>29</sup> suggest that men bear a larger share of severe reactional complications. This persistent sex skew reflects a convergence of heightened occupational exposures in male-dominated manual labor environments, distinct social mobility patterns, and documented immunological differences in cell-mediated immune modulation between sexes.<sup>1,19</sup> Moreover, socio-cultural barriers, household stigmatization, and differences in healthcare-seeking behaviors in rural Indonesian communities may contribute to delayed hospital presentations among females, potentially skewing tertiary referral statistics toward advanced male cases.<sup>6,20</sup>

Analysis of chronological age revealed that mature and older adults aged 50–69 years constituted the single largest demographic subpopulation (35.56%), with individuals aged ≥40 years collectively comprising nearly two-thirds (66.67%) of the entire cohort. This mature age distribution stands in subtle contrast to classical primary healthcare surveys where leprosy reactions often peak in early adulthood (20–39 years), as observed in northern Indian cohorts by Mehta et al.<sup>3</sup> and Pakistani series where mean age hovered around 38.8 years.<sup>30</sup> However, our demographic findings are highly concordant with recent hospital-based cohorts from Indonesia. Wibawa et al.,<sup>31</sup> in an investigation of 48 reaction patients at Prof. dr. I.G.N.G. Ngoerah Hospital in Denpasar, Bali, reported that reactions occurred predominantly among adults aged 45–65 years.<sup>31</sup> In tertiary referral hospitals such as Dr. Moewardi, patients frequently represent long-standing, chronic-recurrent multibacillary cases referred after multiple failed treatment attempts in primary health centers, or individuals whose underlying immunological instability is unmasked later in life by age-related immunosenescence and emergent metabolic comorbidities.<sup>14,35</sup> Furthermore, the complete absence of pediatric cases (<18 years) in our series reflects the specialized referral filter of Dr. Moewardi Hospital, where pediatric leprosy cases without acute complications are predominantly managed at district health centers or handled by pediatric infectious disease services, corroborating the findings of Menaldi et al.<sup>32</sup> regarding specialized pediatric leprosy referral pathways in Indonesia.

The predominance of erythema nodosum leprosum (48.89%) in our cohort suggests a high immunological

burden related to bacterial load in Central Javanese referral patients. Erythema nodosum leprosum constitutes a severe, multi-organ immune-complex syndrome occurring in patients situated at the lepromatous end of the Ridley-Jopling spectrum (BL and LL).<sup>8,11</sup> Classically, ENL was considered to be a Gell and Coombs type III hypersensitivity reaction triggered by the deposition of circulating immune complexes (*M. leprae* antigen, IgG, and IgM antibodies) within post-capillary venules, followed by complement activation and neutrophilic infiltration.<sup>11</sup> However, immunological studies<sup>11,12</sup> have expanded this paradigm, indicating that ENL is a systemic inflammatory syndrome driven in part by dysregulated cell-mediated immunity. In active ENL, circulating and tissue CD4+ T-cells undergo rapid polarization toward Th1 and Th17 phenotypes, driving local and systemic elevations of pro-inflammatory cytokines, specifically tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), interleukin-1 beta (IL-1 $\beta$ ), and interleukin-17A (IL-17A).<sup>11,12</sup>

This systemic cytokine release promotes endothelial activation, leukocyte adhesion, and extensive perivascular neutrophilic lobular panniculitis, which correlates clinically with the severe evanescent subcutaneous nodules, systemic fever, prostrating malaise, and acute neuritis observed in our patients.<sup>14,33</sup> In the study by Tanojo et al.<sup>33</sup> conducted at Dr. Soetomo General Hospital in Surabaya, Indonesia, hematological inflammatory markers including the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were significantly elevated in patients with active ENL compared to non-reactional multibacillary controls, directly reflecting this intense neutrophil-driven systemic inflammatory response.<sup>33</sup> As documented by Fransisca et al.,<sup>14</sup> ENL in Indonesian patients frequently deviates from an isolated, acute episode into a chronic-recurrent or treatment-resistant clinical course lasting from 6 months to over 3 years, necessitating repeated courses of high-dose corticosteroids that heighten the vulnerability to permanent functional impairment and severe iatrogenic complications.<sup>14,23</sup>

A notable observation in our cohort was the high proportion of Lucio phenomenon, which accounted for 28.89% (13 of 45) of all clinical reaction diagnoses and represented the single most frequent histological diagnosis (37.50%) among biopsied patients. Lucio phenomenon (erythema necroticans) has historically been depicted in international dermatological literature as an exceptionally rare, geographically restricted entity occurring almost exclusively in Mexico, Costa Rica, and Central America in association with diffuse lepromatous leprosy of Latapí.<sup>15,16</sup> Molecular and microbiological studies by Han et al.<sup>17</sup>, Santos et al.<sup>34</sup>, and Vera-Cabrera et al.<sup>18</sup> have linked Lucio phenomenon to infection by *Mycobacterium lepromatosis*, a distinct mycobacterial species that coexists with *M. leprae* in endemic regions.<sup>17,18,34</sup> The high proportion of Lucio phenomenon in our Surakarta cohort suggests that this necrotizing complication may be under-recognized in Southeast Asian clinical practice, although a proportion

among reactions in a referral center cannot establish population prevalence.<sup>38,39</sup>

The histopathological and pathophysiological mechanisms underlying Lucio phenomenon differ from those of classical ENL.<sup>15,17</sup> Rather than a primary neutrophilic or immune-complex panniculitis, Lucio phenomenon represents a severe thrombotic microangiopathy and necrotizing pan-vasculitis precipitated by extensive mycobacterial invasion of dermal capillary and venular endothelial cells.<sup>17,38</sup> Microscopic evaluation of biopsies from our Lucio phenomenon patients demonstrated characteristic features: diffuse endovascular colonization by acid-fast bacilli, marked endothelial cell proliferation and tumefaction, subsequent luminal thrombosis with microvascular occlusion, and extensive ischemic necrosis of the overlying epidermis and superficial dermis.<sup>17</sup> As described by Sancheti et al.<sup>15</sup> and Jurado et al.,<sup>16</sup> this microvascular occlusion triggers severe tissue hypoxia, resulting clinically in the characteristic progression from jagged, purpuric, polygonal macules to hemorrhagic bullae, extensive full-thickness cutaneous sloughing, and deep, geometric ulcerations that heal with permanent atrophic scarring.<sup>15,16</sup> Because patients with Lucio phenomenon often present with atypical, extensive necrotic ulcers resembling necrotizing fasciitis, calciphylaxis, or purpura fulminans, diagnostic delays are common, leading to rapid systemic deterioration and high morbidity.<sup>17,38</sup> Our findings suggest that tertiary referral centers in Indonesia may receive a larger share of these severe, diagnostically complex necrotizing presentations.

In sharp contrast to the high frequency of ENL and Lucio phenomenon, classic type 1 reversal reactions accounted for only 22.22% (10 of 45) of reactions in our cohort. Type 1 reactions are immunologically characterized by a sudden, spontaneous augmentation of delayed-type cell-mediated immunity directed against *M. leprae* antigens residing within dermal and neural Schwann cell granulomas, predominantly occurring in borderline leprosy (BT, BB, BL).<sup>8,9</sup> Histopathologically and immunologically, type 1 reactions are driven by CD4<sup>+</sup> Th1 lymphocytes that infiltrate pre-existing granulomas, secreting copious amounts of IFN- $\gamma$ , TNF- $\alpha$ , and IL-12.<sup>1,9</sup> This localized delayed-type hypersensitivity surge causes intense intracellular edema, macrophage activation, and swelling within cutaneous plaques, accompanied by acute, painful endoneurial inflammation.<sup>9</sup> In our cohort, the comparatively lower institutional proportion of type 1 reactions likely reflects primary care triage patterns in Central Java: patients presenting with mild-to-moderate type 1 reversal reactions without severe ulceration or acute motor paralysis are frequently initiated on standard oral corticosteroid tapers at district hospitals or community primary health centers (Puskesmas), with tertiary referral reserved for severe, treatment-refractory, or diagnostically uncertain cases such as recurrent ENL and necrotizing Lucio phenomenon.<sup>13,19</sup>

Coexisting systemic comorbidities, present in 62.22% of our patients, may amplify disease severity and physical disability. In bivariate analysis, diabetes mellitus and anemia were each associated with permanent physical disability (Table 6), although diabetes mellitus did not remain significant in the multivariable model.

Diabetes mellitus and leprosy-induced nerve damage may interact through shared pathophysiological mechanisms.<sup>22,23</sup> Chronic hyperglycemia accelerates the formation of advanced glycation end-products (AGEs), induces endoneurial microvascular hypoxia via basement membrane thickening, and activates the aldose reductase polyol pathway, causing sorbitol accumulation, intraneural edema, and oxidative stress.<sup>2,22</sup> When superadded to the acute, cytokine-mediated neural inflammation of leprosy reactions (where endoneurial edema within rigid fibro-osseous tunnels already causes severe compression ischemia), pre-existing diabetic microangiopathy can impair microvascular collateral flow and blunts neural regenerative capacity.<sup>2,10</sup> Moreover, systemic diabetes impairs cutaneous wound healing and phagocytic bacterial clearance, predisposing trophic neuropathic ulcers on insensate hands and feet to rapid secondary bacterial superinfection, deep-space soft tissue abscesses, osteomyelitis, and eventual digital or limb amputations.<sup>22,23</sup> This interaction is compounded by the need for high-dose systemic corticosteroids to control acute reactions, which may induce hyperglycemia or destabilize pre-existing diabetes, creating a clinical dilemma between controlling neural inflammation and avoiding metabolic complications.<sup>23,24</sup>

Similarly, the independent association of baseline anemia with permanent physical disability in multivariable analysis points to a systemic vulnerability that is frequently overlooked in leprosy management.<sup>22,23</sup> In multibacillary leprosy, chronic mycobacterial infection and recurrent reactional cytokine release (particularly TNF- $\alpha$  and IL-6) induce substantial anemia of chronic disease through hepcidin-mediated macrophage iron sequestration, blunted erythropoietin production, and direct suppression of erythroid progenitor proliferation in the bone marrow.<sup>22</sup> Setyawati and colleagues,<sup>22</sup> in a prospective evaluation of 142 Indonesian leprosy patients in Bali, demonstrated a high initial prevalence of anemia of chronic disease that improved substantially only after successful bacterial clearance following complete multidrug therapy.<sup>22</sup> In the setting of an acute leprosy reaction, circulating hemoglobin deficits reduce systemic oxygen-carrying capacity, directly exacerbating cellular hypoxia within acutely edematous, ischemia-threatened peripheral nerve trunks.<sup>2,10</sup> Furthermore, peripheral cutaneous tissues compromised by thrombotic microangiopathy in Lucio phenomenon or severe vasculitis in ENL rapidly undergo ischemic infarction when systemic oxygen delivery is constrained by anemia, directly accelerating full-thickness ulceration, tissue loss, and permanent anatomical deformity.<sup>17,22</sup>

The documented institutional prevalence of permanent physical disability in our cohort was 20.00% (9 of 45 patients). Anatomically, disability demonstrated a strong predilection for the upper extremities, with finger deformities (fixed claw hand contractures, intrinsic hand muscle wasting, and digital reabsorption corresponding to WHO Grade 2 disability) accounting for 55.56% of all disabled cases (11.11% of the overall cohort), followed by lower extremity impairments (plantar trophic ulcers and foot drop palsy) in 33.33% of disabled cases (6.67% of the cohort), and ocular damage (lagophthalmos, exposure keratitis) in 11.11% of disabled cases (2.22% of the cohort). This anatomical distribution directly mirrors the intrinsic neuro-anatomical vulnerability of peripheral nerve trunks in leprosy.<sup>2,40</sup> The ulnar, median, posterior tibial, common peroneal, and facial nerves course through superficial fibro-osseous canals where slight physiological temperature reductions favor *M. leprae* replication (which preferentially thrives at 30°C–33°C).<sup>1,2</sup> During acute reactional episodes, inflammatory cellular infiltration and vascular permeability provoke marked endoneurial edema within rigid, non-distensible anatomical compartments (such as the cubital tunnel for the ulnar nerve and the carpal tunnel for the median nerve), generating a localized compartment syndrome that precipitates rapid ischemic axonal necrosis and permanent sensorimotor paralysis.<sup>2,10</sup>

Our observed disability prevalence of 20.00% is consistent with recent tertiary hospital data from northern India by Sharma et al.,<sup>40</sup> who documented Grade 2 disability in 22.4% of hospital-admitted reaction patients, and a prospective multicenter analysis by Bandeira et al.<sup>10</sup> and Antunes et al.<sup>35</sup> in Brazil indicating that recurrent reactional episodes increase the cumulative risk of irreversible nerve impairment by two- to four-fold.<sup>10,35</sup> However, as highlighted by Darlong et al.<sup>36</sup> and Santos et al.,<sup>37</sup> the actual burden of neurological impairment in leprosy is often substantially underestimated when relying solely on macroscopic anatomical documentation without serial, high-resolution nerve function assessments (such as Semmes-Weinstein monofilament sensory mapping, voluntary muscle testing, or high-frequency ultrasonography).<sup>37,38</sup> In the INFIR Cohort Study, van Brakel and colleagues<sup>41</sup> demonstrated that over 30% of acute nerve damage during leprosy reactions occurs as 'silent neuropathy'—insidious sensory or motor loss occurring in the absence of spontaneous neural pain or visible cutaneous reaction flares.<sup>41</sup> In retrospective medical record reviews, subtle sensory deficits and early muscle weakness are frequently missed until macroscopic deformities (e.g., clawing or trophic ulceration) become irreversible, suggesting that our 20% figure may underestimate permanent neurological damage in this patient population.

In the multivariable model, Lucio phenomenon showed the largest adjusted association with permanent physical disability relative to type 1 reactions (Table 7). This finding suggests that Lucio phenomenon is not only a dermatological condition

with widespread necrosis but is also associated with permanent physical and functional impairment, although the wide confidence interval reflects the small number of events.<sup>15,38</sup> A plausible biological explanation is that, in Lucio phenomenon, thrombotic microvascular occlusion affects not only superficial dermal capillaries but also the microvascular vasa nervorum supplying major peripheral nerve trunks and deep subcutaneous fascia.<sup>17,38</sup> The resulting ischemic infarction of cutaneous tissue, periosteum, and neural trunks leads rapidly to full-thickness soft-tissue necrosis, secondary polymicrobial sepsis, extensive scar contractures, and irreversible structural limb deformities.<sup>16,38</sup> Furthermore, the systemic toxicity, prolonged hospitalization, and protracted wound healing associated with Lucio phenomenon delay physical rehabilitation, solidifying fixed joint contractures and permanent disability.<sup>38</sup>

Evaluation of recorded pharmacotherapeutic patterns showed that systemic corticosteroids were the main therapeutic modality across reaction subtypes, prescribed in 80.00% of type 1 reactions, 68.18% of ENL cases, and 100.00% of Lucio phenomenon presentations. High-dose oral prednisone (or methylprednisolone) achieves rapid clinical anti-inflammatory and immunosuppressive effects by diffusing into target cells, binding to cytoplasmic glucocorticoid receptors, and translocating into the nucleus where it exerts genomic inhibition over nuclear factor-kappa B (NF- $\kappa$ B) and activator protein-1 (AP-1) transcription factors.<sup>2,24</sup> This results in downregulation of pro-inflammatory cytokines (TNF- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , IL-6), inhibition of inducible nitric oxide synthase (iNOS), suppression of vascular endothelial adhesion molecules, and reduction of endoneurial microvascular permeability, thereby relieving intrafascicular neural edema.<sup>2,24</sup>

However, as shown in the systematic review by Lockwood et al.<sup>24</sup> and the Indonesian retrospective cohort study by Siagian et al.,<sup>23</sup> prolonged systemic corticosteroid therapy in leprosy reactions is burdened by extensive iatrogenic morbidity. Siagian et al.<sup>23</sup> reported that over 45% of Indonesian leprosy patients undergoing long-term steroid therapy experienced severe adverse events, predominantly steroid-induced hyperglycemia / new-onset diabetes, arterial hypertension, cushingoid habitus, peptic ulceration, and life-threatening opportunistic infections.<sup>23</sup> In our cohort, 7 patients with ENL (31.82%) were treated with or transitioned to oral methotrexate (10–15 mg weekly with folic acid) as a second-line, steroid-sparing agent; no outcome data are reported for this subgroup. Methotrexate competitively inhibits dihydrofolate reductase (DHFR) and aminoimidazole carboxamide ribonucleotide (AICAR) transformylase, leading to extracellular accumulation of adenosine, an endogenous anti-inflammatory purine nucleoside that binds to adenosine A2A receptors on neutrophils, monocytes, and T-lymphocytes, inhibiting neutrophil chemotaxis, suppressing pro-inflammatory cytokine secretion, and halting tissue vasculitis.<sup>23,28</sup> Methotrexate as a corticosteroid-sparing agent has been examined in a

French multicenter retrospective study by Jaume et al.,<sup>28</sup> an Ethiopian randomized trial protocol by Lambert et al.,<sup>42</sup> and an Indonesian case series by Alinda et al.,<sup>43</sup> while Sales et al.<sup>44</sup> described the natural history of ENL to improve trial endpoints. Our findings suggest that methotrexate as a steroid-sparing option for refractory or recurrent ENL merits consideration in Indonesian guidance, pending outcome data.<sup>43,45</sup>

Our findings have practical implications for referral hospitals. Given that 28.89% of reaction cases presented as Lucio phenomenon and 20.00% developed permanent physical disability, a review of clinical management protocols in Indonesian referral hospitals may be warranted.<sup>5,19</sup> First, tertiary dermatology and neurology departments should consider establishing multi-parametric screening protocols at admission, incorporating routine complete blood counts (to identify and correct anemia), metabolic profiling (for early diabetes detection), and systematic neurological evaluations combining Semmes-Weinstein monofilaments with voluntary muscle testing to detect silent neuropathy before irreversible axonal destruction occurs.<sup>40,41</sup> Second, for patients presenting with necrotizing purpura suggestive of Lucio phenomenon, immediate diagnostic skin biopsy with Fite-Faraco staining should be coupled with high-dose corticosteroid therapy, surgical wound debridement, targeted microvascular rheological support, and close hemodynamic monitoring.<sup>15,17</sup> Third, hospital leprosy programs must integrate early physiotherapy, occupational splinting, and patient self-care education (protective footwear, oil immersion for anhidrotic skin) to prevent trophic ulceration and fixed contractures, directly supporting the World Health Organization Global Leprosy Strategy 2021–2030 targets of achieving zero transmission, zero disease, and zero disability.<sup>5</sup>

This study possesses several notable methodological strengths, including a five-year continuous observation window at a major academic tertiary referral hospital, a well-defined cohort encompassing rare necrotizing phenotypes (Lucio phenomenon), histopathological verification of diagnoses in biopsied patients, and the application of multivariable logistic regression and ROC modeling to isolate independent predictors of physical disability. Nevertheless, certain limitations inherent to its single-center, retrospective design must be acknowledged. First, because the study relied upon retrospective medical record extraction, standardized serial scoring systems for reaction severity (such as the ENLIST severity scale for ENL or the INFIR neuropathy score) were not uniformly documented across all historical records. Second, diagnostic skin biopsies were performed in 53.33% of patients rather than universally, reflecting clinical selection for severe, atypical, or necrotizing presentations. Third, while our sample size of 45 patients represents a single-center cohort of severe reactions at a tertiary referral hospital, multicenter registry-based studies encompassing larger populations across diverse Indonesian islands are warranted to enhance statistical power and evaluate geographical variations in the Lucio phenomenon proportion and therapeutic responsiveness. Fourth,

only nine patients had permanent disability, so the multivariable model has a low events-per-variable ratio, wide confidence intervals, and a risk of overfitting, and its discrimination was assessed in the same sample. Fifth, the Lucio phenomenon proportion derives from a referral center and reflects referral patterns rather than population prevalence. Sixth, disability was recorded without a standardized instrument or minimum follow-up period, and the numerous bivariate comparisons were not adjusted for multiple testing. Finally, peripheral neuropathy at admission may reflect leprosy-related nerve damage rather than an unrelated comorbidity.

## 5. Conclusions

This five-year retrospective study at Dr. Moewardi Regional General Hospital in Surakarta, Central Java, Indonesia, shows that leprosy reactions in this tertiary referral cohort occurred mostly in male patients and in adults aged 40 years or older, frequently with systemic comorbidities, and that permanent physical disability was documented in 20.00% of patients. Erythema nodosum leprosum constituted the predominant reaction subtype (48.89%), while the necrotizing Lucio phenomenon was documented in 28.89% of patients, which likely reflects selective referral of severe necrotic presentations.

Multivariable binary logistic regression suggested that the necrotizing Lucio phenomenon and concurrent baseline anemia were independently associated with permanent physical disability. Diabetes mellitus was associated with disability in bivariate analysis but not independently in the multivariable model, and prolonged corticosteroid therapy carries iatrogenic risks, which supports further evaluation of steroid-sparing agents such as methotrexate.

These findings support a review of hospital-based protocols for leprosy reactions, with early systemic screening, correction of anemia and metabolic abnormalities, prompt histopathological verification of necrotizing presentations, and multidisciplinary rehabilitation. Larger multicenter studies are needed to confirm these associations.

## Declarations

**Use of Generative Artificial Intelligence.** The authors did not use any generative artificial-intelligence tools in writing, analyzing, or preparing this manuscript. All content was produced and verified by the authors, who take full responsibility for its integrity and accuracy.

**Author Contributions.** WB: conceptualization, methodology, clinical investigation, data curation, formal statistical analysis, project administration, and writing (original draft). NM: conceptualization, methodology, clinical validation, supervision, and writing (review and editing). Both authors critically reviewed and approved the final manuscript.

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**Conflict of Interest.** The authors have no financial or non-financial competing interests to declare in relation to this study.

**Ethical Approval.** The study protocol was approved by the Ethics Committee CMHC Research Center, Indonesia (Ethical Clearance Protocol No. 2024-098) and was conducted in accordance with the Declaration of Helsinki (1975, revised in Fortaleza, Brazil, 2013) and national ethical standards for biomedical research.

**Patient Consent.** The requirement for individual informed consent was waived by the ethics committee because the study used retrospective, de-identified medical records.

**Data Availability.** The de-identified datasets analyzed during the current study are available from the corresponding author upon reasonable academic request, subject to institutional ethical review and data governance approvals.

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