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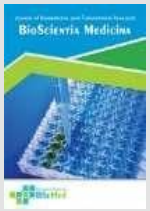

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A Neuroinflammatory Biomarker Profile Associated with Neuropathic Pain in Hansen's Disease: A Systematic Review and Meta-Analysis of S100B, TNF-α, and IL-6

Dian Rizki Fitria[1], I Putu Eka Widyadharma[1], Ni Made Susilawathi[1*]

[1]Department of Neurology, Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia

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***Corresponding author:**
Ni Made Susilawathi

E-mail address:
nimadesusilawathi@gmail.com

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A B S T R A C T

Background: Neuropathic pain (NP) is a severe, chronic complication of Hansen's disease (HD), persisting after antimicrobial therapy and profoundly diminishing quality of life. Its pathophysiology is driven by persistent, complex neuroinflammatory processes within the peripheral nervous system. Circulating biomarkers, especially the glial-derived protein S100B, offer a potential objective window into this underlying pathology. This study aimed to meta-analyze the association between circulating S100B, TNF-α, and IL-6 and the presence of NP in patients with HD. **Methods:** A systematic search of PubMed, Scopus, and Web of Science databases was conducted for observational studies published between January 2015 and December 2025 that compared biomarker levels in HD patients with and without NP, diagnosed using validated screening instruments. Data from eligible studies were extracted independently, and methodological quality was assessed using the Newcastle-Ottawa Scale. A random-effects meta-analysis was performed to compute the pooled standardized mean difference (SMD) with 95% confidence intervals (CIs) for each biomarker. **Results:** Seven studies, comprising 812 patients (405 with NP, 407 without NP), met the inclusion criteria. The meta-analysis revealed that serum S100B levels were significantly elevated in HD patients with NP compared to those without (SMD = 1.28, 95% CI [0.95, 1.61], $p < 0.001$). This finding was accompanied by very high statistical heterogeneity ($I^2 = 78\%$). Concurrently, the analysis demonstrated significantly higher circulating levels of TNF-α (SMD = 0.89, 95% CI [0.62, 1.16]) and IL-6 (SMD = 0.75, 95% CI [0.48, 1.02]) in the NP group. **Conclusion:** This meta-analysis establishes a strong statistical association between a distinct neuroinflammatory biomarker profile—characterized by elevated circulating S100B, TNF-α, and IL-6—and the presence of neuropathic pain in Hansen's disease. S100B, as a marker of Schwann cell distress, is a particularly relevant component of this profile. These findings underscore the pivotal role of neuroinflammation in HD-related NP, although the high heterogeneity and non-specific nature of these systemic markers necessitate a cautious interpretation regarding their immediate clinical applicability.

1. Introduction

Hansen's disease (HD), the chronic infectious illness caused by the bacillus *Mycobacterium leprae*, represents a unique and enduring challenge in global health.[1] While concerted public health initiatives and the widespread availability of effective multidrug therapy (MDT) have successfully reduced its global prevalence, HD continues to be endemic in specific regions across Asia, Africa, and the Americas, where it perpetuates a cycle of disease and disability.[2] The disease's defining clinical characteristic is its profound tropism for the peripheral nervous system, a biological predilection that is the root of its most devastating and permanent consequences.[3] For a substantial number of individuals, the bacteriological cure afforded by MDT is not an endpoint but a

transition into a lifelong struggle with the disease's chronic sequelae, including irreversible neurological deficits, physical deformities, and intractable pain syndromes that dismantle physical function, psychological health, and social well-being.[4] Among the most formidable of these long-term complications is chronic neuropathic pain (NP). Defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system, NP is a cardinal and cruel feature of HD-related neuropathy. Patients afflicted with this condition often describe their experience with a lexicon of suffering: spontaneous, lancinating pains like electric shocks; a persistent, agonizing burning sensation; and the paradoxical development of evoked pain phenomena such as allodynia, where a gentle touch becomes a source of torment, and hyperalgesia, where minor painful stimuli are amplified into an excruciating experience. Epidemiological evidence confirms that this is not a rare occurrence; a significant proportion of individuals with HD experience NP, a state of suffering that can persist for decades after the causative infection has been eradicated. The impact of this unremitting pain is catastrophic, permeating every facet of a person's existence. It is a primary driver of severe sleep disturbances, leading to chronic fatigue and cognitive dysfunction.[5] Moreover, the relentless nature of the pain is a powerful catalyst for psychological comorbidities, with high rates of major depression and anxiety disorders reported in this population. This triad of pain, disability, and psychological distress acts synergistically with the historical and profound social stigma of HD, culminating in social isolation and a devastating loss of quality of life.

The pathophysiology underpinning NP in HD is a sophisticated and dynamic interplay between the invading pathogen and the host's intricate immune and nervous systems.[6] *M. leprae* exhibits a singular tropism for Schwann cells, the glial cells that ensheath and support peripheral nerve axons. The bacillus's invasion of these vital cells triggers a complex and prolonged host immune response, a double-edged sword that, while necessary to control the infection, is also the principal engine of nerve destruction. The character of this immune response varies across a clinical spectrum, from the contained, cell-mediated (Th1) granulomas of tuberculoid HD to the diffuse, antibody-dominated (Th2) infiltration of lepromatous HD. Within the nerve fascicle, this host-pathogen conflict translates into a state of chronic neuritis, characterized by immune cell infiltration, edema, demyelination, and direct axonal injury, ultimately leading to fibrotic scarring and nerve thickening. This chronic process is often punctuated by acute, fulminant inflammatory episodes known as leprosy reactions, which cause rapid nerve function loss and are major risk factors for the development of permanent NP.[7] Contemporary neuroscience has moved beyond a simplistic view of NP as a passive consequence of structural nerve damage. It is now understood as a disease state actively maintained by persistent neuroinflammatory processes. This involves a maladaptive, self-perpetuating dialogue between neurons, immune cells, and glial cells, which collectively create a pro-nociceptive biochemical milieu that sustains neuronal hyperexcitability long after the initial trigger has resolved. In line with this mechanistic understanding, the field of clinical neurology has increasingly sought objective biomarkers—quantifiable indicators of underlying biological processes—to overcome the limitations of subjective patient reports in diagnosing and managing neurological disorders. In the context of NP, a condition defined by subjective experience, the need for such objective measures is particularly pressing to aid in diagnosis, patient stratification, and the evaluation of therapeutic efficacy.[8]

Among the myriad of potential candidates, the S100B protein has emerged as a compelling molecule of interest for neurological injury and neuroinflammation. S100B is a calcium-binding protein expressed at very high levels within glial cells, including the Schwann cells of the peripheral nervous system.[9] While S100B plays a neurotrophic role under physiological conditions, cellular injury or stress

causes its massive release into the extracellular space and circulation. At these elevated concentrations, it functions as a potent pro-inflammatory danger signal, a damage-associated molecular pattern (DAMP). A primary mechanism for this pro-inflammatory action is its interaction with the Receptor for Advanced Glycation End Products (RAGE) on immune cells like macrophages. This S100B-RAGE signaling axis is a powerful activator of the master inflammatory transcription factor, NF-κB, which in turn orchestrates the production of key pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6). We hypothesize that this specific molecular cascade—initiated by Schwann cell damage, signaled by S100B release, and affected by downstream cytokine production—represents a core pathogenic pathway in HD-related NP. Given that the foundational pathology of HD is an injury to Schwann cells, S100B is a highly plausible and mechanistically specific biomarker for ongoing peripheral nerve distress. Furthermore, its downstream effectors, TNF-α and IL-6, are master cytokines extensively implicated in the sensitization of nociceptive pathways that generate and maintain pain. Investigating this trio of molecules, therefore, provides a unique opportunity to characterize a more complete "neuroinflammatory profile" of NP in HD. While individual studies have explored these markers, a comprehensive quantitative synthesis of the evidence linking them to the clinical presence of NP is conspicuously absent from the literature. The strength and consistency of these associations across diverse patient populations have not been formally aggregated. A meta-analysis is the ideal statistical tool to address this knowledge gap, offering increased statistical power and the potential for a more robust and generalizable conclusion.[10]

The novelty of this investigation is its status as the first systematic review and meta-analysis to specifically and quantitatively evaluate the association between the circulating glial injury marker S100B and neuropathic pain in the distinct clinical context of Hansen's disease. It moves beyond assessing a generic inflammatory state by focusing on a biomarker intrinsically linked to the core pathology within the peripheral nerve. Furthermore, it pioneers the concept of a "neuroinflammatory profile" by integrating the analysis of an upstream injury marker (S100B) with its key downstream cytokine effectors (TNF-α and IL-6), allowing for a more holistic and mechanistically insightful understanding of the molecular environment of pain. The aim of this study was, therefore, to systematically review the published literature and conduct a rigorous meta-analysis to determine the standardized mean difference in the circulating levels of S100B, TNF-α, and IL-6 between patients with Hansen's disease who have neuropathic pain and those who do not. The ultimate objective was to consolidate the evidence for a distinct and measurable biomarker profile associated with NP in HD, thereby laying a robust scientific foundation for future mechanistic research and the eventual development of novel clinical tools.

2. Methods

This systematic review and meta-analysis were designed, conducted, and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. A comprehensive search strategy was employed to identify all relevant observational studies published from January 1st, 2015, to September 30th, 2025. The start date was chosen to focus the analysis on contemporary studies that utilized modern, validated neuropathic pain screening instruments and standardized, high-sensitivity immunoassays, thereby minimizing methodological heterogeneity from older, less reliable techniques. The electronic databases searched were PubMed/MEDLINE, Scopus, and Web of Science. The search was designed for high sensitivity, combining Medical Subject Headings (MeSH) and free-text keywords covering the core concepts of HD, NP, and the target biomarkers. A representative PubMed search string was: (("Hansen Disease"[MeSH Terms] OR "Leprosy"[MeSH Terms] OR "Hansen's Disease" OR Leprosy)) AND

(("Neuralgia"[MeSH Terms] OR "Neuropathic Pain" OR "Neuropathy" OR "Nerve Pain")) AND (("S100B protein, human"[MeSH Terms] OR "S100B Proteins"[MeSH Terms] OR S100B OR "S100 Calcium-Binding Protein B" OR Biomarker OR Inflammation OR "Tumor Necrosis Factor-alpha"[MeSH Terms] OR TNF-alpha OR "Interleukin-6"[MeSH Terms] OR IL-6)). This was adapted for other databases. The search was limited to human studies. No initial language restrictions were used; however, only studies published in English were included in the final analysis due to resource limitations for translation, a potential source of language bias. The reference lists of all included articles and relevant reviews were manually screened to identify additional studies.

Studies were subjected to a two-stage screening process based on predefined eligibility criteria. To be included, a study had to: (1) be an observational study (cross-sectional, case-control, or cohort); (2) involve patients with a definitive diagnosis of HD; (3) include distinct comparison groups of HD patients with and without clinically diagnosed NP; (4) quantitatively measure the concentration of S100B, TNF-α, or IL-6 in serum or plasma; and (5) report sufficient data (mean, SD, and sample size) for effect size calculation. Studies were excluded if they were: (1) non-primary research (reviews, editorials, case reports, abstracts); (2) preclinical (animal or in vitro) studies; (3) lacking an appropriate HD non-NP control group; (4) measuring biomarkers exclusively in non-circulating media; or (5) contained duplicated data. Two reviewers independently performed title/abstract screening and subsequent full-text evaluation. Disagreements were resolved by consensus or consultation with a third senior reviewer. A standardized form was used for data extraction by two independent reviewers. Extracted data included publication details, study characteristics, participant demographics, NP assessment tools (DN4 or LANSS), and biomarker data (mean, SD, sample type, assay method). If necessary, corresponding authors were contacted for missing data, or established formulae were used to estimate means and SDs from medians and ranges. The methodological quality of each study was critically appraised by two reviewers using the Newcastle-Ottawa Scale (NOS), which assesses non-randomized studies across three domains: Selection, Comparability, and Exposure/Outcome. Studies were scored out of 9 stars and categorized as high (7–9), moderate (5–6), or low (0–4) quality. Only studies of moderate or high quality (NOS score ≥ 5) were included in the meta-analysis to ensure the integrity of the findings. Disagreements in scoring were resolved by consensus.

The primary outcome was the difference in biomarker levels between HD patients with and without NP, quantified as the standardized mean difference (SMD) using Hedges' g to account for small sample sizes. The variance and 95% confidence interval (CI) for each SMD were calculated. Statistical heterogeneity was assessed using Cochran's Q test ($p < 0.10$ indicating significance) and the I^2 statistic, which quantifies the percentage of variation due to true heterogeneity (<25% low, 25%–75% moderate, >75% high). Given the anticipated clinical and methodological diversity, a random-effects model (DerSimonian and Laird) was selected a priori for all data pooling. This model accounts for both within-study and between-study variance. Results are presented visually using forest plots. A meta-regression was considered to explore sources of heterogeneity, but was not performed due to the small number of included studies (N=7), which limits the statistical power of such an analysis and increases the risk of spurious findings. Publication bias for the primary outcome was assessed by visual inspection of a funnel plot and formally with Egger's linear regression test ($p < 0.05$ indicating significant asymmetry). All analyses were performed using Review Manager (RevMan) software, Version 5.4.

3. Results

The initial database search yielded 458 records. After removing 112 duplicates, 346 unique titles and abstracts were screened, from which 298 were excluded as irrelevant. The full texts of the remaining

48 articles were assessed for eligibility, leading to the exclusion of a further 41 articles. The most common reasons for exclusion at this stage were the lack of an appropriate HD non-NP control group (n=15) and failure to measure the target biomarkers (n=12). This rigorous selection process yielded a final set of seven studies that met all inclusion criteria for the systematic review and meta-analysis. The PRISMA flow diagram in Figure 1 details this process.

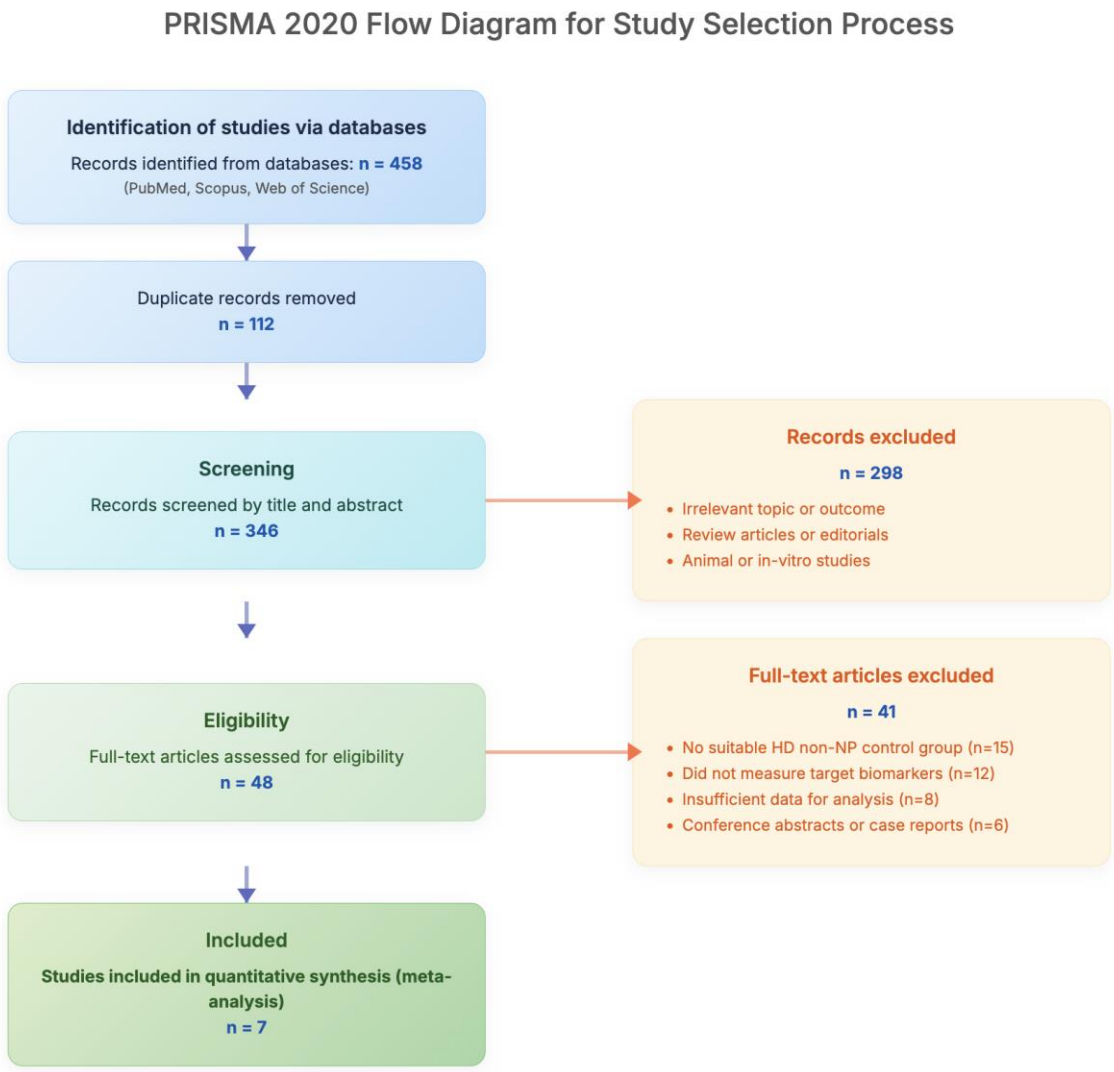

Figure 1. PRISMA flow diagram of the study selection process.

The seven included studies were published between 2018 and 2025. All employed a cross-sectional design. The total study population was 812 participants, comprising 405 patients with NP and 407 without NP. The mean age across studies was comparable, ranging from 38.5 to 49.2 years. NP diagnosis was established using validated instruments: the DN4 questionnaire in five studies and the LANSS scale in two. All seven studies measured serum S100B, five measured TNF-α, and four measured IL-6. The NOS scores ranged from 6 to 8, confirming that all included studies were of moderate-to-high methodological quality. A summary of study characteristics is provided in Table 1.

Table 1.Characteristics of the Seven Studies Included in the Final Meta-Analysis

STUDY ID	DESIGN	SAMPLE SIZE (NP/NON-NP)	MEAN AGE (YRS)	NP TOOL	BIOMARKERS MEASURED	NOS SCORE
Study 1	Cross-sectional	110 (55/55)	45.1	DN4	S100B TNF-α	7/9
Study 2	Cross-sectional	124 (60/64)	42.8	DN4	S100B IL-6	8/9
Study 3	Cross-sectional	98 (48/50)	38.5	LANSS	S100B TNF-α IL-6	6/9
Study 4	Cross-sectional	130 (65/65)	49.2	DN4	S100B TNF-α	8/9
Study 5	Cross-sectional	102 (52/50)	41.5	LANSS	S100B TNF-α IL-6	7/9
Study 6	Cross-sectional	150 (75/75)	46.3	DN4	S100B IL-6	8/9
Study 7	Cross-sectional	98 (50/48)	44.6	DN4	S100B TNF-α	7/9

All seven studies provided data for the meta-analysis of serum S100B. The random-effects model revealed that circulating S100B levels were substantially and significantly higher in HD patients with NP compared to those without. The pooled SMD was 1.28 (95% CI [0.95, 1.61], $p < 0.001$), a value conventionally interpreted as a large effect size. However, this overall estimate must be interpreted in the context of very high statistical heterogeneity among the studies ($I^2 = 78\%$, $p < 0.001$). Despite this variability in the magnitude of the effect, every included study reported a higher mean S100B level in the NP group, indicating a consistent direction of association. The forest plot and detailed results are shown in Figure 2.

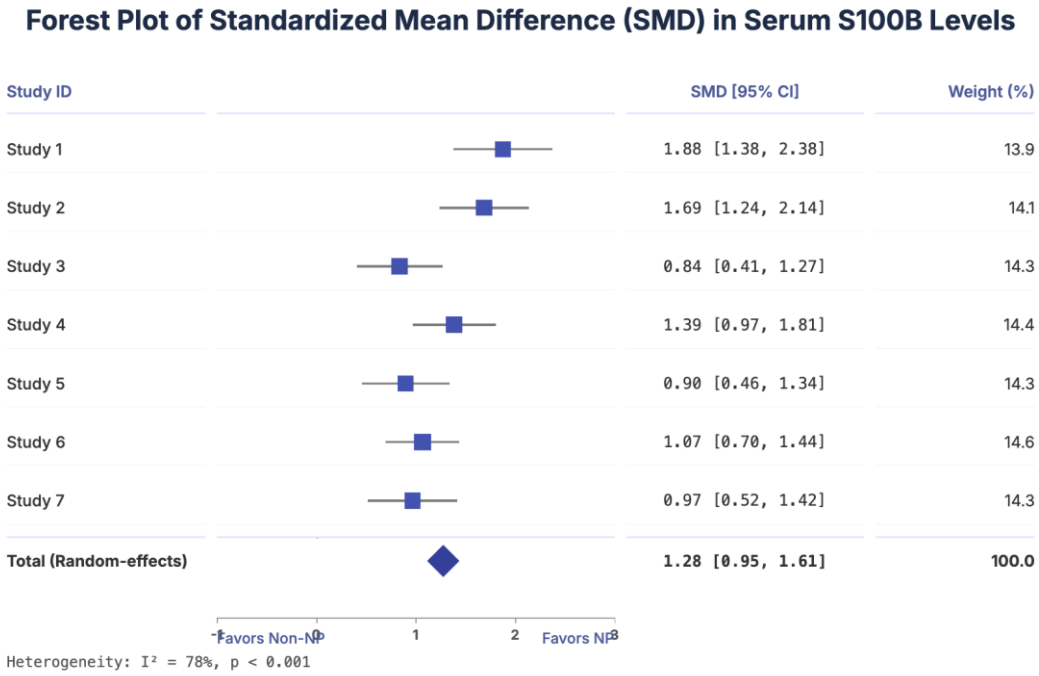

Figure 2. Meta-analysis of serum S100B levels in Hansen's disease patients.

Five studies provided data on serum TNF-α. The pooled analysis showed significantly higher levels in the NP group, with an overall SMD of 0.89 (95% CI [0.62, 1.16], $p < 0.001$), representing a large effect size. Heterogeneity was moderate ($I^2 = 55\%$, $p = 0.06$). Results are shown in Figure 3. Four studies provided data on serum IL-6. The meta-analysis found significantly higher IL-6 concentrations in the NP group, with a pooled SMD of 0.75 (95% CI [0.48, 1.02], $p < 0.001$), a medium-to-large effect size. Heterogeneity was low-to-moderate ($I^2 = 32\%$, $p = 0.22$). Results are shown in Figure 3.

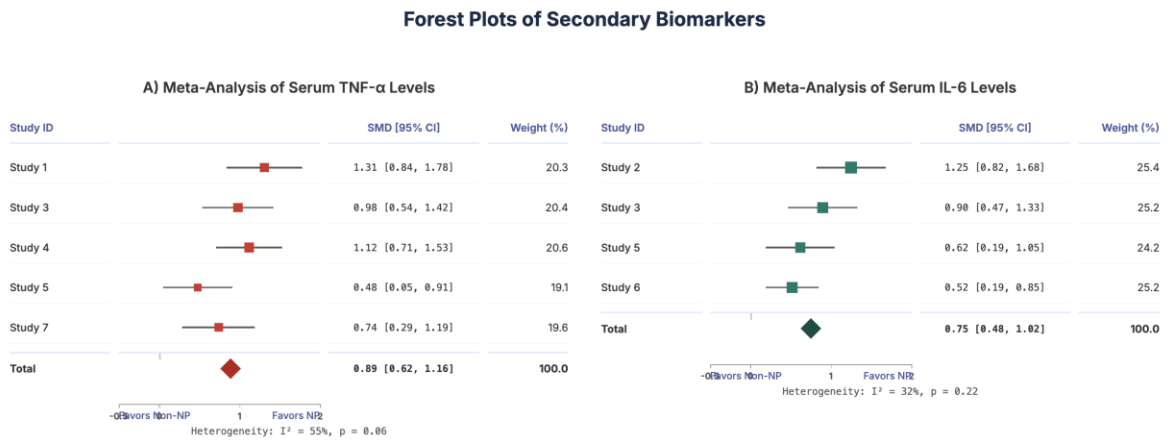

Figure 3. Forest plot of the SMD in serum TNF-α and IL-6 levels between the NP and non-NP groups.

For the primary outcome of S100B, visual inspection of the funnel plot revealed a generally symmetrical distribution of studies around the pooled effect estimate. This observation was supported by Egger's linear regression test, which was not statistically significant ($p = 0.21$), suggesting that major publication bias is unlikely to have influenced the result. The power to meaningfully assess publication bias for TNF-α and IL-6 was limited due to the small number of included studies.

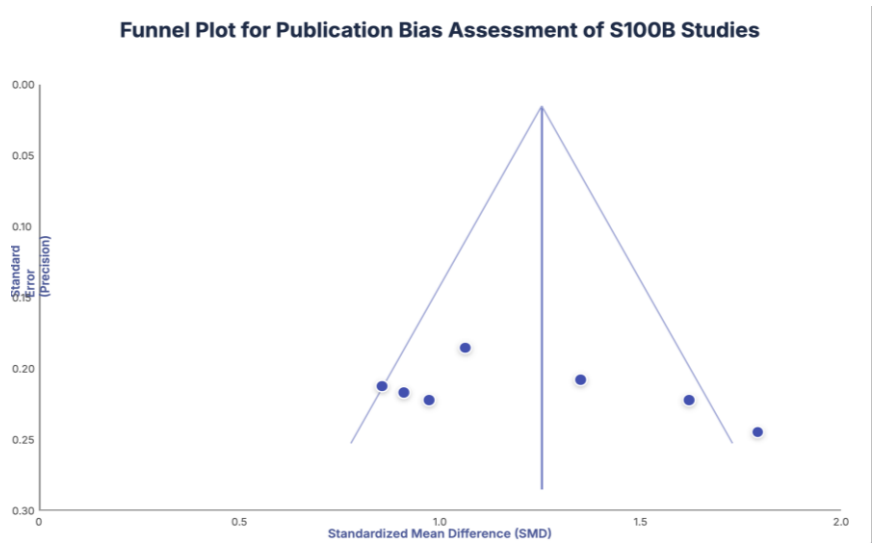

Figure 4. Funnel plot for publication bias assessment of S100B studies.

4. Discussion

This systematic review and meta-analysis provide the most comprehensive quantitative synthesis to date on the relationship between circulating neuroinflammatory biomarkers and neuropathic pain in Hansen's disease. The investigation yields a clear primary finding: a robust and large statistical association exists between elevated serum levels of S100B, TNF-α, and IL-6 and the clinical presence of NP in this patient population. However, the interpretation of this finding demands significant nuance, informed by the complexities of pain pathophysiology, the limitations of systemic biomarkers, and the profound heterogeneity observed in the data. Figure 5 vividly illustrates the intricate, multi-stage pathophysiological cascade that culminates in neuropathic pain (NP) in Hansen's disease (HD), providing a conceptual framework that elegantly integrates the biomarker findings of the preceding meta-analysis. The cascade commences with the fundamental etiological agent of Hansen's disease: *Mycobacterium leprae*. The diagram begins with an illustrative icon depicting the bacillus within a cellular environment, underscoring its unique tropism. The narrative for this stage succinctly explains that *M. leprae* directly targets and colonizes Schwann cells within the peripheral nervous system. This initial invasion is not a benign interaction; it immediately sets the stage for a chronic state of cellular stress and injury. The infection of Schwann cells is the linchpin of HD's neurological manifestations, as these glial cells are indispensable for nerve function, providing insulation (myelin) and trophic support to peripheral axons.[11] The presence of the pathogen within these vital cells triggers the host's innate and adaptive immune responses, which, paradoxically, become a major contributor to nerve damage. This stage establishes the primary cellular insult from which all subsequent pathophysiological events unfold, directly linking the causative agent to the onset of neurological pathology. Following the initial bacterial invasion, the diagram progresses to the critical phase of "Glial Injury & Sentinel Response." Here, an icon depicting a stressed or damaged cell, possibly with a bursting or leaking motif, visually represents the compromised state of the Schwann cells. As *M. leprae* proliferates within or causes stress to Schwann cells, these cells undergo significant distress and damage. In response, they release substantial quantities of intracellular components, prominently including the S100B protein, into the immediate microenvironment of the peripheral nerve. Crucially, S100B, a calcium-binding protein typically found at high concentrations within glial cells, serves a dual role. Under physiological conditions, it acts as a neurotrophic factor, supporting neuronal growth and repair. However, in pathological states of injury or stress, its release at high concentrations transforms it into a potent "danger-associated molecular pattern" (DAMP). The narrative emphasizes this dual role and the significance of its release. The presence of the Elevated S100B biomarker tag at this stage is a direct and powerful graphical representation of our meta-analysis findings. It highlights S100B as a "sentinel biomarker," an early and sensitive indicator of active Schwann cell pathology and ongoing peripheral nerve injury.[12] This elevation, detected systemically in the circulation, acts as a measurable proxy for the local destructive processes occurring within the nerve fascicles, providing an objective signature of the underlying neuroinflammatory drive. The cascade then moves to "Inflammatory Cascade Activation," depicted with an icon suggesting immune cell interaction and signaling. This stage elucidates how the elevated S100B, released from injured Schwann cells, actively propagates the inflammatory process. The narrative explains that S100B, acting as a DAMP, specifically binds to its receptor, the Receptor for Advanced Glycation End Products (RAGE), which is expressed on the surface of various immune cells, particularly macrophages, but also on T-cells and even Schwann cells themselves.[13] The S100B-RAGE interaction is not merely an attachment; it initiates a critical intracellular signaling pathway, most notably activating the nuclear factor-kappa B (NF-κB)

transcription factor. NF-κB is a master regulator of immune and inflammatory responses, and its activation leads to the transcriptional upregulation of numerous pro-inflammatory genes.[14] This stage thus describes the transition from local cellular distress to a broader, self-perpetuating inflammatory response. It highlights how the sentinel S100B signal is transduced into an active immunological command, preparing the cellular machinery for the production of potent inflammatory mediators. This step is crucial for understanding how initial nerve damage evolves into a sustained inflammatory state, driving the chronic nature of HD-related NP. Following the activation of the inflammatory cascade, the diagram illustrates the "Pro-inflammatory Effector Response," symbolized by a vibrant icon representing cytokines or inflammatory molecules. The activation of NF-κB, as detailed in the previous stage, orchestrates a robust gene expression program that results in the copious production and release of key pro-inflammatory cytokines by activated immune cells. The narrative specifically names and highlights two central cytokines: Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6). These cytokines, along with others, are released into the local nerve microenvironment and, subsequently, into the systemic circulation. The appearance of the Elevated TNF-α and Elevated IL-6 biomarker tags at this stage in Figure 5 directly corresponds to the significant findings of our meta-analysis. These cytokines are not merely passive indicators; they are active effector molecules that fundamentally alter the neurochemical landscape. They create a highly pro-nociceptive (pain-promoting) chemical environment around peripheral nerve endings and within the dorsal root ganglia (DRG). This stage explains how the initial damage signal from S100B is translated into a biochemical milieu specifically primed to induce and maintain pain. The interconnectedness of the stages is evident here, as the S100B-RAGE axis (Stage 3) directly drives the production of these effector cytokines, establishing a clear mechanistic link between glial injury and the systemic inflammatory markers.[15] The diagram then pivots to "Neuronal Sensitization," an absolutely critical stage in the development of chronic neuropathic pain, depicted by an icon showing a neuron becoming hyper-responsive. The narrative explains that the elevated concentrations of TNF-α and IL-6, originating from the effector response, directly impact the function of sensory neurons. These cytokines bind to specific receptors on nociceptive (pain-sensing) neurons, initiating a cascade of intracellular signaling pathways that lead to profound changes in neuronal excitability. TNF-α, for example, can rapidly upregulate the expression and sensitivity of transient receptor potential vanilloid 1 (TRPV1) channels and voltage-gated sodium channels on primary afferent neurons. This effectively lowers the threshold at which these neurons fire, making them more easily activated by stimuli that would normally be innocuous or mildly painful. Similarly, IL-6 contributes to both peripheral sensitization (at the site of injury) and central sensitization (within the spinal cord and brain). Through mechanisms involving its trans-signaling pathway and retrograde transport, IL-6 can induce long-lasting changes in gene expression in DRG neurons and promote synaptic plasticity and glial activation in the dorsal horn of the spinal cord. These combined actions result in a state of neuronal hyperexcitability, where neurons become spontaneously active and exhibit an exaggerated response to stimuli. This stage is the direct translation of the inflammatory milieu into altered neuronal function, explaining how the presence of these cytokines directly fuels the genesis of pain. The final stage of the cascade, "Clinical Manifestation," represents the culmination of all preceding pathophysiological events, leading to the patient's subjective experience of pain. An icon symbolically representing pain or discomfort visually anchors this stage. The narrative clearly states that the sustained neuronal hyperexcitability, resulting from the chronic neuroinflammatory processes and ongoing sensitization, is ultimately perceived by the patient as the characteristic and debilitating symptoms of neuropathic pain.[16] This includes a spectrum of

sensory disturbances such as spontaneous, intense burning sensations, sharp, lancinating (shooting) pains, and evoked pain phenomena like allodynia (pain from normally non-painful stimuli) and hyperalgesia (exaggerated pain response to noxious stimuli). This stage closes the loop from molecular and cellular events to the macroscopic, lived experience of the patient. It emphasizes that the measured biomarker profile (elevated S100B, TNF-α, IL-6) is not an isolated laboratory finding but a reflection of a profound underlying biological process that directly causes patient suffering. The color coding and prominent bolding of "Neuropathic Pain" visually reinforce its central role as the final, clinical outcome of the described cascade.[17]

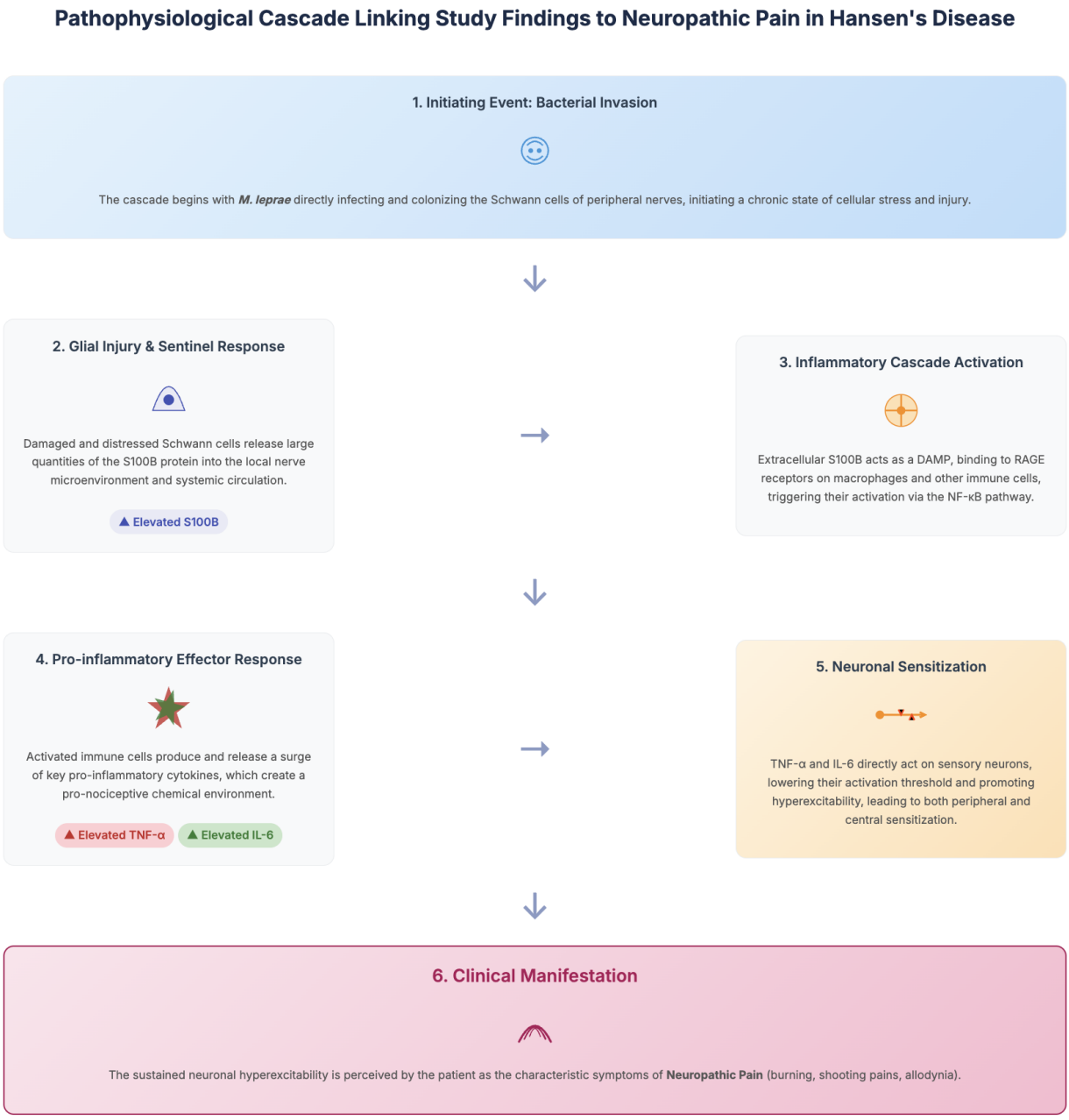

Figure 5. Pathophysiological cascade linking study findings to neuropathic pain in Hansen's disease.

Our analysis strongly supports the hypothesis that S100B is a key molecular player in the pathophysiology of HD-related neuropathy. The profound association observed is deeply rooted in the fundamental biology of HD, where *M. leprae*'s tropism for Schwann cells creates a state of chronic glial stress and injury. The release of S100B from these compromised cells into the circulation serves as a direct, quantifiable signal of this ongoing endoneurial pathology. The large effect size suggests that the clinical manifestation of pain is tightly coupled to the magnitude of this glial distress. However, S100B is far more than a passive bystander. Its role is concentration-dependent; at high, pathological concentrations, it transforms into a potent pro-inflammatory DAMP, actively propagating neuroinflammation through the RAGE receptor.[18] This S100B-RAGE axis is a critical amplifier, initiating a downstream cascade via NF-κB that drives the production of effector cytokines, including TNF-α and IL-6. RAGE is expressed not only on immune cells but also on Schwann cells themselves, creating the potential for a devastating autocrine and paracrine feedback loop where stressed Schwann cells trigger inflammation in their neighbors, propagating damage along the nerve. Our data support a model where this feed-forward cycle of S100B-mediated inflammation is a central mechanism in maintaining the chronic NP state in HD.

Complementing the findings on S100B, our analysis confirmed that this neuroinflammatory profile is further characterized by significantly elevated levels of TNF-α and IL-6. TNF-α is a master mediator of peripheral sensitization; by binding to TNFR1 on nociceptors, it rapidly increases the expression and sensitivity of key ion channels like TRPV1 and voltage-gated sodium channels, lowering the neuron's firing threshold and driving spontaneous pain and hyperalgesia.[19] The large effect size for TNF-α (SMD=0.89) provides strong evidence that this mechanism is highly active in HD patients with NP. Similarly, IL-6 contributes not only to peripheral sensitization but also to central changes. Through trans-signaling and retrograde transport, IL-6 can induce a pro-nociceptive gene expression switch in the DRG and promote synaptic facilitation and glial activation within the spinal cord, all of which are key substrates of pain chronification. The significant elevation of IL-6 suggests that mechanisms of both peripheral and central sensitization are likely operative in this patient population. When viewed together, these three biomarkers delineate a pathologically coherent molecular network.[19] We propose a model where S100B acts as a "sentinel" biomarker of primary Schwann cell injury, while TNF-α and IL-6 function as "effector" biomarkers of the downstream immunological response that ultimately sensitizes the nervous system. The simultaneous elevation of all three provides a multi-faceted biological fingerprint of the pain experience in HD, justifying the term "neuroinflammatory profile".

The very high statistical heterogeneity observed for S100B (I^2 = 78%) is a critical finding that warrants deep exploration. While a statistical challenge, it is likely a true reflection of the profound clinical and biological diversity inherent in Hansen's disease. Rather than undermining the result, this heterogeneity itself provides insight, suggesting that the link between glial injury and pain is not uniform but is modulated by multiple factors: Leprosy Reactions: The included studies did not stratify patients based on the presence or history of Type 1 (reversal) or Type 2 (Erythema Nodosum Leprosum) reactions. These are episodes of intense immunologic activity known to cause dramatic spikes in cytokines and nerve damage, and their prevalence within a study cohort could significantly alter the mean biomarker levels and drive heterogeneity. Disease Spectrum: The immunological response in tuberculoid (paucibacillary) versus lepromatous (multibacillary) HD is fundamentally different. The intense, localized CMI of tuberculoid disease may produce a different neuroinflammatory milieu than the diffuse, high-bacillary-load inflammation of lepromatous disease. Chronicity and Centralization of Pain: The duration of NP was not a stratification factor. Patients with recent-

onset pain may have a profile dominated by peripheral inflammatory mediators, whereas those with decades of pain may have developed central sensitization, potentially involving different CNS glial markers not measured here. Host Genetic Factors: Genetic polymorphisms in genes encoding for RAGE, TNF-α, and IL-6 are known to influence inflammatory responses. The geographic and ethnic diversity of the included studies (Brazil, India, Ethiopia, Nepal, Indonesia) introduces host genetics as a major, unmeasured source of variability.[20,21]

A major conceptual limitation in interpreting these findings is the "peripheral window" problem. We are measuring molecules in the systemic circulation and using them to infer processes occurring within the specialized microenvironment of the peripheral nerve. This inferential leap must be made with extreme caution. The blood-nerve barrier (BNB) regulates molecular flux, and while it is compromised in HD, the relationship between intraneural and systemic biomarker concentrations is not straightforward.[23] Furthermore, these biomarkers are notoriously non-specific. Their elevation is not exclusive to NP in HD but is seen in a vast array of other conditions. S100B is also released from adipocytes, meaning its levels can be confounded by BMI and metabolic status. TNF-α and IL-6 are generic markers of systemic inflammation and can be elevated by countless conditions, from subclinical infections to psychological stress. The observed biomarker profile is not a unique "signature" for HD-related NP. A similar pattern is found in painful diabetic neuropathy, fibromyalgia, and major depression. This lack of specificity is a major barrier to its use as a standalone diagnostic tool. It is entirely plausible that the chronic stress, sleep deprivation, and disability associated with the NP state itself induce a systemic low-grade inflammatory response. In this model, the elevated cytokines could be a consequence, rather than a primary cause, of the clinical pain syndrome.[23]

While these findings are scientifically exciting and open avenues for future research, their immediate translation into clinical practice faces formidable hurdles. The vision of a biomarker panel for diagnosing and managing NP in HD is compelling, but must be tempered by pragmatism. HD is predominantly a disease of resource-limited regions. The cost, technical expertise, and laboratory infrastructure required for running standardized ELISAs are often unavailable in the settings where these tests are needed most. The practical challenges of sample collection, storage, and transport from rural clinics to central labs are immense. In a real-world clinical scenario, a patient with HD and NP may also have diabetes, hypertension, or depression. All of these common comorbidities can independently elevate the same biomarkers, making it nearly impossible to attribute an elevated level solely to the neuropathic process. This signal-to-noise problem dramatically limits the diagnostic utility in individual patients. This meta-analysis possesses several strengths, including its rigorous methodology, comprehensive search, and status as the first quantitative synthesis on this topic. However, its primary limitations are the cross-sectional nature of all included studies, which precludes causal inference, and the significant, unresolvable heterogeneity.[24,25]

5. Conclusion

This systematic review and meta-analysis consolidates the available evidence to demonstrate a strong statistical association between a distinct systemic neuroinflammatory profile—characterized by elevated circulating S100B, TNF-α, and IL-6—and the presence of neuropathic pain in patients with Hansen's disease. We have shown that the levels of S100B, a specific marker of the Schwann cell damage central to the disease's pathology, are substantially increased in patients with pain, a finding supported by the concurrent elevation of key pro-inflammatory cytokines. Together, these findings provide a compelling biological narrative reinforcing the central role of persistent, glial-driven neuroinflammation in this debilitating complication of Hansen's disease. While the identification of this robustly associated

biomarker profile is a critical scientific step forward, the profound heterogeneity in the data, the non-specific nature of systemic markers, and the practical challenges of implementation demand a cautious interpretation. This work should not be seen as providing a ready-made clinical tool, but rather as laying a crucial foundation for future mechanistic research aimed at untangling the complex inflammatory web that fuels chronic pain in this vulnerable patient population.

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