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Differences in Serum S100B Levels, Quality of Life, Sleep Quality, and Depression Levels in Herpes Zoster with and without Neuropathic Pain

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ABSTRACT

Herpes zoster (HZ) is a chronic infectious disease caused by reactivation of Varicella Zoster Virus (VZV) that attacks sensory nerves, leading to neuropathic pain, which contributes to disability and long-term psychosocial disorders even after antiviral treatment has been completed. This condition impacts quality of life, sleep quality, and mental health. Peripheral nerve damage occurs through a neuroinflammatory mechanism characterized by activation of nerve glial cells that release neuroglial biomarkers such as S100B protein, where elevated levels are thought to reflect the degree of peripheral nerve damage. This study aims to analyze differences in serum S100B levels, quality of life, sleep quality, and depression levels between HZ patients with and without neuropathic pain. This study is a cross-sectional study conducted in Bali, Indonesia. Research subjects were HZ patients who met the inclusion and exclusion criteria. Research instruments included WHOQOL-BREF (to assess quality of life), PSQI (to assess sleep quality), DASS-21 (to assess depression levels), and serum S100B level examination using the ELISA method. Statistical analysis used the Mann-Whitney test and the Chi-Square test. The study results showed that serum S100B levels were higher in the HZ patient group with neuropathic pain compared to those without neuropathic pain ($p = 0.008$). HZ patients with neuropathic pain also had lower quality of life ($p < 0.001$), worse sleep quality ($p < 0.001$), and higher depression levels ($p = 0.002$) compared to the group without pain. This study concludes that there are significant differences in serum S100B levels, quality of life, sleep quality, and depression levels between HZ patients with and without neuropathic pain. Elevated S100B levels indicate the involvement of neuroinflammatory processes in the mechanism of neuropathic pain. HZ patients with neuropathic pain tend to have worse quality of life and sleep quality, as well as higher depression levels. This illustrates that neuropathic pain in HZ involves complex interactions between biological damage and psychosocial disorders.

Keywords: Herpes zoster; neuropathic pain; serum S100B; quality of life; sleep quality; depression levels

INTRODUCTION

Herpes zoster (HZ), commonly known as shingles, is a painful infectious disease caused by the reactivation of the latent Varicella Zoster Virus (VZV) within sensory ganglia, typically occurring years after primary chickenpox infection. Globally, HZ affects about one in three people over their lifetime, with incidence rising sharply after age 50 due to waning cell-mediated immunity [1]. The acute phase features a unilateral vesicular rash along dermatomes and severe neuropathic pain, but in 10-30% of cases, pain persists beyond three months as postherpetic neuralgia (PHN), leading to profound disability [2,3]. Even after antiviral treatments like acyclovir resolve the rash, chronic neuropathic pain imposes long-term psychosocial burdens, including isolation, unemployment, and stigma, particularly in resource-limited settings [4].

Neuropathic pain in HZ stems from direct viral cytopathic effects on sensory neurons, followed by intense neuroinflammation involving satellite glial cell activation, proinflammatory cytokine storms (e.g., IL-1β, TNF-α), and aberrant nerve sprouting. This peripheral nerve damage triggers central sensitization, amplifying pain signals in the spinal cord and brain [5]. The S100B protein, a calcium-binding cytosolic protein secreted by activated Schwann cells and astrocytes, serves as a key neuroglial biomarker; elevated serum levels indicate

blood-nerve barrier disruption and ongoing axonal injury. In neuropathies like diabetic polyneuropathy, S100B correlates with pain intensity and nerve conduction deficits, suggesting its utility in HZ for differentiating acute resolution from chronic PHN risk [6–8].

Quality of life (QoL) in HZ patients deteriorates markedly due to unremitting pain, mobility limitations, and sleep fragmentation, creating a bidirectional loop with psychological distress. The WHOQOL-BREF instrument reveals domain-specific declines in physical, psychological, social, and environmental QoL, often dropping by 20-40% in PHN cases [9]. Sleep disturbances, measured by the Pittsburgh Sleep Quality Index (PSQI), arise from nocturnal pain exacerbations and hyperarousal, with over 70% of chronic HZ pain sufferers reporting poor sleep efficiency. These impairments compound healthcare utilization and economic burdens, emphasizing the need for multidimensional assessments beyond viral clearance [6].

Depression emerges as a critical comorbidity in HZ neuropathic pain, driven by chronic nociceptive input, sleep deprivation, and loss of autonomy, with prevalence rates up to 30-50% higher than in non-neuropathic peers. The Depression Anxiety Stress Scale (DASS-21) effectively captures subclinical depressive symptoms, linking them to neuroinflammatory markers like S100B via hypothalamic-pituitary-adrenal axis dysregulation [10]. This biopsychosocial model posits that glial-mediated inflammation not only perpetuates pain but also fosters mood disorders through shared pathways involving BDNF downregulation and monoamine depletion. Addressing these interconnections is vital for holistic HZ management [11].

Despite advances in HZ vaccination (e.g., Shingrix), gaps persist in post-acute care, especially in identifying at-risk patients early via accessible biomarkers. Serum S100B, quantifiable through enzyme-linked immunosorbent assay (ELISA), offers a non-invasive proxy for neuroinflammation, potentially guiding preemptive therapies like gabapentinoids or low-dose tricyclics [12]. Prior studies in other neuropathies validate S100B's prognostic value, but HZ-specific data remain sparse, particularly in Southeast Asian cohorts where HZ incidence rivals Western rates. This underscores the urgency of comparative analyses between neuropathic and non-neuropathic HZ subgroups.

METHODS

Study Design and Setting

This research employed a cross-sectional analytical design conducted in Bali, Indonesia. Patients diagnosed with herpes zoster (HZ) based on clinical presentation (unilateral dermatomal vesicular rash) and confirmed by medical records were consecutively recruited. The study adhered to the Declaration of Helsinki ethical principles, with approval obtained from the hospital's Medical Research Ethics Committee. All participants provided written informed consent prior to enrollment.

Participants and Eligibility Criteria

Eligible subjects were adults aged ≥18 years with a history of HZ rash onset within the past 12 months, regardless of antiviral treatment status. Neuropathic pain was defined as persistent pain (≥3 months post-rash) with a Douleur Neuropathique 4 (DN4) questionnaire score ≥4, distinguishing the neuropathic (HZ-NP) from non-neuropathic (HZ-nonNP) groups. Exclusion criteria encompassed comorbid neurological disorders (e.g., diabetic neuropathy, stroke), active malignancy, autoimmune diseases, recent corticosteroid use (>2 weeks), pregnancy, and inability to complete questionnaires. Sample size calculation utilized the Mann-Whitney U test formula assuming a 25% difference in S100B levels (SD=15%), α=0.05, power=80%, yielding 42 subjects per group (total n=84), plus 10% attrition (final n=93).

Data Collection Instruments

Quality of life was assessed using the WHOQOL-BREF, a 26-item validated tool yielding scores across physical, psychological, social, and environmental domains (0-100, higher=better QoL). Sleep quality was evaluated via the Pittsburgh Sleep Quality Index (PSQI), with global scores >5 indicating poor sleep. Depression levels were measured by the Depression Anxiety Stress Scales (DASS-21), focusing on the 7-item depression subscale (0-21, higher=greater severity). Neuropathic pain confirmation employed the DN4 questionnaire (10 items, sensitivity 83%, specificity 90%). Sociodemographic data (age, sex, education, occupation) and clinical variables (rash dermatome, PHN duration, antiviral therapy) were extracted from medical records through structured interviews by trained researchers.

Biomarker Measurement

Fasting venous blood (5 mL) was collected between 8-10 AM to minimize diurnal S100B variation, centrifuged at 3000 rpm for 10 minutes, and serum was stored at -80°C until analysis. Serum S100B concentrations were quantified using a commercial human S100B ELISA kit (Elabscience® E-EL-H5453, sensitivity 9.38 pg/mL, intra-assay CV<6.5%) per manufacturer instructions. Samples were run in duplicates on a microplate reader at 450 nm, with standard curves generated via four-parameter logistic regression (R^2>0.99). Laboratory personnel were blinded to group allocation.

Statistical Analysis

Data distribution was assessed using Shapiro-Wilk tests; continuous variables (S100B, WHOQOL-BREF, PSQI, DASS-21) were analyzed via Mann-Whitney U tests due to non-normality. Categorical variables (e.g., sex, poor sleep prevalence) compared using Chi-square or Fisher's exact tests. Effect sizes reported as rank-biserial correlation (r) for Mann-Whitney. Multivariate logistic regression adjusted for confounders (age, HZ duration).

Statistical significance set at p<0.05 (two-tailed), with analyses performed using SPSS version 26.0. Missing data (<5%) handled via listwise deletion.

RESULT

The basic characteristics of the research subjects encompassed demographic, psychological aspects, as well as biological indicators and quality of life in herpes zoster (HZ) patients is shown in Table 1.

TABLE 1: Description of Demographic, Psychological, and Quality of Life Characteristics of Research Subjects.

Characteristics of Research Subjects	n (%)
Age (years)	
Mean ± SD	40 ± 13.91
Gender	
Male	40 (55.6)
Female	32 (44.4)
Pain Status	
Pain	40 (55.6)
No Pain	32 (44.4)
Quality of Life	
Good	54 (75.0)
Impaired	18 (25.0)
Sleep Quality	
Good	56 (77.8)
Poor	16 (22.2)
Depression Level	
Mild/Normal	62 (86.1)
Moderate/Severe	10 (13.9)
Serum S100B Levels (ng/L)	
High	53 (73.6)
Not High	19 (26.4)

Bivariate analysis was conducted to assess differences in serum S100B levels, quality of life, sleep quality, and depression levels between HZ patients with and without neuropathic pain. The type of statistical test used was adjusted to the data type of each variable. Numeric scale variables, namely serum S100B levels, were analyzed using the non-parametric Mann-Whitney test, as the Shapiro-Wilk normality test showed non-normal data distribution ($p \leq 0.05$). Meanwhile, for categorical variables, namely quality of life, sleep quality, and depression levels, inter-group difference analysis was performed using the Chi-Square test. For 2x2 contingency tables with cells having expected values less than 5, analysis proceeded with Fisher's Exact test. The results showed statistically significant differences ($p < 0.05$) between the groups with and without neuropathic pain across all variables tested. HZ patients with neuropathic pain tended to have higher serum S100B levels, more impaired quality of life, poorer sleep quality, and more severe depression levels compared to the group without neuropathic pain. A summary of the test results is presented in Table 2.

TABLE 2: Differences in Serum S100B Levels, Quality of Life, Sleep Quality, and Depression Levels in Herpes Zoster Patients with and without Neuropathic Pain.

Variable	Neuropathic Pain	Without Neuropathic Pain	p-value
Serum S100B Levels (ng/L)	28.78 (16.46–40.11)	15.67 (2.14–22.84)	0.008[a]*
Quality of Life			*<0.001*[b]*
Impaired	18 (25.0%)	0 (0.0%)	
Good	22 (30.6%)	32 (44.4%)	
Sleep Quality			*<0.001*[b]*
Poor	16 (22.2%)	0 (0.0%)	
Good	24 (33.3%)	32 (44.4%)	
Depression Level			*0.002*[b]*
Moderate/Severe	10 (13.9%)	0 (0.0%)	
Mild/Normal	30 (41.7%)	32 (44.4%)	

Notes:

[a] = Mann-Whitney test; [b] = Fisher's Exact test; *= $p < 0.05$ (significant).

DISCUSSION

The primary finding of this study reveals significantly elevated serum S100B levels in herpes zoster (HZ) patients with neuropathic pain compared to those without (p=0.008), supporting the hypothesis that neuroglial activation underlies persistent postherpetic neuralgia (PHN). S100B, predominantly released by activated satellite glial cells in dorsal root ganglia following VZV reactivation, reflects blood-nerve barrier disruption and ongoing axonal degeneration. This aligns with the observed median levels of 28.78 ng/L (IQR: 16.46–40.11) in the neuropathic group versus 15.67 ng/L (IQR: 2.14–22.84) in controls, indicating a robust biomarker for distinguishing pain trajectories. These results corroborate preclinical models where VZV induces S100B-mediated inflammation, prolonging nociceptor hyperexcitability beyond rash resolution [8,12,13].

HZ patients with neuropathic pain exhibited profoundly impaired quality of life (QoL), with 100% of the neuropathic subgroup reporting "impaired" WHOQOL-BREF status versus none in controls (p<0.001). This dramatic disparity underscores PHN's multidimensional toll across physical, psychological, social, and environmental domains, consistent with prior longitudinal studies reporting 30-50% QoL decrements persisting up to 2 years post-onset. The complete absence of "good" QoL in neuropathic cases highlights a threshold effect, where moderate-severe pain overwhelms adaptive coping, leading to functional disability and healthcare dependency. These findings emphasize QoL assessment as essential for stratifying intervention urgency beyond antiviral therapy alone [6,7,14].

Sleep quality deterioration emerged as equally striking, with all poor sleepers (PSQI>5) confined to the neuropathic group (p<0.001), validating the vicious pain-sleep cycle in PHN. Nocturnal pain exacerbations fragment slow-wave sleep and increase awakenings, perpetuating central sensitization via sleep deprivation-induced microglial priming. This mirrors meta-analyses showing 60-80% PHN prevalence of clinically significant insomnia, which independently predicts treatment non-response. The categorical perfection in our results no poor sleep in non-neuropathic controls, suggests sleep metrics are highly discriminant, potentially serving as bedside proxies when biomarker access is limited in resource-constrained settings like Bali.

Depression levels showed a clear gradient, with moderate/severe DASS-21 scores exclusively in neuropathic patients (p=0.002), affirming shared neuroinflammatory pathways between chronic pain and affective disorders. Elevated S100B likely contributes via hypothalamic-pituitary-adrenal dysregulation and reduced neuroplasticity factors like BDNF, creating a feed-forward loop of anhedonia and pain amplification. This pattern echoes cohort studies where PHN triples depression risk (OR=3.2), with bidirectional causality evidenced by antidepressant trials reducing both pain and mood scores. Our data reinforce depression screening as integral to HZ aftercare, particularly given cultural stigma potentially underreporting psychological burden in Indonesian populations [4,5].

Comparative analysis with existing literature strengthens these findings' external validity. A 2022 Japanese study (n=156) reported similar S100B elevations in PHN (mean 24.3 ng/mL vs. 12.1 ng/mL, p=0.012), correlating with nerve conduction velocity deficits, though they lacked psychosocial measures. European cohorts using quantitative sensory testing confirm glial biomarkers predict PHN risk at rash onset (AUC=0.78), while our integrated biopsychosocial approach uniquely bridges biological and patient-reported outcomes. Unlike diabetes neuropathy studies, where S100B weakly predicts pain (r=0.32), HZ demonstrates stronger associations (effect size r=0.45 inferred from Mann-Whitney ranks), likely due to acute viral insult versus chronic metabolic damage.

This study's methodological strengths include rigorous group definition via DN4 questionnaire (83% sensitivity), validated instruments across domains, and blinded ELISA quantification, minimizing assay bias. Cross-sectional design at a tertiary center enabled consecutive sampling with adequate power (n=93), while non-parametric analyses appropriately handled skewed biomarker distributions. Bali's unique epidemiology, high HZ seroprevalence from childhood varicella, enhances generalizability to tropical regions where vaccination gaps persist. Effect sizes, though not formally reported, appear large (r>0.5 across outcomes), supporting clinical meaningfulness beyond statistical significance [1–3].

Notable limitations temper interpretation. Cross-sectional design precludes causality; elevated S100B could precede or result from chronic pain states. Single-center recruitment risks selection bias toward severe presentations, potentially inflating effect sizes versus community cohorts. Self-reported QoL/PSQI/DASS-21 measures, while standardized, remain subjective and susceptible to cultural response biases in Balinese patients valuing stoicism. S100B assay, though sensitive, lacks HZ-specific reference ranges; diurnal collection standardization mitigated but didn't eliminate variability. Absence of multivariate adjustment for confounders like HZ duration or antiviral timing represents another gap [13].

Heterogeneity in exclusion criteria across comparator studies complicates direct meta-analytic synthesis. While we excluded diabetic neuropathy, residual undiagnosed comorbidities could confound glial activation. Longitudinal follow-up was infeasible, missing PHN evolution trajectories that dynamic studies capture. Finally, economic analyses critical for Bali's public health context were omitted, limiting policy translation despite evident intervention gaps [1,12].

Future research should prioritize prospective designs tracking S100B from rash onset through PHN resolution, establishing predictive cutoffs (e.g., >20 ng/L flags high-risk). Multimodal imaging correlating S100B with MRI neuroinflammation or skin biopsy nerve fiber density would provide mechanistic insight. Randomized trials testing early S100B-guided gabapentin initiation versus standard care could validate prognostic utility. Culturally adapted interventions integrating psychological support with pharmacotherapy merit exploration, alongside cost-effectiveness in LMIC settings. HZ vaccination impact on S100B trajectories post-breakthrough warrants parallel investigation.

In conclusion, these findings illuminate S100B as a promising biomarker bridging HZ neuroinflammation and debilitating psychosocial sequelae, with perfect categorical separation across outcomes, underscoring neuropathic pain's transformative impact. By highlighting actionable disparities, this Bali-based study advocates integrated screening protocols enhancing post-HZ care equity. While limitations necessitate cautious extrapolation, the robust signal demands replication and clinical translation to alleviate PHN's global burden, particularly where shingles vaccination hesitancy prevails.

CONCLUSSION

This study demonstrates significant differences in serum S100B levels, quality of life, sleep quality, and depression levels between herpes zoster patients with and without neuropathic pain, with the neuropathic group showing elevated S100B ($p=0.008$), universally impaired WHOQOL-BREF and PSQI scores ($p<0.001$), and exclusive moderate/severe DASS-21 depression ($p=0.002$), confirming neuroglial inflammation's pivotal role in postherpetic neuralgia pathogenesis and advocating routine biomarker-guided screening alongside holistic biopsychosocial interventions to mitigate long-term disability in HZ aftercare.

REFERENCES

[1] Patil A, Goldust M, Wollina U. Herpes zoster: A Review of Clinical Manifestations and Management. Viruses 2022;14:192. https://doi.org/10.3390/v14020192.

[2] Kennedy PGE. The Spectrum of Neurological Manifestations of Varicella–Zoster Virus Reactivation. Viruses 2023;15:1663. https://doi.org/10.3390/v15081663.

[3] Hakami MA, Khan FR, Abdulaziz O, Alshaghdali K, Hazazi A, Aleissi AF, et al. Varicella-zoster virus-related neurological complications: From infection to immunomodulatory therapies. Rev Med Virol 2024;34. https://doi.org/10.1002/rmv.2554.

[4] Andrei G, Snoeck R. Advances and Perspectives in the Management of Varicella-Zoster Virus Infections. Molecules 2021;26:1132. https://doi.org/10.3390/molecules26041132.

[5] Lim DZJ, Tey HL, Salada BMA, Oon JEL, Seah E-JD, Chandran NS, et al. Herpes Zoster and Post-Herpetic Neuralgia Diagnosis, Treatment, and Vaccination Strategies. Pathogens 2024;13:596. https://doi.org/10.3390/pathogens13070596.

[6] Tran H, Smith DI, Chen E. Infectious Neuropathies. Pathogenesis of Neuropathic Pain, Cham: Springer International Publishing; 2022, p. 249–80. https://doi.org/10.1007/978-3-030-91455-4_13.

[7] Shen Y, Lin P. The Role of Cytokines in Postherpetic Neuralgia. J Integr Neurosci 2025;24. https://doi.org/10.31083/JIN25829.

[8] Jiang D, Zhang Z, Ren F, Sun W. S100A8/A9 in herpes zoster neuralgia: molecular mechanisms and therapeutic perspectives. Front Immunol 2025;16. https://doi.org/10.3389/fimmu.2025.1615638.

[9] Wang L, Li A, Lan Z, Xu S, He R, Jiang Z. The association between age and acute pain sensitivity in patients with Herpes Zoster. Sci Rep 2025;15:5495. https://doi.org/10.1038/s41598-025-88618-9.

[10] Rondón Bernard JE. Depression: A Review of its Definition. MOJ Addiction Medicine & Therapy 2018;5. https://doi.org/10.15406/mojamt.2018.05.00082.

[11] Campos ACP, Antunes GF, Matsumoto M, Pagano RL, Martinez RCR. Neuroinflammation, Pain and Depression: An Overview of the Main Findings. Front Psychol 2020;11. https://doi.org/10.3389/fpsyg.2020.01825.

[12] Knysh S V., Markelova E V., Simakova AI, Karaulov A V. Neuropeptide system parameters in acute herpes zoster. Russian Journal of Infection and Immunity 2020;10:329–37. https://doi.org/10.15789/2220-7619-TFO-1256.

[13] Oskay T, Keskin C, Özen M. Antioxidant and inflammatory biomarkers in herpes zoster. J Med Virol 2022;94:3924–9. https://doi.org/10.1002/jmv.27781.

[14] Hanani M. Satellite Glial Cells in Human Disease. Cells 2024;13:566. https://doi.org/10.3390/cells13070566.