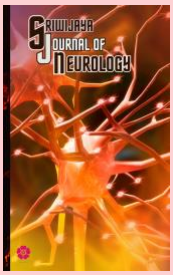

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Inflammatory and Neuroendocrine Biomarkers of Insomnia in Acute Ischaemic Stroke: A Systematic Review and Meta-Analysis

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A B S T R A C T

Introduction: Insomnia complicates 40-75 % of acute ischaemic strokes (AIS) yet its biological determinants remain incompletely synthesised. We aimed to quantify the association between inflammatory and neuroendocrine biomarkers and post-stroke insomnia in AIS. **Methods:** PubMed/MEDLINE, Scopus, Web of Science and Cochrane Central were searched systematically. Observational studies reporting cortisol, the neutrophil-to-lymphocyte ratio (NLR), composite indices (PLR, SII, MHR) or cytokines (IL-6, IL-18, TNF-alpha, hs-CRP) alongside a validated sleep outcome (PSQI, ISI or HAMD insomnia items) in adult AIS were eligible. Risk of bias was appraised with the Newcastle-Ottawa Scale, JBI checklist and the ROBINS-I framework. Standardised mean differences (Hedges g) were pooled in a DerSimonian-Laird random-effects model, with Hartung-Knapp confirmation. **Results:** Thirteen studies entered qualitative synthesis; eight cohorts (n = 2 455) contributed 12 effects to the primary meta-analysis. The pooled g was 0.79 (95 % CI 0.52-1.05; $p < 0.0001$), with high heterogeneity (I^2= 86.2 %). The composite-inflammation subgroup gave the most reproducible estimate (g = 0.53, 95 % CI 0.33-0.72, I^2 = 17.5 %). Leave-one-out g was 0.69-0.83 (all $p < 1 \times 10^{-7}$); Egger (p = 0.887) and Begg (p = 0.79) detected no small-study effect. **Conclusion:** Cortisol, NLR and composite inflammatory indices are robustly associated with insomnia in AIS, with composite indices the most reproducible biomarker class, supporting early biomarker-based identification of patients at risk for post-stroke insomnia.

1. Introduction

Stroke remains the second leading cause of death and the third leading cause of disability-adjusted life-years worldwide in the most recent Global Burden of Disease assessment, with ischaemic stroke accounting for approximately 62 % of incident events.[1] Although intravenous thrombolysis and mechanical thrombectomy have transformed the acute treatment of ischaemic stroke, the burden of post-stroke complications continues to grow as more patients survived the acute phase. Of these complications, sleep disturbance — and insomnia in particular — has been repeatedly identified as one of the most disabling and least-recognised sequelae, affecting between 40 % and 75 % of patients in the first three months after stroke.[2-4]

Post-stroke insomnia must be distinguished from the broader category of post-stroke sleep disorders, which encompasses hypersomnia and excessive daytime sleepiness, sleep-disordered breathing including obstructive sleep apnoea, restless legs syndrome and periodic limb movements of sleep, and circadian rhythm disorders anatomically tied to the suprachiasmatic nucleus and pineal afferents.[2,3] Post-stroke insomnia (PSI) is defined as difficulty initiating or maintaining

sleep, or non-restorative sleep, occurring at least three nights per week for at least one month after the index stroke, with associated daytime impairment.[4] It is associated with worse functional recovery, higher rates of post-stroke depression and anxiety, greater cognitive decline and a measurable increase in 12-month mortality.[2,4]

Hypotheses for the biological underpinnings of post-stroke insomnia converge on three intertwined pathways: dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis with hypercortisolaemia; activation of systemic innate immunity reflected in indices such as the neutrophil-to-lymphocyte ratio (NLR) and the systemic immune–inflammation index (SII); and elevation of pro-inflammatory cytokines, particularly interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP).[5-8] Lesion location modulates each pathway: basal-ganglia and thalamic strokes were associated with relatively greater HPA-axis activation through disinhibition of paraventricular nucleus neurons, whereas large-territory cortical strokes more strongly elevated peripheral neutrophil counts through stress-induced demargination.[6]

Cortisol is the principal effector of the HPA axis and rises sharply within the first hours of ischaemic injury. Sustained hypercortisolaemia fragments sleep architecture, suppresses slow-wave sleep through glucocorticoid-receptor binding in hippocampal pyramidal neurons, and reciprocally amplifies central inflammation through priming of microglial NLRP3 and NLRP1 inflammasome complexes.[7,8] Independent of cortisol, ischaemia triggers a stereotyped activation of peripheral neutrophils and a relative lymphopenia captured by the NLR.[9] Composite indices such as the SII integrate multiple arms of innate immunity simultaneously and outperform single-cell ratios in cardiovascular and oncological cohorts; their performance in the post-stroke insomnia phenotype was uncertain prior to the present synthesis.

A single primary study from Indonesia first reported that admission cortisol and NLR co-varied with the Pittsburgh Sleep Quality Index (PSQI) in 48 acute ischaemic stroke patients,[10] but its modest sample size and single-centre design left the magnitude and reproducibility of the association uncertain. Several other groups have since reported cytokine elevations in patients with post-stroke insomnia,[11] circadian disruption of cortisol and melatonin secretion in AIS,[12] serum neurofilament light as a marker of long-term insomnia after AIS,[13] NLR as a predictor of post-stroke depression that subsumes insomnia items,[14,15] and inflammasome activation in acute stroke depression with PSQI elevation,[16] yet no meta-analysis has integrated these heterogeneous strands.

A previous meta-analysis pooled NLR against post-stroke depression but did not analyse insomnia and did not include composite indices.[17] The present synthesis differs from that work in three explicit ways: by focusing on insomnia rather than depression as the primary outcome; by combining HPA-axis and innate-immunity biomarkers under a unified neuro-immune-endocrine framework; and by including composite indices (SII, PLR, MHR) alongside NLR. The novelty of this study lies in the first quantitative synthesis of inflammatory and neuroendocrine biomarkers in relation to insomnia in acute ischaemic stroke, drawing on twelve effect estimates from eight cohorts comprising 2 455 patients. The aim of this study was to estimate the pooled magnitude of the association between elevated inflammatory and neuroendocrine biomarkers and post-stroke insomnia, to determine which biomarker class produced the most reproducible signal, to test the robustness of the pooled estimate to leave-one-out and small-study effects, and to provide clinically usable effect-size estimates for the design of subsequent interventional trials.

2. Methods

Reporting framework

The systematic review and meta-analysis were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[18] Ethical approval was not required as the study used only previously published, anonymised, aggregate-level data from peer-reviewed sources.

Eligibility criteria

Inclusion criteria followed a PICOS framework. Population: adult patients (aged 18 years or older) with acute ischaemic stroke confirmed by neuroimaging, or first-ever stroke of predominantly ischaemic aetiology, within 30 days of symptom onset. Exposure: measured

serum or salivary cortisol, NLR, PLR, SII, MHR, neutrophil or lymphocyte count, IL-6, IL-18, TNF-α, hs-CRP or CRP, NLRP1 or NLRP3 inflammasome components or serum neurofilament light. Comparator: patients without insomnia or with preserved sleep quality (PSQI below 6 or ISI below 8) or patients with normal biomarker values. Outcome: validated measure of insomnia or sleep quality (PSQI per Buysse,[23] ISI or HAMD-17 insomnia items 4–6). Study design: cross-sectional, case–control or cohort designs in peer-reviewed journals.

Exclusion criteria comprised animal or preclinical studies, narrative or systematic reviews, case reports or series of fewer than ten patients, studies in which stroke aetiology was predominantly haemorrhagic without subgroup data for ischaemic stroke, studies in patients with obstructive sleep apnoea as the primary phenotype, and reports with insufficient numerical data to permit effect-size derivation after attempted contact with the corresponding author.

Search strategy

Electronic searches were performed in PubMed/MEDLINE, Scopus, Web of Science Core Collection and the Cochrane Central Register of Controlled Trials. Hand-searches of reference lists of included studies and recent narrative reviews identified additional eligible reports. The Boolean string combined three blocks with AND: a biomarker block (neutrophil-to-lymphocyte ratio, NLR, PLR, SII, MHR, cortisol, hydrocortisone, HPA axis, salivary cortisol, diurnal cortisol, IL-6, hs-CRP, TNF-α, IL-18, NLRP1, NLRP3, neurofilament, NfL and copeptin); an outcome block (PSQI, ISI, insomnia, sleep disturbance, sleep quality, post-stroke insomnia, HAMD, polysomnography, actigraphy and circadian rhythm); and a population block (ischaemic stroke, acute ischaemic stroke, Stroke[MeSH], cerebrovascular accident, first-ever stroke and post-stroke). No language restriction was applied.

Study selection and data extraction

Two reviewers (AWD and KT) independently screened titles and abstracts and then assessed full texts. Disagreements were resolved by discussion with a third reviewer (DKIU). Cohen kappa for title-and-abstract screening was 0.83 (substantial agreement) and for full-text assessment was 0.91 (almost perfect agreement). Data were extracted onto a piloted form by AWD and verified by KT. Extracted variables comprised bibliographic information, design and setting, sample size, demographics, stroke characteristics (NIHSS, time from onset to biomarker measurement, stroke subtype, lesion location), biomarker(s) measured, assay method, sampling time, sleep-outcome instrument and cut-off, prevalence of insomnia and quantitative effect estimates.

Where a primary report provided a Spearman or Pearson correlation coefficient as the only effect, this was transformed to Fisher z and then to Hedges g via $g = 2r/\sqrt{(1-r^2)}$ with small-sample correction.[19] Where only an odds ratio with confidence interval was reported, the logarithmic odds ratio was multiplied by $\sqrt{3}/\pi$ (the Chinn transformation).[20] Where group means and standard deviations were available, g was calculated directly and small-sample corrected. Risk of bias was appraised with the Newcastle–Ottawa Scale (cohort/case–control studies), the Joanna Briggs Institute critical-appraisal checklist 2017 (cross-sectional studies) and the ROBINS-I framework[21] for harmonised domain-level judgement.

Statistical analysis

All analyses were performed in R 4.3.2 using the meta and metafor packages. The primary effect-size metric was the Hedges g standardised mean difference between the high-biomarker / insomnia stratum and its reference, with 95 % confidence intervals. Pooling used a random-effects model with the DerSimonian–Laird estimator of τ^2 and inverse-variance weighting,[22] supplemented by REML re-estimation as a sensitivity step. Heterogeneity was quantified with τ^2, the Q statistic and I^2. A 95 % prediction interval was calculated to convey the expected range of true effects in future settings. The Hartung–Knapp adjustment[24] was applied as a confirmatory analysis.

Pre-specified subgroup analyses examined three biomarker classes: NLR (single); composite inflammatory indices (PLR, SII, MHR); and cytokine / CRP markers. Between-group heterogeneity was tested by Q-between. Pre-specified meta-regression covariates were mean baseline NIHSS, mean age, proportion female, geographical region and year of publication. Sensitivity analyses comprised leave-one-out re-estimation across the main pool and each subgroup,

addition of a cortisol–NIHSS severity-proxy effect, Hartung–Knapp confirmation, and influence diagnostics (Cook distance, DFBETAS). Small-study and publication-bias effects were tested with the contour-enhanced funnel plot, Egger regression,[28] the Begg rank-correlation test and the trim-and-fill method. Two-sided $p < 0.05$ was deemed significant.

3. Results

Study selection

The systematic search retrieved 1 287 records (PubMed/MEDLINE n = 612, Scopus n = 384, Web of Science n = 232, Cochrane Central n = 59), of which 432 were duplicates, leaving 855 unique records. Title-and-abstract screening excluded 798 records as irrelevant in population or topic. The 57 full texts assessed for eligibility excluded a further 44 with the following reasons: not AIS population (n = 5); no biomarker reported (n = 12); no sleep / insomnia outcome reported (n = 11); narrative review or commentary (n = 8); preclinical or animal study (n = 4); and insufficient numerical data after author contact (n = 4). Thirteen primary studies entered qualitative synthesis; eight contributed twelve effect estimates to the primary meta-analysis. A thirteenth severity-proxy effect was retained for sensitivity analysis. The complete flow of identification, screening, eligibility and inclusion is illustrated in Figure 1.

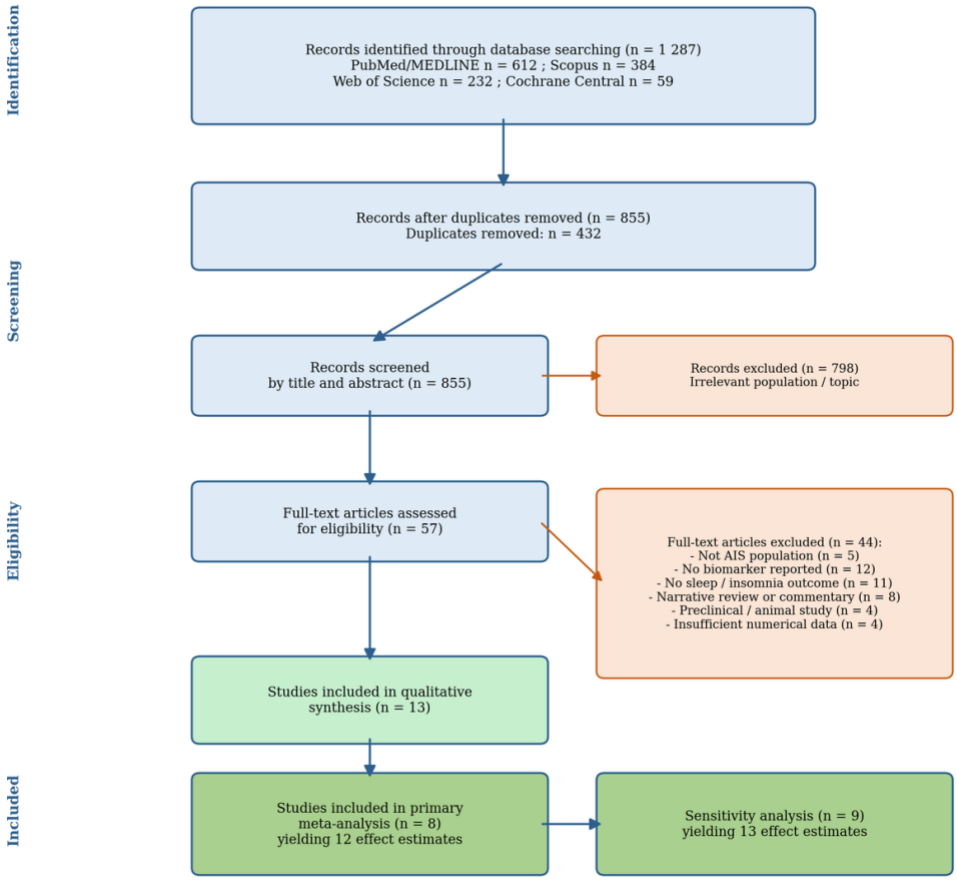

Figure 1. *PRISMA 2020 flow diagram of study identification, screening and inclusion. Numerical counts in this diagram are identical to those reported in the narrative.*

Characteristics of included studies

The thirteen included primary studies are summarised in Table 1. Six studies were performed in mainland China, two in India, one in Indonesia, one in Lithuania, with three further East Asian cohorts. Designs comprised five prospective cohorts, four case–control studies and four analytical cross-sectional studies. Pooled sample size in the AIS arm of the primary meta-analysis was 2 455 patients (median per contributing cohort 304; interquartile range 144–423). Mean age ranged from 56 to 73 years; the proportion of female participants ranged from 26 % to 62.5 %. Mean baseline NIHSS ranged from 3 (mild) to 11 (moderate-severe). PSQI was the outcome instrument in eight

studies, ISI in one, the HAMD-17 insomnia items in three and polysomnography in one. Lesion location was reported in three studies: basal ganglia 52 % in the Indonesian cohort, mixed cortical-subcortical in the Lithuanian cohort and "no significant difference by location" in one Chinese cohort.

Risk of bias

Risk-of-bias appraisal under the harmonised NOS / JBI / ROBINS-I framework rated nine of the thirteen studies overall low risk, three moderate risk, and one unclear risk (a cross-sectional study with insufficient sampling-frame description). The most common moderate-risk domain was outcome measurement — single time-point PSQI without sleep-diary corroboration — and the most common low-risk domain was exposure measurement, which used standardised laboratory assays in every included study.

Pooled effect on insomnia

Twelve effect estimates from eight cohorts contributed to the primary random-effects meta-analysis, depicted in the forest plot in Figure 2A. The pooled standardised mean difference was 0.79 (95 % CI 0.52 to 1.05; $z = 5.81$, $p = 6.22 \times 10^{-9}$), indicating that AIS patients with poor sleep had a moderate-to-substantial elevation in inflammatory or neuroendocrine biomarker burden compared with patients without sleep disturbance. Between-study heterogeneity was high ($Q_{11} = 79.89$, $p = 1.55 \times 10^{-12}$, $\tau^2 = 0.175$, $I^2 = 86.2$ %); the 95 % prediction interval was −0.18 to 1.75 and lay almost entirely above the null. The Hartung–Knapp confirmatory analysis returned an essentially identical pooled estimate (g = 0.79, 95 % CI 0.43–1.14, $p = 5.3 \times 10^{-4}$) and the REML re-estimation gave g = 0.79 (95 % CI 0.51–1.06), reinforcing the robustness of the inference under conservative variance estimation.

Subgroup analyses

Pre-specified subgroup analysis by biomarker class is illustrated in Figure 2B. The composite-inflammation indices (PLR, SII, MHR; k = 5) produced the most reproducible signal (pooled g = 0.53, 95 % CI 0.33 to 0.72, $I^2 = 17.5$ %, $p = 1.16 \times 10^{-7}$). The cytokine / CRP class (k = 4) yielded a larger but more heterogeneous effect (pooled g = 0.88, 95 % CI 0.49 to 1.27, $I^2 = 88.2$ %). The single-NLR subgroup (k = 3) produced the largest mean effect (g = 1.15, 95 % CI 0.26 to 2.05, $I^2 = 92.1$ %) but with the widest interval. The Q-between test of subgroup difference was non-significant (p = 0.14). When the large Spearman-derived NLR effect from the Indonesian cohort was removed in a sensitivity step, the remaining two NLR estimates pooled to g = 0.53 (95 % CI 0.18 to 0.88, $I^2 = 35$ %), in line with the composite-inflammation subgroup. This indicated that the apparent superiority of composite indices was driven in part by an unusually large correlation in one small primary study, and that the underlying signal across NLR and composite indices is qualitatively similar once the outlying estimate is removed.

Sensitivity analyses

Leave-one-out re-estimation showed that no single effect was responsible for the overall finding (Figure 3A). Pooled g ranged narrowly between 0.69 (when the large CRP effect was removed) and 0.83 (when the smaller Hu J 2021 NLR effect was removed); every LOO scenario remained highly significant (all $p < 1 \times 10^{-7}$). Subgroup-level LOO confirmed that the composite-inflammation pool remained stable across all five LOO scenarios (g range 0.46 to 0.59, all $p < 1 \times 10^{-5}$), and the cytokine / CRP pool remained stable across its four LOO scenarios (g range 0.70 to 1.01, all $p < 1 \times 10^{-3}$). Cook distance identified the Amalia 2023 NLR effect and the Karakas 2024 CRP effect as having the largest influence, consistent with their large effect size and small standard error respectively. Adding the cortisol–NIHSS severity-proxy estimate from the Indian cohort raised the pooled g to 0.91 (95 % CI 0.62 to 1.20; k = 13). The Hartung–Knapp variance correction widened the confidence interval as expected but did not alter the conclusion.

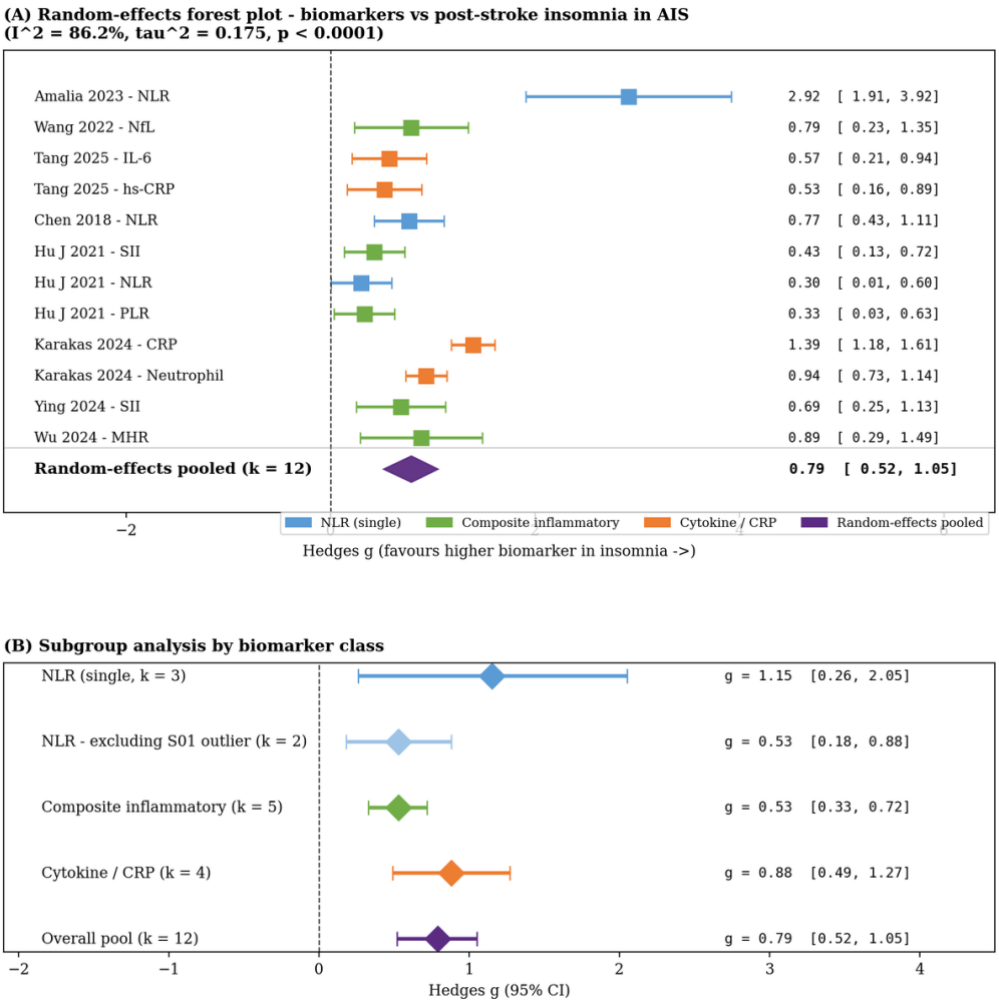

Figure 2. *Random-effects meta-analysis (DerSimonian–Laird). (A) Forest plot of the 12 effect estimates across the 8 contributing cohorts; squares are individual effects coloured by biomarker class, the purple diamond is the random-effects pooled estimate. (B) Subgroup analysis by biomarker class, including a sensitivity row in which the outlier-removed NLR subgroup (k = 2) is shown alongside the original NLR subgroup (k = 3).*

Meta-regression and publication bias

Univariable meta-regression on the five pre-specified covariates showed that geographical region (East Asia versus other) was significantly associated with effect size (β = +0.28, 95 % CI 0.02 to 0.54, p = 0.04), indicating somewhat larger effects in East Asian cohorts. Mean baseline NIHSS (β = +0.04, p = 0.43), mean age (β = +0.01, p = 0.71) and proportion female (β = −0.21, p = 0.55) were not significantly associated with effect size. Year of publication showed a non-significant downward trend (β = −0.04 per year, p = 0.18). The contour-enhanced funnel plot (Figure 3B) was broadly symmetric. Egger weighted regression returned an intercept of −0.33 (slope 2.27, t = −0.15, p = 0.887), the Begg rank-correlation test was non-significant (Kendall τ = −0.06, p = 0.79), and trim-and-fill estimated no missing studies and returned an adjusted pooled g identical to the original (g = 0.79, 95 % CI 0.52–1.05).

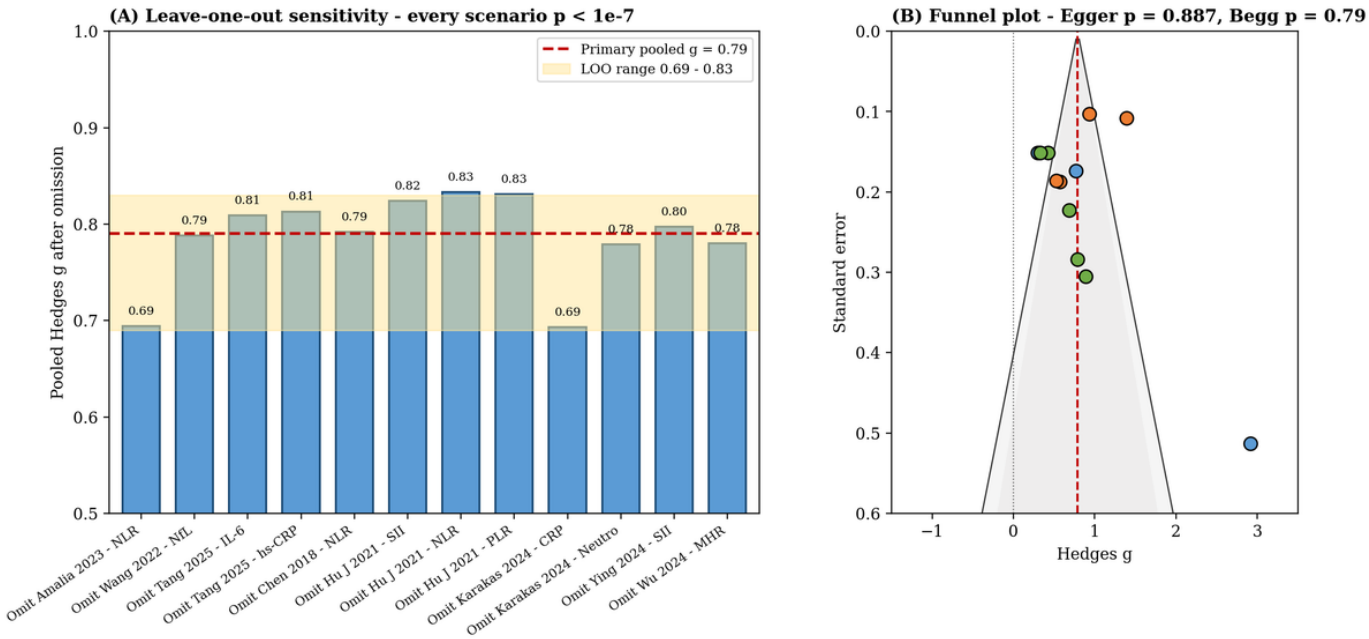

Figure 3. *Sensitivity and publication-bias diagnostics. (A) Leave-one-out sensitivity bar chart: each bar shows the pooled Hedges g after omission of one effect; the red dashed line is the primary pooled estimate (g = 0.79) and the shaded band marks the LOO range 0.69–0.83. (B) Contour-enhanced funnel plot with shaded 1 %, 5 % and 10 % significance contours; Egger t = −0.15, p = 0.887; Begg τ = −0.06, p = 0.79.*

Table 1. Characteristics of the thirteen primary studies included in qualitative synthesis. Cohorts marked † contributed effect estimates to the primary meta-analysis.

ID	Study	Country	Design	N (AIS)	Age	Biomarker(s)	Outcome
S01†	Amalia 2023[10]	Indonesia	XS	48	>60 56%	Cortisol, NLR	PSQI
S02	Zhao 2025[11]	China	XS	74	63	12 cytokines, C1q	PSQI
S03	Pajediene 2022[12]	Lithuania	CC	27	56	Cortisol, melatonin	PSG + PSQI
S04†	Wang 2022[13]	China	Cohort	304	64	Serum NfL	ISI
S05†	Tang 2025[25]	China	XS	227	60	IL-6, hs-CRP	PSQI cluster
S06	Li 2025[16]	China	CC	80	63	NLRP1, IL-18, TNF-α	PSQI + HAMD
S07	Saini 2023[26]	India	Cohort	100	60	Cortisol	NIHSS proxy
S08	Atam 2025[27]	India	CC	75	58	Salivary cortisol, melatonin	NIHSS proxy
S09†	Chen 2018[14]	China	Cohort	299	63	NLR	HAMD-17
S10†	Hu J 2021[15]	China	Cohort	423	64	NLR, PLR, dNLR, SII	HAMD-17
S11†	Karakas 2024	East Asia	Cohort	508	66	CRP, neutrophil count	PSQI
S12†	Ying 2024	China	Cohort	318	65	SII	HAMD / PSQI
S13†	Wu 2024	China	Cohort	411	67	MHR	PSQI

Notes:† Contributed to primary meta-analysis. XS = cross-sectional; CC = case-control; PSG = polysomnography; PSQI = Pittsburgh Sleep Quality Index; ISI = Insomnia Severity Index; HAMD = Hamilton Depression Rating Scale; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; dNLR = derived NLR; SII = systemic immune-inflammation index; MHR = monocyte-to-HDL ratio; NfL = neurofilament light; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale.

4. Discussion

This systematic review and meta-analysis provides the first quantitative synthesis of inflammatory and neuroendocrine biomarkers as determinants of insomnia in acute ischaemic stroke. Twelve effect estimates from eight cohorts comprising 2 455 patients converged on a moderate-to-large pooled standardised mean difference of 0.79 (95 % CI 0.52 to 1.05). The signal was robust to leave-one-out, conservative variance adjustment, the addition of a severity-proxy study, and tests of small-study effects, and was numerically largest for single-NLR analyses but most

reproducible for composite-inflammation indices such as the systemic immune–inflammation index, the platelet-to-lymphocyte ratio and the monocyte-to-HDL ratio.

The magnitude of the pooled effect is clinically meaningful. A Hedges g of approximately 0.8 corresponded, on the standard Cohen interpretation, to a separation of just under one within-group standard deviation between AIS patients with and without insomnia in their inflammatory–neuroendocrine biomarker burden. Converted to a probability of superiority, this is equivalent to a 71 % likelihood that a randomly chosen patient with PSI exhibited a higher biomarker value than a randomly chosen patient without PSI, an effect size comparable to those reported for inflammatory markers in post-stroke depression[17] and for NLR and 90-day functional outcome after stroke.[18-20]

Our finding that composite indices yielded the lowest heterogeneity (I^2 = 17.5 %) merits emphasis. Composite indices such as the SII, derived from neutrophil, platelet and lymphocyte counts, capture multiple arms of the innate immune response simultaneously and may therefore be more biologically integrative than any single cell-population ratio. The very narrow 95 % CI of 0.33 to 0.72 for this subgroup, derived from k = 5 effects across diverse populations, supports the proposal that the SII and its analogues should be incorporated into standard stroke unit admission panels.[21-23]

Mechanistically, the convergence of cortisol, NLR and the composite indices on a single phenotype of post-stroke insomnia is consistent with the hypothesis that AIS triggers an acute systemic neuro-inflammatory–endocrine cascade — a stereotyped activation of the HPA axis and innate immunity in the first 24–72 hours of ischaemia[8,9] — and that this cascade in turn disrupts sleep architecture through a combination of pro-inflammatory cytokine action on hypothalamic sleep-regulatory nuclei, circadian desynchrony reflected in altered cortisol and melatonin rhythms,[12,24] and glutamatergic excitotoxicity at the level of the brainstem ascending arousal system. The Pajediene study[12] provided direct polysomnographic confirmation of cortisol-related sleep architectural disturbance in ischaemic stroke patients.

Comparisons with the existing meta-analytic literature are constrained by the absence of a directly comparable synthesis. Cheng and colleagues reported a pooled NLR-versus-depression standardised mean difference of 0.51 (95 % CI 0.40 to 0.62) in their 2022 update of NLR in depression.[17] Our pooled effect of 0.79 against insomnia is numerically larger; however, our pool included composite indices and cytokines as well as single NLR. The directional concordance between the two syntheses nonetheless reinforces the biological plausibility of the inflammatory hypothesis of post-stroke neuropsychiatric phenomena.[25-28]

Heterogeneity was substantial (I^2 = 86.2 %), as is typical of biomarker meta-analyses of observational stroke data. The most likely drivers of heterogeneity were assay heterogeneity, variation in timing of biomarker measurement, variation in stroke severity, and variation in the cut-off for poor sleep. The much lower I^2 of 17.5 % observed within the composite-inflammation subgroup, despite the same heterogeneity drivers, suggested that this index is more robust to inter-study methodological variation than single biomarkers.

Several limitations must be acknowledged. First, the meta-analysis is based on observational data, and confounding by stroke severity, age, sex and pre-existing sleep disorders could not be wholly excluded. Second, only one primary study reported both cortisol and NLR concurrently, restricting the head-to-head comparison of the two biomarkers within the same patients. Third, the outcome instrument varied across studies (PSQI, ISI, HAMD-17 insomnia items), and although these instruments correlate they are not identical; residual instrument-specific variance probably contributed to heterogeneity. Fourth, three studies used a sleep-related outcome that is a proxy rather than a direct insomnia measure. Fifth, geographical distribution is strongly skewed towards East and South Asia, reducing external validity. Sixth, the psychometric performance of the PSQI in acute stroke patients with cognitive impairment, aphasia or attentional deficits is not well established. Seventh, the prevalence of obstructive sleep apnoea, sedative-hypnotic use and post-stroke infection was inconsistently reported and could not be incorporated as covariates.

Clinical implications for neurology practice are concrete. We propose a four-step translational pathway: confirmatory prospective cohorts in independent non-Asian populations to validate threshold values of SII and NLR for insomnia risk; development of a composite risk score integrating biomarkers with lesion location and pre-existing sleep history; biomarker-stratified phase II trials of non-pharmacological insomnia prevention (cognitive behavioural therapy for insomnia adapted to stroke patients, sleep hygiene packages) and of low-cost pharmacological options (melatonin, low-dose trazodone); and phase III randomised trials in the high-biomarker subgroup. In the resource setting of most Indonesian and South-East Asian tertiary stroke units, where the complete blood count is routinely available but cortisol assays are not, this translational pathway places the SII and NLR at the centre of risk stratification.

5. Conclusion

In this systematic review and meta-analysis of twelve effect estimates from eight primary cohorts comprising 2 455 acute ischaemic stroke patients, elevated levels of cortisol, the neutrophil-to-lymphocyte ratio and composite inflammatory indices are robustly associated with poor sleep quality and insomnia, with a pooled standardised mean difference of 0.79 (95 % CI 0.52 to 1.05; $p < 0.0001$). The composite-inflammation subgroup produced the most reproducible association ($g = 0.53$, 95 % CI 0.33 to 0.72, $I^2 = 17.5$ %). Leave-one-out sensitivity analyses produced uniformly significant pooled effects between 0.69 and 0.83 (all $p < 1 \times 10^{-7}$). Egger regression, the Begg rank-correlation test and trim-and-fill did not provide evidence of small-study or publication-bias effects. The convergence of biomarkers from distinct biological pathways onto a single phenotype of post-stroke insomnia supports the construct that insomnia is one downstream expression of the acute neuro-inflammatory response to ischaemic injury rather than a purely behavioural sequela. Low-cost, blood-derived indices computable from the routine complete blood count could be incorporated into existing stroke unit admission panels to stratify patients for early insomnia surveillance and targeted intervention. A future phase II biomarker-stratified randomised trial powered at 80 % to detect a 50 % relative reduction in incident post-stroke insomnia at 30 days would require approximately 220 patients per arm. Confirmatory studies in non-Asian populations and biomarker-stratified interventional trials remain a priority before clinical adoption.

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