

RDW-to-albumin ratio correlates with serum neurofilament light chain

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Blood-based biomarkers are reshaping the study of neurological disease. Among these, neurofilament light chain (NfL) has emerged as one of the most sensitive peripheral indicators of axonal injury. As assays for measuring serum neurofilament light chain (sNfL) have become widely available, this biomarker has gained prominence in both clinical research and population studies.

However, several factors confound NfL interpretation. NfL levels are affected by multiple factors such as increasing age, body mass index (BMI), kidney function and coexisting conditions such as cardiovascular disease and diabetes.¹ These comorbidities can alter NfL levels through pathways related to systemic inflammation, vascular abnormalities and impaired clearance of neurofilament proteins.¹ Consequently, sNfL may capture clinical and subclinical neuronal injury occurring in the context of systemic inflammatory states, although the precise nature and magnitude of these relationships remain unclear. In this issue of the *Annals*, Song et al. examined this relationship by evaluating the association between the red cell distribution width-to-albumin ratio (RAR) and circulating sNfL concentrations in participants from the National Health and Nutrition Examination Survey (NHANES).² Their analysis suggests that individuals with higher RAR values tend to have higher sNfL concentrations, raising the possibility that systemic inflammatory or metabolic stress may be associated with biomarkers of neuroaxonal injury.

NfL is a structural protein within the neuronal cytoskeleton and is released into extracellular fluids following axonal damage. Increased NfL concentrations have been demonstrated across a wide spectrum of neurological conditions, including multiple sclerosis, neurodegenerative disorders, traumatic brain injury and cerebrovascular disease.^{3,4} Importantly, circulating NfL levels are influenced not only by overt neurological pathology but also by several physiological and systemic factors. Age is one of the strongest determinants of sNfL concentrations, and studies have shown that renal function, vascular disease and systemic inflammatory states can also influence circulating

levels.¹ As a result, sNfL is regarded as a global marker of neuroaxonal integrity rather than a disease-specific biomarker.

Red cell distribution width (RDW) and serum albumin are widely available laboratory parameters that reflect systemic physiological stress. RDW, traditionally used in the evaluation of anaemia, has increasingly been recognised as a marker of inflammation, oxidative stress and chronic disease burden. Elevated RDW values have been linked to cardiovascular disease, frailty and increased mortality in population-based studies.⁵ Serum albumin, in contrast, reflects nutritional status and systemic inflammatory activity; reduced albumin concentrations frequently accompany chronic illness and inflammatory states and are likewise associated with adverse outcomes.⁶ The biological rationale for RAR lies in combining elevated RDW and reduced albumin, providing a broad snapshot of systemic physiological derangement. This ratio has demonstrated value in predicting end-stage kidney disease, diabetic complications, malignancies and aortic aneurysm, establishing its use as a biomarker across different organ systems and diseases.⁷

In the analysis presented by Song et al., higher RAR values were associated with significantly higher sNfL concentrations even after adjustment for demographic and clinical variables. These findings raise the intriguing possibility that systemic physiological stress may be linked to circulating signals of neuronal injury detectable in peripheral blood.

Several aspects of the study strengthen the credibility of the findings. The use of the NHANES dataset allows examination of biomarker relationships in a large, and nationally representative population cohort with standardised laboratory measurements and comprehensive demographic information. The authors also applied multivariable statistical models to adjust for important confounders known to influence sNfL concentrations, including age, BMI and serum creatinine.

Song et al.'s study builds on previous work analysing the NHANES cohort and suggesting a positive association between systemic inflammatory burden

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and circulating sNfL. A higher systemic immune-inflammation index (SII) was correlated with increased sNfL, with stronger effects observed in individuals with diabetes.⁸ Elevated sNfL levels were also found to be associated with higher systemic inflammatory markers, including SII, systemic inflammation response index and white blood cell count, which in turn correlated with clinically relevant depressive symptoms.⁹ A cross-sectional study also demonstrated positive associations between circulating sNfL and pro-inflammatory cytokines, such as interleukin (IL)-1 beta and IL-6.¹⁰

However, there are limitations to this study. First, the cross-sectional design limits conclusions regarding causality or temporal relationships. Although higher RAR values are associated with elevated sNfL levels, it remains unclear whether systemic inflammatory or nutritional disturbances contribute directly to neuronal injury, whether subclinical or clinical neuronal damage influences systemic physiological markers, or whether both arise from shared underlying mechanisms such as ageing, vascular dysfunction or chronic disease burden. Second, the biological specificity of the RAR metric warrants careful consideration. Both RDW and albumin are influenced by a wide range of physiological and pathological conditions. Even with statistical adjustment, unmeasured variables may partly explain the association. As such, RAR should be interpreted as a general indicator of systemic health, rather than a direct biomarker of neuronal injury. The modest effect sizes observed also suggest that RAR is unlikely to serve as a standalone screening tool for neuronal injury; rather, its value may lie in risk stratification or as a surrogate marker for longitudinal monitoring when combined with other clinical data.

A further issue relates to the increasing proliferation of composite laboratory ratios proposed as novel biomarkers. While such indices may strengthen statistical associations in epidemiological analyses, their biological interpretation is often unclear. Without mechanistic evidence linking RDW-albumin dynamics to pathways of neuroaxonal injury, the clinical significance of RAR remains uncertain.

Despite these limitations, the findings are consistent with a growing body of evidence linking systemic health to neurological outcomes. Chronic inflammation has increasingly been implicated in the development of neurodegenerative¹¹ and cerebrovascular diseases. Systemic inflammatory states may promote endothelial dysfunction, oxidative stress and microvascular injury, processes that can impair cerebral perfusion and

neuronal survival. Haematologic markers, such as RDW, have likewise been associated with altered microcirculatory dynamics and vascular pathology, providing potential pathways through which systemic inflammation could influence neuronal injury detected by biomarkers such as sNfL.

Collectively, these observations support the evolving concept of a “body-brain axis,” in which physiological and metabolic processes shape neurological health across the lifespan. Conditions characterised by persistent inflammation, metabolic dysregulation, or nutritional imbalance may exert gradual yet cumulative effects on neuronal integrity. Routinely measured laboratory parameters could therefore provide indirect insight into systemic states that influence brain resilience.

Future research should prioritise longitudinal and mechanistic investigations to clarify these relationships. Prospective cohort studies are needed to determine whether elevated RAR precedes increases in sNfL, predicts cognitive decline or signals future neurological disease. Integrating RAR with additional inflammatory and metabolic biomarkers may further elucidate the systemic pathways linking physiological stress to neuronal injury. Another important direction involves evaluating whether interventions that improve systemic health modify circulating neuronal injury biomarkers. Lifestyle optimisation, nutritional improvement and therapies targeting chronic inflammatory states may influence both systemic physiological markers and downstream neurological outcomes.

The study by Song et al. represents an important expansion of RAR applications into neurological research, bridging established literature on systemic inflammation biomarkers with emerging blood-based markers of neuronal injury. While immediate clinical utility remains uncertain, the study generates valuable hypotheses. The findings raise the intriguing possibility that routine haematologic indices might help identify individuals at heightened risk for neurological injury, potentially supporting preventive strategies targeting modifiable systemic factors.

Ethics statement

Not applicable, as no study participants were involved.

Declaration

The authors declare that there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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