

**Original research article**

**A NOVEL INFLAMMATORY MARKER OF DIAGNOSTIC IMPORTANCE IN DIABETIC SENSORY-MOTOR NEUROPATHY: SYSTEMIC IMMUNE INFLAMMATION INDEX**

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**Abstract**

Diabetic sensory-motor neuropathy (DSMN) is a prevalent complication of diabetes mellitus characterized by nerve damage leading to sensory deficits, motor dysfunction, and neuropathic pain. This abstract examines the clinical and diagnostic significance of the Systemic Immune Inflammation Index (SII) in DSMN. Recent research has highlighted the association between systemic inflammation and the pathogenesis of DSMN. The SII, calculated based on peripheral blood cell counts, serves as a composite marker reflecting the balance between systemic immune responses and inflammatory status. Clinical studies have demonstrated a positive correlation between elevated SII levels of DSMN. Patients with higher SII values exhibit more pronounced neuropathy symptoms and impaired nerve conduction velocities, indicating a potential link between inflammation-mediated processes and neuropathic damage. Furthermore, the SII has emerged as a valuable diagnostic tool for predicting DSMN related inflammatory sequel and monitoring disease progression. Its non-invasive nature and cost-effectiveness make it a promising biomarker for identifying individuals at risk of developing neuropathic complications in diabetes. This abstract underscores the clinical relevance of the SII in enhancing our understanding of the inflammatory mechanisms underlying DSMN and its potential utility in early detection and management strategies. Further investigation into the predictive value and therapeutic implications of the SII in DSMN is warranted to optimize patient care and outcomes. The present study aims to evaluate the potential role of SII in predicting inflammation in patients with Diabetic Sensory-motor Neuropathy.

**Keywords:** Diabetes Mellitus, Inflammation, Systemic Immune Inflammation Index, Neuropathy

**Introduction**

India's struggle with diabetes is an imperative and inescapable global health crisis. With one of the highest rates in the world, it's time to take action and address this issue head-on. Peripheral neuropathy is one of the major microvascular consequences of type 2 diabetes mellitus (T2DM) It is more common than nephropathy or retinopathy secondary to T2DM, and is the leading cause of lower limb amputation in Western countries <sup>[1-3]</sup>. Diabetic sensory-motor neuropathy (DSMN) may have variable manifestations based on the nervous system involved, resulting in a complicated spectrum of symptoms. However, peripheral neuropathy is the most frequent feature and, as clearly outlined by recent guidelines, it might affect almost half of patients with T2DM during their lifetime <sup>[1,4]</sup>.

DSMN can present in various forms such as symmetric sensory-motor axonal neuropathy, proximal asymmetric painful motor neuropathy, mononeuropathy, or autonomic neuropathy. The latter occurs mainly due to the involvement of small fibers <sup>[1]</sup>. The pathogenesis is characterized by inflammatory damage to the peripheral neurons that transmit motor and sensory impulses <sup>[1,5]</sup>. This damage is mostly seen in the longest nerve fibers, hence known as "length-dependent" neuropathy <sup>[1,6]</sup>.

The Systemic Immune Inflammation Index (SII) is a measure used to assess the balance of host inflammatory and immunological status. It was initially designed to predict the outcome in patients with hepatocellular carcinoma <sup>[7]</sup>. However, recent studies have shown that it can also be used as a prognostic factor for various malignancies and inflammatory conditions <sup>[8-11]</sup>. Some researchers believe that the increasing rates of diabetes can be partly attributed to low-grade chronic inflammation and the resulting insulin resistance <sup>[12]</sup>. SII is an effective and non-invasive biochemical marker that can be readily obtained through routine blood work, making it an economical alternative to other markers.

Various health conditions, including malignancies, cardiovascular diseases, and hepatic steatosis, have been linked to the Systemic Immune-Inflammation Index (SII). Despite being a common complication of diabetes, the link between SII and DSMN is still not well comprehended and has not been methodically studied. We need to be involved in more research to explore this relationship and gain a better understanding of this debilitating condition. Studies are insufficient on this topic from the eastern region of the country at present. The objective of our is to explore the potential of SII as a novel indicator of inflammation in Diabetes Mellitus. We aim to gain a better understanding of how this marker can be of assistance in diagnosing and managing the disease more effectively.

**Materials & Methods**

A study was conducted for a year on 100 patients with T2DM in a city hospital located in eastern part of India. The study included individuals aged between 18 to 80 years, who were diagnosed with Type 2 diabetes as per the 1999 World Health Organization Diagnostic Standards for Diabetes Patients. Only those individuals who voluntarily agreed to participate were included in the study. However, patients with acute diabetic complications or undergoing acute stress states, patients with non-healing diabetic foot ulcers, patients with severe cardiac, liver, or renal insufficiency, and patients diagnosed with cancer, recent infections, immune system disorders, or blood system diseases were

excluded from the study.

All patients underwent a Nerve Conduction Study (NCS) examination. The NCS was performed in the unilateral upper and lower extremities. Motor NCS was performed in the nerves of the upper extremities including median and ulnar. They were also done in the peroneal and tibial nerves of the lower extremities. For each nerve, the F-waves were recorded. Sensory NCS were attained from the median, ulnar, and sural nerves. H-reflex studies were also completed. Based on the NCS report, the patients were subsequently categorized into two groups the diabetic neuropathy group (n=50) and the diabetic non-neuropathy group (n=50).

A Sysmex XN 100 analyzer was used to conduct a Comprehensive Blood Count (CBC), which measured the total count of white blood cells, platelets, neutrophils, and lymphocytes. Subsequently, the Systemic Immune-Inflammation Index (SII) was calculated by multiplying the total platelet count by the total neutrophil count and dividing the result by the total lymphocyte count.

Statistical scrutiny of the compiled data was accomplished by using SPSS 24.0 software. The measurement data that trailed a normal distribution were represented in terms of measures of central tendency. Group contrasts were achieved using two independent samples t-tests. When analyzing non-normally distributed measurement data and expressing it as the median and quantile spacing, it becomes a reliable approach. To perform group comparisons, the Mann-Whitney U-test is a proven and effective method. Trusting these methods one can ensure accurate and meaningful insights from the data analysis.

The Mantel-Haenszel analysis was used for the chi-square trend test, for observing the drift of the study. We used restrictive cubic spline analysis to investigate the non-linear relationships between the risk of DSMN in patients with type 2 diabetes (T2DM) and systemic immune-inflammation index (SII). Additionally, we evaluated the diagnostic value of SII for DSMN in T2DM patients by analyzing the Receiver Operating Characteristic (ROC) curve, including the calculation of the area under the curve (AUC). We considered statistical significance at  $P < 0.05$  for all analyses.

## **Results**

Among all T2DM patients, patients with DSMN exhibited significantly higher SII levels, when compared to non-DSMN patients ( $P < 0.001$ ). The incidence of DSMN was higher among male patients compared to the non-DSMN group ( $P = 0.025$ ). DSMN patients had a significantly longer duration of diabetes compared to non-DSMN patients ( $p = 0.025$ ).

We categorized patients into four groups based on quartile intervals of the SII quartile spacing level (I, II, III & IV) to convert SII into ordered multi-classification variables and each group comprised 25 patients. The SII intervals were Group I ( $SII < 311$ ), group II ( $311 < SII < 428$ ), group III ( $428 < SII < 555$ ), and Group IV ( $SII > 555$ ).

We performed a Mantel-Haenszel chi-square trend test on the four patient groups. Upon grouping, a linear trend was evident between SII and the occurrence of DSMN ( $P < 0.001$ ). A moderate positive correlation was found between SII and DSMN, with a correlation coefficient of 0.3 and a P-value of less than 0.001. The incidence of DSMN demonstrated an escalating pattern with increasing SII quartile levels with rates of 27.8%, 44.8%, 61.2%, and 74.2% in Groups I, II, III, and IV, respectively (Table 1).

**Table 1: Mantel-Haenszel Chi-Square Trend**

Mantel-Haenszel Chi-Square Trend				
Groups	I	II	III	IV
DSMN %	27.8	44.8	61.2	74.2

For SII, a significant linear relationship with the incidence of DSMN was observed (P total trend <0.001, P nonlinear = 0.06). DSMN incidence significantly increased when SII > 428, and it increased linearly with higher SII values. The ROC curve analysis revealed that SII exhibited the highest accuracy in evaluating DSMN, with an AUC of 0.80, a sensitivity of 76.1%, and a specificity of 71.6%.

### Discussion

This study represents the first assessment of the association between SII and Diabetic sensory-motor neuropathy in a cohort of Indian adults. When examining the cohort as a whole, we found a positive relationship between SII and DSMN.

In recent times, SII and system inflammation response index (SIRI) have emerged as novel markers of inflammation. Studies have indicated that SII and SIRI encompass platelets and various inflammatory cells present within white blood cells, including diverse immune regulatory pathways in the body. In comparison to individual white blood cells and platelets, these indices are less affected by the physiological and pathological states of the body, thereby offering a more consistent reflection of the overall inflammatory condition<sup>[13, 14]</sup>. It is noteworthy that the calculation methods for SII and SIRI are simple and affordable, requiring only common blood routine parameters. It's important to note that the Systemic Immune-Inflammation Index (SII) can be used to evaluate diabetic patients who have limited mobility or cognitive disorders because it doesn't require their active involvement.

Research shows that there is a strong connection between SII, SIRI, and diabetes. SII can also be used to predict and assess conditions like diabetic nephropathy and depression<sup>[14, 15]</sup>. Our findings are consistent with previous studies that have identified a positive correlation between SII and diabetes or its complications. For example, a study by Nie Y *et al.* found that SII was positively associated with diabetes<sup>[16]</sup>. Another study by Ozer Balin S *et al.* found a moderately positive relationship between the SII index and Diabetic Foot Infection<sup>[17]</sup>.

However, it's important to acknowledge the limitations of this study. Our investigation was limited to a specific community and included a relatively small number of participants. Therefore, it's not possible to generalize these findings to a wider population of patients. Further correlation studies, including extensive clinical trials, are necessary to validate the associations between SII, SIRI, and individuals with DSMN.

## Conclusion

Our study concluded that there is a positive correlation between the Systemic Immune Inflammation Index and diabetic sensory-motor neuropathy. To our knowledge, this study is the first to utilize prospective cohort data in examining the correlation between sensory-motor neuropathy in T2DM patients and SII levels. The study was conducted among adults in a city-based hospital in Eastern India, and the findings suggest that SII may act as an independent and early marker of inflammation factor for sensory-motor neuropathy. Higher levels of SII may hold promise as useful indicators of this condition in T2DM patients.

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