

Original Article

Serum interleukin-6 as an inflammatory biomarker in type 2 diabetes mellitus: correlation with diabetic peripheral neuropathy and diagnostic performance

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Abstract

Diabetic peripheral neuropathy (DPN) is a common, debilitating complication of type 2 diabetes mellitus (T2DM); interleukin-6 (IL-6) has been increasingly implicated in its pathogenesis, yet Iraqi data remain scarce. We compared serum IL-6 between T2DM patients with and without DPN, assessed its correlation with neuropathy severity, and evaluated its diagnostic performance. A cross-sectional study was conducted on 90 patients with T2DM, equally divided into two groups based on DPN status assessed using the Michigan Neuropathy Screening Instrument (MNSI). Serum IL-6 was measured by ELISA and analysed using the Mann-Whitney U test, Spearman correlation, ROC curve analysis, and multivariable logistic regression. Median serum IL-6 was higher in DPN patients (194.38 pg/mL; IQR: 144.16–338.89) than in those without DPN (97.01 pg/mL; IQR: 71.39–148.26; $p < 0.001$) and correlated strongly with MNSI score ($\rho = 0.693$, $p < 0.001$), with no correlation to HbA1c or fasting glucose. IL-6 independently predicted DPN (OR=1.020; 95% CI: 1.010–1.031; $p < 0.001$), with good diagnostic accuracy (AUC=0.843; 95% CI: 0.763–0.922; cut-off 110.34 pg/mL; sensitivity 91.1%; specificity 64.4%). Serum IL-6 is significantly elevated in DPN and correlates with its severity independent of glycaemic control, showing good diagnostic accuracy as a potential adjunctive screening biomarker in resource-limited settings.

Keywords: inflammation, cytokines, Michigan neuropathy screening instrument, cross-sectional studies, roc curve, Iraq

Introduction

Diabetes mellitus is one of the most serious non-communicable diseases worldwide, with an estimated 537 million adults affected in 2021, projected to reach 783 million by 2045 [1]. The Middle East and North Africa (MENA) region carries the highest comparative prevalence globally at 18.1% [1]. In Iraq, local studies report a type 2 diabetes mellitus (T2DM) prevalence of up to 19.7% in adults, yet epidemiological data on diabetic complications remain limited [2].

Diabetic peripheral neuropathy (DPN) is the most common and disabling complication of diabetes, af-

fecting nearly 50% of all diabetic patients over their lifetime [3, 4]. It is a leading cause of pain, foot ulceration, and lower-limb amputation [5]. In the MENA region, DPN prevalence is particularly high and largely underdiagnosed: a large multicentre study from Qatar, Kuwait, and Saudi Arabia found that 33.3% of T2DM patients had DPN, of whom 53.6% were previously undiagnosed [6]. In Iraq, a cross-sectional study in Erbil reported a DPN prevalence of 31.2% using the Michigan Neuropathy Screening Instrument (MNSI) [7].

For decades, DPN was viewed mainly as a downstream consequence of hyperglycaemia-driven metabolic and vascular injury. Over the past two decades,



however, this view has shifted, and chronic low-grade systemic inflammation is now recognized as an independent contributor to peripheral nerve damage. IL-6, a pleiotropic cytokine released by macrophages, endothelial cells, and adipocytes, appears central to this process: it activates NF- κ B, MAPK, and JAK2/STAT3 signaling in peripheral nerves and, through these pathways, promotes Schwann-cell dysfunction, impaired axonal transport, and demyelination [8, 9]. The strongest evidence for a causal role comes from the KORA F4/FF4 cohort, where elevated serum IL-6 predicted incident DPN over 6.5 years of follow-up, even after full adjustment for HbA1c and other metabolic risk factors — indicating that inflammation actively drives neuropathic progression rather than simply following in its wake [10].

To our knowledge, no study from Al-Anbar Governorate has measured serum IL-6 and related it to MNSI scores in a structured cross-sectional design; the Iraqi data available on this association come from other cities. Given how much DPN goes undiagnosed in Iraq, and how inaccessible nerve conduction studies remain in many local health centers, a biomarker with genuine diagnostic value would fill a real clinical gap. This study therefore compared serum IL-6 levels between T2DM patients with and without DPN, examined its correlation with neuropathy severity, and evaluated its diagnostic performance for identifying DPN.

Material and methods

Study design and ethical approval

This cross-sectional observational study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Anbar Health Directorate, Ministry of Health, Iraq (Approval No. 320, dated 19 May 2025). Written informed consent was obtained from all participants prior to enrolment.

Study population

A total of 90 patients with confirmed T2DM were recruited from internal medicine outpatient clinics and public hospitals in Ramadi City, Al-Anbar Governorate, Iraq, between June and September 2025. Participants were purposively allocated into two equal groups of 45 each based on DPN status — patients with DPN and patients without DPN — to facilitate group comparison.

Participants were eligible if they had a confirmed diagnosis of T2DM, were aged 18 years or older, and were receiving oral hypoglycaemic therapy. Patients receiving insulin therapy were not excluded, but insulin use was not systematically recorded. Patients were excluded if they had type 1 diabetes mellitus, other known causes of peripheral neuropathy (e.g., vitamin B12 deficiency, hypothyroidism, chronic kidney disease), or acute inflammatory or infectious conditions that could affect IL-6 levels.

Assessment of diabetic peripheral neuropathy

Peripheral neuropathy was assessed using the questionnaire component of the Michigan Neuropathy Screening Instrument (MNSI), a validated and widely used clinical screening tool for the detection of DPN [11]. The questionnaire includes eight items assessing neuropathic symptoms including numbness, burning pain, tingling, muscle cramps, and loss of sensation in the feet. Each abnormal response was scored as 1, with a total score ranging from 0 to 8. A score of ≥ 4 was used to define the presence of DPN, a threshold validated in regional studies and consistent with published modified MNSI criteria [7, 11]. The physical examination component of the MNSI was not performed in this study due to logistical constraints.

Blood sample collection and laboratory analysis

Venous blood samples (5 mL) were collected from each participant after an overnight fast of at least 8 hours. Samples were allowed to clot at room temperature, centrifuged at 3000 rpm for 10 minutes, and the separated serum was stored at -20°C until analysis. Samples were analyzed within three months of collection. Serum IL-6 concentrations were measured using a quantitative ELISA kit (Human IL-6 ELISA Kit, Sunlong Biotech Co., Ltd., Hangzhou, China; detection range: 3.12–200 pg/mL; minimum detectable concentration: <1.0 pg/mL) according to the manufacturer's instructions, using a four-parameter logistic (4PL) calibration curve. Samples with optical density values exceeding the highest standard were diluted, re-assayed according to the manufacturer's protocol, and the measured concentrations were multiplied by the corresponding dilution factor to obtain the final serum IL-6 concentrations. Results were expressed in picograms per milliliter (pg/mL). Fasting blood sugar (FBS) was measured by the enzymatic colorimetric method, glycated haemoglobin (HbA1c) by an automated

clinical chemistry analyzer, and serum creatinine by the Jaffé method.

Statistical analysis

Data were analysed using IBM SPSS Statistics version 26.0. Normality was assessed by the Shapiro-Wilk test; non-normal variables, including IL-6, were expressed as median (IQR) and compared with the Mann-Whitney U test, and normally distributed variables as mean±SD compared with the independent t-test. Categorical variables were compared with the Chi-square test, and Spearman correlation assessed associations between IL-6 and clinical variables. ROC analysis (cut-off by Youden index) evaluated diagnostic accuracy, and multivariable logistic regression (Enter method; DPN as the dependent variable; IL-6, age, diabetes duration, HbA1c, and FBS as covariates) identified independent predictors, with results reported as adjusted OR (95% CI) and model fit assessed via the Omnibus Chi-square test, Nagelkerke R², and Hosmer-Lemeshow test. Significance was set at p<0.05; no data were missing.

Results

General characteristics of study participants

The study included 90 patients with T2DM (57 males, 33 females), equally divided into two groups. The demographic and clinical characteristics are presented in Table 1. Patients with DPN were significantly older than those without DPN (55.40±6.99 vs. 50.73±

9.84 years; p=0.006) and had a significantly longer duration of diabetes (8.04±4.24 vs. 5.47±2.67 years; p=0.003). There were no significant differences between the two groups in sex distribution, fasting blood sugar, HbA1c, or creatinine levels (p > 0.05 for all). The MNSI score was significantly higher in the neuropathy group (5.60±1.25 vs. 2.60±0.50; p<0.001).

Serum IL-6 levels

Serum IL-6 levels were significantly higher in patients with DPN compared to those without DPN (median 194.38 pg/mL, IQR: 144.16–338.89 vs. median 97.01 pg/mL, IQR: 71.39–148.26; Mann-Whitney U=318.5, p<0.001). The full distribution of IL-6 levels in both groups is shown in Figure 1 (range: 21.17–315.32 pg/mL in the No DPN group vs. 67.29–1413.75 pg/mL in the DPN group).

Correlation between serum IL-6 and clinical variables

Spearman rank correlation analysis revealed a strong positive correlation between serum IL-6 and MNSI score (Spearman's rho=0.693, p<0.001), indicating that higher IL-6 levels are associated with greater neuropathy severity. No significant correlations were found between IL-6 and HbA1c, fasting blood glucose, age, or duration of diabetes (Table 2).

Diagnostic performance of serum IL-6

ROC curve analysis demonstrated good diagnostic accuracy for serum IL-6 in identifying DPN (AUC=0.843;

Table 1: Demographic and clinical characteristics of study participants.

Characteristic	No DPN (n=45)	DPN (n=45)	p-value
Age (years), mean±SD	50.73±9.84	55.40±6.99	0.006 *
Sex (male/female)	30/15	27/18	0.662 †
DM duration (years), mean±SD	5.47±2.67	8.04±4.24	0.003 *
FBS (mg/dL), mean±SD	264.04±144.79	240.96±104.42	0.695
HbA1c (%), mean±SD	8.23±1.61	8.60±1.51	0.144
Creatinine (mg/dL), mean±SD	0.97±0.10	1.00±0.08	0.084
MNSI score, mean±SD	2.60±0.50	5.60±1.25	<0.001 *
IL-6 (pg/mL), median (IQR)	97.01 (71.39–148.26)	194.38 (144.16–338.89)	<0.001 *

Note: * – Statistically significant (p<0.05). † – Chi-square test. Mann-Whitney U test used for non-normally distributed variables; independent samples t-test for normally distributed variables. DM – diabetes mellitus; FBS – fasting blood sugar; IQR – interquartile range; SD – standard deviation.

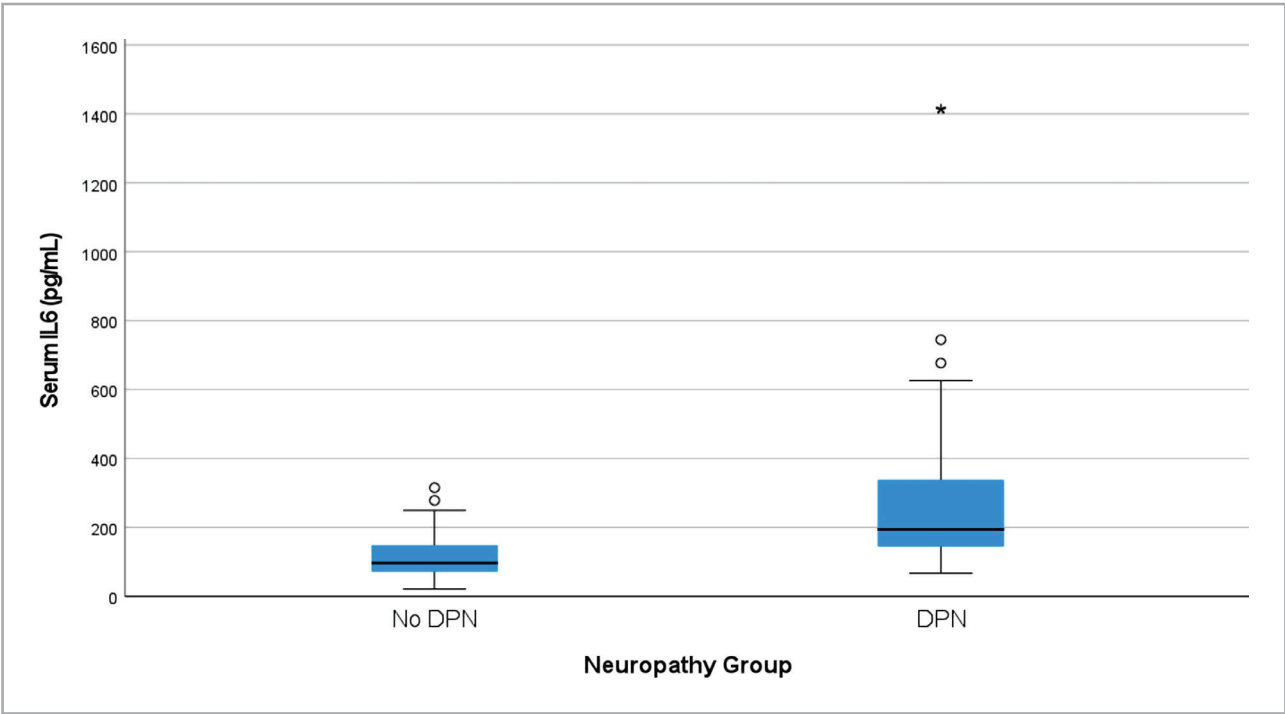


Figure 1: Serum IL-6 levels in patients with and without DPN (Mann-Whitney U test, $p < 0.001$).

95% CI: 0.763–0.922; $p < 0.001$). The optimal cut-off value, determined by the Youden index, was 110.34 pg/mL, yielding a sensitivity of 91.1% and a specificity of 64.4%. Diagnostic performance parameters are summarized in Table 3, and the ROC curve is presented in Figure 2.

Multivariable logistic regression analysis

Multivariable binary logistic regression (Enter method, $N = 90$) was performed to determine whether serum IL-6 remained an independent predictor of DPN after controlling for age, diabetes duration, HbA1c, and FBS. Serum IL-6 emerged as a statistically significant independent predictor of DPN (OR=1.020; 95% CI: 1.010–1.031; $p < 0.001$), indicating that each 1 pg/mL increase in serum IL-6 was associated with a 2.0% increase in the adjusted odds of DPN, independent of

all other covariates. Diabetes duration was also independently associated with DPN (OR=1.334; 95% CI: 1.085–1.641; $p = 0.006$). Age showed a trend toward significance (OR=1.074; $p = 0.059$) but did not reach the pre-defined threshold. HbA1c (OR=1.104; $p = 0.618$) and FBS (OR=1.000; $p = 0.864$) were not independently associated with DPN after adjustment. The overall model demonstrated good fit: Omnibus $\chi^2 = 54.955$ ($df = 5$, $p < 0.001$), Nagelkerke $R^2 = 0.609$, Hosmer-Lemeshow $\chi^2 = 5.240$ ($df = 8$, $p = 0.732$), and overall classification accuracy of 81.1%. Full results are presented in Table 4.

Discussion

This study examined serum IL-6 as an inflammatory biomarker in T2DM patients from Al-Anbar

Table 2: Spearman rank correlation between serum IL-6 and clinical variables.

Variable	Spearman's rho	p-value	Result
IL-6 vs. MNSI score	0.693	<0.001 *	Significant
IL-6 vs. HbA1c (%)	0.057	0.596	Not significant
IL-6 vs. FBS (mg/dL)	-0.137	0.199	Not significant
IL-6 vs. Age (years)	0.054	0.614	Not significant
IL-6 vs. DM duration (years)	0.051	0.631	Not significant

Note: * – Statistically significant ($p < 0.05$). FBS – fasting blood sugar; MNSI – Michigan Neuropathy Screening Instrument.

Table 3: Diagnostic performance of serum IL-6 for identifying diabetic peripheral neuropathy.

Parameter	Value	95% CI
AUC	0.843	0.763–0.922
Optimal cut-off	110.34 pg/mL	—
Sensitivity	91.1%	—
Specificity	64.4%	—
p-value	<0.001	—

Note: AUC – area under the curve; CI – confidence interval. Optimal cut-off determined by Youden index.

Governorate. Three findings stand out: serum IL-6 was markedly higher in patients with DPN, it correlated strongly with neuropathy severity independently of glycaemic control, and ROC analysis showed good diagnostic accuracy for identifying DPN.

Patient characteristics

Patients with DPN were older and had lived with diabetes longer than those without neuropathy — an

expected finding, since cumulative hyperglycaemic exposure progressively damages peripheral nerve fibers [12, 13]. What stands out is that HbA1c did not differ between the two groups. This is not really a paradox once one considers that neuropathy tracks the cumulative, fluctuating glycaemic burden accumulated over years rather than a single HbA1c snapshot; Saibi et al. [14] showed in a ten-year prospective study that glycaemic variability, not mean HbA1c, independently predicted DPN incidence.

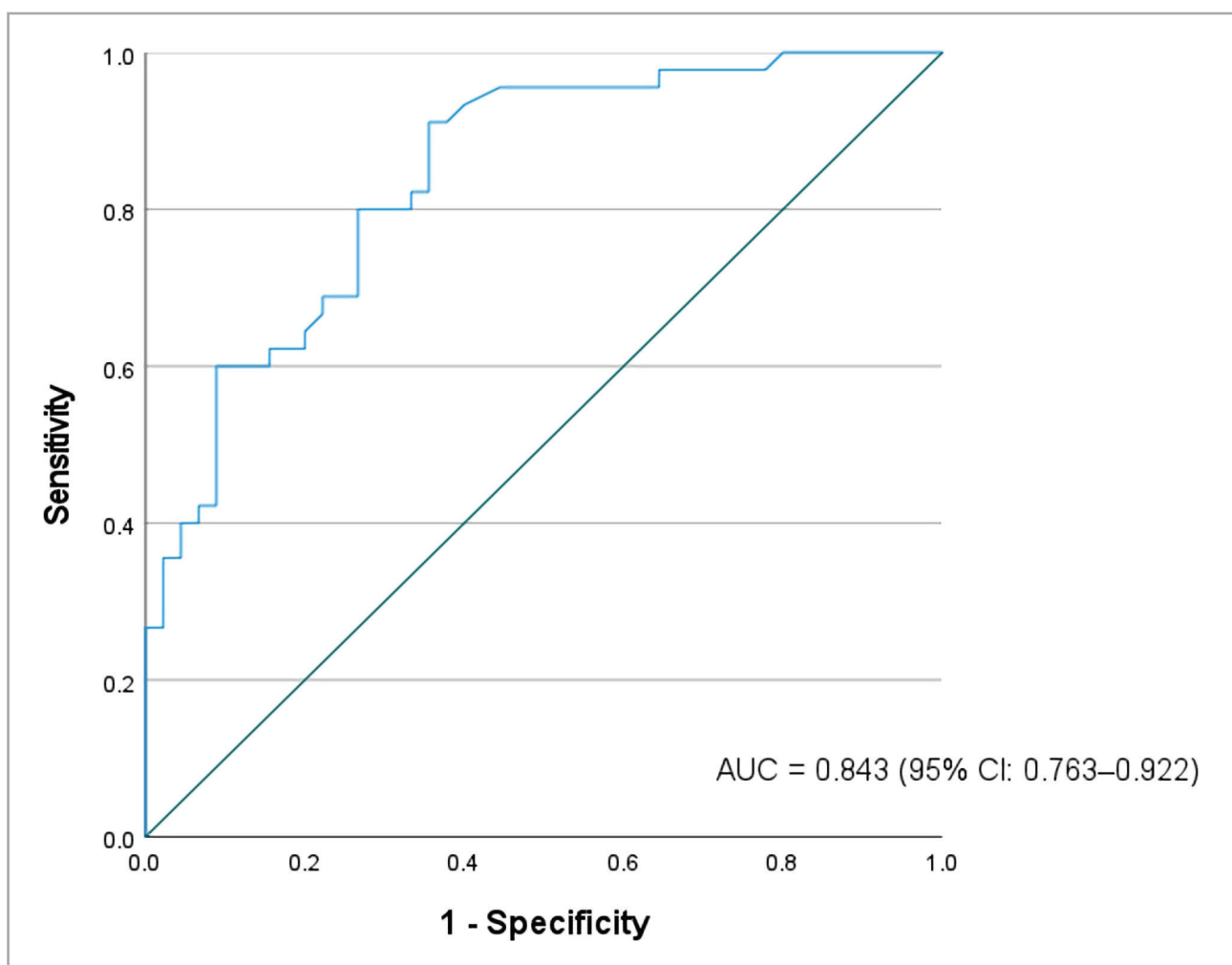


Figure 2: ROC curve for serum IL-6 in identifying DPN (AUC=0.843; 95% CI: 0.763–0.922).

Table 4: Multivariable binary logistic regression analysis: independent predictors of diabetic peripheral neuropathy (N=90).

Variable	B (SE)	Wald	p-value	OR (95% CI)
Serum IL-6 (pg/mL)	0.020 (0.005)	14.68	<0.001*	1.020 (1.010–1.031)
Age (years)	0.072 (0.038)	3.56	0.059	1.074 (0.997–1.158)
DM Duration (years)	0.288 (0.106)	7.44	0.006*	1.334 (1.085–1.641)
HbA1c (%)	0.099 (0.198)	0.25	0.618	1.104 (0.749–1.626)
FBS (mg/dL)	–0.000 (0.002)	0.03	0.864	1.000 (0.995–1.004)

Note: * – Statistically significant ($p<0.05$). OR – odds ratio; CI – confidence interval; B – regression coefficient; SE – standard error; DM – diabetes mellitus; FBS – fasting blood sugar. Model fit: Omnibus $\chi^2=54.955$, $df=5$, $p<0.001$; Nagelkerke $R^2=0.609$; Hosmer-Lemeshow $\chi^2=5.240$, $df=8$, $p=0.732$; Overall classification accuracy=81.1%.

Serum IL-6 and diabetic peripheral neuropathy

Even the No DPN group had elevated IL-6 (median 97.01 pg/mL) — well above the 2–7 pg/mL typical of healthy individuals. This fits what is already known about T2DM itself: adipose tissue dysfunction, advanced glycation end-products, and hyperglycaemia-driven oxidative stress keep patients in a state of chronic low-grade inflammation regardless of neuropathic status [8, 9]. That IL-6 rose further still in the DPN group, on top of this already-elevated baseline, points to an additional neuroinflammatory process acting specifically on peripheral nerve tissue. Mechanistically this is plausible: IL-6 drives Schwann-cell dysfunction, impairs axonal transport, and promotes demyelination through its downstream inflammatory signaling [8]. This mirrors the KORA F4/FF4 findings of Herder et al. [10], who showed that systemic inflammation actively drives neuropathic progression rather than simply following in its wake.

Similar findings have been reported regionally: Karahmet et al. [15] in Bosnia and Herzegovina found elevated IL-6 in T2DM patients with polyneuropathy, and Fadel et al. [16] in Egypt showed IL-6 rising progressively with neuropathy severity, with good diagnostic performance. More directly relevant, Abdulrhman et al. [17] studied 140 T2DM patients at Al-Numan Teaching Hospital in Baghdad and likewise found significantly higher serum IL-6 in those with DPN, concluding it was a useful indicator of neuropathy in an Iraqi population; the same group also reported elevated TGF- β and TNF- α in Iraqi DPN patients, suggesting the pro-inflammatory dysregulation extends beyond IL-6 alone [18]. Together, these two Iraqi studies point to the same association holding across different clinical settings in the country. Our absolute IL-6 values, however, were considerably higher than those report-

ed elsewhere — 97.01 and 194.38 pg/mL in the No DPN and DPN groups, compared with 32.91 and 52.34 pg/mL in Chanda et al.’s Indian cohort [19], and lower still in the European KORA F4/FF4 cohort [10]. Such differences between populations likely reflect disease severity, BMI, genetic background, ELISA kit sensitivity, and patient selection, rather than a fundamentally different biology.

Correlation between IL-6 and neuropathy severity

The correlation between IL-6 and MNSI score was strong (Spearman’s $\rho=0.693$, $p<0.001$), and biologically this makes sense: as inflammatory signaling intensifies, Schwann-cell dysfunction and axonal injury accumulate, moving patients from subclinical changes to the clinically detectable sensory deficits that the MNSI captures. In other words, IL-6 tracks severity rather than simply flagging the presence or absence of neuropathy — a pattern also described by Samakidou et al. [20] and, more recently, by Stoian et al. [21] and Panou et al. [22], who reviewed IL-6 alongside other cytokines, chemokines, and adipokines as candidate biomarkers for staging DPN. IL-6 did not correlate with HbA1c or fasting glucose, which fits the idea that this inflammatory pathway operates independently of glycaemic control at any given moment; HbA1c only reflects the preceding three months, after all, and likely underestimates the cumulative metabolic injury that drives the nerve damage seen here.

Diagnostic value of serum IL-6

After adjusting for age, diabetes duration, HbA1c, and fasting glucose, serum IL-6 remained an independent predictor of DPN (OR=1.020; 95% CI: 1.010–1.031; $p<0.001$). In practical terms, the elevated IL-6 in DPN

patients is not simply a proxy for being older or having had diabetes longer — both differed significantly between groups — but reflects an inflammatory signal contributing to the neuropathic process in its own right. This fits the wider literature on DPN risk modeling: Liu et al. [23], using LASSO regression in a cohort of 1,185 diabetic patients, also identified diabetes duration as a consistent independent risk factor, matching our own finding (OR=1.334; $p=0.006$), while Fadel et al. [16] similarly found IL-6 to independently predict neuropathy severity after adjusting for glycaemic and demographic variables in Egyptian patients.

The model itself performed well. A Nagelkerke R^2 of 0.609 means the five variables together explain roughly 61% of the variance in DPN status, and a Hosmer-Lemeshow p -value of 0.732 indicates good calibration between predicted and observed risk [24]. The AUC of 0.843 falls in the “good” range by Hajian-Tilaki’s criteria [24], and the 91.1% sensitivity at the 110.34 pg/mL cut-off matters clinically: for a screening test, missing a patient with undiagnosed neuropathy who later progresses to foot ulceration is the costlier error, so prioritizing sensitivity over specificity makes sense here. The trade-off is a more modest 64.4% specificity, unsurprising given that IL-6 rises in many conditions besides DPN [20, 21]. It is worth noting that a 2024 review of inflammatory biomarkers in DPN reported typical AUC values of 0.65–0.75 for IL-6, TNF- α , and hs-CRP [21]; our AUC of 0.843 exceeds that range, possibly because our cohort had more established, severe neuropathy, or because of differences in ELISA sensitivity between studies. A similarly designed 2026 study comparing serum neurofilament light chain and Tau for DPN screening reported single-marker AUCs of 0.825–0.829, with only their combined panel reaching 0.896 [25], suggesting that a single well-validated marker such as IL-6 can perform comparably to newer neuro-specific biomarkers without requiring a multi-marker panel.

Taken together, these results support serum IL-6 as a first-line screening adjunct rather than a stand-alone diagnostic test, particularly where nerve conduction studies are unavailable, as in much of Iraqi primary and secondary care [7, 11]. It should complement, not replace, existing clinical assessment tools for identifying patients who need closer follow-up.

Several limitations should be considered. The cross-sectional design cannot establish causality or temporal sequence between IL-6 elevation and DPN development. With only 90 patients from a single governorate, statistical power and generalizability are limited.

DPN status relied on the MNSI questionnaire alone, without the physical examination component or electrophysiological confirmation by nerve conduction studies, still the reference standard for DPN diagnosis [3, 11]. The deliberate 1:1 allocation into DPN and No DPN groups, while useful for statistical comparison, introduces a selection bias and means our data cannot be used to estimate the true prevalence of DPN in this population. Insulin use was not systematically recorded, a potential confounder given that insulin therapy can independently affect serum IL-6. We also measured IL-6 alone rather than a broader inflammatory panel (TNF- α , IL-1 β , hs-CRP), and although the regression model adjusted for age, diabetes duration, HbA1c, and FBS, residual confounding from unmeasured factors — BMI, smoking, physical activity, complete medication histories — cannot be ruled out. Larger multicenter cohorts with electrophysiological confirmation, a broader biomarker panel, and longitudinal follow-up would help validate and extend these findings.

Conclusion

Serum IL-6 was significantly elevated in T2DM patients with diabetic peripheral neuropathy and correlated strongly with neuropathy severity on the MNSI, independent of glycaemic control. ROC analysis confirmed good diagnostic accuracy, with high sensitivity at a cut-off of 110.34 pg/mL. Serum IL-6 therefore appears to be a clinically useful and accessible adjunctive biomarker for DPN screening in resource-limited settings such as Iraqi primary and secondary care facilities. Larger, longitudinal, multicenter studies with electrophysiological confirmation are needed to validate these findings and to assess the prognostic value of serum IL-6 in Iraqi diabetic populations.

Conflict of interest

The authors declare no conflict of interest.

AI-assisted language editing

AI-assisted paraphrasing tools were used for language editing and text improvement. The author thoroughly reviewed and verified all content, taking full responsibility for the accuracy and integrity of the final manuscript.

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