

Clinical Significance of Serum CCR2 and IDO1 in Diabetic Peripheral Neuropathy

Yubin Liu, Qiaoe Yang

Department of Endocrinology and Diabetes, Cangzhou Hospital of Integrated Traditional Chinese Medicine and Western Medicine of Hebei, Cangzhou, Hebei, People's Republic of China

Correspondence: Qiaoe Yang, Department of Endocrinology and Diabetes, Cangzhou Hospital of Integrated Traditional Chinese Medicine and Western Medicine of Hebei, No. 31 Huanghe West Road, Cangzhou, Hebei, 061000, People's Republic of China, Email YangQiaoe_01@outlook.com

Objective: To quantify circulating levels of C-C chemokine receptor-2 (CCR2) and indoleamine-2,3-dioxygenase-1 (IDO1) in patients with type 2 diabetes mellitus (T2DM) complicated by diabetic peripheral neuropathy (DPN) and to evaluate their potential as early biomarkers for DPN detection.

Methods: In this retrospective observational study, 367 patients with T2DM admitted to Cangzhou Hospital of Integrated Traditional Chinese Medicine and Western Medicine of Hebei between January 2021 and November 2024 were consecutively enrolled. Participants were stratified into a DPN group ($n = 108$) and a non-DPN group ($n = 259$) based on the presence or absence of DPN. Clinical baseline data were collected, and serum CCR2 and IDO1 levels were determined by enzyme-linked immunosorbent assays (ELISA). Their associations with DPN and predictive performance were evaluated using Spearman correlation, multivariate logistic regression, random-forest modeling, and receiver operating characteristic (ROC) curve analyses.

Results: Median serum CCR2 (7.32 ng/mL) and IDO1 (9.77 ng/mL) concentrations were both significantly higher in the DPN cohort than in the non-DPN group ($P < 0.05$ for each) and were positively correlated ($r = 0.384$, $P < 0.001$). Multivariable logistic regression identified elevated CCR2 (OR 1.460, 95% CI 1.047–2.035) and IDO1 (OR 1.317, 95% CI 1.220–1.421) as independent risk factors for DPN. In a random forest model, CCR2 and IDO1 ranked as the third and fourth most important predictors, respectively. ROC analysis yielded areas under the curve (AUCs) of 0.728 for CCR2 and 0.749 for IDO1 individually; combining the two biomarkers increased the AUC to 0.786 (95% CI 0.729–0.844), with 62.0% sensitivity and 89.6% specificity.

Conclusion: Serum CCR2 and IDO1 are significantly up-regulated in patients with DPN and represent independent risk factors for its development. Their combined measurement enhances early detection accuracy, offering a clinically useful biomarker panel for DPN.

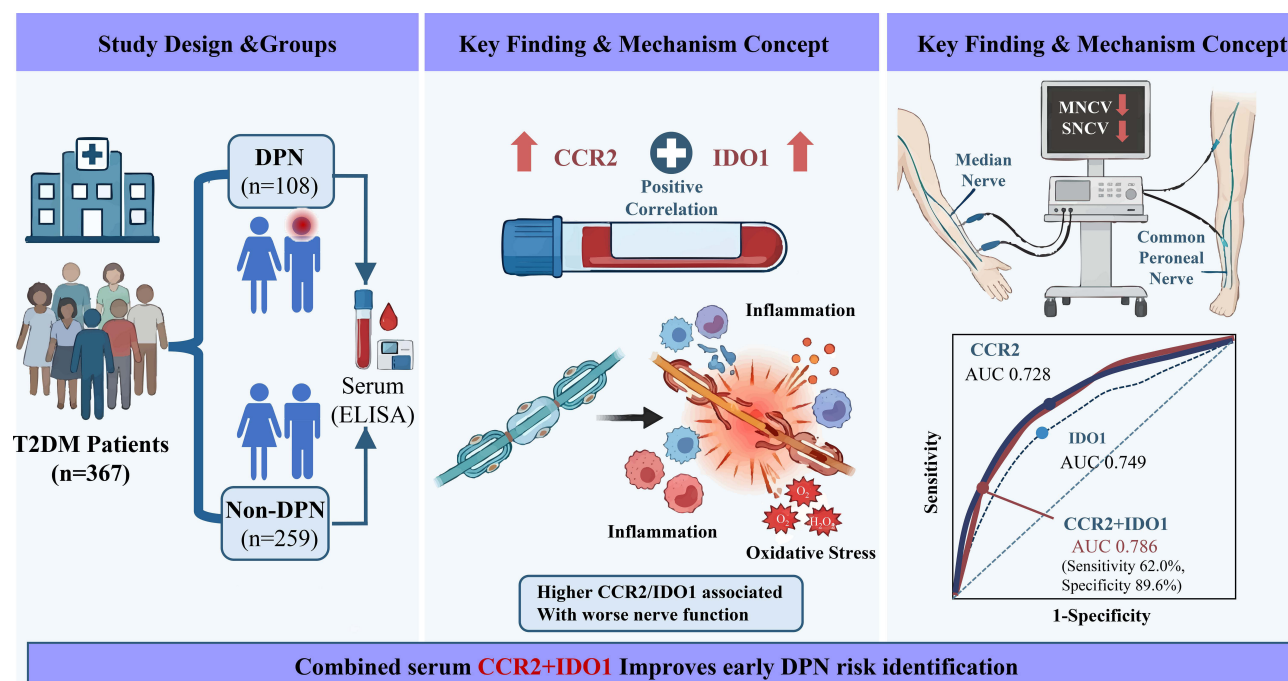
Keywords: C-C chemokine receptor-2, indoleamine-2,3-dioxygenase-1, diabetic peripheral neuropathy, biomarkers, clinical utility

Introduction

Type 2 diabetes mellitus (T2DM) is frequently accompanied by a spectrum of chronic micro- and macrovascular complications, of which diabetic peripheral neuropathy (DPN) is the most prevalent. Epidemiological studies indicate that DPN is highly prevalent among individuals with diabetes, and this burden is rising in parallel with the global escalation of diabetes mellitus.¹ DPN is a multifactorial disorder whose precise etiology and pathogenesis remain incompletely understood. Current consensus implicates chronic hyperglycemia, lipid-metabolism disturbances, and insulin resistance as central drivers; these factors converge to trigger inflammatory signaling, exacerbate oxidative stress, and impair microvascular function, collectively producing neuronal and glial injury with demyelination of nerve fibers and constituting the principal mechanisms underlying DPN. DPN is now recognized as the commonest and least tractable diabetic complication, imposing the largest share of direct medical costs and accounting for a substantial proportion of diabetes-related disability and excess mortality.²

DPN is subclassified into diffuse neuropathy, mononeuropathy, autonomic neuropathy, and radiculoplexus neuropathy. At present, management centers on strict glycemic control supplemented by symptomatic agents such as pregabalin and duloxetine, together with foot-care education and early detection of acute foot complications.

Graphical Abstract



Nevertheless, no intervention has yet been shown to reverse established nerve injury.³ Pathologically, DPN is characterized by progressive, length-dependent axonal degeneration and segmental demyelination that simultaneously affects sensory, motor and autonomic nerve fibers. The resulting sensory deficit and motor impairment constitute the principal risk factors for diabetic foot ulceration and subsequent lower-extremity amputation; moreover, neuropathic pain, autonomic cardiac dysfunction and falls-related injury further amplify morbidity and mortality. Current screening and diagnosis of DPN rely on clinical presentation combined with ancillary tests; nerve conduction studies (NCS) remain the diagnostic gold standard. Patients with T2DM should undergo annual DPN screening from the time of diagnosis.⁴

Importantly, subclinical neuropathy is already detectable in the prediabetic state, but its early manifestations are subtle and frequently elude routine clinical assessment. Current screening tools exhibit limited sensitivity, leading to under-diagnosis and missed opportunities for intervention.⁵ Consequently, the identification of robust early diagnostic biomarkers and the discovery of molecular targets amenable to disease-modifying therapy are urgent unmet clinical needs.

CC chemokine receptor 2 (CCR2), a class-A G-protein-coupled receptor, is predominantly expressed on classical inflammatory monocytes, tissue macrophages and a subset of effector T lymphocytes.⁶ Studies have revealed that CCR2⁺ inflammatory monocytes robustly infiltrate the retina during the early stages of diabetes, amplifying retinal inflammation and identifying CCR2 as a potential therapeutic target for diabetic retinopathy.⁷

Beyond ocular complications, ligand-activated CCR2 orchestrates the systemic trafficking of monocytes and macrophages to metabolically stressed organs, thereby potentiating tissue-specific inflammatory loops and oxidative injury that drive maladaptive remodeling in the myocardium, renal parenchyma and peripheral nerves. Consequently, CCR2-mediated innate immune signaling contributes to the pathogenesis of diabetic cardiomyopathy, chronic kidney disease and progressive peripheral neurodegeneration.⁸

Indoleamine 2,3-dioxygenase 1 (IDO1) is a heme-dependent enzyme that catalyzes the conversion of tryptophan to kynurenine. Expressed by multiple cell lineages—most notably dendritic cells, monocytes, and macrophages—it exerts immunoregulatory effects through local depletion of tryptophan and generation of immunomodulatory kynurenine metabolites.⁹ IDO1 has been shown to be activated during chronic inflammatory conditions—including autoimmune

diseases, bacterial and viral infections, and many cancers—thereby driving immunosuppression.¹⁰ In high-glucose-stimulated murine peritoneal macrophages, selective IDO1 inhibitors attenuate pro-inflammatory cytokine expression; accordingly, IDO1 has been validated as a diagnostic and prognostic biomarker for diabetic kidney disease, underscoring its therapeutic potential.¹¹

Currently, the respective contributions of circulating CCR2 and IDO1 to DPN remain insufficiently characterized. Therefore, the present study was designed to delineate the association between serum CCR2/IDO1 levels and DPN, to evaluate their potential as minimally invasive biomarkers, and to provide both a risk-stratification tool for early detection and a rationale for targeting these molecules therapeutically.

Materials and Methods

Sample-Size Calculation

On the basis of a previously reported DPN prevalence of 28.73% among adults with T2DM,¹² we estimated the required sample size for the present cross-sectional investigation. Setting an absolute allowable error of 5% (corresponding to a 10% two-sided 95% confidence interval width) and $\alpha = 0.05$ (two-tailed), power analysis was performed with PASS 15.0 software. The computation indicated that a minimum of 333 participants would be required to guarantee adequate statistical precision and scientific rigor.

Study Participants

We consecutively enrolled 367 patients with T2DM admitted to Cangzhou Hospital of Integrated Traditional Chinese Medicine and Western Medicine of Hebei between January 2021 and November 2024.

Inclusion criteria were as follows: (1) T2DM defined according to internationally accepted thresholds:¹³ fasting plasma glucose ≥ 7.0 mmol/L, or 2-h plasma glucose ≥ 11.1 mmol/L during a 75-g oral glucose-tolerance test (OGTT), or random plasma glucose ≥ 11.1 mmol/L in the presence of classic diabetic symptoms; (2) DPN diagnosed using the validated algorithm:¹⁴ ① definite diabetes mellitus; ② neuropathic symptoms or signs developing at or after the diagnosis of diabetes; ③ presence of neuropathic symptoms (pain, numbness, or paresthesia) and abnormality in ≥ 1 of five clinical tests (ankle reflex, vibration, pressure, temperature, or pin-prick sensation); in asymptomatic individuals, ≥ 2 abnormal tests are required; ④ exclusion of other causes of peripheral neuropathy; ⑤ NCS demonstrating ≥ 2 parameter abnormalities in each of ≥ 2 distinct nerves (typically including lower-limb nerves); (3) age 30–75 years; (4) complete clinical and laboratory data available.

Exclusion criteria were: (1) acute hyperglycemic crises or active severe infection; (2) diabetes types other than T2DM; (3) significant cardiac, hepatic or renal insufficiency, malignancy, autoimmune disease, or any other disorder known to cause peripheral neuropathy; (4) co-existing diabetic retinopathy or diabetic nephropathy; (5) pregnancy or lactation; (6) medications potentially confounding neuropathy assessment within the preceding 3 months; (7) alcohol or drug abuse.

Of the 367 patients recruited, 108 met the criteria for DPN (DPN group) and 259 did not (non-DPN group). The flowchart of participant enrollment in this study is shown in [Figure 1](#).

This retrospective analysis of de-identified human serum was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of Cangzhou Hospital of Integrated TCM-WM HEBEI (Approval No. CZX2024-KY-107.1). Due to the retrospective nature of the research utilizing biobank-stored serum samples, informed consent was waived by the approving institution. All data were handled with strict confidentiality to ensure the anonymity of participants.

Clinical Data Collection

Comprehensive baseline characteristics were extracted from the electronic medical record, comprising age, sex, body-mass index (BMI), systolic and diastolic blood pressure, smoking status, alcohol consumption, and documented history of hypertension or dyslipidemia. Diabetes-related variables included disease duration, fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c). Routine biochemical parameters comprised serum creatinine (Scr), uric acid (UA),

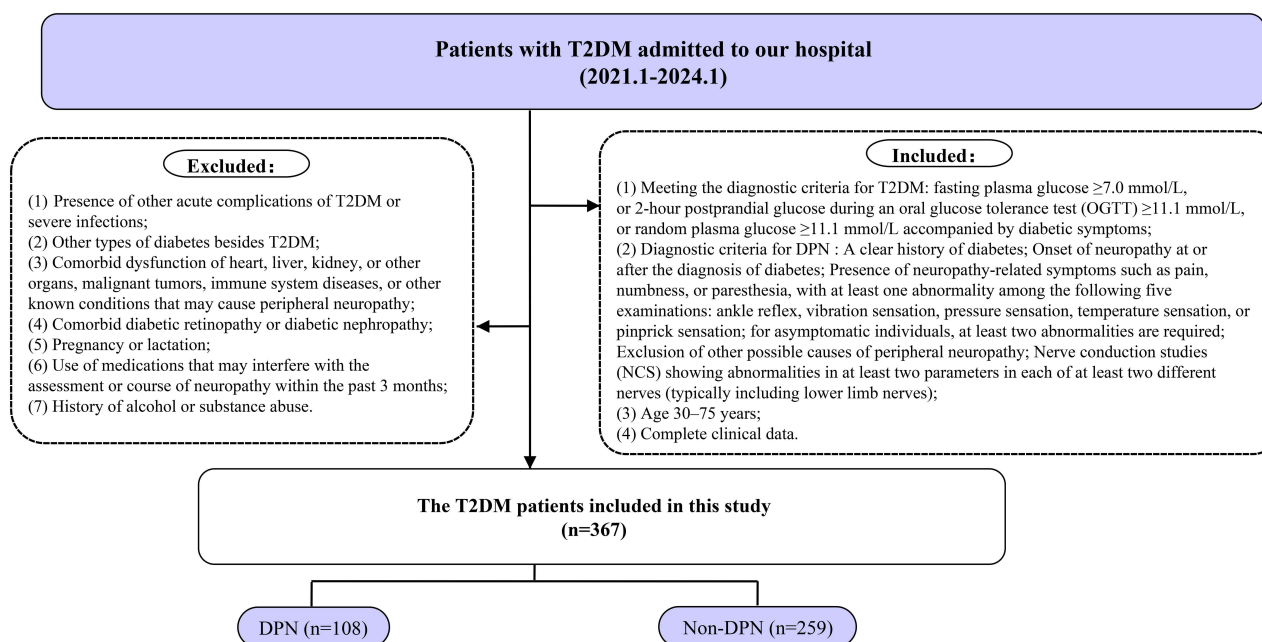


Figure 1 Flowchart of Participant Enrollment in This Study.

estimated glomerular filtration rate (eGFR), total cholesterol (TC), triglycerides (TG), high-density-lipoprotein cholesterol (HDL-C), low-density-lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Nerve Conduction Velocity Measurement

Motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV) of the median and common peroneal nerves were measured with the patient awake and lying supine in a quiet, temperature-controlled room, using a Keypoint 9033A07 electromyography/evoked-potential system (Dantec, Denmark).

Measurement of Serum CCR2 and IDO1 Concentrations

Serum samples retrieved from the institutional biobank were subjected to a single freeze–thaw cycle. CCR2 and IDO1 levels were quantified in duplicate by commercial enzyme-linked immunosorbent assays (ELISA) purchased from Amjettech (Wuhan, China; catalogues abx570562 and abx251114, respectively), following the manufacturer's instructions verbatim. Absorbance was read at 450 nm, and concentrations were interpolated from four-parameter logistic standard curves. Intra- and inter-assay coefficients of variation were both $<10\%$. Samples were randomly coded, and all assays were executed by laboratory personnel blinded to clinical data, ensuring strict masking throughout the analytical phase.

Statistical Analysis

All analyses were performed with SPSS 26.0 (IBM, Armonk, NY, USA). Categorical variables are presented as n (%) and were compared by χ^2 -test. Continuous variables were first examined for normality (Shapiro–Wilk). Normally distributed data are expressed as mean $\pm$ SD and compared by independent-samples t test; non-normally distributed data are reported as median (inter-quartile range, P_{25} – P_{75}) and analyzed with the Mann–Whitney U -test. The correlation between serum CCR2 and IDO1 concentrations was assessed by Spearman's rank correlation. Variables differing significantly between groups were screened for multicollinearity (variance inflation factor < 5) and then entered into a multivariable logistic regression model to identify independent determinants of DPN in patients with T2DM. A random-forest algorithm implemented in R (v4.3.0) was used to rank variable importance. Diagnostic performance

of serum CCR2 and IDO1 was evaluated by receiver-operating-characteristic (ROC) curve analysis. Two-tailed P values < 0.05 were considered statistically significant.

Results

Baseline Characteristics of the DPN and Non-DPN Groups

Patients with DPN were significantly older, had a longer duration of diabetes, higher FPG, glycated HbA1c and serum UA, and a lower eGFR than those without DPN (all $P < 0.05$). No statistically significant differences were observed between the two groups in sex distribution, body-mass index, systolic or diastolic blood pressure, smoking or alcohol consumption, prevalence of hypertension or dyslipidemia, serum urea, creatinine, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, alanine aminotransferase or aspartate aminotransferase (all $P > 0.05$, Table 1).

Comparison of Nerve Conduction Velocity Between the Two Groups

The DPN group had significantly lower MNCV and SNCV in both the median and common peroneal nerves than the non-DPN group ($P < 0.05$, Table 2).

Serum CCR2 and IDO1 Concentrations in the DPN and Non-DPN Groups

Quantitative ELISA revealed that patients with DPN exhibited significantly higher circulating levels of both CCR2 and IDO1 than those without DPN ($P < 0.05$, Figure 2A and B). Spearman correlation analysis revealed a positive association between serum CCR2 and IDO1 levels in patients with DPN ($r = 0.384$, $P < 0.001$) (Figure 2C).

Table 1 Comparison of Baseline Characteristics Between the DPN and Non-DPN Groups

Variable	DPN Group (n=108)	Non-DPN Group (n=259)	$\chi^2/Z/t$	P
Age (year)	64 (62, 67)	56 (54, 59)	-12.732 [^]	0.000
Gender[n (%)]			0.333 [#]	0.564
Male	64 (59.26)	145 (55.98)		
Female	44 (40.74)	114 (44.02)		
BMI (kg/m ²)	23.36±1.35	23.58±1.25	-1.476*	0.141
Systolic blood pressure (mm Hg)	130.44±15.98	128.85±15.32	0.898*	0.370
Diastolic blood pressure (mm Hg)	80.21±9.34	81.21±9.78	-0.901*	0.368
Smoking history [n (%)]	27 (25.00)	77 (29.73)	0.840 [#]	0.360
Alcohol consumption [n (%)]	39 (36.11)	87 (33.59)	0.215 [#]	0.643
Hypertension [n (%)]	47 (43.52)	103 (39.77)	0.444 [#]	0.505
Dyslipidaemia [n (%)]	32 (29.63)	67 (25.87)	0.547 [#]	0.459
Duration of diabetes (year)	9 (8, 10)	5 (4, 6)	-13.007 [^]	0.000
FPG (mmol/L)	8.4 (7.3, 9.48)	7.8 (7, 8.4)	-4.411 [^]	0.000
HbA1c (%)	9.09±1.44	8.17±1.42	5.590*	0.000
Serum urea (mmol/L)	5.62±0.91	5.48±1.07	1.167*	0.244
Scr (μmol/L)	60.12±10.88	57.91±9.75	1.910*	0.057
UA (μmol/L)	312.88±57.14	286.15±44.94	4.335*	0.000
GFR (mL/min)	76.88±8.19	84.14±9.64	-7.332*	0.000
TC (mmol/L)	4.75 (3.99, 5.54)	4.75 (4.06, 5.55)	-0.230 [^]	0.818
TG (mmol/L)	1.43±0.39	1.51±0.45	-1.609*	0.108
HDL-C (mmol/L)	1.07 (0.92, 1.20)	1.01 (0.87, 1.15)	-1.902 [^]	0.057
LDL-C (mmol/L)	2.59±0.67	2.68±0.59	-1.281*	0.201
ALT (U/L)	20.81±5.66	21.26±5.83	-0.671*	0.503
AST (U/L)	20.36±5.19	19.81±4.98	0.953*	0.341

Notes: * denotes the t-value, ^ denotes the Z-value, and # denotes the χ^2 -value.

Abbreviations: BMI, body-mass index; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; Scr, serum creatinine; UA, uric acid; GFR, glomerular filtration rate; TC, total cholesterol; TG, triglycerides; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 2 Nerve Conduction Velocity: Comparison Between DPN and Non-DPN Groups

Variable	DPN Group (n=108)	Non-DPN Group (n=259)	Z	P
Median nerve				
MNCV (m/s)	41.86 (40.13, 43.70)	55.66 (52.66, 58.46)	-15.017	0.000
SNCV (m/s)	39.51 (37.71, 41.58)	48.54 (46.06, 51.75)	-14.344	0.000
Common peroneal nerve				
MNCV (m/s)	35.38 (33.47, 37.34)	46.64 (43.69, 49.71)	-14.702	0.000
SNCV (m/s)	35.67 (33.98, 37.65)	47.82 (44.80, 50.90)	-14.534	0.000

Abbreviations: MNCV, motor nerve conduction velocity; SNCV, sensory nerve conduction velocity.

Correlation of Serum CCR2 and IDO1 with Clinical Variables in the DPN Group

Spearman correlation analysis showed that, within the DPN group, serum CCR2 and IDO1 levels were unrelated to age or diabetes duration ($P > 0.05$). Both biomarkers exhibited positive correlations with FPG, HbA1c, and UA, and inverse correlations with GFR ($P < 0.001$) (Figure 3).

Correlation of Serum CCR2 and IDO1 with Nerve Conduction Velocity

Spearman correlation analysis showed that serum CCR2 and IDO1 levels were inversely correlated with MNCV and SNCV of both the median and common peroneal nerves ($P < 0.001$) (Figure 4).

Multivariate Logistic Regression: Predictors of DPN in T2DM

Age, diabetes duration, FPG, HbA1c, serum uric acid, eGFR, CCR2 and IDO1 were entered as independent variables into a binary logistic model with DPN status as the dependent variable (DPN = 1, non DPN = 0). Variance-inflation factors were all < 2 , excluding significant multicollinearity. Advanced age, longer diabetes duration, elevated FPG, higher HbA1c, increased uric acid, reduced eGFR, and elevated serum CCR2 and IDO1 concentrations emerged as independent risk factors for DPN (all $P < 0.05$, Table 3).

Random-Forest Modelling

A random-forest classifier was constructed with age, diabetes duration, FPG, HbA1c, UA, eGFR, CCR2 and IDO1 as predictors and incident DPN as the binary outcome. The model exhibited excellent performance, achieving an F1-score of 0.973, precision 97.6%, accuracy 97.3% and recall 97.3%. Variable-importance analysis ranked the contributors as follows: age $>$ diabetes duration $>$ CCR2 $>$ IDO1 $>$ eGFR $>$ UA $>$ FPG $>$ HbA1c (Figure 5).

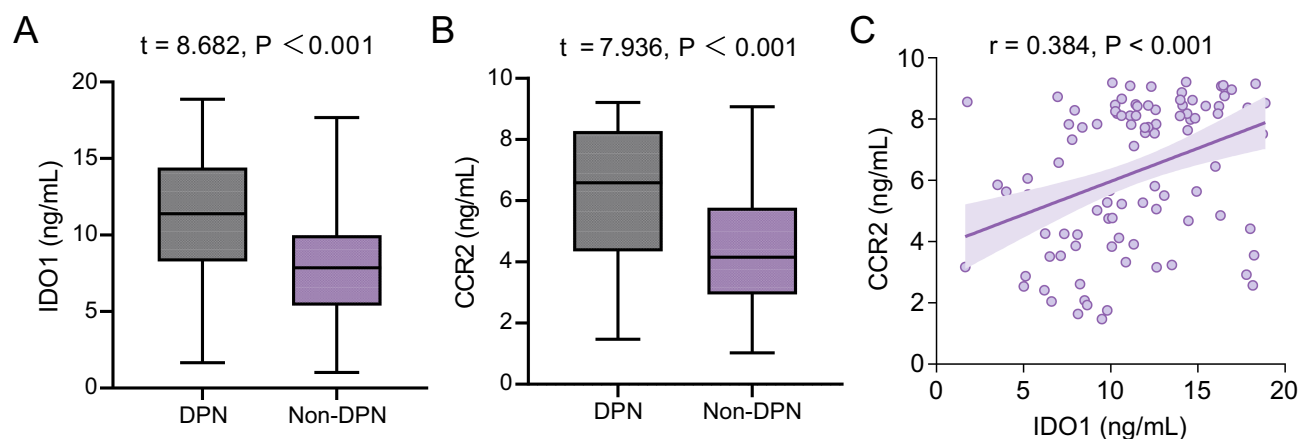


Figure 2 Comparison of serum CCR2 and IDO1 levels between the DPN and non-DPN groups.

Notes: (A) serum CCR2 levels; (B) serum IDO1 levels; (C) correlation analysis between serum CCR2 and IDO1.

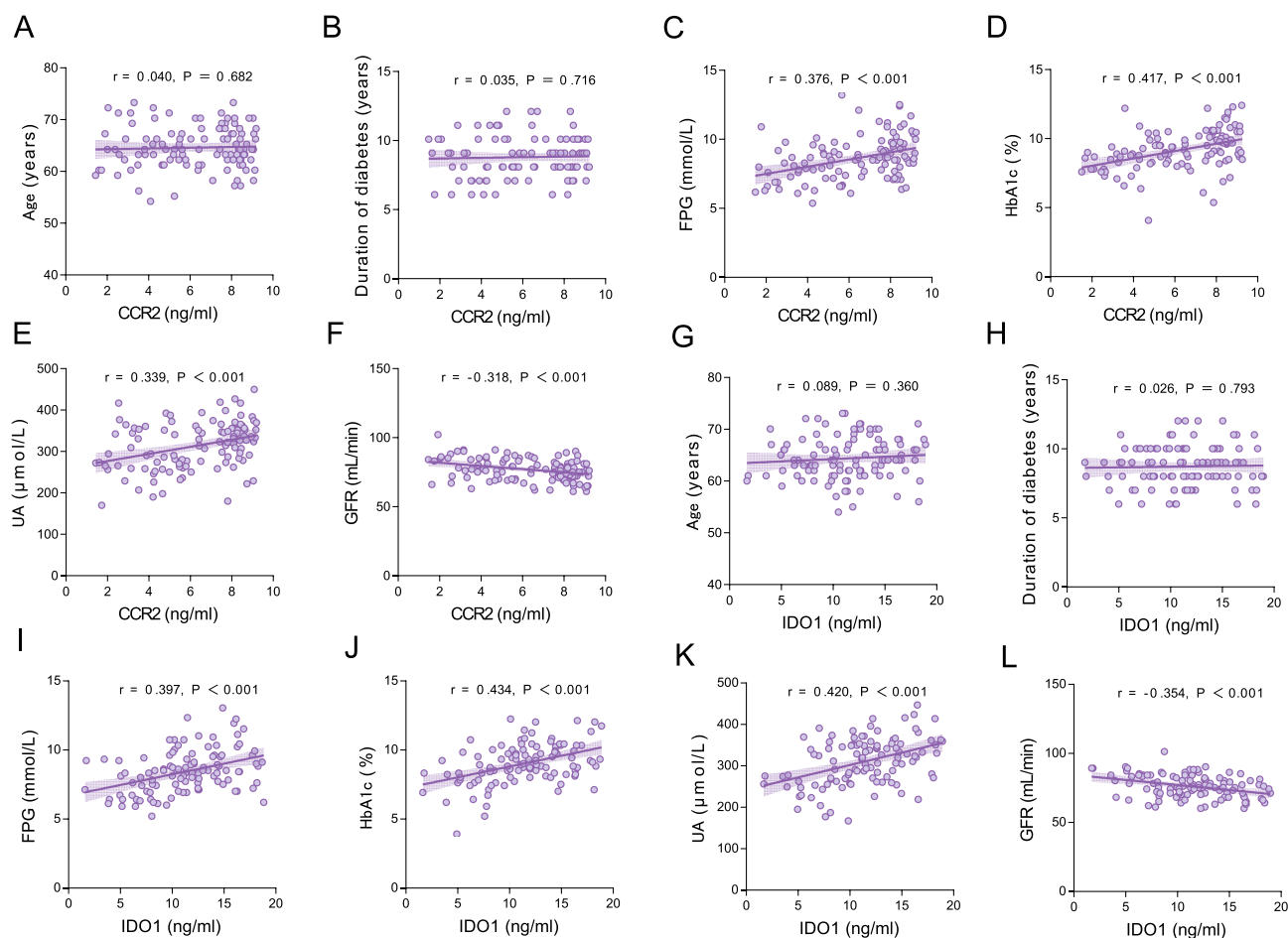


Figure 3 Correlation of serum CCR2 and IDO1 with clinical variables in the DPN group.

Notes: (A–F) correlations between serum CCR2 and clinical variables; (G–L) correlations between serum IDO1 and clinical variables.

Diagnostic Performance of Serum CCR2 and IDO1 for DPN: ROC Analysis

ROC curves were constructed to quantify the discriminative ability of serum CCR2 and IDO1 for incident DPN. The AUC was 0.728 (95% CI 0.669–0.787) for CCR2 alone, 0.749 (95% CI 0.692–0.806) for IDO1 alone, and 0.786 (95% CI 0.729–0.844) for the two biomarkers combined (all $P < 0.001$). The composite model exhibited superior discrimination to either marker in isolation (Table 4 and Figure 6).

Discussion

DPN is a common and disabling microvascular complication of T2DM, causing progressive sensory-motor deficits, pain, and reduced quality of life. With no disease-modifying therapies currently available, identification of early diagnostic biomarkers represents an urgent unmet clinical need.^{15–19} This study identified significantly elevated serum CCR2 and IDO1 as independent risk factors for DPN in T2DM patients, with both biomarkers correlating negatively with nerve conduction velocity. These findings highlight the involvement of CCR2 and IDO1 in DPN pathophysiology, providing a basis for future validation studies of these minimally invasive indicators.

Chronic, low-grade inflammation is now recognized as a fundamental driver of both the onset and progression of diabetes mellitus, with inflammatory and metabolic circuits operating as an integrated pathogenic axis in DPN.²⁰ DPN arises from the synergistic effects of sustained hyperglycemia and systemic inflammation that jointly amplify neurodegeneration; pro-inflammatory cytokines trigger oxidative stress, disrupt the blood–nerve barrier and degrade myelin, culminating in irreversible neural damage.²¹

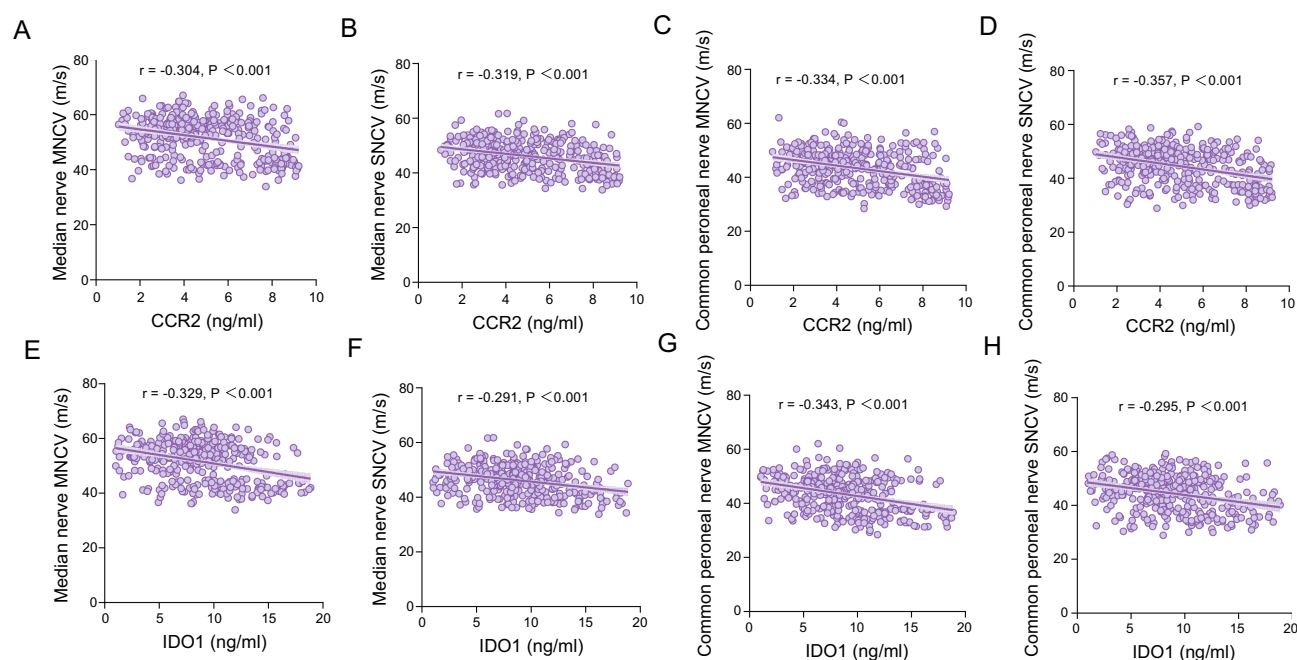


Figure 4 Correlation of serum CCR2 and IDO1 with nerve conduction velocity.

Notes: (A–D), correlations between serum CCR2 and nerve conduction velocity; (E–H), correlations between serum IDO1 and nerve conduction velocity.

In the present study, multivariable logistic regression identified elevated serum CCR2 and IDO1 as independent risk factors for DPN. Spearman correlation analysis indicated that serum CCR2 and IDO1 levels were positively correlated with each other in DPN patients and that both were significantly negatively correlated with MNCV and SNCV of the median and common peroneal nerves, suggesting that serum CCR2 and IDO1 levels are not only associated with the presence of DPN but also closely linked to the severity of peripheral nerve function impairment—the higher their levels, the slower the nerve conduction velocity and the more severe the neurological dysfunction—implying that CCR2 and IDO1 may, through synergistic or mutually reinforcing inflammatory-metabolic mechanisms, jointly promote the development and progression of DPN.

Previous work in paclitaxel-induced peripheral neuropathy documented marked up-regulation of CCR2 in dorsal-root-ganglion sensory neurons, mediating mechanical hypersensitivity and neurodegeneration.²² In lepromatous leprosy lesions, *Mycobacterium leprae* cooperates with IFN- γ to induce high IDO1 expression in macrophages/dendritic cells and thereby suppresses local immunity.²³ Given that the same organism also infiltrates along nerves, intraneural up-

Table 3 Multivariate Logistic Regression Analysis of Factors Associated with DPN in Patients with T2DM

Variable	β	S.E	Walds	P	OR	95% CI	VIF
Age	0.679	0.134	25.612	0.000	1.973	1.516~2.566	1.355
Duration of diabetes	1.225	0.246	24.899	0.000	3.405	2.104~5.511	1.398
FPG	0.670	0.287	5.448	0.020	1.953	1.113~3.427	1.073
HbA1c	0.498	0.100	24.620	0.000	1.646	1.352~2.004	1.076
UA	0.021	0.008	6.290	0.012	1.021	1.005~1.038	1.068
GFR	-0.203	0.055	13.611	0.000	0.816	0.733~0.909	1.070
CCR2	0.378	0.170	4.970	0.026	1.460	1.047~2.035	1.156
IDO1	0.275	0.039	50.033	0.000	1.317	1.220~1.421	1.182

Abbreviations: FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; Scr, serum creatinine; UA, uric acid; GFR, glomerular filtration rate; CCR2, CC chemokine receptor 2; IDO1, Indoleamine 2,3-dioxygenase 1.

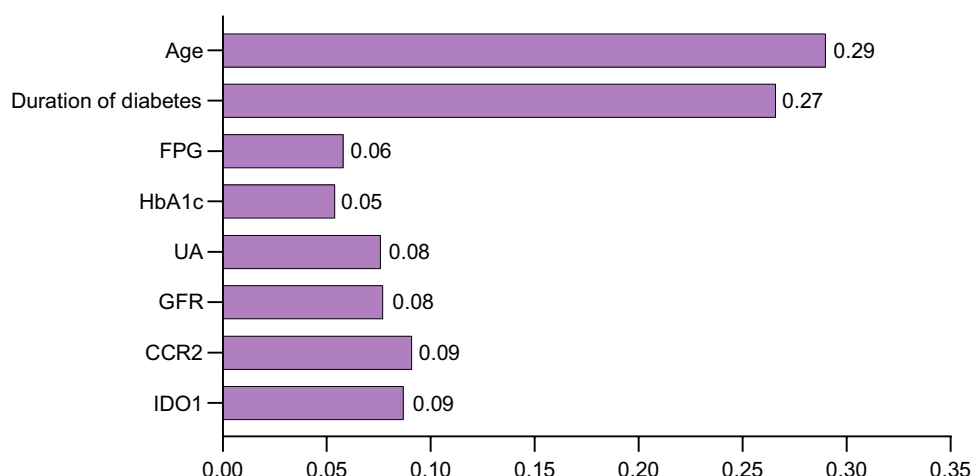


Figure 5 Variable-importance ranking from the random-forest prediction model analyzing risk factors for DPN development in patients with T2DM.

regulation of IDO1 may be associated with the persistent inflammation, axonal degeneration, and progressive peripheral neuropathy observed in lepromatous leprosy. Although CCR2 and IDO1 have been implicated sporadically in other neuropathies, direct comparison of their circulating levels between DPN and non-DPN individuals remains unreported. The present study provides the first exploration of their combined involvement in DPN, demonstrating that both molecules are closely tied to disease presence and progression; this finding offers novel immune-inflammatory targets and a theoretical framework for early recognition and directed immunotherapy of DPN.

CCR2, a G-protein-coupled receptor, orchestrates the chemotaxis of monocytes and other immune cells, thereby shaping inflammatory and tumor-immune responses.²⁴ After subarachnoid hemorrhage, neuronal CCR2 is markedly up-regulated and contributes to neuro-inflammation and apoptosis; genetic or pharmacologic inhibition of CCR2 improves neurological recovery.²⁵ In white adipose tissue, increased CCR2 expression fuels obesity-related inflammation and systemic insulin resistance, whereas CCR2 deletion reduces food intake, fasting glucose and insulin levels and ameliorates glucose tolerance.²⁶ CCR2 expression is up-regulated in peripheral-blood monocytes from diabetic patients and increases with poorer glycemic control, indicating that hyperglycemia may directly drive CCR2 induction.²⁷ In streptozotocin-diabetic rats, long-term hyperglycemia up-regulates CCR2 in dorsal-root-ganglion nociceptors independently of monocyte infiltration; the magnitude of CCR2 induction parallels gastric hypersensitivity, and intrathecal CCR2 antagonism rapidly reverses both visceral hyperalgesia and the attendant pro-inflammatory milieu.²⁸

IDO1, a tryptophan-catabolizing enzyme transcriptionally activated by inflammatory cues, exerts immunoregulatory effects through local depletion of tryptophan and generation of bioactive kynurenine metabolites that facilitate immune escape in cancer.²⁹ Under high-glucose conditions, IDO1 is up-regulated in human and murine retinal microglia; its downstream metabolite quinolinic acid accumulates in the retina and precipitates neuronal dysfunction and death via multiple mechanisms.³⁰ Hyperglycemia also induces high IDO1 expression in dendritic cells and monocytes, accelerating the conversion of tryptophan to kynurenine. Resultant metabolites activate the aryl-hydrocarbon receptor (AhR) and N-methyl-D-aspartate (NMDA) receptors, thereby triggering excitotoxicity, oxidative stress and sustained low-grade inflammation that collectively promote neuronal loss.³¹

Table 4 Diagnostic Performance of Serum CCR2 and IDO1 for DPN in Patients with T2DM

Variable	Cut-Off	Sensitivity %	Specificity %	AUC	95% CI
CCR2	7.315	0.472	0.911	0.728	0.667~0.789
IDO1	9.765	0.694	0.734	0.749	0.691~0.807
CCR2+ IDO1	–	0.620	0.896	0.786	0.729~0.844

Abbreviations: CCR2, CC chemokine receptor 2; IDO1, Indoleamine 2,3-dioxygenase 1.

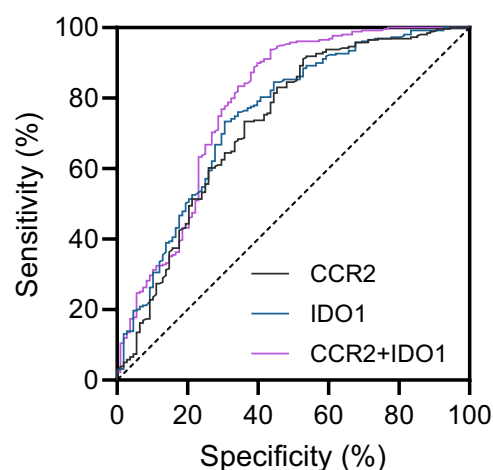


Figure 6 ROC curves assessing the value of serum CCR2 and IDO1 levels for identifying DPN in patients with T2DM.

We found that serum CCR2 and IDO1 levels correlated positively with FPG, HbA1c, and UA and negatively with GFR, suggesting that metabolic derangements such as hyperglycemia and declining kidney function may jointly trigger CCR2- and IDO1-mediated inflammatory pathways and thereby contribute to the neuroimmune dysregulation underlying DPN. Multivariable logistic regression further confirmed that advanced age, longer diabetes duration, elevated FPG, higher HbA1c, increased serum UA and reduced eGFR are independent determinants of DPN. The tight association between age and DPN accords with prior epidemiological data.³² Likewise, disease duration is a well-established risk factor: each additional decade of diabetes raises DPN probability by 39%.³³

Persistent hyperglycemia saturates neuronal hexokinase, forcing glucose into the polyol pathway where aldose reductase reduces it to sorbitol at the expense of NADPH. The resulting fall in intracellular NADPH disrupts the $\text{NADP}^+/\text{NADPH}$ redox couple, fueling oxidative stress.³⁴ Because sorbitol cannot freely cross cell membranes, its intracellular accumulation creates osmotic imbalance, drives passive efflux of inositol and depletes the precursor required for phosphatidylinositol synthesis and Na^+/K^+ -ATPase activity; the ensuing bioenergetic failure underlies progressive nerve dysfunction.³⁵

HbA1c integrates ambient glycaemia over the erythrocyte lifespan; its elevation denotes chronic metabolic dysregulation. Sustained hyperglycemia activates not only the polyol cascade but also the protein-kinase-C (PKC) axis and advanced glycation end-product (AGE) formation, amplifying oxidative injury and sustaining low-grade inflammation within peripheral nerves.³⁶ Consequently, higher HbA1c correlates with increased neuropathic risk, whereas intensive glycemic control significantly curbs DPN incidence and progression.³⁷

UA amplifies inflammatory cascades by activating multiple pro-inflammatory pathways; elevated UA levels can precipitate tissue ischemia and impair peripheral nerve function, thereby fostering the onset and progression of chronic disorders and are closely linked to the development of diabetic microvascular complications.³⁸ Concomitant glucose dysmetabolism, oxidative stress, and inflammatory injury affect both glomeruli and peripheral nerves, while declining renal function allows uremic toxins to accumulate, further exacerbating nerve damage and increasing the risk of DPN.³

In summary, serum CCR2 and IDO1 demonstrated certain discriminative value for DPN; however, several limitations remain in this study. First, the cross-sectional design precludes determining whether elevated serum CCR2 and IDO1 levels are the cause or consequence of nerve injury, and prospective studies are required to validate whether they predict the onset or progression of DPN. Second, the single-center data source may limit external validity. Moreover, the lack of racial and geographic diversity means the study population cannot represent the characteristics of the overall T2DM population, potentially overestimating the effect size of the biomarkers. Third, nerve conduction studies primarily reflect large-fiber nerve function and may miss early small-fiber lesions; therefore, the correlation between serum CCR2/IDO1 and small-fiber neuropathy remains to be determined. Furthermore, this study lacked functional validation of CCR2 and IDO1, with no *in vitro* cellular experiments or *in vivo* animal models conducted, leaving mechanistic insights into the

specific roles of CCR2 and IDO1 in DPN fragmented. Thus, large-scale prospective cohort studies and functional investigations are warranted to integrate and extend these findings.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Statement

This study involving human participants was conducted in accordance with the Declaration of Helsinki and received ethical approval from the Cangzhou Hospital of Integrated TCM-WM HEBEI (Approval Number: CZX2024-KY-107.1). Due to the retrospective nature of the research utilizing biobank-stored serum samples, informed consent was waived by the approving institution. All data were handled with strict confidentiality to ensure the anonymity of participants.

Author Contributions

Yubin Liu: Conceptualization, Investigation, Methodology, Project administration, Resources, Funding acquisition, Writing – review & editing. Qiaoe Yang: Data curation, Formal analysis, Investigation, Software, Supervision, Validation, Visualization, Writing – original draft. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

No potential conflict of interest was reported by the authors.

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