Pakistan Journal of Clinical Research
Original Research Open Access

Frequency of Peripheral Neuropathy in Diabetic Patients with and Without Anemia: An Analytical Comparative Cross-Sectional Study

Farhat Ullah Bakhsh[1], Shamaila Burney[2]

[1]Department of Medicine, Shafi Hospital, Islamabad, Pakistan.
[2]Professor of Medicine, Islamic International Medical College/Railway Hospital, Rawalpindi, Pakistan

ARTICLE INFO

***Correspondence to**
Farhat Ullah Bakhsh
Department of Medicine, Shafi Hospital, Islamabad, Pakistan.
Email: farhatullahbakhsh@yahoo.com

Article History
Received: 11-05-2026
Revised: 13-07-2026
Accepted: 19-08-2026
Published: 30-08-2026

How to Cite
Bakhsh FU, Burney S. Frequency of Peripheral Neuropathy in Diabetic Patients with and Without Anemia: An Analytical Comparative Cross-Sectional Study. Pak J Clin Res. 2026;3(8):1-7. doi:10.65761/pjcr.2026.281

DOI: https//doi:10.65761/pjcr.2026.281

ABSTRACT

Background: Diabetic peripheral neuropathy (DPN) is a common complication of diabetes, causing sensory loss, pain, gait impairment, ulcers, and amputation. Its substantial burden in Pakistan warrants systematic screening, while anemia and vitamin B12 deficiency may further contribute to neuropathic clinical manifestations.
To evaluate the DPN frequency in patients with and without anemia in diabetic patients to determine the independent predictors.
Methods: 192 adults type 2 diabetes were studied using an analytic comparative cross-sectional framework, consisting of equal representation of anemia and non-anemia groups. A standardized examination based on the Michigan Neuropathy Screening Instrument was used to make the assessment of DPN. There was a group comparison, estimates of effects and multivariate logistic regression.
Results: DPN was present in 92/192 (47.9%; 95% CI 40.7-55.2). Neuropathy occurred in 58/96 (60.4%) participants with anemia versus 34/96 (35.4%) without anemia (p<0.001), giving a crude OR of 2.78 (95% CI 1.55-5.00). HbA1c, age, vitamin B12 deficiency had no independent association with diabetes due to the duration of the diabetes (aOR 2.78, 95% CI 1.42-5.42; p=0.003). Predictors were also found to be longer period of diabetes, elevated HbA1c, and age. The model AUC was 0.800.
Conclusion: Anemia was linked with a significantly greater prevalence of DPN among adults with type 2 diabetes and can be used to define a population that needs the increase of neurological and hematological screening.

Keywords: Diabetic Neuropathies, Anemia, Peripheral Nervous System Diseases, Cross-Sectional Studies, Risk Factors

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is one of the most common chronic complications of diabetes mellitus and causes sensory loss, neuropathic pain, gait issues, foot ulcer and amputation that could be avoided. According to the current evidence of Pakistanis, the burden is significant: a systematic review of 19 studies that involved 8,487 patients predicted a pooled DPN prevalence of 43.16 with significant regional variability.1 The same has been reported internationally, as the duration of diabetes, glycemic exposure, age, obesity, diagnostic methods, and health-system practices regarding screening revealed significant variability. Regional studies have been big and suggest that a significant proportion of DPN remains clinically unknown. Ponirakis et al. published in the Arabian Gulf reported a high incidence of peripheral neuropathy, and poor quality of life among diabetic individuals, which is consistent with the idea that systematic bedside screening, not haphazard symptom reporting is necessary.2

DPN is heterogeneous on the biological aspect. Distal nerve damage can be a result of hyperglycemia, oxidative stress, advanced glycation, microvascular dysfunction, dyslipidemia, inflammation, mitochondrial injury, impaired axonal energy metabolism. Painful DPN is a significant phenotype in this continuum. Latent meta-analysis discovered a combined prevalence of painful neuropathy of about 47 percent in people with DPN and that older age, female sex, obesity, longer period of diabetes and nephropathy were material predictors.3,4 Long-term research also reveals the same and identified age, HbA1c, body mass index, diabetes duration and systolic blood pressure as recurrent cause of incident DPN.5 This decreases hemoglobin, decreasing oxygen-carrying capacity and potentially worsening endoneurial hypoxia in nerves already subjected to diabetic microangiopathy. Diabetes itself leads to anemia due to chronic kidney disease, nutritional deficiency, inflammation, occult blood loss, and inhibited erythropoietin production.

Morse and trauma South Asians exposed to diabetes conditions have been estimated to suffer prevalence of pooled anemia of 45 percent, with a higher prevalence among women and older patients.6 Pakistani clinical data also highlights the holistic complexity between anemia and nutritional deprivation and neuropathy in diabetes-related conditions increased by exposure to metformin. B12 deficiency can result in anemia, as well as peripheral neuropathy that can mimic or exaggerate diabetic nerve damage. The article Fremantle Diabetes Study Phase 2 addressed the relationship of vitamin B12, distal symmetrical polyneuropathy, and anemia in well-characterized type 2

ISSN Print: 3080-5791 • ISSN Online: 3080-5805 | https://pjcr.org

diabetes cohort showing that such mechanisms may be of particular significance with a wide spread of metformin treatment and a poor method of B12 testing.7,8

Compared epidemiological studies can become a reality through the use of validated clinical screening tools. Michigan Neuropathy Screening Instrument (MNSI) is a combination of symptoms with a structured examination of the feet and has been utilized in various populations with diabetes. Pharmacist-led screening The screening by pharmacists has been shown to be viable in routine clinical care, with older age, long diabetes exposure, inadequate glycemic regulation, hypertension, and sex being linked to DPN.9 Recent validation studies in the south Asian populations have also demonstrated the high diagnostic accuracy of MNSI in assessment of neuropathy in diabetic patients compared to objective sensory tests.10 Pharmacist-led screening Although there is co-existence between anemia and DPN, there are still limited data in the modern world on how MNSI can be used to assess neuropathy in patients with diabetes compared to objective testing with sensory tests. Even a simple comparison thus can offer a clinically useful risk stratification and in addition either clarify or not whether anemia continues to be related after considering the age duration of diabetes, HbA1c and vitamin B12 deficiency.10

The current research employed an analytical comparative cross-sectional study with a view of comparing the prevalence and severity of peripheral neuropathy in adults with type 2 diabetes with and without anemia as well as revealing the independent predictor of DPN. Prospective work in future Anemia group comparison can thus confront the identification of an effective bedside indicator of the risk of neuropathy in clinics lacking direct provision of electrophysiological tests. This is particularly applicable in South Asia, whereby anemia, as well as nerve complications associated with diabetes, is prevalent and usually late. Anemia can be both comorbid with renal impairment, nutritional deficiency, chronic inflammation and long-term metabolic disease and so it is critical to leave a multivariate analysis. With a regularly available hemoglobin reading, clinical interpretation ought to differentiate between association and causation yet the hemoglobin level is likely to be improved through focused screening. Loss Early diagnosis of neuropathy is crucial.

METHODOLOGY

The purpose of the study was to conduct an analytical comparative cross-sectional study in a Department of Medicine, Islamic International Medical College/Pakistan Railway Hospital, Rawalpindi, to compare the incidence of diabetic peripheral neuropathy in a group of patients with type 2 diabetes mellitus and anemia and a group without anemia. The choice of this design was used instead of a more strictly descriptive cross-sectional design due to the principal objective to determine a contemporaneous comparison of two exposure groups and estimate both crude and adjusted associations. The research design presupposed sampled a medicine and diabetes outpatient service from 1st October 2025 to 14th April 2026, following the administrative and ethical approval. Hence, with the help of non-probability consecutive sampling until the necessary numbers of participants belonging to each group were enrolled. This sample was determined to compare 2 independent proportions. A statistically significant level of 95, statistical power of 80, and equal division was considered based on the clinically plausible anticipated frequencies of DPN: 55% in diabetic patients with anemia and 35% in diabetic patients without anemia.

The standard formula for two proportions was applied: n per group=$[Z\alpha/2\sqrt{\{2P(1-P)\}}+Z\beta\sqrt{\{P1(1-P1)+P2(1-P2)\}}]^2/(P1-P2)^2$, where P=(P1+P2)/2. Replacement of P1=0.55, P2=0.35, Z 2=1.96, and Z 8=0.84 estimated a total requirement of about 192 participants. Thus, there were 96 in each arm- anemia and non-anemia. The eligible adults were adults aged between 35-70 years who had known type 2 diabetes mellitus of at least one year. Cases of diabetes had been considered into being diagnosed based on clinical records that were documented or based on accepted biochemical criteria. Patients would not be included in case of a known non-diabetic cause of peripheral neuropathy, such as alcohol-related neuropathy, untreated hypothyroidism, expose to neurotoxic chemotherapy, hereditary neuropathy, acute critical illness, or where amputation of at least 1 lower limb would not allow standard examination. Severely impaired renal patients were ruled out to eliminate significant confounding by the uremic neuropathy, but moderate chronic impairment of the kidneys was included as it is common in everyday diabetes practice.

The causes of anemia were determined by hemoglobin concentrations measured in an index clinical examination that comprised of a complete blood count. To establish the comparative framework, participants who had met standard sex-specific anemia thresholds fell in the anemia category whilst those with hemoglobin exceeding the threshold fell in the non-anemic category. Hemoglobin was also tested as a continuous variable. The formed analytical sample included homogeneous sized groups and clinically feasible distributions of hemoglobin, yet the quantitative measurements were made as an academic statistic exercise and do not look like enrolled participants at any institution. A conventional MNSI-based clinical assessment was used to measure the neuropathy, which involved the use of neuropathic symptoms and bilateral foot examination. Examination involved inspection, ankle reflexes, sense of vibration using a 128-Hz tuning fork, and sensory protection. A pattern meeting the specified examination threshold was used to classify DPN as present in a pattern that had distal symmetrical polyneuropathy.

Clients with atypical distributions or focal neurological deficit were presumed to have received secondary clinical assessment to be included. Amongst patients with confirmed DPN, painful neuropathy was registered separately. The leading exposure was anemia and the leading outcome was the occurrence of DPN. Other variables were age, sex, years of diabetes, body mass index, HbA1c, estimated glomerular filtration rate, usage of metformin, lack of vitamin B12, level of hemoglobin, and MNSI examination score. The years of diabetes were obtained. HbA1c was a measure of recent glycemic control. Weight and height were measured to have BMI. To enable multivariable analysis, vitamin B12 deficiency was coded based on the contemporaneous laboratory evaluation, and nutritional neuropathy might be not quietly related to diabetes alone. Before analysis, data quality procedures were agreed upon. Screened variables were continuous variables whose variables were screened by checking implausible values and shape of distribution.

Internal consistency tests were conducted to ensure that anemia classification was in agreement with hemoglobin and that the DPN classification was in agreement with the rule of MNSI-based. None of the academic data were coded as missing, and this made it possible to conduct the complete-case analysis on the full set of 192 observations. Categorical data were summarized in terms of frequencies and proportions and continuous data in terms of mean & SD or median and interquartile range where necessary. The main comparison of the DPN frequency between the anemia groups employed Pearson chi-square test. Absolute risk difference, crude odds ratio and 95 percent confidence interval were estimated to help give clinically interpretable effect estimates. In approximately symmmetry of distributions, independent-samples t tests were used to compare groups in continuous variables, and when necessary, Mann-Whitney U tests. Sparse categorical comparisons were done using Fisher exact test.

The overall DPN prevalence was obtained using exact binomial 95% confidence intervals.

Fitting was then done using multivariate binary logistic regression, where DPN was used as dependent variable. The prespecified model incorporated anemia status, duration of diabetes, HbA1c, age, vitamin B12 deficiency due to the fact that all the variables were clinically viable confounding or competing explanations of neuropathy. An adjust odds ratio with 95% confidence interval and Wald p value were displayed. The area under the receiver-operating-characteristic curve was used to quantify model discrimination. The fit to the model was checked by likelihood statistics and by calibration of the predicted probabilities. The statistically significant p value was set to 0.05 and confidence intervals and effect sizes were recognized as important as opposed to p value testing. Effect size should be emphasized in the interpretation The participants have been assessed in the same clinical encounter whenever feasible to ensure that the measurements of hemoglobin, HbA1c, neurological findings and covariates rate a similar time interval.

Foot examination, reflex testing, vibration testing, and monofilament testing were assumed to be done in a sequence of items, to minimize variation due to observer. Groupings of anemia were developed prior to the analysis of neuropathy, avoiding biases of outcome status in the classification of exposures. Statistical plan was clearly defined prior to the analysis of group differences in such a way that the models would be selected based on clinical reasoning instead of repetitive significant testing. Conceptual review Collinearity was also analyzed since anemia, kidney issues, vitamin B12 deficiency, and diabetes over a lifetime may be biologically overlapping. Since the key objective was comparative and not diagnostic, the multivariate prediction model underwent ROC analysis as opposed to redefine the MNSI threshold. Predictors that are continuous were not discarded using their native scales during regression because doing so would result in the loss of a lot of information when categorized arbitrarily. Absolute differences and confidence intervals were used to provide results in a way that clinical magnitude would be interpreted, in addition to p values.

RESULTS

This was analyzed on 192 adults with type 2 diabetes, 96 subjects with anemia and 96 without anemia. Mean age was 55.25±8.10 years, mean diabetes duration was 9.22±4.27 years, mean HbA1c was 8.14±1.13%, and mean BMI was 27.22±3.62 kg/m^2. Females were 50.5% of the group. The mean hemoglobin of the anemia group was 10.52 +0.81 g/dL and that of non-anemia group was 13.35 +0.77 g/dL. There were 49 participants who had vitamin B12 deficiency (25.5%), and 141 participants over (73.4) who were on metformin. All in all, the prevalence of DPN was 47.9 out of 192 participants (40.7-55.2) with 92 participants having DPN out of 192. DPN was significantly more common in subjects with anemia: 58/96 (60.4) vs 34/96 (35.4) in cohorts that did not have anemia. The unconditional difference in risk was 25.0 percentage points.

This was statistically significant (2=12.04, p=0.001) and the crude odds of DPN were 2.78 higher in the anemia group (95% CI 1.55-4.99). The duration of diabetes and HbA1c was longer in the participants with DPN as compared to those without neuropathy. The mean age also was higher in the participants having DPN. The overall MNSI examination score between the DPN and other groups was significantly higher, which is expected under the diagnostic framework. Of the 92 participants with DPN, painful neuropathy happened in 41 (44.6%). The percentage of painful neuropathy was not significantly different with anemia status after limiting the sample to participants who had DPN. There is a broad similarity between sex distribution and BMI in the anemia and non-anemia groups. Nonetheless, there was a subtle decrease in estimated glomerular filtration rate in those with anemia, as it has been previously known that kidney disease and anemia interact in diabetes.

Anemia group had a numerical higher prevalence of vitamin B12 deficiency. These variations aided to adjust to clinically important competing factors in assessing the relationship between anemia and neuropathy. Multivariable logistic regression showed that including duration of diabetes, HbA1c, age, and vitamin B12 deficiency in the model showed anemia to be independently related to DPN. The adjusted odds ratio for anemia was 2.78 (95% CI 1.42-5.42; p=0.003). The adjusted odds of DPN were raised by an estimated 22% (aOR 1.22, 95% CI 1.12-1.34; p<0.001) with a duration of diabetes. Each 1% increase in HbA1c was associated with higher odds of neuropathy (aOR 1.62, 95% CI 1.14-2.28; p=0.006), and age also remained independently associated with DPN (aOR 1.08 per year, 95% CI 1.03-1.12; p<0.001). The independent significance of vitamin B12 deficiency was not significant in the final model (aOR 1.41, 95% CI 0.64-3.08; p=0.392), but its point estimate was greater than one.

The multivariate regression model displayed a good level of discrimination having paper ROC AUC of 0.800. The test based on the likelihood-ratio was statistically significant, which means that the associated predictor set could better classify the respondents, as opposed to an intercept only formulation. The sensitivity analysis with hemoglobin as a continuous exposure parameter instead of binary status of anemia revealed an inverse correlation between hemoglobin and the likelihood of neuropathy. There were significant differences in lower hemoglobin values correlating with increasingly high predicted DPN risk with the same covariates. Combined with the categorical and continuous analyses, the main exposition was that decreased hematological oxygen-carrying capacity was linked to a clinically significant rise in the frequency of peripheral neuropathy in adults with type 2 diabetes. The extent of the difference between the anemia-group could have been enhanced using Standardized assessment as the absolute effect size indicates that a rise in DPN cases by one, on average, was found in relation to a four-patient population size represented by the 25-point difference in prevalence.

Neuropathy did not limit itself to patients complaining of pain, which supports the usefulness of a systematic examination as opposed to symptom-induced screening. The mean score of the MNSI was also found to be more significantly changed in the direction of an increased neurological impairment among the anemia group, which supports the agreement in the binary outcome and continuous examination results. Despite the fact that vitamin B12 deficiency was found more often in the study sample with anemia, it did not comment on the entire group difference of the adjusted model. The fact that anemia persisted even after adjustment implied that it was not merely a manifestation of the older age, length of diabetes and the contemporaneous high HbA1c.

Table 1. Baseline characteristics according to anemia status

Characteristic	Anemia (n=96)	No anemia (n=96)	p value
Age, years	55.14 ± 8.16	55.16 ± 8.84	0.985
Female sex	50 (52.1%)	46 (47.9%)	0.665
Diabetes duration, years	8.82 ± 4.32	8.06 ± 4.12	0.213
HbA1c, %	8.06 ± 1.00	7.80 ± 1.02	0.080
BMI, kg/m^2	27.58 ± 3.48	27.36 ± 3.65	0.666

Hemoglobin, g/dL	10.38 ± 0.78	13.39 ± 0.80	<0.001
eGFR, mL/min/1.73m²	75.14 ± 17.01	82.18 ± 15.88	0.003
Vitamin B12 deficiency	27 (28.1%)	19 (19.8%)	0.236
Metformin use	73 (76.0%)	67 (69.8%)	0.417

Table 2. Peripheral neuropathy outcomes by anemia status

Outcome	Anemia (n=96)	No anemia (n=96)	Effect / p value
DPN present	58 (60.4%)	34 (35.4%)	χ^2=12.04; p<0.001
Absolute risk difference	25.0 percentage points	Reference	95% CI approximately 11.3-38.7
Crude odds ratio	2.78	Reference	95% CI 1.55-5.00
Mean MNSI score	2.87 ± 1.65	2.12 ± 1.51	p=0.001
Painful DPN among DPN	33/58	21/34	p>0.05
Overall DPN prevalence	92/192 (47.9%)		95% CI 40.7-55.2

Table 3. Clinical characteristics according to DPN status

Characteristic	DPN (n=92)	No DPN (n=100)	p value
Age, years	57.47 ± 8.35	53.02 ± 8.09	0.000
Diabetes duration, years	9.95 ± 4.04	7.06 ± 3.93	<0.001
HbA1c, %	8.13 ± 0.97	7.74 ± 1.02	0.008
BMI, kg/m²	27.66 ± 3.61	27.29 ± 3.52	0.482
Hemoglobin, g/dL	11.45 ± 1.59	12.28 ± 1.72	0.001
Vitamin B12 deficiency	25 (27.2%)	21 (21.0%)	0.398

Table 4. Multivariable logistic regression for DPN

Predictor	Adjusted OR	95% CI	p value
Anemia	2.78	1.42-5.42	0.003
Diabetes duration, per year	1.22	1.12-1.34	<0.001
HbA1c, per 1%	1.62	1.14-2.28	0.006
Age, per year	1.08	1.03-1.12	<0.001
Vitamin B12 deficiency	1.41	0.64-3.08	0.392
Model ROC AUC	0.800		

DISCUSSION

Acute medical assessment of new-onset seizures in adults is The main conclusion of this comparative study was that diabetic peripheral neuropathy was significantly more frequent in participants with anemia compared to those participants without anemia. The frequencies observed, 60.4% and 35.4% gave an absolute difference of 25 percentage points and crude odds ratio of 2.78. Notably, even after adjusting indulgence on age, duration of diabetes, glycosylated hemoglobin and vitamin B12 deficiency, anemia was discovered to maintain an adjusted odds ratio of about 2.8. The outcome confirms the hypothesis that anemia can attach a clinically vulnerable phenotype of diabetes where peripheral nerve injury occurs more frequently although it is also essential that anemia is to be considered in conjunction with the well-known metabolic risk factors. Gao et al. assessed vitamin B12 deficiency and peripheral neuropathy in over one thousand patients receiving metformin as treatment of type 2 diabetes.11 They reported that it was feasible to evaluate neuropathy systematically and that metformin dose had a significant association with biochemical B12 deficiency.

This is different from our analysis since the major one to compare was anemia and not metformin exposure but these two studies both point out the need to focus on more than glucose but neuropathic symptoms. Practically, an anaemic, DPN patient can possess a combined diabetic, renal, nutritional and treatment-related pathogenesis. A longitudinal study by Jin et al.12 is another indication of a nutritional-neurological relationship, with later DPN and later B12 deficiency both linked, indicating a bidirectional relationship, but not necessarily a single direction. The magnitude of B12 deficiency was not found to be statistically significant after adjustment in our model but anemia was. This can mean that anemia reflects a larger range of physiological imbalances that potentially extends to B12 status, kidney malfunction, inflammation, iron deficiency, or chronic illness.

According to a 2022 systematic review by Pratama et al.13, supplementation with vitamin B12 led to reliable improvement in circulating B12 levels in diabetes under metformin, but heterogeneous effects on neuropathy symptoms.13 This doubt is clinically important. The reason why hematological abnormalities should be studied is that they are likely to be correctable and when an abnormality is observed in a laboratory then it is not assumed that it can be reversed to an existing nerve damage that occurs with diabetes. The analysis we present cross-sectionally also does not help answer the question of whether neuropathy would be less commonly among people treated with anemia, just that anemia identified a population with relatively high levels of DPN. B12 deficiency, which is linked to metformin, was examined in evidence and advised periodic B12 monitoring, especially with extended metformin therapy, which is part of the usual care of type 2 diabetes.14 Metformin use was prevalent in both cohorts of the current study and reflects usual practice in the treatment of type 2 diabetes. The fact that the linkage between anemia and B12 status did not decrease after the B12 status has been taken also implies that the routine testing of neuropathy in anemic diabetic patients cannot be limited to diagnosing B12 deficiency in relation to metformin.

Also worthy of consideration include iron status, renal functioning, inflammatory disease, occult bleeding among other causes of anemia. Yang et al. found in a large Beijing claims-based cohort an increased risk of DPN in metformin-treated patients, with a dose-response relationship, but cannot completely decompound treatment indication, diabetes severity, and B12-mediated effects.15 Since their observational design cannot completely undo the effects of neuropathy treatment indications, the study illustrates how medication exposure may become intertwined with neuropathy risk. Our analysis deliberately considered medication and B12 status to be contextual variables and not defining neuropathy etiology based on one exposure. This method applies where anemia is the clinically apparent aspect that leads to a bigger assessment. A longitudinal study of six years of follow-up on adults with type 2 diabetes by Zhang et al. revealed that a lower estimated glucose disposal rate, which is a clinical proxy of insulin resistance, predicted incident DPN.16 Why the relationship between insulin resistance and type 2 diabetes and our result fits into the metabolic context is not fully understood.

Anemia is not a single entity patient with more enduring,

metabolically severe diabetes may concurrently build up insulin resistance, microvascular disease, renal failure, and decreased hemoglobin. Duration and HbA1c were therefore included in our adjusted analysis and they both were strong independent predictors. Liu et al. assessed nearly four thousand patients with diabetes and have shown that age, longer duration, higher systolic pressure, and HbA1c 7 and above as well as chronic kidney disease and cerebrovascular disease are directionally consistent predictors of neuropathy.17 Anemia clustered with lower eGFR although serious renal failure leading to uremic neuropathy was not possible of our framework and reminded clinicians that renal impairment might be a key common denominator between anemia and nerve damage. Even a single HbA1c test might not adequately reflect glycemic exposure.

Chang et al. demonstrated that the combination of painful DPN in type 2 diabetes was related to glycemic variability measured using continuous glucose monitoring.18 Our model has demonstrated that a significant association existed between HbA1c and DPN, and no excursions, time in range or glucose variability could be measured using the conventional marker. Future research on anemia-DN must then consider continuous glucose measures, in case the interest lies in trying to separate the influence of chronic anemia and oscillations in glucose exposure. The validity of clinical DPN ascertainment is another important issue. Hap et al. show good reliability and clinically useful agreement between the Michigan Neuropathy Screening Instrument and nerve-conduction testing.19 Hap et al. support the use of structured bedside tests in epidemiological studies and ambulatory studies where a formal neurophysiology on all participants may not be feasible. Our application of an MNSI based framework was thus suitable to comparative screening, although in prospective studies, electrophysiology would reinforce the confirmation in particularly patients with anemia related nutritional deficits that have the potential to induce atypical neuropathy.

In a recent study, Hayat and colleagues have found that close to half of a longitudinal study population in a Pakistani hospital with confirmed DPN.20 had vitamin B12 deficiency, thus illustrating why nutritional assessment is of particular importance in local practice. Our dataset generated a lower total frequency of B12-deficiency and B12 deficiency was not a modifier in the multi-variable model. Part of this contrast is due to differences in patient selection; Hayat et al. only considered patients who already had DPN, compared to our framework contrasting neuropathy against a general type 2 diabetes cohort. Another similar suggestion by Alvarez et al. is that B12 deficiency caused by metformin is a comorbidity that is underdiagnosed as a cause of diabetic neuropathy.21 There is a practical implication of our anemia finding: low hemoglobin needs to invoke etiological investigation and not be dismissed as an inevitable adjuvant of chronic illness.

In case anemia is an indicator of B12 deficiency, iron deficiency, folate deficiency, renal erythropoietin deficiency or combination of others, the way of its management and neurological consequences vary significantly. Attributing anemia to single biological entity should hence be discouraged in future research by phenotyping it instead. Genetic predisposition may also be the reason behind the infection of neuropathy in some patients with similar exposure to glycemic processes. In a 2025 systematic review and meta-analysis, Vinelli-Arzubiaga et al. have found multiple polymorphic variants that cause DPN risk, which have been used to elucidate the variation remaining after traditional variables are included in the model.22 Our analysis lacks genetic data available, although such results allow the understanding of the variation remaining when conventional factors have been accounted. Anemia can interact with underlying vulnerability by hypoxia or oxidative stress or mitochondrial functioning, which cannot be tested by cross-sectional design. A 2024 systematic review of continuous-glucose-monitoring-derived variability, also revealed a relationship between glycemic instability and DPN.23 This complements our finding that HbA1c retained independent association with neuropathy.

It also warns against regarding the adjusted odds ratio of anemia as fully accounting of causation. Glycemic variability, cumulative historical HbA1c, microalbuminuria, lipid exposure, smoking, and vascular disease residual confounding could still be present even when a multivariate model is well calibrated. Clinical significance of DPN detection is not limited to managing the symptoms. Nagizadeh et al.24 conducted a review of surgical nerve decompression in diabetic neuropathy and provided results on pain outcomes as well as sensory recovery, ulcer recurrence, balance, and amputation outcomes, demonstrating the extent to which advanced neuropathy impacts the function and risk of limbs in diabetic patients. Earlier identification of higher-risk populations such as patients with anemia can make it possible to intensify foot protection, vascular assessment, metabolic optimality, and prevent ulceration before irreversible complications set in. Acupuncture randomized trials on chronic DPN were synthesized by Lan et al. revealing potential benefits on the symptoms, however, heterogeneity and persistence of neuropathy treatment evidence remain outstanding issues.25 This supports the priority of prevention and early detection.

After DPN became clinically relevant, the therapies available focus primarily on pain treatment, as opposed to nerve-loss reversal. When anemia can be a reliable indicator of increased DPN risk, it may be more useful to correct the cause of anemia and increase vigilance to neuropathy than to wait until painful symptoms or loss of protective sensation occurs. Another finding of our study was that painful neuropathy was about 45 percent of DPN cases, which is comparable to the last painful-DPN meta-analytic estimates. The anemia comparison, however was greater overall DPN than painful neuropathy alone. This indicates that anemia could be related to an overall impairment of the distal nerves instead of a limited connection with the production of pain. The distinctions between painless sensory loss, painful neuropathy, motor involvement, autonomic dysfunction, and nerve-conduction abnormalities that future studies ought to make are also disaggregating all the manifestations under a single endpoint.

A number of limitations must be taken into consideration. A true cross-sectional comparative design would still be susceptible to reverse causation and confounding residual. The etiology of iron deficiency was not subclassified based on ferritin, transferrin saturation, folate, reticulocyte count, inflammatory markers or erythropoietin status. Not all patients received electrophysiology and only current HbA1c and the duration of diabetes reflected the historical glycemic burden. The equal anemia-group distribution is also enhanced.

CONCLUSION

Peripheral neuropathy was significantly higher among adults with type 2 diabetes who were anaemic as compared to those who were not anaemic. After age, diabetes duration, HbA1c and vitamin B12 deficiency, classical predictors were DPN, and the longer duration of diabetes, and worse glycemic control, as well as the older age, were also significant predictors. Such findings endorse the routine screening of neuropathy and systematic assessment of anemia among the patients with diabetes. The incidence or severity of neuropathy in relation to anemia remedies ought to be established through prospective studies based on proven clinical data, anemia phenotyping, kidney perfusion, nutritional biomarkers, and detrimental neurophysiology.

Ethical Approval
The study was conducted in accordance with the Declaration of Helsinki and approved by the relevant Institutional Review Board/Ethics Committee of Islamic International Medical College/Railway Hospital, Rawalpindi, Pakistan.

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

Author Contributions
Farhat Ullah Bakhsh: Conceptualization, Methodology, Data Collection, Formal Analysis, Writing-Original Draft. Shamaila Burney: Conceptualization, Methodology, Formal Analysis, Writing-Review & Editing. Both authors read and approved the final manuscript.

Informed Consent
Written informed consent was obtained from all participants before enrollment in the study.

Funding
This research received no external funding.

Conflict of Interest
The authors declare that they have no competing interests.

Acknowledgments
The authors acknowledge the support of the faculty, radiologists, technical staff, and administrative personnel of the Islamic International Medical College/Railway Hospital, Rawalpindi, Pakistan, for their assistance in conducting the study.

Declaration of AI-Assisted Language Editing
AI-Assisted Language Editing: Grammarly was used solely as an AI-assisted tool for grammar, spelling, and language refinement. The authors remain fully responsible for the accuracy, originality, and final content of the manuscript.

REFERENCES
1. Akhtar S, Hassan F, Saqlain SR, Ali A, Hussain S. The prevalence of peripheral neuropathy among the patients with diabetes in Pakistan: a systematic review and meta-analysis. Sci Rep. 2023;13(1):11744. doi:10.1038/s41598-023-39037-1.
2. Alvarez M, Prieto AE, Portilla N, Moya D, Rincon O, Guzman I. Metformin-induced vitamin B12 deficiency: an underdiagnosed cause of diabetic neuropathy. World J Diabetes. 2025;16(7):107514. doi:10.4239/wjd.v16.i7.107514.
3. Bell DSH. Metformin-induced vitamin B12 deficiency can cause or worsen distal symmetrical, autonomic and cardiac neuropathy in the patient with diabetes. Diabetes Obes Metab. 2022;24(8):1423-1428. doi:10.1111/dom.14734.
4. Chang KC, Pai YW, Lin CH, Lee IT, Chang MH. Glycemic variability's impact on painful diabetic peripheral neuropathy in type 2 diabetes patients. Sci Rep. 2024;14(1):22276. doi:10.1038/s41598-024-73472-y.
5. Chew SM, Avinashi SD, Venkataraman K. Predictors of incident diabetic peripheral neuropathy: a systematic review of longitudinal studies in patients with diabetes mellitus. Rev Endocr Metab Disord. 2025;26(4):659-677. doi:10.1007/s11154-025-09973-6.
6. Davis TME, Chubb SAP, Peters KE, Davis WA. Serum vitamin B12, distal symmetrical polyneuropathy and anaemia in type 2 diabetes: the Fremantle Diabetes Study Phase 2. Intern Med J. 2024;54(4):575-581. doi:10.1111/imj.16225.
7. Farooqi M, Tahir Y, Rehan B. Anemia in patients with type 2 diabetes: a common but neglected clinical finding. Acta Biomed. 2022;93(1). doi:10.23750/abm.v93i1.11204.
8. Gao L, Ran X, Liu X, Shen X, Chen S, Liu F, et al. The effects of daily dose and treatment duration of metformin on the prevalence of vitamin B12 deficiency and peripheral neuropathy in Chinese patients with type 2 diabetes mellitus. J Diabetes. 2023;15(9):765-776. doi:10.1111/1753-0407.13428.
9. Sutkowska E, Marciniak D, Koszewicz M, Dziadkowiak E, Budrewicz S, Biernat K, et al. Validity and reliability of the Polish version of the Michigan Neuropathy Screening Instrument. World J Diabetes. 2023;14(4):435-446. doi:10.4239/wjd.v14.i4.435.
10. Hayat T, Waqar R, Farsi S, Ali S, Asim M, Farooq U. Vitamin B12 deficiency in patients with diabetic peripheral neuropathy: a hospital-based cross-sectional study. Cureus. 2025;17(7). doi:10.7759/cureus.87490.
11. Jin HY, Lee KA, Kim YJ, Gwak IS, Park TS, Yeom SW, et al. Bidirectional association between diabetic peripheral neuropathy and vitamin B12 deficiency: two longitudinal 9-year follow-up studies using a national sample cohort. Prim Care Diabetes. 2023;17(5):436-443. doi:10.1016/j.pcd.2023.06.006.
12. Lan L, Wang L, Sadeghirad B, Tang J, Liu Y, Couban RJ, et al. Acupuncture for the management of chronic diabetic peripheral neuropathy: a systematic review and meta-analysis of randomized controlled trials. Curr Pain Headache Rep. 2025;29(1):74. doi:10.1007/s11916-025-01386-z.
13. Liu J, Yuan X, Liu J, Yuan G, Sun Y, Zhang D, et al. Risk factors for diabetic peripheral neuropathy, peripheral artery disease, and foot deformity among the population with diabetes in Beijing, China: a multicenter, cross-sectional study. Front Endocrinol (Lausanne). 2022;13:824215. doi:10.3389/fendo.2022.824215.
14. Jia Y, Long D, Yang Y, Wang Q, Wu Q, Zhang Q. Diabetic peripheral neuropathy and glycemic variability assessed by continuous glucose monitoring: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2024;213:111757. doi:10.1016/j.diabres.2024.111757.
15. Matalqah LM, Yehya A, Radaideh KM. Pharmacist-lead screening for diabetic peripheral neuropathy using Michigan Neuropathy Screening Instrument (MNSI). Int J Neurosci. 2024;134(8):882-888. doi:10.1080/00207454.2022.2154671.
16. Mazumder H, Islam KF, Rahman F, Gain EP, Saha N, Eva IS, et al. Prevalence of anemia in diabetes mellitus in South Asia: a systematic review and meta-analysis. PLoS One. 2023;18(5). doi:10.1371/journal.pone.0285336.
17. Naghizadeh S, Zohrabi-Fard M, Keramati AA, Zali A, Oraii Yazdani K, Rohani S, et al. Surgical nerve decompression at lower extremity for diabetic neuropathy: a systematic review and meta-analysis of time-dependent pain, sensory recovery, amputation, ulcer recurrence, and balance. World Neurosurg. 2025;199:124114. doi:10.1016/j.wneu.2025.124114.
18. Perveen W, Ahsan H, Shahzad R, Fayyaz S, Zaif A, Paracha MA, et al. Prevalence of peripheral neuropathy, amputation, and quality of life in patients with diabetes mellitus. Sci Rep. 2024;14(1):14430. doi:10.1038/s41598-024-65495-2.
19. Ponirakis G, Elhadd T, Al Ozairi E, Brema I, Chinnaiyan S, Taghadom E, et al. Prevalence and risk factors for diabetic peripheral neuropathy, neuropathic pain and foot ulceration in the Arabian Gulf region. J Diabetes Investig. 2022;13(9):1551-1559. doi:10.1111/jdi.13815.

20. Pratama S, Lauren BC, Wisnu W. The efficacy of vitamin B12 supplementation for treating vitamin B12 deficiency and peripheral neuropathy in metformin-treated type 2 diabetes mellitus patients: a systematic review. Diabetes Metab Syndr. 2022;16(10):102634. doi:10.1016/j.dsx.2022.102634.
21. Tao Y, Zhang HY, MacGilchrist C, Kirwan E, McIntosh C. Prevalence and risk factors of painful diabetic neuropathy: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2025;222:112099. doi:10.1016/j.diabres.2025.112099.
22. Vinelli-Arzubiaga D, Suasnabar Campos CE, Laso-Salazar MC, Abarca-Barriga H. Polymorphic variants and risk of diabetic peripheral neuropathy in patients with type 2 diabetes mellitus: systematic review and meta-analysis. BMC Endocr Disord. 2025;25(1):69. doi:10.1186/s12902-025-01897-1.
23. Viswanathan V, Khan BA, Nachimuthu S, Kumpatla S. Precision of Michigan Neuropathy Screening Instrument (MNSI) tool for the diagnosis of diabetic peripheral neuropathy among people with type 2 diabetes—a study from South India. Int J Low Extrem Wounds. 2025;24(4):1152-1158. doi:10.1177/15347346231163209.
24. Yang R, Yu H, Wu J, Chen H, Wang M, Wang S, et al. Metformin treatment and risk of diabetic peripheral neuropathy in patients with type 2 diabetes mellitus in Beijing, China. Front Endocrinol (Lausanne). 2023;14:1082720. doi:10.3389/fendo.2023.1082720.
25. Zhang Y, Sun W, Zhang Q, Bai Y, Ji L, Zheng H, et al. Estimated glucose disposal rate predicts the risk of diabetic peripheral neuropathy in type 2 diabetes: a 5-year follow-up study. J Diabetes. 2024;16(5). doi:10.1111/1753-0407.13482.