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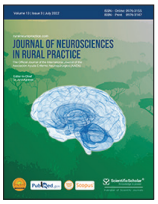

Original Article

Development of risk prediction scores for diabetic peripheral neuropathy patients

Mathukumalli Sai Laxmi[1], Orsu Prabhakar[2]

[1]Department of Pharmacology, Max Institute of Pharmaceutical Sciences, Khammam, Telangana, [2]Department of Pharmacology, GITAM Deemed to be University, GITAM School of Pharmacy, Visakhapatnam, Andhra Pradesh, India.

ABSTRACT

Objectives: Risk prediction scores are important for early diagnosis and treatment of diseases. Diabetic peripheral neuropathy (DPN) is a common complication of type 2 diabetes, but the early diagnosis is challenging. This study developed a risk prediction model for DPN based on modifiable risk factors.

Materials and Methods: The study included 315 type 2 diabetes patients with and without DPN. Demographic, biochemical, and diagnostic data were collected. Multinomial logistic regression analysis was used to identify independent risk factors for DPN.

Results: Hemoglobin% and total red blood cells were identified as independent risk factors for DPN, used to develop a risk prediction score.

Conclusion: The risk prediction score developed in this study can be used by physicians to quickly assess a patient's risk of DPN and select appropriate therapeutic options. Routine monitoring of modifiable risk factors can improve DPN prognosis. Patients stratified by risk scores can better understand their risk and seek appropriate care.

Keywords: Risk prediction, Prediction score, Peripheral neuropathy, Hemoglobin

INTRODUCTION

A risk prediction score is a mathematical formula that calculates the likelihood of a healthcare outcome based on patient risk factors. Risk prediction models have various applications in medicine, public health, and epidemiology.[1] India ranks second worldwide with a prevalence of 10.5–32.2% in the type 2 diabetes population (T2DM) and 26% to 51% of diabetic peripheral neuropathy (DPN).[2]

The early diagnosis of DPN is challenging due to the need for advanced diagnostic tools, thorough clinical examination, and scoring systems, which can be time-consuming for physicians. Electrophysiological tests such as vibration perception threshold (VPT) scores generated by biothesiometers are crucial for objectively diagnosing DPN, but their routine use is impractical for asymptomatic patients or in resource-limited rural areas, making risk prediction models valuable in facilitating early oversight and intervention.[3] Differences in baseline disease risk, disease subtype distribution, and risk factor exposure levels exist due to regional and ethnic diversity.[4] Validated risk prediction models support health-care practitioners in tailoring medical decisions by identifying candidates for intensive preventive interventions or further testing.[5] To the best of our knowledge, available studies in India have identified age, hemoglobin A1C (HbA1c), and hemoglobin (Hb)% among others, as risk factors for DPN, but there is a lack of developed risk prediction models specific to India.[6] This study aimed to investigate clinical characteristics, identify DPN risk factors, and develop risk prediction scores for physicians to stratify patients and prioritize treatment across diverse populations.

MATERIALS AND METHODS

This study, conducted from November 2021 to January 2023 in a Telangana, India tertiary care hospital, obtained prior Ethical Committee approval (Rc. No.MRD/280/2021) and followed the Declaration of Helsinki guidelines. Informed written consent was obtained in both Telugu and English. A sample size of 315 (N) was calculated considering a power of 80%, an absolute precision of 5% (E), confidence level of

***Corresponding author:** Mathukumalli Sai Laxmi, Department of Pharmacology, Max Institute of Pharmaceutical Sciences, Khammam, Telangana, India. msailaxmi@gmail.com

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95%, and a DPN prevalence rate(P) of 25% among Indian diabetic patients and 10% of sample size were added to manage for dropouts or loss in follow-up and calculated using the formula $N = Z^2PQ/E^2$ where Q = 1-P, Z = Z statistic (1.96 at 95% confidence interval), and E = absolute prevalence.

This study included T2DM patients (≥18 years, both genders). Exclusions were type 1 diabetes, <18 years, pregnant/lactating women, other diabetic comorbidities, and non-diabetic peripheral neuritis. Sociodemographic, anthropometric, and diagnostic information was collected. A fasting blood sample (5 mL) was drawn for biochemical analyses. Blood parameters were estimated using the ERBA Chem-7 plus analyzer (One call medical systems, Hyderabad), HbA1C by AGAPPE-MISPAi2 (AGAPPE, India), urinary parameters by URIT-31URINE ANALYZER (micro enterprises, India), and Ankle Brachial Index (ABI) and Tibial Brachial Index (TBI) with a Doppler. Total cholesterol/HDL, LDL/HDL, A/G, and albumin to creatinine ratio were calculated. Patients with T2DM were diagnosed with DPN based on the American Diabetes Association's definition and assessed using Toronto clinical scoring system (TCSS) and VPT scores.[7,8] TCSS score is from 0 to 19. 0–5 score is considered without DPN, 6–8 is mild, 9–11 is moderate, and 12–19 is severe.[9] VPT scores were measured using a Poly-Neuro Digital Biothesiometer (Diabetic Foot Care India Pvt Ltd, India). Score of 0 to 9.5 is without DPN (WDPN), 10 to 15.5 is mild DPN, 16 to 25.5 is moderate DPN and 26 to 50 is severe DPN.

In a study of 1000 patients with diabetes, univariate analysis was performed using SPSS software to identify variables associated with DPN. Variables with $P < 0.05$ were selected for binary logistic regression, while variables with $P < 0.2$ were selected for multinomial logistic regression. Variables with $P < 0.05$ and corresponding regression coefficients (β) were considered. Rankings were assigned based on the lowest β value, with subsequent variables ranked in increasing order to develop risk stratification scores. Independent variables were subcategorized by gender, coded as 0 for the normal range and 1 for the abnormal range, with the midpoint calculated as the reference value. The risk scoring system employed the formula β(m-mref)/B, where B is obtained by multiplying the least β value by 5 (Framingham constant). In this study, B was calculated as 1.66*5 = 8.3. The process was repeated for each variable, assigning a score accordingly. Aggregate scores were used to stratify patients into moderate- and high-risk groups.

RESULTS

Results show 188 of WDPN patients and 127 of DPN patients and males outnumbered the females (160–155). VPT-based stratification of DPN groups are: mild (n = 31), moderate (n = 40), severe (n = 56), and very severe DPN (WDPN) (n = 188). Results of univariate analysis are shown in [Table 1]. Body mass index, triglyceride, and C-reactive protein (CRP) were some of the variables with odds >1. The variables with $P < 0.2$ were Hb%, total red blood cells (RBC), CRP, TCSS, urine creatinine, urine albumin, and ABI, moved to next step. The multinomial logistic regression analysis's final step enables one to comprehend that the variables with $P < 0.05$ were Hb%, total RBC, CRP, and TCSS. [Table 2] shows the equation variables B, m_{ref}, m, and β for each of these predictors along with scores. Hb% had the lowest β value and was assigned rank 1, followed by total RBC (rank - 2), CRP (rank - 1), and TCSS (rank - 3). Gender-specific normal and abnormal ranges were established for these variables. Mid values were calculated with the normal range for each coded as 0 and taken as the reference mid value for substitution in the formula. For example, in our study the least β was 1.66. This is multiplied with Framingham's constant 5 gives the value of B (1.66*5 = 8.3). β regression was −2.279.

If mid value is 8.5, score is given by β (m-mref)/B. Score = -2.279(6.5- 8.5)/8.3 = 0.549. The scores for the other variables were calculated in a similar manner.

Based on the total score obtained, patients can be categorized into either a high-risk group (scores of −3 to −1) or a moderate-risk group (score of 1) for DPN.

DISCUSSION

The prognosis of DPN relies on the identification of significant risk factors and early screening through comprehensive diagnosis. However, diagnostic challenges arise, particularly in remote areas lacking access to sophisticated electro diagnostic equipment.[10]

Risk prediction scores using modifiable risk predictors are crucial in identifying high-risk patients and aiding clinicians in making treatment decisions. Our study found a higher DPN prevalence (40.3%) compared to the national proportion (32.4%), potentially due to diagnostic criteria and sample size differences. Increasing age was found as a significant demographic predictor of DPN, consistent with the previous studies.[11] Age-related axonal injury or demyelination is thought to accumulate molecular and cellular damage over time, contributing to DPN.[12] Our study supported earlier research that uncontrolled hyperglycemia increases the risk of DPN in T2DM, and that glycemic control can slow the progression of DPN.[13]

Our study confirmed previous findings[14,15] that DPN is more prevalent among individuals with dyslipidemia, and that elevated triglyceride levels are associated with a loss in myelinated fiber density, regardless of age, disease duration, or control. Potassium levels were lower in the DPN group, and as reported, hypokalemia was associated with hyperexcitability, pain, and abnormal nerve function, which

Table 1: Biochemical parameters differentiating DPN and without DPN groups – univariate regression analysis.

Biochemical parameter (normal value)	B	S.E.	Wald	df	Sig.	Exp (B)
BMI (kg/m^2)	1.02	0.23	18.40	1	0.81	2.770
FBG	0.32	0.26	1.55	1	0.21	1.38
Hb%	−0.10	0.29	0.05	1	0.005	0.93
Total RBC (mill/cmm)	−0.55	0.41	1.81	1	0.17	0.58
Tch (<200)(mg/dL)	0.51	0.23	4.850	1	0.02	1.67
HDL (30–60)	−0.55	0.24	5.01	1	0.03	0.58
Total ch/HDL	0.38	0.240	2.50	1	0.11	1.46
LDL/HDL	0.49	0.24	4.38	1	0.04	1.64
Blood urea (10–45)	−1.12	0.42	7.32	1	0.007	0.33
K (3.5–5)	−0.48	0.25	3.69	1	0.06	0.62
Total bilirubin (0.1–1.2) (mg/dL)	−0.51	0.25	4.24	1	0.040	0.60
Indirect bilirubin (0.2–0.8)	−0.67	0.25	6.96	1	0.01	0.51
A/G (1–2)	0.66	0.3	4.94	1	0.03	1.94
SGOT (5–40) (IU/L)	−0.88	0.34	6.52	1	0.011	0.42
SGPT (5–36)	−0.82	0.29	7.860	1	0.01	0.44
ACR (mg/g)	0.51	0.23	4.82	1	0.03	1.67
CRP (0.3–1 mg/dL)	1.600	0.300	28.52	1	<0.000	4.95
TCSS	3.3	0.34	96.69	1	<0.000	28.000
Urine creatinine (mg/dL)	1.06	0.24	19.380	1	<0.000	2.89

DPN: Diabetic peripheral neuropathy, BMI: Body mass index, FBG: Fasting blood glucose, Hb%: Hemoglobin, Tch: Total cholesterol, TG: Triglycerides, HDL: High-density lipoproteins, LDL: Low-density lipoproteins, Na: Sodium, K: Potassium, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, AP: Alkaline phosphatase, ACR: Albumin creatinine ratio, CRP: C-reactive protein, TCSS: Toronto clinical scoring system

Table 2: Risk stratification scores and severity grades for DPN patients.

Clinical characteristic	B	Categories	Mid value	Scoring=β(m-mref)/B	Point/rank
Hb%	−2.279	6–11 (1)	8.5	1=−2.2790 (6.5–8.5)/8.3 = 0.549	1
		>12 (0)	6.50 m_{ref}	0	
Total RBC	1.66	4.2–5.9 (0)	5.05 m_{ref}	0	
		>5.9 (1)	2.95	=1.66 (2.95–5.05)/8.3=−0.42	−2
CRP	−1.402	1–3 (0)	2.00 m_{ref}		
		>3 (1)	1.5	=−1.402 (1.50–2)/8.3=−0.0844	−1
TCSS	−1.676	0–5 (0)	2.50 m_{ref}	0	
		6–19 (1)	12.5	=−1.676 (12.50–2.50)/8.3=−2.019	−3

Constant B = 1.66*5 = 8.3; m_{ref} = mid value of the reference range; m = mid value of the category considered. DPN: Diabetic peripheral neuropathy, Hb%: Hemoglobin %, Total RBC: Total red blood cell count, CRP: C-reactive protein, TCSS: Toronto clinical scoring system

have been attributed to injury, inflammation, or neuropathic lesions that reorganize membrane ion channels.[16] Our study found decreased SGOT and SGPT levels in the DPN group, but there was no correlation between DPN and liver function.[16,17] Binary and multinomial regression analysis narrowed down the variables to four: Hb%, total red blood cell count, CRP, and TCSS.

Lower Hb% was related to DPN, and as reported,[18,19] a decrease in red blood cell count impairs their ability to change shape and adapt to the tissue microenvironment, leading to damage in large nerve fibers. CRP induces vascular endothelial factor elevation, altering blood flow in small blood vessels. In addition, it promotes WBC growth, complement activation, and cell death.[20] Urine albumin, beyond representing renal disease, signifies widespread vascular damage throughout the body.[21]

The diagnostic scores of VPT and TCSS showed a strong correlation, suggesting their interchangeability in distinguishing between individuals with and without DPN. Thus, TCSS can be used as an alternative to VPT in areas lacking biothesiometers, although this finding is less commonly reported.

Our study developed risk scores for DPN patients based on Hb%, red blood cell count, CRP, and TCSS. Regularly monitoring these risk factors improves prognosis and prevents unnecessary medication use.

CONCLUSION

There are numerous potential uses for risk prediction models and can be applied to risk-adjust outcome data, define intervention thresholds, and simplify clinical decision making. The prognosis for DPN, a disabling complication of type 2 diabetes, would be favorable if modifiable risk factors were routinely monitored. Patients who are given a risk score based on a risk prediction model for DPN can better manage their condition.

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Declaration of patient consent

The authors certify that they have obtained all appropriate consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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