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ORIGINAL RESEARCH

Construction of a Risk Prediction Model and Associative Path Analysis for Impaired Awareness of Hypoglycemia in People with Diabetes

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Video abstract

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Purpose: We aimed to develop a risk prediction model for impaired awareness of hypoglycemia (IAH) in diabetes and explore the associations with clinical variables, providing a basis for targeted screening and personalized intervention.

Patients and Methods: This cross-sectional study included 280 hospitalized people with diabetes (73.2% type 2 and 42.9% female) who experienced hypoglycemia between October 2023 and February 2024. We defined IAH as a Gold Scale score ≥4. We used binary logistic regression to construct the prediction model and structural equation modeling to analyze the associated pathways. Sensitivity analysis stratified by diabetes type verified the robustness of the results.

Results: IAH affected 60.4% of the participants. Multivariate analysis revealed lower total cholesterol (TC) levels (aOR=0.819; 95% CI: 0.684–0.981; P=0.030) as independent correlates. The model, which incorporated BMI, TC level, serum albumin level, peripheral neuropathy (PN) incidence, glomerular filtration rate (GFR), age, sex, and insulin use, showed moderate discriminative ability (AUC=0.630, P<0.001), with high sensitivity (87.0%) and good calibration (Hosmer–Lemeshow test: P=0.743). Path analysis revealed that age indirectly influenced IAH risk (β=0.243) by decreasing the GFR (β=−0.419; P<0.001) and increasing PN risk (β=0.352; P<0.001) and that a lower GFR (β=−0.133; P=0.024) and TC level (β=−0.131; P=0.024) were directly correlated with IAH risk. The serum albumin level was maintained by preserving the GFR (β=0.203; P<0.001) and reducing PN risk (β=−0.139; P=0.012).

Conclusion: Higher BMI and lower TC are key correlates of IAH in hospitalized patients with diabetes. Age, GFR, serum albumin, and PN interact through direct and indirect pathways to affect the risk of IAH. This model, based on routine clinical indicators and with high sensitivity, represents a practical screening tool. Clinicians should perform early risk assessment and intervention in diabetic patients with higher BMI, lower TC, advanced age, malnutrition, renal insufficiency, or PN.

Keywords: diabetes mellitus, hypoglycemia, impaired awareness of hypoglycemia, risk prediction model, path analysis

Introduction

Hypoglycemia is a common clinical event in the management of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). Recurrent episodes of hypoglycemia can lead to impaired awareness of subsequent hypoglycemic events, forming a vicious positive feedback loop that increases the risk of morbidity and mortality.[1] Impaired awareness of hypoglycemia (IAH) is an acquired syndrome associated with insulin therapy[2] and can lead to reduced intensity of, alterations in, or complete loss of the warning symptoms of hypoglycemia. The incidence of IAH increases as diabetes progresses.[3] It is estimated that up to 40% of T1DM patients develop IAH,[4] with a three- to sixfold risk of severe

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hypoglycemia,[5] while the incidence of IAH in T2DM patients is 22%.[6] Despite improvements in diabetes management strategies, approximately 30% of T1DM patients still suffer from IAH.[7]

According to the American Diabetes Association Standards of Care in Diabetes-2025, patients at risk of hypoglycemia should undergo annual screening for IAH and implement interventions to prevent IAH.[8] Currently, the pathogenesis of IAH remains incompletely understood,[6] but it has been hypothesized that increased cerebral glucose transport, the integration of alternative energy sources, and alterations in hypothalamic signaling may contribute to its development.[9] Previous studies have shown that the occurrence of IAH in T2DM patients is associated with sociodemographic factors (such as age, body mass index, race, marital status, education level, and type of healthcare facility visited), clinical disease factors (including disease duration, glycated hemoglobin A1c, complications, insulin treatment regimen, sulfonylurea use, and the frequency and severity of hypoglycemia), and behavioral and lifestyle factors (such as smoking status and medication compliance).[6] However, the relative contributions and interactions among these factors remain unclear, and the underlying biological mechanisms are still controversial.[10–13] Li et al[7] reported that patients with type 2 diabetes and a body mass index (BMI) ≥30 kg/m^2 had a significantly elevated risk of impaired awareness of hypoglycemia (IAH) (P<005, OR=0.73), a finding subsequently validated by van Meijel et al[14] and Besen et al[15] in patients with type 1 diabetes, a comparable association was also identified, with Wellens et al[16] reporting that increased BMI was a significant independent risk factor for IAH. Naito et al[17] reported no differences in baseline indicators (age, disease duration, and HbA1c) among patients with type 1 diabetes, yet psychological traits (alexithymia and maladaptive perfectionism) and cognitive–behavioral barriers were linked to IAH. Olsen et al[10] reported that IAH in adults with type 1 diabetes (T1D) is unrelated to autonomic dysfunction or peripheral neuropathy (contrary to earlier hypotheses) and emphasized the need to explore alternative underlying mechanisms. Therefore, further research is urgently needed to optimize risk stratification and intervention strategies for this condition.

Given the serious burden of IAH on people with diabetes and the urgent need for early identification and targeted intervention strategies for this disease, this study aimed to develop a dynamic IAH risk prediction model by integrating multidimensional clinical indicators such as renal function, nutritional status and inflammatory markers, and neuropathy parameters. Path analysis was used to quantify the direct and indirect effects of key variables on IAH risk. This study provides a theoretical basis for the identification of intervention targets and, by elucidating relevant mechanisms through path analysis, supports the development of personalized prevention and management strategies for IAH, ultimately improving the long-term outcomes of patients with diabetes.

Materials and Methods

Study Design and Participants

In this cross-sectional study, patients with diabetes hospitalized in the endocrinology department of a Grade A Class 3 hospital in China between October 1, 2023, and February 1, 2024, were recruited through convenience sampling. The inclusion criteria were as follows: (1) a diagnosis of diabetes in accordance with the 2024 American Diabetes Association diagnostic criteria for diabetes;[18] (2) at least one episode of hypoglycemia during hospitalization, defined as a capillary blood glucose level ≤3.9 mmol/L;[8] and (3) written informed consent and agreement to participate in this study. The exclusion criteria were as follows: (1) a current immunosuppressive therapy regimen and (2) advanced-stage malignancies or pregnancy.

Data Collection and Laboratory Analysis

General Information Questionnaire

A self-designed general information questionnaire was used in this study to collect sociodemographic and disease-related data. (1) Sociodemographic data, such as sex, age, education level, smoking history, drinking history, family history of genetic diseases (eg., if one or both parents had diabetes), and body mass index (BMI), were collected at admission. (2) Disease-related data, such as the type and duration of diabetes; type of hypoglycemia; C-peptide levels; the levels of glycated hemoglobin (HbA1c), hemoglobin, albumin, high-density lipoprotein, low-density lipoprotein, triglyceride, total cholesterol (TC), serum creatinine, blood urea nitrogen, and 25-hydroxyvitamin D3; the glomerular filtration rate (GFR);

comorbidities (hypertension, coronary heart disease, cerebral infarction); diabetic complications (diabetic nephropathy, diabetic retinopathy, diabetic foot, lower extremity vascular disease, and peripheral neuropathy); antihyperglycemic regimens (oral hypoglycemic agents, insulin and GLP-1 administration); and continuous glucose monitoring and hypoglycemia classification.

Gold Scale

Proposed by Professor Gold in the United Kingdom in 1994,[2] the Gold Scale is currently the most commonly used tool for assessing IAH. It determines whether a patient has IAH through a single question: "Can you feel when your hypoglycemia is starting?" Responses are rated on a seven-point Likert scale, where 1 indicates always aware of the onset of hypoglycemia, 7 indicates never aware, and a score of ≥4 suggests the presence of IAH. IAH was therefore defined as a Gold scale score of 4 or higher.

Data Collection Method

The sociodemographic and disease-related data of patients in this study were collected by nurses on duty within 1–2 days after hospital admission, and laboratory data were collected from the first set of test results from samples obtained at admission. For patients who met the inclusion and exclusion criteria and signed informed consent forms, relevant data were collected, and a general information questionnaire was completed. The Gold scale was administered when patients developed hypoglycemia. All the collected data were reviewed and managed by a single investigator.

Statistical Analysis

Data entry was performed in Excel. The original data sources were carefully verified, and any data that were logically inconsistent or outside the normal range were individually identified and corrected. To handle variables with a low proportion of missing variables (less than 5%), measurement data were processed using the mean imputation method, whereas categorical variables were processed using the mode imputation method. For variables with a high proportion of missing values (5%-10%), multiple imputations were applied, considering information from other relevant variables. Variables with an excessive proportion of missing values (>10%) were excluded from the analyses to ensure data accuracy. Statistical analysis was performed using SPSS version 26.0. Measurement data are expressed as the mean ± standard deviation (X ± S), and comparisons between groups were performed using the independent-sample *t* test for normally distributed data and the nonparametric rank-sum test otherwise. Categorical data are expressed as percentages (%) and were compared using the chi-square test. We treated age, BMI, diabetes duration, C-peptide level, HbA1c level, hemoglobin level, albumin level, high-density lipoprotein level, low-density lipoprotein level, triglyceride level, total cholesterol level, serum creatinine level, blood urea nitrogen level, the GFR, and 25-hydroxyvitamin D3 level as continuous variables for all analyses.

Univariable analysis was conducted using IAH as the dependent variable. Variables with statistical significance ($P<0.1$) in the univariable analyses were further subjected to binary logistic regression analysis. Two confounders (sex and insulin administration) were incorporated for adjustment to control for confounding effects. To ensure the robustness of the primary findings, a sensitivity analysis stratified by diabetes type was performed. $P<0.05$ was considered to indicate statistical significance. The Hosmer–Lemeshow goodness-of-fit test was used to evaluate the calibration of the prediction model, and the area under the curve (AUC) was plotted using receiver operating characteristic (ROC) analysis to evaluate the predictive power of the model.[19] We used IBM SPSS Amos software to construct a structural equation model with IAH as the outcome variable, incorporating variables with statistical significance in the univariable analysis as associative variables. We generated a weighted path diagram, estimated the path coefficients, and quantified the direct and indirect associations among the variables. A weighted path diagram was generated, and the path coefficients were estimated to reveal the direct and indirect effects among the variables. On the basis of the weighted path diagram of the model, the goodness of fit between the model and the observed data was evaluated using multiple indices, including the chi-square/degrees of freedom ratio (χ^2/df), goodness-of-fit index, comparative fit index, and root mean square error of approximation.[20,21]

Results

Baseline Characteristics

A total of 351 people with diabetes were initially recruited. After individuals with other types of diabetes, incomplete records, and missing data were excluded, 280 people with diabetes were ultimately included in the reanalysis, of whom 169 (60.4%) had IAH and 111 (39.6%) had a normal awareness of hypoglycemia. In the IAH group, 42.9% of the patients were female, with a mean age of 56.4±14.8 years. A total of 73.2% had T2DM, and the mean duration of diabetes was 11.6±8.4 years. Univariable analysis revealed statistically significant ($P<0.1$) differences in age, BMI, peripheral neuropathy incidence, serum albumin level, total cholesterol level, and glomerular filtration rate (GFR) between the IAH and non-IAH groups (Table 1).

Table 1 Baseline Characteristics of Patients with Diabetes Grouped by IAH

Variables	Total	IAH	Non-IAH	*P* value
N,%	280	169(60.4)	111(39.6)	
Sex (female, n, %)	120(42.9)	70(41.4)	50(45.0)	0.359
Age, years	56.4±14.8	57.8±14.8	54.4±14.7	0.082*
Educational Level (college and above, n, %)	83(29.6)	47(27.8)	36(32.4)	0.686
Smoking History (n, %)	125(44.6)	79(46.7)	46(41.4)	0.763
Drinking History (n, %)	78(27.9)	51(30.2)	27(24.3)	0.285
Family History of Diabetes (n, %)	104(37.1)	61(36.1)	43(38.7)	0.201
Body Mass Index, kg/m^2	22.6±3.4	22.9±3.7	22.0±2.9	0.028**
Duration of Diabetes, Years	11.6±8.4	12.0±8.5	10.9±8.2	0.256
Type of Diabetes (T2DM, n, %)	205(73.2)	127(75.1)	78(70.3)	0.816
Hypertension (n, %)	97(34.6)	62(36.7)	35(31.5)	0.786
Coronary Heart Disease (n, %)	27(9.6)	21(12.4)	6(5.4)	0.182
Cerebral Infarction (n, %)	9(3.2)	8(4.7)	1(0.9)	0.152
Peripheral Neuropathy (n, %)	161(57.5)	98(58.0)	63(56.8)	0.042**
Peripheral Vascular Disease (n, %)	199(71.1)	125(74.0)	74(66.7)	0.188
Diabetic Nephropathy (n, %)	66(23.6)	44(26)	22(19.8)	0.231
Diabetic Retinopathy (n, %)	87(31.1)	51(30.2)	36(32.4)	0.159
Diabetic Foot (n, %)	6(2.1)	4(2.4)	2(1.8)	0.749
C-Peptide, ng/mL	1.2±1.9	1.3±2.2	1.1±1.4	0.736
Glycated Hemoglobin, %	9.3±2.5	9.1±2.5	9.4±2.6	0.265
Hemoglobin, g/L	125.9±20.8	124.7±22.4	127.7±18.2	0.441
Albumin, g/L	38.1±5.1	37.8±5.2	38.6±4.9	0.080*
High-Density Lipoprotein, mmol/L	1.4±0.7	1.3±0.4	1.5±1.1	0.957
Low-Density Lipoprotein, mmol/L	2.6±1.0	2.5±1.0	2.7±1.1	0.195
Triglycerides, mmol/L	1.6±1.6	1.5±1.2	1.8±2.2	0.587
Total Cholesterol, mmol/L	4.8±1.5	4.6±1.3	5.0±1.7	0.079*
Serum Creatinine, μmol/L	87.9±56.4	93.0±65.7	80.2±37.0	0.235
Blood Urea Nitrogen, mmol/L	6.8±3.7	7.1±4.1	6.4±2.9	0.370
Glomerular Filtration Rate, mL/(min ·1.73 m^2)	84.8±28.2	81.6±29.7	89.6±25.2	0.030**
25-Hydroxyvitamin D3, nmol/L	50.3±20.1	51.6±20.0	48.3±20.1	0.207
Oral hypoglycemic agents (n, %)	201(71.8)	126(74.6)	75(67.6)	0.204
Insulin administration (n, %)	239(85.4)	146(86.3)	93(83.8)	0.364
GLP-1 administration (n, %)	30(10.7)	23(13.6)	7(6.3)	0.183
Continuous glucose monitoring (n, %)	130(46.4)	68(40.2)	62(55.9)	0.101
Hypoglycemia classification (level 2, n, %)	47(16.8)	25(14.9)	22(19.8)	0.281

Note: Patients who have quit smoking are classified as having a smoking history; patients who consume alcohol daily are classified as having a drinking history. A family history of diabetes was defined as having at least one family member (including grandparents, parents, and immediate siblings) with diabetes. Hypoglycemia classification: level 1: <3.9 mmol/l and ≥3.0 mmol/l; level 2: < 3.0 mmol/l. *P < 0.1, **P < 0.05.
Abbreviation: GLP-1, glucagon-like peptide-1.

Table 2 Binary Logistic Regression Analysis of Factors Associated with IAH

Variable	Model A (Initial)			Model B (Adjusted for Sex & Insulin Administration)		
	B (SE)	OR (95% CI)	*P* value	B (SE)	aOR (95% CI)	*P* value
BMI	0.075 (0.038)	1.078(1.000–1.163)	**0.049****	0.075 (0.038)	1.078(1.000–1.162)	0.051*
Total Cholesterol	−0.200 (0.092)	0.819(0.684–0.981)	**0.030****	−0.199 (0.092)	0.819(0.684–0.981)	**0.030****
Serum Albumin	−0.037 (0.026)	0.964(0.916–1.014)	0.156	−0.037 (0.026)	0.964(0.916–1.014)	0.156
Peripheral Neuropathy	0.303 (0.282)	1.354(0.779–2.354)	0.283	0.305 (0.282)	1.357(0.780–2.361)	0.279
GFR	−0.009 (0.006)	0.991 (0.980–1.003)	0.130	−0.008 (0.006)	0.992(0.980–1.003)	0.150
Age	0.008 (0.010)	1.008(0.988–1.029)	0.425	0.009 (0.010)	1.009(0.988–1.030)	0.408
Sex (Male)	/	/	/	0.069 (0.261)	1.071(0.643–1.785)	0.791
Insulin administration	/	/	/	−0.323 (0.362)	0.724(0.356–1.473)	0.373
Constant	1.243 (1.601)	3.468	0.475	1.166 (1.632)	3.210	0.475

Note: **P*<0.05, ***P*<0.01.
Abbreviations: B, unstandardized regression coefficient; SE, standard error; aOR, adjusted odds ratio; CI, confidence interval; body mass index, BMI; GFR, glomerular filtration rate.

Construction of the IAH Risk Prediction Model

In Model A, which included variables significant in univariate analysis, a higher body mass index (BMI) (odds ratio [OR] = 1.078, 95% CI: 1.000–1.163, P = 0.049) and lower total cholesterol levels (OR = 0.819, 95% CI: 0.684–0.981, P = 0.030) were identified as significant factors associated with IAH. In the final Model B, after further adjustment for sex and age, the association with a higher BMI became borderline significant (aOR = 1.078; 95% CI: 1.000–1.162; P = 0.051), whereas the association with lower total cholesterol levels remained significant (aOR = 0.819; 95% CI: 0.684–0.981; P = 0.030). No significant associations were found for peripheral neuropathy incidence, the GFR, serum albumin concentration, sex, or age in this fully adjusted model (Table 2). On the basis of the final adjusted model (Model B), the risk prediction formula for IAH was derived as follows:

P(IAH) = 1/[1 + exp(- (1.166 + 0.075 × BMI - 0.037 × Albumin - 0.199 × Total Cholesterol + 0.305 ×Peripheral Neuropathy - 0.008 × GFR + 0.009 × Age+ 0.069 × Gender-0.323 × Insulin administration))] The model (Model B) demonstrated a statistically significant but modest discriminative ability, with an area under the receiver operating characteristic curve value of 0.630 (95% CI: 0.564–0.696, P < 0.001). At the conventional probability cutoff of 0.5, the model had a sensitivity of 87.0% and a specificity of 62.9%. The model was statistically significant overall (Omnibus test: χ^2 = 17.796, P = 0.038) and showed good calibration, as indicated by a nonsignificant Hosmer–Lemeshow goodness-of-fit test (χ^2 = 5.139, P = 0.743). A prespecified sensitivity analysis was performed by stratification by diabetes type (Table 3). In the type 2 diabetes subgroup (n=205), the directions of association with BMI (aOR=1.078; P=0.086) and total cholesterol levels (aOR=0.821; P=0.081) were consistent with those in the main analysis, although the difference was not statistically significant. In the type 1 diabetes (n=48) and other special types (unclassified diabetes and specific

Table 3 Sensitivity Analysis Stratified by Diabetes Type

Variable	Type 2 Diabetes (n=205)		Type 1 Diabetes (n=48)		Other Types of Diabetes (n=27)	
	aOR (95% CI)	*P* value	aOR (95% CI)	*P* value	aOR (95% CI)	*P* value
BMI	1.078(0.989–1.174)	0.086	1.034(0.819–1.305)	0.781	1.082(0.803–1.459)	0.604
Total Cholesterol	0.821(0.657–1.025)	0.081	0.801(0.517–1.240)	0.319	**0.619(0.248–1.545)**	**0.304**
Serum Albumin	0.967(0.912–1.006)	0.271	0.938(0.812–1.083)	0.379	0.987(0.803–1.213)	0.897
Peripheral Neuropathy	1.334(0.701–2.539)	0.380	2.006(0.521–7.727)	0.312	0.571(0.052–6.224)	0.646
GFR	0.993(0.980–1.006)	0.259	0.986(0.961–1.012)	0.986	0.991(0.935–1.051)	0.765
Age	1.001(0.973–1.029)	0.968	1.024(0.980–1.071)	0.293	1.021(0.941–1.108)	0.622

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; body mass index, BMI; GFR, glomerular filtration rate.

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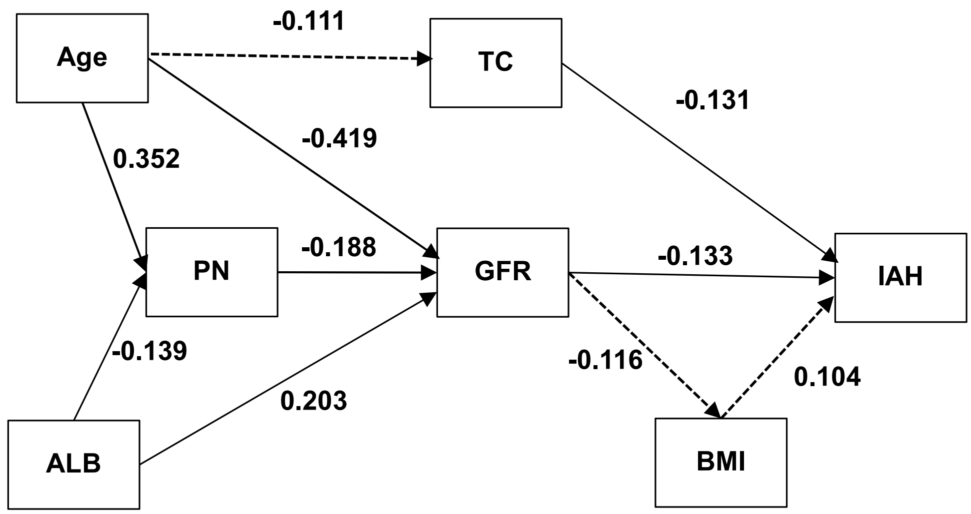

Figure 1 Path Analysis Diagram of the Risk Prediction Model for IAH.
Note: Rectangles represent observed variables. The arrows indicate hypothesized directional associations. The numbers adjacent to the arrows are standardized path coefficients (β). The solid arrows denote statistically significant paths (P< 0.05). The dashed arrow indicates a borderline significant association (P<0.1).
Abbreviations: ALB, serum albumin; BMI, body mass index; GFR, glomerular filtration rate; IAH, impaired awareness of hypoglycemia; PN, peripheral neuropathy; TC, total cholesterol..

types of diabetes) (n=27) subgroups, no statistically significant associations were observed for any variable, which is likely attributable to the severely limited sample size and statistical power in these subgroups.

Path Analysis of the Risk Model for IAH

On the basis of the results of the univariable analysis, a structural equation model for IAH was established, and a corresponding path analysis diagram was generated (Figure 1). The model fitting results revealed a chi-square/degrees of freedom ratio (χ^2/df) =1.173<3, a goodness-of-fit index of 0.987, a comparative fit index of 0.989 (all three fit indices > 0.90), and a root mean square error of approximation of 0.025 (<0.08), indicating an excellent fit of the model to the observed data. The standardized path coefficients (Table 4) revealed that age had a strong negative direct effect on the glomerular filtration rate (GFR) (β = −0.419, P < 0.001) and a positive direct effect on peripheral neuropathy (PN) incidence (β = 0.352, P < 0.001). Serum albumin (ALB) was positively associated with the GFR (β = 0.203; P < 0.001) and negatively associated with PN incidence (β = −0.139; P = 0.012). In terms of direct effects on IAH, both lower

Table 4 Path Coefficients of the Final Structural Equation Model for IAH

Path (X → Y)	Standardized Estimate (β)	Unstandardized Estimate	SE	CR	*P* value
Direct Paths to IAH					
GFR → IAH	−0.133	−0.002	0.001	−2.264	**0.024***
TC → IAH	−0.131	−0.044	0.019	−2.251	**0.024***
BMI → IAH	0.104	0.015	0.008	1.773	0.076
Mediating Paths					
Age → GFR	−0.419	−0.796	0.100	−7.921	**<0.001****
Age → PN	0.352	0.012	0.002	6.359	**<0.001****
Age → TC	−0.111	−0.011	0.006	−1.873	0.061
ALB → GFR	0.203	1.117	0.275	4.062	**<0.001****
ALB → PN	−0.139	−0.013	0.005	−2.515	**0.012***
PN → GFR	−0.188	−10.701	3.037	−3.524	**<0.001****
GFR → BMI	−0.116	−0.014	0.007	−1.959	**0.050**

Note: ** and * indicate significance levels of 1% and 5%, respectively.
Abbreviations: Age, patient age; ALB, serum albumin level; BMI, body mass index; GFR, glomerular filtration rate; IAH, impaired awareness of hypoglycemia; PN, peripheral neuropathy; TC, total cholesterol; SE, standard error; CR, critical ratio.

Table 5 Effect Sizes of Each Variable on IAH

Variable	Total Effect	Direct Effect	Indirect Effect
Age	0.243	/	0.243
GFR	−0.133	−0.133	/
TC	−0.131	−0.131	/
BMI	0.104	0.104	/
ALB	−0.009	/	−0.009
PN	0.025	/	0.025

Note: "/" denotes "none".
Abbreviations: BMI, body mass index; IAH, impaired awareness of hypoglycemia; ALB, serum albumin level; TC, total cholesterol; GFR, glomerular filtration rate; PN, peripheral neuropathy.

GFR (β = −0.133, P = 0.024) and lower total cholesterol (TC) levels (β = −0.131, P = 0.024) were significantly associated with a greater likelihood of IAH, whereas a higher body mass index (BMI) had a borderline positive direct association (β = 0.104, P = 0.076). The data in Table 5 indicate that age exerted a notable total indirect effect on IAH risk (β = 0.243), which was mediated through its effects on the GFR, TC levels, and the pathways associated with the GFR and BMI. In contrast, the GFR, TC level, and BMI influenced IAH risk primarily through direct effects.

Discussion

IAH in People with Diabetes Requires Urgent Attention

Hypoglycemia is a common clinical event in people with diabetes. Patients with IAH are unable to perceive the occurrence of hypoglycemia, which often leads to severe hypoglycemic episodes and even hypoglycemic coma. Two cross-sectional studies reported prevalences of IAH in patients with T1DM of 19.1%[10] and 22%,[22] whereas a meta-analysis revealed that the pooled prevalence of IAH in patients with T2DM was 22%.[6] Notably, 60.4% of people with diabetes in the present study were identified as having impaired awareness of hypoglycemia (IAH). This substantially high prevalence underscores the critical need for clinical attention to this high-risk population. Consistent with the emphasis stated in current clinical guidelines that highlight the importance of systematic IAH screening and targeted interventions, elucidating IAH-related factors and developing practical identification tools are of urgent clinical relevance.

Through an analysis of hospitalized people with diabetes who developed impaired awareness of hypoglycemia (IAH), an IAH risk prediction model was successfully constructed in this study, and structural equation modeling was applied to elucidate the complex associative network among key clinical variables. Our primary findings revealed that lower total cholesterol (TC) levels are independent risk factors for IAH. Furthermore, path analysis revealed that age, renal function (assessed via the glomerular filtration rate (GFR)), nutritional status (represented by serum albumin levels), and peripheral neuropathy (PN) incidence collectively form an associative system that influences IAH risk through both direct and indirect pathways.

Key Associated Factors and Potential Pathways in IAH

The association between a higher BMI and IAH risk observed in the present study aligns with findings from a recent meta-analysis focusing on type 2 diabetes (T2DM),[7] which also documented a positive link between an elevated BMI and increased IAH risk in this population. An elevated BMI—particularly in the obese range (≥30 kg/m^2)—is a well-recognized correlate of diabetes and associated cardiometabolic comorbidities, including hypertension and dyslipidemia.[23] The bidirectional interplay between diabetes and obesity often perpetuates a positive feedback loop of metabolic dysregulation, potentially exacerbating the progression of complications. However, our findings are not fully consistent with those reported by Lian A van Meijel et al,[14] who reported that a BMI <30 kg/m^2 was associated with a greater likelihood of IAH This discrepancy may stem from key differences in the study population: their analysis

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focused exclusively on insulin-treated patients with T2DM. Additionally, we did not categorize BMI into predefined ranges, which limits direct comparability with their stratified analysis.

On the other hand, lower TC levels are associated with a higher IAH risk. Lower TC levels may accompany conditions such as malnutrition or chronic catabolism, which could influence neurometabolic homeostasis and increase the risk of IAH. In contrast, Olsen et al[10] reported no significant association between lipid levels and IAH risk in a cohort of 103 patients with type 1 diabetes, and differences in the study population and sample size may have contributed to this discrepancy. Overall, these associations highlight the relevance of maintaining appropriate body weight and lipid profiles in diabetes management, which may support metabolic stability and hypoglycemia awareness.

Furthermore, the path analysis derived from the structural equation model in this study significantly advances our understanding of the interactive relationships among these seemingly isolated factors. The analysis clearly demonstrated that advancing age indirectly but robustly increased IAH risk (total indirect effect β=0.243) by significantly impairing renal function (reducing the GFR) and increasing the likelihood of peripheral neuropathy. This delineates a potential associative pathway: "aging→renal dysfunction/neural impairment→diminished hypoglycemia defense capacity." Compared with older adults without diabetes, those living with diabetes are more prone to functional impairments; have a higher incidence of comorbidities such as hypertension, chronic kidney disease (CKD), coronary heart disease, and stroke; and face an increased risk of cognitive decline.[24,25] When the glomerular filtration rate falls below 60 mL/min/1.73 m^2, CKD-related complications and cardiovascular events become more prevalent, with the severity of these complications increasing as CKD progresses.[26]

Peripheral neuropathy (PN) incidence was indirectly associated with IAH risk (β=0.025) because of its negative effect on the glomerular filtration rate (GFR) (β=−0.188; P<0.001). Martine-Edith G et al[27] reported that people with IAH experience fewer autonomic symptoms than those without impaired hypoglycemia awareness do (OR=0.43). Our findings are consistent with those of Sakane et al,[9] who demonstrated that PN increases the risk of IAH in patients with type 1 diabetes (T1DM) However, Olsen et al[10] reported no association between IAH and PN incidence in adults with T1DM. The mechanisms underlying the link between PN and IAH remain unclear, but it is plausible that PN-induced sensory deficits may lead to cognitive impairments, thereby compromising the ability to perceive hypoglycemia.

Moreover, serum albumin (ALB) acts as a protective factor, and serum ALB concentrations were positively correlated with the GFR (β=0.203; P<0.001) and negatively correlated with peripheral neuropathy (PN) incidence (β=−0.139; P=0.012). As an integrated marker of nutritional status and systemic inflammation, low serum ALB levels may indicate underlying malnutrition, which in turn impairs neural and renal function, indirectly increasing the risk of IAH. These findings suggest that maintaining optimal nutritional status may indirectly protect against normal hypoglycemia awareness by supporting renal function and safeguarding neural integrity.

Performance, Positioning and Clinical Translation Potential of the Prediction Model

The clinical prediction model developed in this study exhibits performance characteristics with clear clinical utility: while it demonstrates moderate discriminative ability (AUC=0.630), it is well calibrated, with predicted probabilities showing high consistency with actual observed outcomes. Notably, the model achieves high sensitivity (87.0%) at the conventional cutoff value, despite its relatively limited specificity (62.9%). This performance profile indicates that the model can effectively identify the vast majority of people at risk of impaired awareness of hypoglycemia (IAH), making it a valuable tool for preliminary clinical screening. A key advantage lies in its ability to enable rapid risk assessment solely on the basis of routine inpatient laboratory indicators, requiring no additional costs. This facilitates the initial identification of high-risk individuals who need further specialized evaluation from the broader population of people with diabetes—even in resource-constrained settings—thereby providing a practical and objective reference for early detection and stratified management.

Strengths and Weaknesses

This study has several notable strengths. First, in terms of its methodological comprehensiveness, we employed not only binary logistic regression to identify independent associated factors but also structural equation modeling for path analysis, enabling us to quantify and visualize the direct and indirect effects of key variables on IAH incidence and deepen the understanding of the underlying associative mechanisms. Second, our study has high clinical translatability. The prediction model is built on routinely collected indicators from electronic medical records, requiring no additional testing costs and facilitating rapid implementation across healthcare settings at all levels. Third, through rigorous analytical approaches, we validated the robustness of our findings through sensitivity analysis stratified by diabetes type and thoroughly assessed model calibration and goodness-of-fit using the Hosmer–Lemeshow test and multiple fit indices, enhancing the credibility of our conclusions. Nevertheless, the study has inherent limitations that must be acknowledged. First, the cross-sectional design represents fundamental constraint-all findings reflecting associations, and no causal relationships can be inferred. Second, despite conducting subgroup analyses, the small sample sizes of participants with type 1 diabetes and other special types of diabetes prevented the detection of significant associations in these important subgroups, limiting the generalizability of the conclusions and suggesting that the model may be primarily applicable to populations dominated by people with type 2 diabetes. Third, owing to practical constraints, this study did not include psychosocial or cognitive factors such as fear of hypoglycemia, anxiety, and depression, all of which are known variables potentially associated with IAH risk. Finally, as a single-center study, the external validity of the model urgently requires validation in prospective cohorts across diverse populations and healthcare centers.

Conclusion

In summary, this study revealed key clinical factors associated with impaired awareness of hypoglycemia (IAH) in hospitalized individuals with diabetes, including a higher body mass index (BMI) and lower total cholesterol (TC) levels, and a risk prediction model suitable for preliminary screening was developed. More importantly, through path analysis, we preliminarily revealed how age, nutritional status, renal function, and peripheral neuropathy (PN) incidence are interrelated and collectively influence IAH risk. This highlights that clinicians should exercise heightened vigilance for IAH risk in people with diabetes who present with a higher BMI, lower TC levels, advanced age, malnutrition, renal insufficiency, or PN and should conduct targeted assessments accordingly. Future research should focus on four key areas: 1) conducting multicenter, prospective cohort studies to validate the temporality of these associations and tentatively explore potential causal directions; 2) validating and optimizing this prediction model in larger cohorts, particularly among people with type 1 diabetes (T1DM); 3) integrating psychosocial and cognitive assessments to develop a more comprehensive and accurate risk prediction system; and 4) ultimately developing and validating targeted interventions based on such risk models to bridge the gap from risk identification to effective prevention of IAH.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Shenzhen People's Hospital (Approval number: LL-KY-2022422-01), and all participants signed informed consent forms.

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Author Contributions

Xuexian Wen and Liyan Chen: Conceptualization, Supervision, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing; Jun Wang: Methodology, Supervision, Writing – Review & Editing, Project Administration; Yali Mo, Hongzhen Guo, Rui Pei, Yuan Lyu and Huiqiong Luo: Investigation, Data Curation, Writing – Original Draft. The corresponding author confirms the accuracy of and agreement on all reported contributions. All the 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 the aspects of the work.

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Disclosure

The author(s) report no conflicts of interest in this work.

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