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Prevalence and risk factors of hypertensive retinopathy in South Korea based on national health survey data

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This study investigated the prevalence and risk factors of moderate to severe hypertensive retinopathy among non-diabetic South Korean adults using data from the Korea National Health and Nutrition Examination Survey (KNHANES) 2008–2011. Hypertensive retinopathy was defined through standardized retinal image grading. A multivariable logistic regression model was developed using weighted analysis and predictor selection based on pathophysiological relevance and multicollinearity diagnostics. Final model features included age, systolic blood pressure, HbA1c, total cholesterol, creatinine, and hemoglobin. Among 5,075 participants, the weighted prevalence of moderate to severe hypertensive retinopathy was 0.8%. The prevalence rate increased with higher systolic blood pressure levels. The model demonstrated moderate discrimination, with an average area under the receiver operating characteristic curve (AUC) of 0.721 in 5-fold cross-validation and 0.679 in external validation using the KNHANES 2012 dataset. External validation was performed using averaged predictions from the five internally validated models. The relatively low prevalence of hypertensive retinopathy compared to Western populations may reflect differences in hypertension control, lifestyle, or genetic susceptibility. Future research should explore retinal image analysis and longitudinal datasets to enhance early detection and clarify the systemic implications of hypertensive retinopathy.

Keywords Hypertensive retinopathy, Prevalence study, Risk factors, Prediction model, Systolic blood pressure

Hypertensive retinopathy is a retinal manifestation of systemic hypertension, reflecting damage to the microvasculature due to elevated blood pressure[1]. Since the retina is the only organ where the arteriovenous vasculature can be directly visualized, hypertensive retinopathy provides an opportunity to observe systemic vascular changes in detail[2]. It serves as a valuable marker for systemic vascular health and an indicator of end-organ damage[3]. With the global prevalence of hypertension steadily increasing due to aging populations, urbanization, and changing lifestyles, the burden of hypertensive retinopathy is expected to change[4]. Moreover, as healthcare accessibility improves and lifestyles evolve, the prevalence patterns of hypertensive retinopathy may also shift, emphasizing the need for updated epidemiological data and analysis.

Hypertensive retinopathy encompasses a spectrum of findings, ranging from mild arteriolar changes to severe retinal damage[5]. However, mild hypertensive retinopathy is often excluded from epidemiological studies because of its subjective nature and the challenges associated with consistent detection. Features such as arteriovenous nicking and focal arteriolar narrowing are difficult to measure quantitatively, limiting their utility in large-scale studies[6]. In contrast, moderate to severe hypertensive retinopathy, characterized by more conspicuous retinal changes such as flame-shaped hemorrhages, cotton-wool spots, hard exudates, and optic disc edema, can be more reliably identified. These advanced stages are clinically significant, as they are strongly associated with an elevated risk of cardiovascular events and other systemic complications. Previous major epidemiological studies have also focused on moderate to severe hypertensive retinopathy due to its clinical relevance and diagnostic reliability[7].

Distinguishing hypertensive retinopathy from diabetic retinopathy presents a significant challenge due to overlapping retinal features, such as hemorrhages and exudates[8]. This overlap has hindered research and

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diagnosis of hypertensive retinopathy, as hypertension and diabetes often coexist, with hypertension frequently contributing to kidney damage in diabetic patients[9]. The resulting complex interplay of pathophysiological mechanisms can obscure the boundaries between the two conditions, complicating their differentiation in clinical and research settings. To address this issue and ensure accurate assessment, many studies have deliberately excluded individuals with diabetes[7,10]. This approach effectively eliminates the confounding effects of DR, enabling a clearer evaluation of hypertensive retinopathy directly related to hypertension. By focusing exclusively on non-diabetic individuals, researchers can achieve a more precise understanding of hypertensive retinopathy, facilitating the identification of its distinct characteristics and risk factors within the context of systemic hypertension.

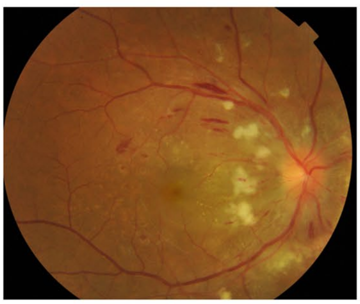
The objectives of this study are to determine the prevalence of moderate to severe hypertensive retinopathy among non-diabetic adults in South Korea (Fig. 1), and to identify independent risk factors for hypertensive retinopathy. By addressing the limitations of existing diagnostic criteria and providing robust epidemiological data, this study aims to enhance the understanding and clinical management of hypertensive retinopathy in the era of rising hypertension prevalence. This study utilized data from the Korea National Health and Nutrition Examination Survey (KNHANES), a comprehensive national health database that includes fundus photographs assessed by qualified ophthalmologists. Using this dataset, hypertensive retinopathy was assessed, with a focus on moderate to severe cases that could be reliably identified through standardized screening protocols.

Methods

We utilized comprehensive health data from the KNHANES, a nationwide cross-sectional survey conducted by the Korea Disease Control and Prevention Agency (KDCA). The study protocol was approved by the institutional review board of KDCA, and informed consent was obtained from all participants prior to their participation in the survey. The data are publicly available for research purposes at the KNHANES website, which exempts this study from requiring additional institutional review board approval. The study adhered to the principles of the Declaration of Helsinki. KNHANES participants were selected to represent the Korean population using stratified random sampling based on demographic factors, including sex, age, and region of residence. This national health dataset includes fully digitized health records encompassing medical history, sociodemographic information, laboratory test results, and ophthalmological examination findings. For this study, we utilized data from 2008 to 2011, as these years include ophthalmological examination data with detailed retinal evaluations critical to our analysis.

We conducted our study on adult participants without diabetes. Figure 2 depicts the sequential selection process for the final non-diabetic study population derived from the Korea National Health and Nutrition Examination Survey (KNHANES) 2008–2011 dataset. Out of 37,753 initial participants, 19,148 were excluded due to missing retinal findings or being under 19 years old. Among the remaining 18,605 participants, 12,388 were excluded due to missing data on blood pressure, HbA1c, or other variables. Additionally, 22 participants with wet age-related macular degeneration were excluded, leaving 6,195 eligible participants. Finally, 1,120 diabetic participants, defined by HbA1c levels ≥ 6.5%, were excluded to eliminate the potential confounding

(A)



Hypertensive retinopathy (Grade: Severe)

(B)

Grade	Signs	Opinion
Mild	- Generalized arteriolar narrowing - Focal arteriolar narrowing - Arteriovenous nicking - Opacification of the arteriolar wall (silver or copper wiring) - Combination of these signs	- Subjective and may vary depending on the imaging modality used for fundus photography. - Arteriovenous nicking is commonly observed even in healthy individuals.
Moderate	- Signs of mild retinopathy plus: - Retinal hemorrhages (blot, dot, or flame-shaped) - Microaneurysms - Cotton-wool spots - Hard exudates - Combination of these signs	- Typically evaluated objectively by ophthalmologists using fundus photographs. - However, features may overlap with other retinal diseases, such as diabetic retinopathy.
Severe (Malignant)	- Signs of moderate retinopathy plus Optic disc edema - Presence of severely elevated blood pressure	- Mild optic disc edema is often difficult to identify on fundus photographs. - May require additional imaging or clinical assessment to confirm.

• **Study Focus:** Moderate to Severe Stages Only

Fig. 1. Hypertensive Retinopathy and Grading System. (**A**) Fundus photograph showing severe hypertensive retinopathy. Key findings include flame-shaped hemorrhages, cotton-wool spots, and optic disc edema, characteristic of the severe stage. (**B**) Grading system for hypertensive retinopathy from Wong and Mitchell[1]. Mild hypertensive retinopathy is characterized by generalized or focal arteriolar narrowing, arteriovenous nicking, and arteriolar wall opacification. Moderate hypertensive retinopathy includes additional findings such as retinal hemorrhages, microaneurysms, and hard exudates. Severe hypertensive retinopathy is defined by the presence of optic disc edema and signs of critically elevated blood pressure. The study focuses on moderate to severe stages due to their objective and clinically significant features.

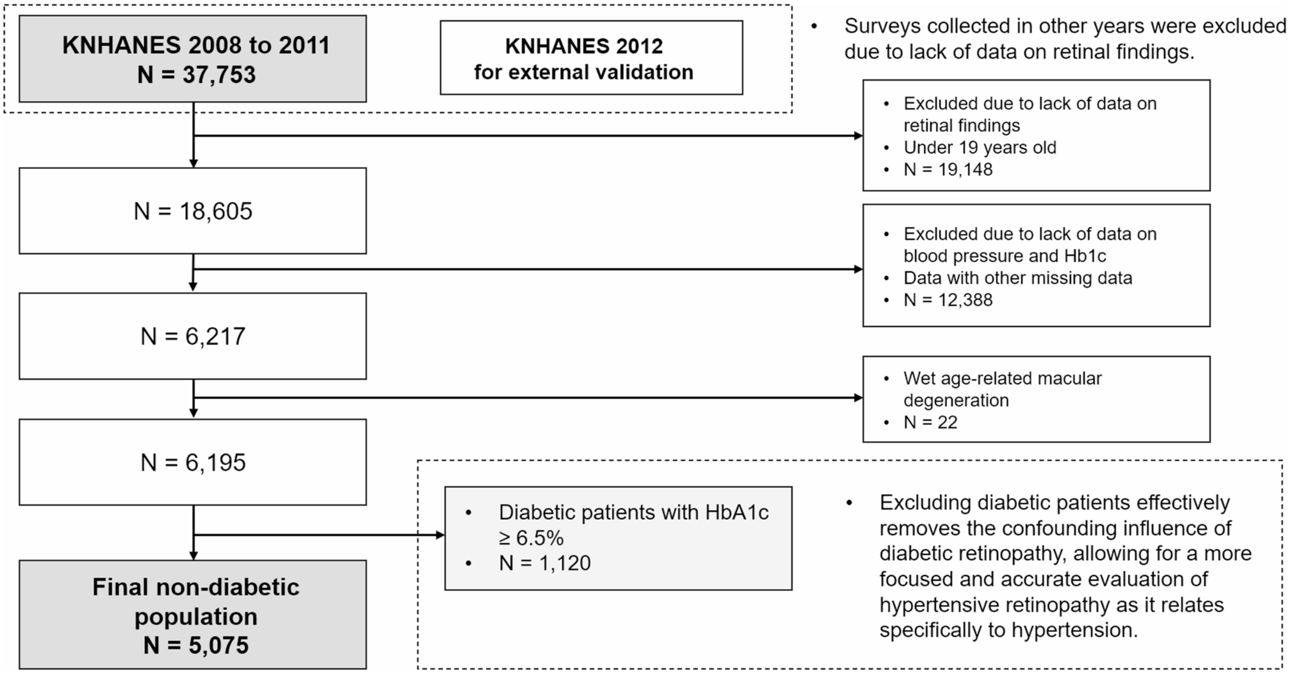


Fig. 2. Flowchart of Study Population Selection. This flowchart illustrates the selection process for the final non-diabetic population from the Korea National Health and Nutrition Examination Survey (KNHANES) 2008–2011 dataset. Excluding diabetic patients minimized confounding effects from diabetic retinopathy, enabling a focused evaluation of hypertensive retinopathy as it relates specifically to hypertension.

effect of diabetic retinopathy. This process resulted in a final study population of 5,075 non-diabetic participants, enabling a more accurate assessment of hypertensive retinopathy as it relates specifically to hypertension. Well-controlled diabetes mellitus patients, those with HbA1c < 6.5%, were included in this study to enhance its applicability to real-world clinical settings where hypertension and DM frequently coexist[11]. This inclusion minimizes the potential overlap with diabetic retinopathy while allowing for a more comprehensive evaluation of hypertensive retinopathy in patients managing their glycemic levels effectively. Similarly, the external validation cohort was constructed from the KNHANES 2012 dataset, resulting in a final sample of 4,114 non-diabetic participants (Supplementary Fig. 1).

Potential risk factors

Potential risk factors were identified based on evidence from prior literature[10–13]. Retinal microvascular changes have been shown to correlate with various systemic biomarkers, reflecting broader cardiovascular and metabolic dysfunction[14]. Possible risk factors were extracted from previous studies. Blood pressure was assessed three times on the right arm using a mercury sphygmomanometer (Baumanometer; Baum, Copiague, NY, USA)[15]. Measurements were taken while participants were seated and had rested for at least 5 min. The final systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were calculated as the average of the second and third readings, rounded to the nearest 2 mmHg. Information on age, sex, smoking habits, and comorbid conditions was gathered through a standardized health questionnaire, which also included details on hypertension medication and diabetes. Participants underwent fasting overnight prior to blood sampling, which was conducted to analyze lipid profiles and liver enzyme levels. Serum levels of creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) were measured using a Hitachi Auto Analyzer 7600 (Hitachi, Tokyo, Japan). Hematological parameters, including white blood cell (WBC) count, hemoglobin, and platelet levels, were measured using an ADVIA 120 hematology system (Bayer, Pittsburgh, PA, USA). Glycated hemoglobin (HbA1c) levels were determined through high-performance liquid chromatography using the Variant II system (Bio-Rad Laboratories, Hercules, CA, USA).

Definition of hypertensive retinopathy

Given the challenges in directly diagnosing hypertensive retinopathy, we estimated its presence by excluding other retinal pathologies such as diabetic retinopathy from fundus-based diagnostic findings. Detailed protocols for ocular examinations in the KNHANES have been previously reported[16]. The quality of eye examinations was overseen by the Epidemiologic Survey Committee of the Korean Ophthalmologic Society (KOS). Participating ophthalmologists and residents were periodically trained by acting staff members of the National Epidemiologic Survey Committee of the KOS to ensure standardization and consistency. Data collection and quality assurance protocols were further verified by the KDCA. Digital fundus images were obtained using a digital nonmydriatic fundus camera (TRC-NW6S; Topcon) under physiological mydriasis. For each participant, one 45° nonmydriatic digital retinal image centered on the fovea was taken for each eye (two images per person). The optic nerve configuration and any retinal pathologic findings were recorded during the examination. Each fundus image underwent a two-stage grading process. Preliminary grading was conducted onsite by ophthalmologists or ophthalmologic residents trained by the KOS. This was followed by detailed final grading performed by retinal specialists from the KOS[17]. Specific findings on retinopathy were labeled and categorized separately to ensure accurate documentation and analysis.

As in previous studies, the diagnosis of moderate to severe hypertensive retinopathy was based on the presence of flame-shaped hemorrhages, blot and dot hemorrhages, microaneurysms, cotton wool spots, hard exudates, or disc hemorrhages[7]. Patients were classified as having hypertensive retinopathy if these findings were observed in at least one eye. To avoid diagnostic confusion, patients with wet age-related macular degeneration, which can also present with retinal hemorrhages or exudation, were excluded from the analysis. Additionally, diabetic retinopathy was effectively excluded by removing participants with diabetes (HbA1c ≥ 6.5%), defined by HbA1c levels meeting the diagnostic threshold.

Statistical analysis

All analyses were performed using R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria). To ensure representativeness of the Korean population, sampling weights provided by the KNHANES were applied in both prevalence estimation and logistic regression modeling. Group differences between individuals with and without hypertensive retinopathy were assessed using the Wilcoxon rank-sum test for continuous variables and the χ^2 test for categorical variables. To identify independent risk factors for hypertensive retinopathy, weighted multivariable logistic regression was performed, and odds ratios (ORs) were reported under three modeling strategies including (1) crude ORs (unadjusted), (2) fully adjusted model including all candidate variables, and (3) model selected via backward feature elimination. While statistical feature selection was initially performed, the final variables included in the prediction model were determined based on a combination of clinical and pathophysiological relevance, pairwise correlation analysis, and multicollinearity diagnostics using the variance inflation factor (VIF). This approach was adopted to enhance both interpretability and model stability. Internal validation was conducted via 5-fold cross-validation using the KNHANES 2008–2011 dataset. For external validation, the average predicted probabilities from the five models generated during cross-validation were applied to the independent KNHANES 2012 dataset. The final logistic regression model was used to derive a risk prediction formula, which was implemented as a web-based risk calculator using HTML and JavaScript[18]. The model's discrimination was evaluated using the area under the receiver operating characteristic curve (AUC). Calibration performance and validation plots were also calculated for both internal and external validation. A two-tailed P value < 0.05 was considered statistically significant. All analyses were conducted in R unless otherwise specified.

Results

Table 1 summarizes the demographic and clinical characteristics of the study population, comparing participants with hypertensive retinopathy and those without. Among the 5,075 non-diabetic participants included in the study, 56 (1.1%) had hypertensive retinopathy. Participants with hypertensive retinopathy were significantly older (60.2 ± 14.6 years) than those without hypertensive retinopathy (48.8 ± 15.9 years, $P < 0.001$). The proportion of females was slightly lower in the hypertensive retinopathy group (50.0%) compared to the non-hypertensive retinopathy group (58.0%), though this difference was not statistically significant ($P = 0.276$). SBP was markedly higher in participants with hypertensive retinopathy (129.1 ± 19.9 mmHg) compared to those without hypertensive retinopathy (117.8 ± 16.7 mmHg, $P < 0.001$), whereas diastolic blood pressure (DBP) showed no significant difference ($P = 0.921$). Participants with hypertensive retinopathy were more likely to use hypertension medication (48.2% vs. 17.6%, $P < 0.001$). Additionally, fasting glucose and HbA1c levels were significantly elevated in the hypertensive retinopathy group ($P = 0.001$ and $P = 0.003$, respectively). BUN levels were higher in the hypertensive retinopathy group (17.6 ± 6.0 mg/dL) compared to the non- hypertensive retinopathy group (14.2 ± 4.1 mg/dL, $P < 0.001$), and creatinine levels trended higher but did not reach statistical significance ($P = 0.110$). Other clinical variables did not differ significantly between the two groups.

Table 2 presents the prevalence of moderate to severe hypertensive retinopathy among non-diabetic adults, stratified by age group and sex. Among the 5,075 participants included in the analysis, the overall weighted prevalence of hypertensive retinopathy was 0.8%, corresponding to 56 observed cases. The prevalence of hypertensive retinopathy increased substantially with advancing age. In individuals younger than 40 years, the adjusted prevalence was 0.4%, while it peaked at 3.1% among those aged 71 years and older. A similar age-related trend was observed in both sexes. Among males, the prevalence rose from 0.3% in the < 40 age group to 1.6% in the ≥ 71 age group. Among females, the increase was more pronounced, from 0.4 to 4.1%, respectively. Among participants aged over 40 years, the adjusted prevalence was 1.2% overall. In the subgroup aged over 50 years, the prevalence increased to 1.9% in males and 1.8% in females.

Figure 3 illustrates the crude and sex- and age-adjusted ORs for hypertensive retinopathy across SBP categories. In the crude analysis, the odds of hypertensive retinopathy increased significantly with higher SBP levels. Compared to the reference group (SBP < 130 mmHg), participants with SBP of 130–140 mmHg had an OR of 2.85 (95% CI: 1.15–5.62, $P = 0.002$), those with SBP of 140–160 mmHg had an OR of 3.96 (95% CI: 2.00–7.81, $P < 0.001$), and those with SBP > 160 mmHg had the highest OR of 5.77 (95% CI: 1.72–19.38, $P = 0.005$). A significant linear trend ($P < 0.001$) was observed, indicating a progressive increase in hypertensive retinopathy risk with higher SBP levels. In the sex- and age-adjusted analysis, the increasing trend persisted. The adjusted ORs for hypertensive retinopathy were 1.88 (95% CI: 0.94–3.69, $P = 0.082$) for SBP of 130–140 mmHg, 2.38 (95% CI: 1.21–4.64, $P = 0.019$) for SBP of 140–160 mmHg, and 3.15 (95% CI: 0.90–10.83, $P = 0.074$) for SBP > 160 mmHg, compared to the reference group. The linear trend remained significant ($P < 0.001$), highlighting the

	Total (N = 5075)	Hypertensive retinopathy (N = 56)	No hypertensive retinopathy (N = 5019)	P-value
Sex (Female, N, %)	2939 (57.9)	28 (50.0)	2911 (58.0)	0.276
Age (years)	48.9 ± 15.9	60.2 ± 14.6	48.8 ± 15.9	< 0.001
BMI (kg/m2)	23.5 ± 3.3	23.5 ± 3.2	23.5 ± 3.3	0.893
Current smoker (N, %)	909 (17.9)	6 (10.7)	903 (18.0)	0.218
SBP (mmHg)	117.9 ± 16.8	129.1 ± 19.9	117.8 ± 16.7	< 0.001
DBP (mmHg)	75.7 ± 10.3	75.9 ± 13.6	75.7 ± 10.2	0.921
Hypertension medication (N, %)	909 (17.9)	27 (48.2)	882 (17.6)	< 0.001
Fasting glucose (mg/dL)	93.7 ± 12.2	104.3 ± 23.0	93.5 ± 12.0	0.001
HbA1c (%)	5.6 ± 0.4	5.8 ± 0.5	5.6 ± 0.4	0.003
Total cholesterol (mg/dL)	189.8 ± 35.9	181.9 ± 44.7	189.9 ± 35.8	0.188
HDL (mg/dL)	50.9 ± 13.0	49.8 ± 15.3	50.9 ± 13.0	0.582
Triglycerides (mg/dL)	129.3 ± 107.1	167.3 ± 365.5	128.9 ± 100.6	0.435
AST (U/L)	22.1 ± 11.3	23.2 ± 9.3	22.1 ± 11.3	0.379
ALT (U/L)	20.4 ± 14.7	21.7 ± 12.4	20.4 ± 14.7	0.460
BUN (mg/dL)	14.3 ± 4.1	17.6 ± 6.0	14.2 ± 4.1	< 0.001
Creatinine (mg/dL)	0.83 ± 0.2	1.03 ± 0.9	0.83 ± 0.2	0.110
WBC (10^3/μL)	6.0 ± 1.7	6.0 ± 1.9	6.0 ± 1.7	0.929
Hemoglobin (g/dL)	14.0 ± 1.6	13.5 ± 2.0	14.0 ± 1.6	0.124
Platelets (10^3/μL)	253.3 ± 58.9	244.8 ± 74.5	253.4 ± 58.7	0.393

Table 1. Demographic and clinical features of the study population. AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, BMI: Body Mass Index, BUN: Blood Urea Nitrogen, DBP: Diastolic Blood Pressure, HDL: High-Density Lipoprotein Cholesterol, SBP: Systolic Blood Pressure, WBC: White Blood Cells.

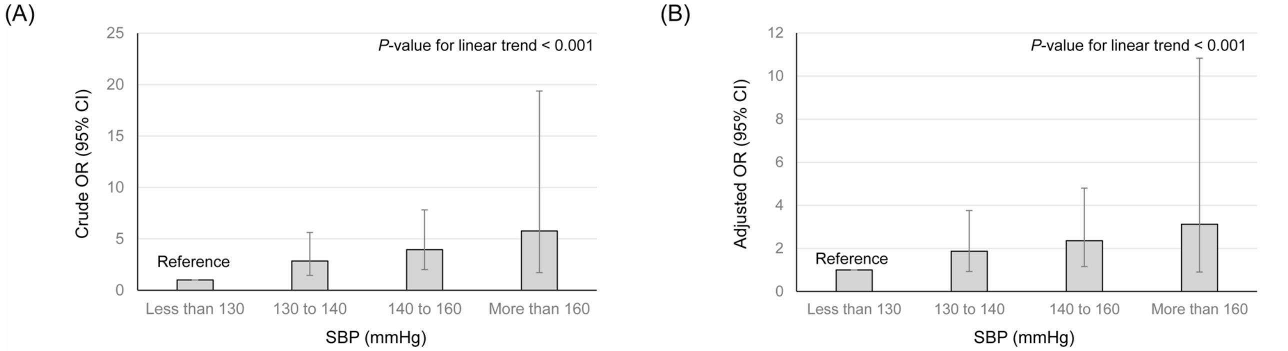
	All persons			Male			Female		
Age (year)	Case/total	Raw Prevalence (%)	Adjusted Prevalence (%)*	Case/total	Raw Prevalence (%)	Adjusted Prevalence (%)*	Case/total	Raw Prevalence (%)	Adjusted Prevalence (%)*
Age groups									
19 to 40	8/1786	0.4	0.4	4/740	0.5	0.3	4/1046	0.4	0.4
41 to 50	3/935	0.3	0.3	1/387	0.3	0.1	2/548	0.4	0.4
51 to 60	15/995	1.5	1.7	9/415	2.2	2.1	6/580	1.0	1.2
61 to 70	13/793	1.6	1.5	8/359	2.2	2.2	5/434	1.2	0.9
≥ 71	17/566	3.0	3.1	6/235	2.6	1.6	11/331	3.3	4.1
Summary									
Age > 40	48/3289	1.5	1.2	24/1396	1.7	1.2	24/1893	1.3	1.2
Age > 50	45/2354	1.9	1.9	23/1009	2.3	2.1	22/1345	1.6	1.8
Total	56/5075	1.1	0.8	28/2136	1.3	0.8	28/2939	1.0	0.9

Table 2. Prevalence of non-diabetic hypertensive retinopathy in the study population. *Values derived using the sampling weights.

strong association between elevated SBP and increased ORs of hypertensive retinopathy, even after accounting for sex and age.

Table 3 presents the results of univariate (crude), fully adjusted, and backward feature selection logistic regression models examining clinical factors associated with moderate to severe hypertensive retinopathy. In the crude model, increasing age, SBP, fasting glucose, HbA1c, BUN, and creatinine were significantly associated with higher hypertensive retinopathy risk. In the fully adjusted model controlling for all covariates, SBP (adjusted OR: 1.03 per mmHg, $P = 0.006$), fasting glucose (adjusted OR: 1.03 per mg/dL, $P = 0.003$), HDL cholesterol (adjusted OR: 1.03 per mg/dL, $P = 0.009$), and ALT (adjusted OR: 1.02 per U/L, $P = 0.012$) remained significant. Backward feature selection was used to identify a reduced set of variables, and this model included age (adjusted OR: 1.02 per year, $P = 0.089$), SBP (adjusted OR: 1.03, $P = 0.006$), fasting glucose (adjusted OR: 1.03, $P < 0.001$), BUN (adjusted OR: 1.10, $P < 0.001$), HDL (adjusted OR: 1.03, $P = 0.011$), and hemoglobin (adjusted OR: 0.83, $P = 0.047$).

Supplementary Fig. 2 displays the correlation matrix of key clinical and laboratory variables, highlighting several moderate to strong correlations suggestive of potential multicollinearity. Notably, SBP and DBP ($r = 0.67$) and ALT and AST ($r = 0.68$) showed strong positive correlations, indicating possible redundancy. Supplementary Fig. 3 presents the variance inflation factor (VIF) analysis, with all values below the conventional threshold of



(A)

SBP (mmHg)	Less than 130	130 to 140	140 to 160	More than 160
N (Case / Total)	29 / 3988	12 / 587	12 / 426	3 / 74
OR (95% CI)	1.00 (Reference)	2.85 (1.15–5.62)	3.96 (2.00–7.81)	5.77 (1.72–19.38)
P-value	-	0.002	<0.001	0.005

(B)

SBP (mmHg)	Less than 130	130 to 140	140 to 160	More than 160
N (Case / Total)	29 / 3988	12 / 587	12 / 426	3 / 74
OR (95% CI)	1.00 (Reference)	1.88 (0.94–3.69)	2.38 (1.21–4.64)	3.15 (0.90–10.83)
P-value	-	0.082	0.019	0.074

Fig. 3. Crude and Sex- and Age-Adjusted Odds Ratios (ORs) for Hypertensive Retinopathy by Systolic Blood Pressure (SBP) Categories. (**A**) Crude ORs (95% CI) for hypertensive retinopathy across SBP categories: less than 130 mmHg (reference), 130 to 140 mmHg, 140 to 160 mmHg, and more than 160 mmHg. A significant linear trend ($P<0.001$) was observed, with increasing SBP associated with higher odds of hypertensive retinopathy. (**B**) Sex- and age-adjusted ORs (95% CI) for hypertensive retinopathy across SBP categories. After adjusting for sex and age, a significant linear trend ($P<0.001$) was observed.

	Unadjusted models		Fully adjusted model		Backward feature selection model	
Potential risk factors	**Crude OR (95% CI)**	***P*-value**	**Adjusted OR (95% CI)**	***P*-value**	**Adjusted OR (95% CI)**	***P*-value**
Sex (Female)	0.72 (0.43–1.23)	0.230	0.79 (0.32–1.97)	0.619	-	-
Age (per 1 year increase)	1.05 (1.03–1.07)	< 0.001	1.01 (0.98–1.04)	0.458	1.02 (1.00–1.04)	0.089
BMI (per 1 kg/m^2 increase)	0.99 (0.92–1.08)	0.896	0.94 (0.83–1.06)	0.314	-	-
Current smoker	0.55 (0.23–1.28)	0.164	0.50 (0.18–1.40)	0.188	-	-
SBP (per 1 mmHg increase)	1.03 (1.02–1.05)	< 0.001	1.03 (1.01–1.06)	0.006	1.03 (1.02–1.06)	0.006
DBP (per 1 mmHg increase)	1.00 (0.98–1.03)	0.895	0.99 (0.95–1.03)	0.543	-	-
Hypertension medication	4.37 (2.57–7.41)	< 0.001	1.77 (0.68–4.62)	0.243	-	-
Fasting glucose (per 1 mg/dL increase)	1.04 (1.03–1.05)	< 0.001	1.03 (1.01–1.05)	0.003	1.03 (1.01–1.04)	< 0.001
HbA1c (per 1% increase)	4.18 (2.03–8.61)	< 0.001	1.94 (0.54–6.91)	0.307	-	-
Total cholesterol (per 1 mg/dL increase)	0.99 (0.99–1.00)	0.096	0.99 (0.98–1.00)	0.315	-	-
HDL (per 1 mg/dL increase)	0.99 (0.97–1.01)	0.515	1.03 (1.01–1.05)	0.009	1.03 (1.01–1.05)	0.011
Triglycerides (per 1 mg/dL increase)	1.00 (1.00–1.00)	0.013	1.00 (0.99–1.00)	0.771	-	-
AST (per 1 U/L increase)	1.01 (0.99–1.02)	0.462	0.97 (0.92–1.01)	0.171	-	-
ALT (per 1 U/L increase)	1.00 (0.99–1.20)	0.527	1.02 (1.01–1.04)	0.012	-	-
BUN (per 1 mg/dL increase)	1.14 (1.09–1.19	< 0.001	1.06 (1.00–1.13)	0.067	1.10 (1.04–1.15)	< 0.001
Creatinine (per 1 mg/dL increase)	1.97 (1.34–2.89)	< 0.001	1.47 (0.82–2.65)	0.200	-	-
WBC (per 10^3/μL increase)	1.01 (0.86–1.18)	0.919	0.99 (0.81–1.21)	0.936	-	-
Hemoglobin (per 1 g/dL increase)	0.85 (0.72–1.00)	0.045	0.86 (0.67–1.09)	0.204	0.83 (0.68–0.99)	0.047
Platelets (per 10^3/μL increase)	1.00 (0.99–1.00)	0.276	1.00 (0.99–1.00)	0.638	-	-

Table 3. Crude and adjusted odds ratios of clinical variables for hypertensive retinopathy in the study population. AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, BMI: Body Mass Index, DBP: Diastolic Blood Pressure, BUN: Blood Urea Nitrogen, CI: confidence interval, HDL: High-Density Lipoprotein Cholesterol, OR: odds ratio, SBP: Systolic Blood Pressure, WBC: White Blood Cells.

5, suggesting no severe multicollinearity. However, variables with borderline VIF values, such as SBP (2.69), HbA1c (2.44), and ALT (2.33), were carefully evaluated during the final variable selection process.

Table 4 summarizes the process of final variable selection by integrating both statistical diagnostics and pathophysiological relevance. While backward feature selection initially identified several statistically significant predictors, the final model was refined to include only those with clinical relevance and acceptable multicollinearity. Age was retained despite its borderline statistical significance due to its strong biological relevance in vascular aging. SBP was prioritized over DBP and hypertension medication as the primary hemodynamic factor, given its stronger association with retinal microvascular damage and acceptable VIF. HbA1c was selected instead of fasting glucose due to its reflection of long-term glycemic burden and better multicollinearity profile. Although total cholesterol was not statistically significant, it was retained for its potential role in lipid-mediated retinal changes. Similarly, creatinine and hemoglobin were included based on their biologic plausibility in microvascular health, despite borderline statistical significance. Variables such as HDL, BUN, ALT, and smoking were excluded due to either lack of significance or collinearity with more physiologically central variables.

Figure 4 shows the validation performance of the final logistic regression model for predicting hypertensive retinopathy, constructed using six predictors selected based on pathophysiological relevance and multicollinearity diagnostics: age, systolic blood pressure, HbA1c, total cholesterol, creatinine, and hemoglobin (Table 4). Internal validation was performed using 5-fold cross-validation on the KNHANES 2008–2011 dataset, with individual fold AUCs ranging from 0.559 to 0.853 and a mean AUC of 0.721. External validation was conducted using the KNHANES 2012 dataset, based on the averaged predicted probabilities from the five cross-validated models, yielding an AUC of 0.679. The predictive performance of the final model surpassed that of any individual predictor, as demonstrated in both internal and external validation analyses (Supplementary Fig. 4). Supplementary Fig. 5 illustrates the calibration performance of the final logistic regression model for predicting moderate to severe hypertensive retinopathy. The calibration slopes were 6.727 (internal) and 24.715 (external).

Supplementary Fig. 6 demonstrates the interface and functionality of the web-based Moderate to Severe Hypertensive Retinopathy Risk Calculator, developed using the final logistic regression model based on the 2008–2011 KNHANES cohort (available at: https://taekeuntoo.github.io/HypertensiveRetinopathy/; see Supplementary Table 1). The calculator allows users to input six clinical variables, including age, systolic blood pressure, HbA1c, total cholesterol, creatinine, and hemoglobin, to estimate an individual's probability

Domain	Variable	Pathophysiologic justification	Statistical justification	Included in final model
Demographics and lifestyle	Sex	Biological sex influences vascular tone and hormonal modulation	Not significant in the fully adjusted model	X
	Age	Major determinant of microvascular aging and arteriosclerosis	Statistically significant; low VIF	O
	BMI	Related to metabolic syndrome; limited direct association with hypertensive retinopathy	Not significant	X
	Current smoker	Promotes oxidative stress and endothelial dysfunction	Not significant	X
Blood pressure and medication	SBP	Primary driver of hypertensive retinopathy	Statistically significant; acceptable VIF	O
	DBP	Secondary to SBP in determining vascular damage	Correlated with SBP; excluded to avoid multicollinearity	X
	Hypertension medication	Proxy for long-standing or treated hypertension	Correlated with SBP; excluded	X
Glucose metabolism	Fasting glucose	Marker of systemic metabolic stress	Correlated with HbA1c; excluded	X
	HbA1c	Reflects chronic glycemic burden and microvascular injury	Statistically significant; retained over glucose due to collinearity	O
Lipid Profile	Total cholesterol	Associated with atherosclerosis and lipid exudation	Low VIF; non-significant but pathophysiologically relevant; Included instead of HDL	O
	HDL	Anti-inflammatory and endothelial protective functions	Excluded due to statistical contradiction of expected mechanism	X
	Triglycerides	May contribute to exudative retinal changes	Not significant	X
Liver Function	AST	Marker of hepatic metabolic disturbance and systemic inflammation	Not significant; correlated with ALT	X
	ALT	Reflects metabolic inflammation and fatty liver disease-related vascular risk	Not significant; borderline VIF	X
Renal Function	BUN	Associated with microvascular dysfunction and endothelial stress; susceptible to short-term fluctuations	Not significant; moderate correlation	X
	Creatinine	Reflects chronic kidney disease; often coexists with hypertensive retinopathy	Low VIF; non-significant but biologically meaningful	O
Hematologic and Inflammatory	WBC	Marker of systemic inflammation and vascular stress	Not significant	X
	Hemoglobin	Influences oxygen delivery to retinal capillaries	Marginal statistical significance; low VIF	O
	Platelets	Related to thrombosis and vascular turnover	Not significant	X

Table 4. Selected variables for the final model based on pathophysiological relevance and multicollinearity diagnostics. AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, BMI: Body Mass Index, DBP: Diastolic Blood Pressure, BUN: Blood Urea Nitrogen, CI: confidence interval, HDL: High-Density Lipoprotein Cholesterol, OR: odds ratio, SBP: Systolic Blood Pressure, VIF: variance inflation factor, WBC: White Blood Cells.

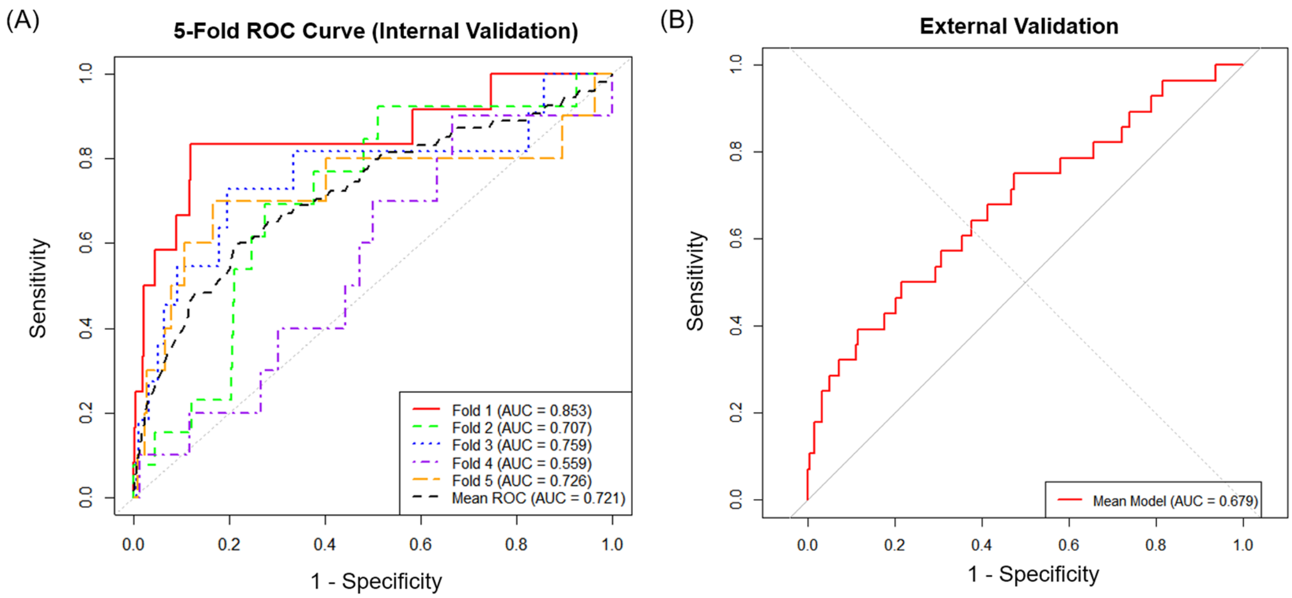


Fig. 4. Internal and external validation of a logistic regression model for predicting hypertensive retinopathy. (**A**) Receiver operating characteristic (ROC) curves from 5-fold cross-validation on the internal dataset from the Korea National Health and Nutrition Examination Survey (KNHANES) 2008–2011. Each fold's ROC curve is shown with a distinct color and line type, and the corresponding area under the curve (AUC) is indicated in the legend. (**B**) ROC curve for external validation using the KNHANES 2012 dataset. The curve is based on the average predicted probabilities from the five models trained on the internal dataset.

of hypertensive retinopathy. Risk probabilities are accompanied by a qualitative risk assessment (e.g., high or moderate risk based on population percentile thresholds), facilitating clinical interpretation and potential prioritization for retinal evaluation.

Discussion

Epidemiological studies on hypertensive retinopathy are crucial, as hypertensive retinopathy is not only a condition that can impair vision but also serves as a significant predictor of cardiovascular disease[2,19]. This study provides valuable insights into the prevalence and risk factors associated with hypertensive retinopathy in South Korea, focusing on a non-diabetic adult population. Using data from the KNHANES 2008–2011, the study identifies a hypertensive retinopathy prevalence of 0.8%, emphasizing the increasing risk with elevated age, SBP, HbA1c, and creatinine levels. Among these, SBP demonstrated the strongest association with disease prevalence. By excluding individuals with diabetes and focusing on clinically meaningful grades of hypertensive retinopathy, the study provides robust population-level data and introduces a practical risk prediction model, thereby supporting improved risk stratification and clinical decision-making in non-diabetic populations.

The findings of this study align with and build upon existing literature, as summarized in Table 5, which highlights the prevalence and risk factors for hypertensive retinopathy across diverse populations and methodologies. The prevalence of hypertensive retinopathy in this study (0.8%) is notably lower than rates reported in non-diabetic populations from Australia (9.8%) and the United States (4.1–7.7%)[7,20]. These differences may be attributed to regional variations in population characteristics, healthcare access, and blood pressure management practices. Consistent across all epidemiological studies, however, is the strong association between elevated blood pressure and the incidence of hypertensive retinopathy[10,21]. The risk factors identified in this study, such as higher SBP, HbA1c, and creatinine level, are consistent with those reported in previous studies, which highlight the roles of uncontrolled hypertension, proteinuria, and other metabolic indicators[22]. Notably, hypertensive retinopathy prevalence is particularly high in patients with chronic kidney disease (CKD), reflecting the severity of systemic vascular damage in this group[23]. A significant prevalence of hypertensive retinopathy was observed in a hypertensive patient population in India[24]. While a Chinese study reported a prevalence of hypertensive retinopathy similar to that observed here[22], it still showed higher rates compared to our findings, likely reflecting differences in study populations and methodologies. These variations emphasize the need for region-specific research and affirm this study's contribution to understanding hypertensive retinopathy in South Korea.

Hypertensive retinopathy develops as a result of persistently elevated blood pressure, which causes damage to the retinal vasculature through both structural and functional changes[25]. Chronic hypertension related to atherosclerosis increases vascular wall tension, leading to endothelial injury, arteriolar narrowing, and eventual remodeling of the blood vessels[26]. These changes reduce blood flow and oxygen supply to the retina, triggering ischemia and vascular leakage. Retinal manifestations such as microaneurysms, hemorrhages, and cotton wool spots reflect the extent of microvascular injury[27]. Additionally, the activation of the renin-angiotensin-aldosterone system from kidney damage contributes to vasoconstriction and inflammation, compounding

Author, year	Population	Definition of hypertensive retinopathy	Prevalence of hypertensive retinopathy	Risk factor of hypertensive retinopathy
Sharp et al., 1995 [11]	Afro-Caribbeans & Europeans	Grade ≥ 1(Keith-Wagener-Barker grading)	11%	Age, higher SBP, Afro-Caribbean ethnicity
Yu et al., 1998 [20]	Non-diabetic older adults, Australia	Retinopathy including retinal hemorrhages or microaneurysms	9.8%	Age, uncontrolled hypertension, increasing BP quartiles
Wong et al., 2003 [7]	Non-diabetic African Americans and Whites, USA	Moderate to severe (Wong and Mitchell grading)	African Americans: 7.7%, Whites: 4.1%	Race, BP levels, ventricular hypertrophy, fasting glucose, BMI
Ong et al., 2013 [10]	Hypertensive patients aged 50–73 years, USA	Moderate to severe (Wong and Mitchell grading)	5.1%	Age, BP control, antihypertensive medication, sex
Chillo et al., 2019 [23]	Non-diabetic CKD patients, Tanzania	Grade 3–4 (Keith-Wagener-Barker grading)	33.4% (grade 3: 19.6%, grade 4: 13.8%)	CKD severity, hypertension grade, alcohol use
Schuster et al., 2020 [21]	Adults aged 35–74 years, Germany (Gutenberg Study)	Moderate to severe (Wong and Mitchell grading)	4.0%	Age, sex, smoking, dyslipidemia, BMI, hypertension, diabetes
Chen et al., 2021 [22]	China Stroke Primary Prevention Trial cohort	Grade 3–4 (Keith-Wagener-Barker grading)	2.39% (grade 3: 2.36%, grade 4: 0.03%)	Higher SBP, DBP, proteinuria, and fasting glucose
Warad et al., 2023 [24]	Hypertensive patients in a teaching hospital, India	Grade 3–4 (Keith-Wagener-Barker grading)	23.6% (grade 3: 20.9%, grade 4: 2.7%)	Duration of hypertension, CKD, sedentary lifestyle, smoking
This study	Non-diabetic adults (HbA1c < 6.5%), South Korea	Moderate to severe (Wong and Mitchell grading)	0.8%	Age, higher SBP, HbA1c, creatinine, hemoglobin

Table 5. Literature review on the prevalence and risk factors of hypertensive retinopathy (mainly moderate to severe grades). BMI: Body Mass Index, BP: blood pressure, CKD: chronic kidney disease; DBP: Diastolic Blood Pressure, SBP: Systolic Blood Pressure.

the damage to retinal vessels. The strong correlation between CKD and hypertensive retinopathy observed in several studies can be attributed to these shared mechanisms[23,24]. SBP emerged as the most significant predictor of hypertensive retinopathy, which is consistent with previous findings and highlights its critical role in the disease process. Elevated levels of HbA1c, and creatinine were also identified as risk factors, pointing to the influence of systemic metabolic disturbances on retinal vascular health[28]. These results are in line with studies from other regions and populations, reinforcing the recognition of hypertensive retinopathy as a global indicator of systemic vascular disease.

Diagnosing and studying hypertensive retinopathy is challenging due to the subjective nature of mild hypertensive retinopathy and the diagnostic overlap between moderate to severe hypertensive retinopathy and diabetic retinopathy. Mild hypertensive retinopathy, characterized by subtle changes such as arteriolar narrowing and arteriovenous nicking, is difficult to evaluate consistently across different observers and imaging modalities, leading to variability in assessments and limiting its inclusion in epidemiological studies. Furthermore, the clinical significance of mild hypertensive retinopathy is less clear compared to moderate or severe grades, which are more strongly associated with systemic vascular complications. Moderate and severe hypertensive retinopathy, on the other hand, share retinal features with diabetic retinopathy, such as hemorrhages and exudates, complicating accurate diagnosis and research[29]. These challenges contribute to the scarcity of reliable epidemiological data and hinder the diagnosis of hypertensive retinopathy in routine clinical practice. To address these limitations, this study focused on moderate to severe hypertensive retinopathy, ensuring the inclusion of cases with clear diagnostic criteria and greater clinical relevance. This approach enabled a more precise evaluation of hypertensive retinopathy prevalence and risk factors. However, there is a pressing need for the development of more objective and quantitative diagnostic tools for hypertensive retinopathy, as well as advanced retinal evaluation methods, such as imaging technologies incorporating artificial intelligence[30]. These innovations could improve diagnostic accuracy, support large-scale epidemiological studies, and enhance the clinical management of hypertensive retinopathy as a marker of systemic vascular health.

Although the prevalence of moderate to severe hypertensive retinopathy in the general non-diabetic population was relatively low, the clinical value of the proposed prediction model lies not in broad population-based screening but in risk stratification. Fundoscopic examination, while recommended in major hypertension guidelines as part of target organ damage assessment, is often underutilized in routine clinical practice due to limited access to ophthalmic equipment and trained personnel. In this context, our model serves as a pragmatic clinical decision support tool that leverages routinely collected health parameters (e.g., blood pressure, creatinine, hemoglobin, cholesterol, HbA1c) to identify individuals at elevated risk of hypertensive retinopathy. By stratifying patients based on predicted risk, the model can guide primary care physicians and internists in prioritizing referrals for fundus examination[31], thereby optimizing the allocation of ophthalmologic resources and reducing missed diagnoses in high-risk individuals.

Regarding feasibility and future clinical utility, the model can be integrated into routine clinical workflows through electronic health records or mobile-based platforms. Such integration would allow automatic calculation of hypertensive retinopathy risk at the point of care, facilitating informed decision-making even in the absence of retinal imaging equipment. The development of a web-based risk prediction calculator significantly enhances the clinical utility of these findings[32], providing an easy-to-use tool for healthcare providers to quickly assess the probability of hypertensive retinopathy in individual patients. This is particularly valuable in resource-limited settings or primary care environments. As portable and smartphone-based fundus cameras become increasingly accessible, the model could serve as an initial triage tool to identify patients who should undergo confirmatory imaging[33]. In this way, the model supports the broader goal of early detection and intervention for hypertension-related complications, contributing to more personalized and preventive cardiovascular care.

Despite its contributions, this study has several limitations. First, its cross-sectional design prevents causal inferences about the relationship between risk factors and hypertensive retinopathy. Longitudinal studies are needed to confirm the temporal associations and predictive validity of the identified risk factors. Second, although this study excluded diabetic participants to minimize confounding with diabetic retinopathy, the inclusion of well-controlled diabetes patients (HbA1c < 6.5%) could still introduce subtle overlaps in pathophysiology. Third, the prevalence of hypertensive retinopathy in this study is relatively low, potentially limiting the generalizability of findings to populations with higher hypertension or metabolic disease burdens. Finally, the reliance on fundus photography may overlook subtle retinal changes detectable by more advanced imaging modalities, such as optical coherence tomography angiography[5]. Future studies integrating more comprehensive imaging techniques and longitudinal follow-up are warranted to address these limitations.

Conclusion

This study highlights the prevalence and risk factors of hypertensive retinopathy in non-diabetic adults in South Korea, contributing valuable insights to the global understanding of this condition. The findings reveal a prevalence of 0.8% for moderate to severe hypertensive retinopathy and identify age, SBP, HbA1c, total cholesterol, creatinine, and hemoglobin as significant risk factors. By focusing on a non-diabetic population from KNHANES, this study provides a clearer picture of hypertensive retinopathy that is not confounded by diabetic retinopathy. The development of a practical risk prediction model further enhances the clinical relevance of the study, offering a tool to identify individuals at higher risk of hypertensive retinopathy. These results emphasize the need for effective blood pressure management and metabolic control to prevent hypertensive retinopathy and related systemic complications. Future studies should consider longitudinal designs and advanced imaging technologies to gain deeper insight into the progression and systemic impacts of hypertensive retinopathy.

Data availability

The data utilized in this study are publicly accessible through the Korea National Health and Nutrition Examination Survey (KNHANES) website at "https://knhanes.kdca.go.kr/knhanes/eng/main.do". All methodologies have been detailed within this manuscript.

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Author contributions
Conceptualization & Methodology: S-H Park, T K Yoo Data collection: D Nam, T K Yoo Data processing: D Nam, J Y, Choi, T K Yoo Investigation & Visualization: D Nam, T K Yoo Supervision: J Y, Choi, T K Yoo Writing—original draft: S-H Park, D Nam, T K Yoo Writing—review & editing: S-H Park, J Y, Choi, T K Yoo.

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Declarations

Competing interests
T K Yoo is an advisory board member of MediWhale and has received consultant fees as part of the standard compensation package. The remaining authors declare no conflicts of interest.

Ethics approval and consent to participate
This study was conducted using anonymized data from the publicly available KNHANES dataset, which was approved by the Institutional Review Board (IRB) of the Korea Centers for Disease Control and Prevention (IRB numbers: 2008-04EXP-01-C, 2009-01CON-03–2 C, 2010-02CON-21-C, 2011-02-CON-06-C, and 2012-01-EXP-01–2 C). Written informed consent was obtained from all participants prior to their inclusion in the survey. As the study exclusively utilized publicly available data, additional IRB approval was not required. The study complied with the principles outlined in the Declaration of Helsinki, ensuring ethical standards were maintained throughout.

Consent for publication
Not applicable, as this study does not include identifiable individual data, images, or personal information requiring consent for publication.

Additional information
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