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Research Article

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Deep learning-based retinal risk stratification for 10-year atherosclerotic cardiovascular mortality in patients with hypertension and diabetes: a retrospective cohort study

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ABSTRACT

Background: Cardiovascular risk stratification in patients with hypertension and diabetes remains suboptimal. We evaluated the prognostic and incremental value of Dr. Noon CVD, a deep learning (DL)-based retinal biomarker, for 10-year atherosclerotic cardiovascular (ASCVD) mortality.
Methods: This retrospective, single-center, primary prevention cohort study included 7,832 Korean patients with hypertension or diabetes diagnosed on or before retinal fundus photography (2005 to 2022). Patients with prior cardiovascular disease were excluded. The primary outcome of 10-year ASCVD mortality and a sensitivity analysis of 5-year mortality were stratified using 4-tier and 3-tier Dr. Noon CVD systems, respectively. Multivariable Cox proportional hazards models were adjusted for traditional risk factors and chronic kidney disease (CKD), and incremental predictive value was assessed using the change in the C-index (ΔC-index) and net reclassification improvement (NRI).
Results: In the overall population, the Dr. Noon CVD score was independently associated with 10-year ASCVD mortality (hazard ratio [HR] trend, 1.49; 95% confidence interval [CI], 1.21 to 1.85; $P < 0.001$) after full adjustment for traditional factors and CKD. Adding Dr. Noon CVD to the clinical model significantly improved discrimination (ΔC-index, 0.030; $P = 0.001$)

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Abbreviations

AI, artificial intelligence; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DL, deep learning; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HR, hazard ratio; HTR, hypertensive retinopathy; ICD-10, International Classification of Diseases, 10th Revision; IRB, Institutional Review Board; non-HDL-C, non-high density lipoprotein cholesterol; NRI, net reclassification improvement; PCE, Pooled Cohort Equations; PREVENT, Predicting Risk of Cardiovascular Disease Events; PY, person-years; SD, standard deviation.

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Competing interest

Nam D, Seo J, Thakur S, Nusinovici S, and Rim TH are employees of Mediwhale Inc. Rim TH, Lee YH, and Lee CJ own stock in Mediwhale Inc. Yoo TK, Jang M, and Joe BH have served as consultants for Mediwhale Inc. Park S reported receipt of personal fees from Viatris Inc., Organon & Co., Boryung Corporation, Handok Inc., Hanmi Pharmaceutical Co., Ltd., Daewoong Pharmaceutical Co., Ltd.,

and risk reclassification (NRI, 0.484; 95% CI, 0.233 to 0.666; $P < 0.001$). This independent prognostic value was consistent in both hypertension (10-year HR trend, 1.48; $P = 0.006$) and diabetes (10-year HR trend, 1.42; $P = 0.003$) subgroups. The reclassification improvement was greater in the diabetes than the hypertension subgroup (10-year NRI, 0.481 vs. 0.413). The score's prognostic value was independent of diabetic retinopathy status.
Conclusions: DL-based retinal imaging provides prognostic value for 10-year ASCVD mortality independent of the available clinical risk factors (age, sex, hypertension, diabetes, and CKD) and consistent under adjustment for available laboratory measures, supporting its role as an accessible opportunistic screening tool for long-term primary prevention in cardiometabolic clinics.

Keywords: Artificial intelligence; Deep learning; Diagnostic imaging; Retina; Cardiovascular diseases; Risk assessment; Diabetes mellitus; Hypertension; Renal insufficiency, chronic

BACKGROUND

Cardiovascular disease (CVD) remains a leading cause of mortality worldwide, and accurate risk stratification is essential for effective primary prevention [1]. Although risk calculators such as the Pooled Cohort Equations (PCE) and the Predicting Risk of Cardiovascular Disease Events (PREVENT) equation are widely used for primary prevention [2-4], significant residual risk remains, and these equations require laboratory and blood-pressure inputs that are not always available in routine practice. This is particularly evident in cardiometabolic disease cohorts where vascular aging often accelerates subclinically [2]. Retinal microvascular changes provide direct insight into systemic vascular health. In diabetes and hypertension, chronic metabolic and hemodynamic burdens induce widespread microvascular deterioration and distinct alterations, including arteriolar narrowing and arteriovenous nicking [5,6]. These retinal microvascular patterns are powerful predictors of cardiovascular events, independent of blood pressure and glucose levels [7,8]. Despite this predictive potential, the integration of quantitative retinal data into routine cardiovascular management remains highly limited.

Advances in oculomics have enabled the development of deep learning (DL) systems capable of predicting CVD risk directly from retinal fundus images [9,10]. Dr. Noon CVD (Mediwhale Inc., Seoul, Republic of Korea) is a commercialized algorithm that estimates cardiovascular risk by analyzing retinal features [11]. While the model has shown predictive performance in previous cohorts [11-13], validation in real-world clinical practice remains insufficient. Prior studies—including those in related conditions such as hypertensive retinopathy (HTR) and retinal vein occlusion—were frequently limited by cross-sectional designs, small sample sizes, or inclusion of patients with established CVD, and largely assessed associations with risk scores rather than incident cardiovascular events [14,15].

Therefore, key questions remain regarding its prognostic utility in these specific clinical populations. Given the reno-retinal axis and the shared microvascular pathology between the eye and kidney [16], it is important to determine whether retinal artificial intelligence (AI) provides prognostic value independent of renal function or if it simply reflects renal dysfunction. It is also uncertain whether these algorithms can provide incremental prognostic value in these high-risk populations independent of their respective standard-of-care assessments. Specifically, the question is whether retinal AI can identify residual cardiovascular

Dong-A ST Co., Ltd., Celltrion Inc., Les Laboratoires Servier, Daiichi Sankyo Co., Ltd., Daewon Pharmaceutical Co., Ltd., Ahn-Gook Pharmaceutical Co., Ltd., and SkyLabs Inc., and owns stock in Mediwhale Inc. Lee M has received lecture honoraria from JW Pharmaceutical Corporation, Boryung Corporation, Eli Lilly and Company, Merck Sharp & Dohme (MSD), HK inno.N Corp., Servier Korea Co., Ltd., Handok Inc., Daewoong Pharmaceutical Co., Ltd., Kukje Pharm Co., Ltd., GC Biopharma Corp., Jeil Pharmaceutical Co., Ltd., and Boehringer Ingelheim. All other authors declare no competing interests.

Availability of data and materials

The datasets used and/or analyzed during the current study are not publicly available due to patient privacy restrictions and institutional data governance policies but are available from the corresponding author on reasonable request and with permission of Severance Hospital, Yonsei University Health System.

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the Institutional Review Board (IRB) of Severance Hospital, Yonsei University Health System (approval number: 4-2022-0531). The requirement for informed consent was waived by the IRB due to the retrospective nature of the study.

Consent for publication

Not applicable.

Authors' contributions

Conceptualization: Nam D, Park S; Data curation: Lee CJ, Kim H, Park S; Formal analysis: Nam D, Lee CJ, Kim H, Park S; Methodology: Lee CJ, Kim H, Park S; Resources: Park S; Supervision: Park S; Writing - original draft: Nam D, Seo J, Thakur S, Nusinovici S, Rim TH, Hwang S; Writing - review & editing: Nusinovici S, Yoo TK, Jang M, Joe BH, Kim HK, Lee M, Lee YH, Park S.

risk in patients with hypertension and diabetes that is currently missed by conventional clinical profiling. If Dr. Noon CVD can stratify long-term mortality risk independent of standard clinical factors and renal function, it could serve as a vital opportunistic screening tool. We evaluated the 10-year predictive performance of Dr. Noon CVD in a rigorously defined primary prevention cohort of Korean patients with cardiometabolic disease and quantified its incremental value over conventional risk factors and chronic kidney disease (CKD).

METHODS

Ethics statement

This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (No. 4-2022-0531), and informed consent was waived. Full details are provided in the Declarations section.

Study design and population

We conducted a retrospective cohort study at Severance Hospital, Yonsei University Health System. We included patients who underwent digital fundus photography between July 1, 2005, and September 30, 2022, and had a diagnosis of hypertension (International Classification of Diseases, 10th Revision [ICD-10] I10–I15) or diabetes (ICD-10 E10–E14) on or before the date of the index fundus examination. Exclusion criteria were age < 20 or > 80 years and poor image quality preventing retinal AI analysis. To establish a definitive primary prevention cohort, patients with a history of CVD prior to baseline, identified by ICD-10 codes for coronary heart disease (I20–I25), cerebrovascular disease (I60–I69), transient ischemic attack (G45), and heart failure (I50, I11.0, I13.0, and I13.2), were also excluded (**Supplementary Fig. 1**).

Retinal imaging and DL-based cardiovascular risk assessment (Dr. Noon CVD)

Digital fundus photographs were captured using various standard non-mydriatic fundus cameras, including the Visucam series (200, PRO NM, 224, NM FA, and 524; Carl Zeiss Meditec AG, Jena, Germany), CR-2 (Canon Inc., Tokyo, Japan), and HOCT-1F (Huvitz Co., Ltd., Anyang, Republic of Korea). These devices provided standard field-of-view images, typically ranging from 30 to 45 degrees.

The Dr. Noon CVD score is a DL-based software as a medical device that predicts cardiovascular risk from retinal fundus photographs of both eyes. The algorithm architecture and reproducibility have been described elsewhere [11,12]. Briefly, it generates a continuous score from 0 to 100, trained to predict the probability of significant coronary artery calcium (CAC). Previous prospective validations have demonstrated excellent precision for this algorithm, with repeatability and reproducibility intraclass correlation coefficients exceeding 0.99 across diverse imaging platforms [17].

For this study, we applied a dual stratification approach based on the clinical follow up horizon. For the primary 10-year ASCVD mortality analysis, the population was stratified into a granular 4-tier system: Group 1a (scores < 41), Group 1b (scores 41 to 45), Group 2 (scores 46 to 50), and Group 3 (scores ≥ 51). For the secondary 5-year sensitivity analysis, we adopted a 3-tier system (Group 1: scores < 46, Group 2: scores 46 to 50, Group 3: scores ≥ 51). All cut-points were prespecified and were not derived from the present outcome data: the 41-point threshold corresponds to a previously validated high-risk cut-point [11,12], while the 46- and

51-point thresholds were operational cut-points from the developer's risk-tiering scheme used for clinical communication. Because the score is floored to an integer, these thresholds map exactly to the score bins; we additionally analyzed the score continuously (per-standard-deviation) and as an ordinal trend, neither of which depends on any threshold.

Covariates and definitions

Baseline clinical characteristics including age and sex were extracted from electronic health records. All comorbidities and clinical conditions were defined exclusively through ICD-10 diagnosis codes and medication prescription history. Hypertension was identified via diagnosis codes (I10–I15) and relevant prescriptions. Diabetes mellitus was defined by diagnosis codes (E10–E14) and medication prescription history. CKD was identified using ICD-10 code N18. Diabetic retinopathy (DR) was identified from ICD-10 codes for diabetic ophthalmic complications (E10.3, E11.3, E12.3, E13.3, E14.3, H28.0, and H36.0) recorded on or before the index fundus examination. In a prespecified sensitivity analysis, available laboratory measures were added as continuous covariates (hemoglobin A1c [HbA1c], non-high-density lipoprotein cholesterol [non-HDL-C], and estimated glomerular filtration rate [eGFR]) to capture the severity of diabetes, dyslipidemia, and renal dysfunction beyond their binary diagnostic indicators. These measures were incompletely recorded across the study period (missing: HbA1c 55.9%, non-HDL-C 56.2%, and eGFR 37.1%; all 3 available in 2,547 patients [32.5%]); missing values were handled by multiple imputation by chained equations (20 imputations), with the complete-laboratory subset (n = 2,547) analyzed as a further sensitivity.

The primary and secondary outcomes were 10-year and 5-year atherosclerotic cardiovascular (ASCVD) mortality, respectively. ASCVD mortality was defined from the death-certificate underlying cause (ICD-10 codes I20–I25, I60–I69, I50, and I10–I13); the broad circulatory definition (I00–I99) was retained as a sensitivity analysis, and non-cardiovascular deaths were censored at the date of death (cause-specific hazards). Mortality data and vital status were verified using linkage to the national death registry database managed by the Korea Disease Control and Prevention Agency.

Statistical analysis

All statistical analyses were performed using R software, version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Baseline characteristics were compared across the Dr. Noon CVD risk groups. Continuous variables were expressed as median with interquartile range and compared using the Kruskal-Wallis test. Categorical variables were presented as numbers with percentages and analyzed using the χ^2 test.

Cumulative incidence of ASCVD mortality was estimated via the Kaplan-Meier method, and differences between risk groups were evaluated using log-rank tests. Cox proportional hazards models were used to determine hazard ratios (HRs) and 95% confidence intervals (CI) across 3 models: an unadjusted model, a traditional risk-adjusted model (adjusting for age, sex, hypertension, and diabetes), and a full-adjusted model (further adjusting for CKD). In the 4-tier model, Group 1a served as the reference, while in the 3-tier model, Group 1 was the reference. Tests for trend were performed by analyzing the categorical risk groups as a continuous numeric variable (HR trend). Subgroup analyses were conducted identically in the hypertension and diabetes populations, with the respective defining disease condition removed from the adjustment models. Incidence rates were expressed as the number of events per 1,000 person-years.

Incremental predictive value was evaluated by comparing nested models. Model 1 adjusted for traditional risk factors (age, sex, hypertension, and diabetes). Model 2 incorporated variables in Model 1 plus CKD. Model 3 added the Dr. Noon CVD risk group to Model 2. Model discrimination was assessed using Harrell's C-index, and the statistical significance of the change in C-index (ΔC-index) was tested. Risk reclassification was quantified by the category-free continuous net reclassification improvement (NRI) for survival data. Total NRI, event NRI, and non-event NRI were calculated. The 95% CIs and 2-sided *P*-values for both ΔC-index and NRI were derived using bootstrap resampling with 2,000 replicates. Statistical significance was defined as a 2-sided *P*-value < 0.05.

In prespecified sensitivity analyses evaluating whether the score merely reflected overt retinal disease, we examined its correlation with ICD-defined DR using Spearman rank correlation, additionally adjusted the full-adjusted model for ICD-defined DR, and repeated the analysis within strata defined by the presence or absence of DR; the proportional-hazards assumption was evaluated using Schoenfeld residuals. The specific underlying causes of cardiovascular death were tabulated from death-certificate codes to characterize the composition of the endpoint.

RESULTS

Baseline demographics and clinical characteristics

A total of 17,771 patients with a hypertension or diabetes diagnosis and gradable digital fundus photography were identified. We first restricted the cohort to the 15,164 patients whose hypertension or diabetes had been diagnosed on or before the index fundus examination, ensuring that exposure was ascertained at baseline; we then excluded 6,501 with a history of CVD and 831 outside the inclusion age criteria, leaving 7,832 patients for the final analysis (**Supplementary Fig. 1**). Among the final cohort, 4,923 patients had hypertension and 5,127 had diabetes (subgroups were not mutually exclusive). The median age was 62 years, and 49.3% were male. Within the 4-tier stratification system, 2,534 patients were in Group 1a, 1,868 in Group 1b, 1,727 in Group 2, and 1,703 in Group 3. Patients in the highest-risk tier (Group 3) were older (median age 68 vs. 54 years in Group 1a) and had a higher prevalence of diabetes (81.3% vs. 53.4%) and CKD (8.5% vs. 6.1%) than the lowest-risk tier. Hypertension prevalence decreased across risk tiers, from 67.1% in Group 1a to 53.6% in Group 3 (**Table 1**).

Prognostic performance for 10-year and 5-year ASCVD mortality

Over 10 years, 100 ASCVD deaths occurred. The 4-tier system demonstrated a clear risk gradient. The incidence per 1,000 person-years increased from 0.72 in Group 1a to 5.48 in Group 3. In the full-adjusted model accounting for age, sex, hypertension, diabetes, and CKD, Group 3 showed a significantly elevated risk of 10-year ASCVD mortality compared with Group 1a (HR, 3.66; 95% CI, 1.69 to 7.89; $P = 0.001$). The test for trend across risk groups was highly significant (HR trend, 1.49; 95% CI, 1.21 to 1.85; $P < 0.001$; per-standard deviation [SD] HR, 1.64; 95% CI, 1.30 to 2.06) (**Table 2**, **Fig. 1A**).

In the 5-year analysis using the 3-tier system, 61 ASCVD deaths occurred. The full-adjusted model demonstrated consistent prognostic value. Group 3 had an approximately 2-fold higher risk than Group 1 (HR, 2.41; 95% CI, 1.25 to 4.66; $P = 0.009$), with a significant trend (HR trend, 1.55; 95% CI, 1.12 to 2.14; $P = 0.008$) (**Table 2**, **Fig. 1B**). Among the 100 ASCVD deaths over 10 years, the underlying causes were cerebrovascular disease (I60–I69, $n = 37$), ischemic

Table 1. Baseline characteristics of the study population stratified by Dr. Noon CVD risk

Variable	Overall (n = 7,832)	Dr. Noon CVD risk group				*P*-value
		Group 1		Group 2	Group 3	
		Group 1a	Group 1b			
Stratified by 4-tier Dr. Noon CVD group		(n = 2,534)	(n = 1,868)	(n = 1,727)	(n = 1,703)	
Age (yr)	62 [53, 70]	54 [44, 62]	62 [54, 69]	66 [58, 72]	68 [61, 74]	< 0.001
Sex (male)	3,860 (49.3)	1,072 (42.3)	945 (50.6)	875 (50.7)	968 (56.8)	< 0.001
Diabetes	5,127 (65.5)	1,354 (53.4)	1,190 (63.7)	1,199 (69.4)	1,384 (81.3)	< 0.001
Hypertension	4,923 (62.9)	1,700 (67.1)	1,237 (66.2)	1,074 (62.2)	912 (53.6)	< 0.001
CKD	604 (7.7)	154 (6.1)	154 (8.2)	151 (8.7)	145 (8.5)	0.002
HbA1c (%)	6.7 [6.0, 7.8]	6.4 [5.8, 7.4]	6.7 [6.0, 7.7]	6.8 [6.1, 8.0]	7.1 [6.4, 8.2]	< 0.001
Missing	4,377 (55.9)	1,364 (53.8)	1,031 (55.2)	980 (56.7)	1,002 (58.8)	
Non-HDL-C (mg/dL)	121 [95, 151]	125 [100, 152]	120 [95, 150]	117 [90, 149]	118 [91, 148]	< 0.001
Missing	4,403 (56.2)	1,155 (45.6)	1,030 (55.1)	1,066 (61.7)	1,152 (67.6)	
eGFR (mL/min/1.73 m^2)	93.4 [73.0, 103.4]	98.9 [82.7, 109.4]	93.7 [74.5, 102.1]	89.6 [68.8, 99.1]	82.2 [59.9, 95.3]	< 0.001
Missing	2,905 (37.1)	634 (25.0)	659 (35.3)	751 (43.5)	861 (50.6)	
Dr. Noon CVD risk score	45 [40, 50]	36 [31, 39]	44 [43, 45]	49 [48, 50]	56 [53, 60]	< 0.001
5-yr ASCVD mortality	61 (0.8)	8 (0.3)	9 (0.5)	15 (0.9)	29 (1.7)	< 0.001
10-yr ASCVD mortality	100 (1.3)	9 (0.4)	15 (0.8)	24 (1.4)	52 (3.1)	< 0.001
Stratified by 3-tier Dr. Noon CVD group		(n = 4,402)		(n = 1,727)	(n = 1,703)	
Age (yr)		58 [48, 65]		66 [58, 72]	68 [61, 74]	< 0.001
Sex (male)		2,017 (45.8)		875 (50.7)	968 (56.8)	< 0.001
Diabetes		2,544 (57.8)		1,199 (69.4)	1,384 (81.3)	< 0.001
Hypertension		2,937 (66.7)		1,074 (62.2)	912 (53.6)	< 0.001
CKD		308 (7.0)		151 (8.7)	145 (8.5)	0.026
HbA1c (%)		6.6 [5.9, 7.5]		6.8 [6.1, 8.0]	7.1 [6.4, 8.2]	< 0.001
Missing		2,395 (54.4)		980 (56.7)	1,002 (58.8)	
Non-HDL-C (mg/dL)		123 [98, 151]		117 [90, 149]	118 [91, 148]	0.002
Missing		2,185 (49.6)		1,066 (61.7)	1,152 (67.6)	
eGFR (mL/min/1.73 m^2)		97.0 [79.3, 106.7]		89.6 [68.8, 99.1]	82.2 [59.9, 95.3]	< 0.001
Missing		1,293 (29.4)		751 (43.5)	861 (50.6)	
Dr. Noon CVD risk score		40 [35, 44]		49 [48, 50]	56 [53, 60]	< 0.001
5-yr ASCVD mortality		17 (0.4)		15 (0.9)	29 (1.7)	< 0.001
10-yr ASCVD mortality		24 (0.5)		24 (1.4)	52 (3.1)	< 0.001

Values are expressed as median [Q1, Q3] for continuous variables and number (percentage) for categorical variables. *P*-values were determined using the Kruskal-Wallis test (continuous) and χ^2 test (categorical). HbA1c, non-HDL-C, and eGFR were used only in the laboratory-adjusted sensitivity analysis; tabulated distributions are among patients with non-missing values (missing fractions indicated).
CKD, chronic kidney disease; HbA1c, hemoglobin A1c; non-HDL-C, non-high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; ASCVD, atherosclerotic cardiovascular disease; Q1, 25th percentile; Q3, 75th percentile.

heart disease (I20–I25, n = 36), heart failure (I50, n = 16), and hypertensive heart disease (I10–I13, n = 11); the broader I00–I99 definition captured 34 additional non-atherosclerotic circulatory deaths, predominantly cardiac arrest (I46, n = 14) and cardiomyopathy (I42, n = 6) (**Supplementary Table 1**). The association was consistent under the I00–I99 definition (10-year HR trend, 1.62; 95% CI, 1.34 to 1.96) (**Supplementary Table 2**).

Risk stratification in high-risk subgroups: hypertension and diabetes

The Dr. Noon CVD score maintained independent prognostic value across both the hypertension (n = 4,923) and diabetes (n = 5,127) subgroups (**Supplementary Tables 3** and **4**). In the hypertension subgroup, 10-year ASCVD mortality occurred in 57 patients. Group 3 had an adjusted HR of 3.15 (95% CI, 1.24 to 8.02; P = 0.016) compared with Group 1a, with a significant trend (HR trend, 1.48; 95% CI, 1.12 to 1.96; P = 0.006) (**Table 3**, **Fig. 2A**). The 5-year analysis in this subgroup showed a significant trend (HR trend, 1.56; 95% CI, 1.04 to 2.33; P = 0.030) (**Supplementary Table 5**, **Supplementary Fig. 2A**).

In the diabetes subgroup, 10-year ASCVD mortality occurred in 79 patients. Group 3 had an adjusted HR of 2.91 (95% CI, 1.25 to 6.77; P = 0.013) compared with Group 1a, with a significant

Table 2. Association of Dr. Noon CVD risk score with 5- and 10-year ASCVD mortality

Dr. Noon CVD group	No.	Cases	PY	Incidence, per 1,000 PY	Unadjusted HR		Traditional risk-adjusted HR		Full-adjusted HR	
					95% CI	*P*-value	95% CI[a]	*P*-value	95% CI[b]	*P*-value
Stratified by 4-tier Dr. Noon CVD risk group (10-yr ASCVD mortality)										
Group 1a	2,534	9	12,465	0.72	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 1b	1,868	15	7,619	1.97	**2.76 (1.21, 6.31)**	**0.016**	1.85 (0.80, 4.31)	0.153	1.81 (0.78, 4.21)	0.171
Group 2	1,727	24	7,468	3.21	**4.47 (2.08, 9.61)**	**< 0.001**	**2.58 (1.16, 5.76)**	**0.020**	**2.52 (1.13, 5.63)**	**0.024**
Group 3	1,703	52	9,487	5.48	**7.45 (3.67, 15.13)**	**< 0.001**	**3.74 (1.73, 8.08)**	**< 0.001**	**3.66 (1.69, 7.89)**	**< 0.001**
HR trend (HR per 1-tier change)[c]					**1.84 (1.52, 2.22)**	**< 0.001**	**1.50 (1.21, 1.86)**	**< 0.001**	**1.49 (1.21, 1.85)**	**< 0.001**
HR per SD					**1.98 (1.64, 2.40)**	**< 0.001**	**1.65 (1.31, 2.08)**	**< 0.001**	**1.64 (1.30, 2.06)**	**< 0.001**
Stratified by 3-tier Dr. Noon CVD risk group (5-yr ASCVD mortality)										
Group 1	4,402	17	14,143	1.20	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1,727	15	5,295	2.83	**2.35 (1.17, 4.70)**	**0.016**	1.69 (0.82, 3.47)	0.156	1.65 (0.80, 3.39)	0.174
Group 3	1,703	29	6,162	4.71	**3.88 (2.13, 7.07)**	**< 0.001**	**2.48 (1.28, 4.79)**	**0.007**	**2.41 (1.25, 4.66)**	**0.009**
HR trend (HR per 1-tier change)[c]					**1.95 (1.46, 2.61)**	**< 0.001**	**1.56 (1.13, 2.16)**	**0.007**	**1.55 (1.12, 2.14)**	**0.008**
HR per SD					**1.89 (1.47, 2.42)**	**< 0.001**	**1.63 (1.21, 2.19)**	**0.001**	**1.60 (1.19, 2.16)**	**0.002**

HR per 1-SD increase in the continuous Dr. Noon CVD score, standardized within the analyzed population. Bold values indicate statistical significance at *P*-value < 0.05.
PY, person-years; HR, hazard ratio; CI, confidence interval; ASCVD, atherosclerotic cardiovascular disease; SD, standard deviation.
[a]Adjusted for age, sex, hypertension, and diabetes; [b]Adjusted for age, sex, hypertension, diabetes, and chronic kidney disease.
[c]The *P*-value listed for 'HR trend' represents the test for trend across risk groups.

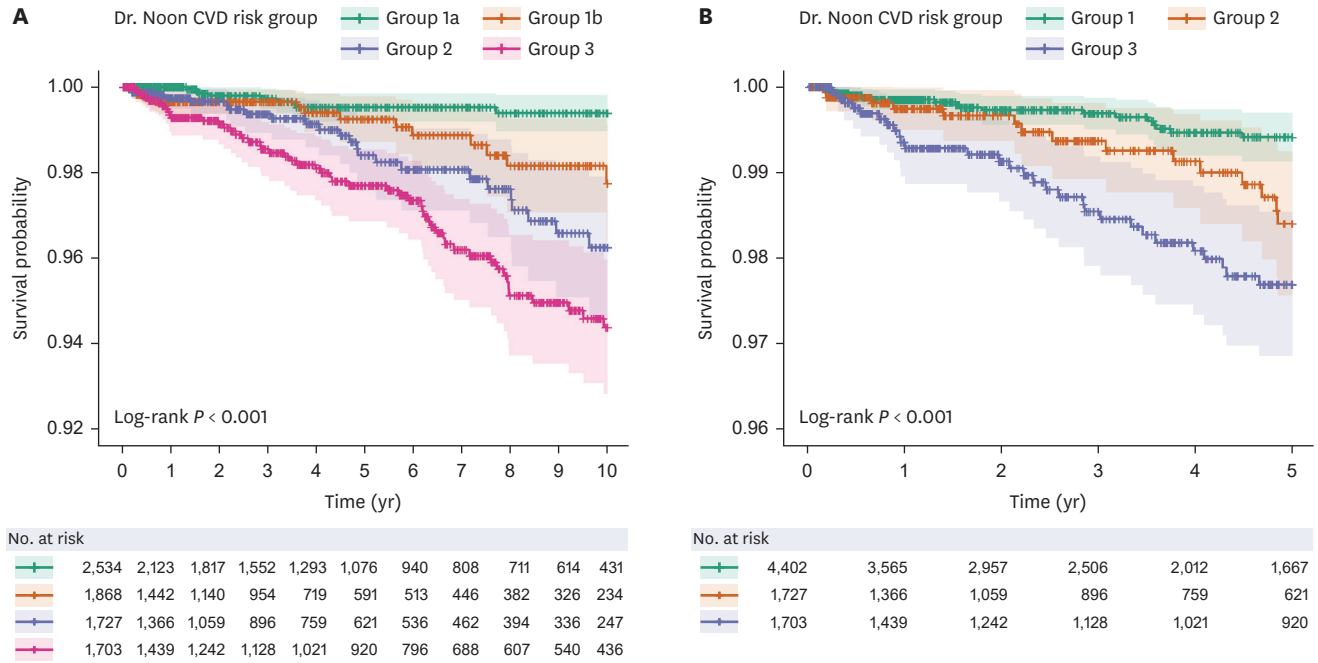


Fig. 1. Kaplan-Meier curves for 10- and 5-year atherosclerotic cardiovascular disease mortality by Dr. Noon CVD groups. (A) Ten-year follow-up analysis comparing 4 risk groups (Group 1a, 1b, 2, and 3). (B) Five-year follow-up analysis comparing 3 risk groups (Group 1, 2, and 3). Shaded bands represent 95% confidence intervals for each survival trajectory. Differences in survival distributions were assessed using the log-rank test.

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Table 3. Dr. Noon CVD risk scores and 10-year ASCVD mortality in hypertension and diabetes subgroups

Dr. Noon CVD group	No.	Cases	PY	Incidence, per 1,000 PY	Unadjusted HR		Traditional risk-adjusted HR		Full-adjusted HR	
					95% CI	*P*-value	95% CI	*P*-value	95% CI	*P*-value
Patients with hypertension stratified by 4-tier Dr. Noon CVD risk group (10-yr ASCVD mortality)										
Group 1a	1,700	7	8,285	0.84	1.00 (Reference)		1.00 (Reference)[a]		1.00 (Reference)[b]	
Group 1b	1,237	9	5,074	1.77	2.13 (0.79, 5.71)	0.134	1.42 (0.51, 3.92)[a]	0.498	1.39 (0.50, 3.83)[b]	0.529
Group 2	1,074	14	4,565	3.07	**3.66 (1.48, 9.06)**	**0.005**	2.06 (0.79, 5.41)[a]	0.140	2.02 (0.77, 5.29)[b]	0.153
Group 3	912	27	4,579	5.90	**6.94 (3.02, 15.94)**	**< 0.001**	**3.25 (1.28, 8.26)[a]**	**0.013**	**3.15 (1.24, 8.02)[b]**	**0.016**
HR trend (HR per 1-tier change)[c]					**1.88 (1.47, 2.40)**	**< 0.001**	**1.49 (1.13, 1.97)[a]**	**0.005**	**1.48 (1.12, 1.96)[b]**	**0.006**
HR per SD					**2.01 (1.54, 2.61)**	**< 0.001**	**1.55 (1.13, 2.14)[a]**	**0.007**	**1.54 (1.12, 2.12)[b]**	**0.008**
Patients with diabetes stratified by 4-tier Dr. Noon CVD risk group (10-yr ASCVD mortality)										
Group 1a	1,354	7	6,642	1.05	1.00 (Reference)		1.00 (Reference)[d]		1.00 (Reference)[e]	
Group 1b	1,190	10	4,706	2.12	2.04 (0.77, 5.35)	0.149	1.48 (0.56, 3.96)[d]	0.431	1.44 (0.54, 3.84)[e]	0.469
Group 2	1,199	19	5,220	3.64	**3.46 (1.46, 8.24)**	**0.005**	2.26 (0.92–5.54)[d]	0.074	2.19 (0.90, 5.37)[e]	0.086
Group 3	1,384	43	7,980	5.39	**5.03 (2.26, 11.18)**	**< 0.001**	**3.01 (1.29, 7.01)[d]**	**0.011**	**2.91 (1.25, 6.77)[e]**	**0.013**
HR trend (HR per 1-tier change)[c]					**1.65 (1.33, 2.06)**	**< 0.001**	**1.43 (1.13, 1.81)[d]**	**0.003**	**1.42 (1.12, 1.80)[e]**	**0.003**
HR per SD					**1.82 (1.46, 2.27)**	**< 0.001**	**1.63 (1.28, 2.08)[d]**	**< 0.001**	**1.61 (1.26, 2.06)[e]**	**< 0.001**

HR per 1-SD increase in the continuous Dr. Noon CVD score, standardized within the analyzed population. Bold values indicate statistical significance at *P*-value < 0.05.
PY, person-years; HR, hazard ratio; CI, confidence interval; ASCVD, atherosclerotic cardiovascular disease; SD, standard deviation.
[a]Adjusted for age, sex, and diabetes; [b]Adjusted for age, sex, diabetes, and chronic kidney disease.
[c]The *P*-value listed for 'HR trend' represents the test for trend across risk groups.
[d]Adjusted for age, sex, and hypertension; [e]Adjusted for age, sex, hypertension, and chronic kidney disease.

trend (HR trend, 1.42; 95% CI, 1.12 to 1.80; $P = 0.003$) (**Table 3**, **Fig. 2B**). The 5-year analysis showed an HR trend of 1.38 (95% CI, 0.97 to 1.96; $P = 0.075$); the continuous per-SD association remained significant (HR, 1.56; 95% CI, 1.13 to 2.14; $P = 0.007$) (**Supplementary Table 5**, **Supplementary Fig. 2B**). The Dr. Noon CVD score was only weakly correlated with ICD-defined DR (median 49 vs 44; Spearman rho = 0.28, $P < 0.001$), and among the 5,562 patients (71%) without coded retinopathy it remained associated with 10-year ASCVD mortality with an effect comparable to the overall cohort (HR trend, 1.47; 95% CI, 1.08 to 2.00), persisting after adjustment for DR (HR trend, 1.41; 95% CI, 1.13 to 1.75) (**Supplementary Tables 6** and **7**). The proportional-hazards assumption was not violated in the overall full-adjusted model (global Schoenfeld test, $P = 0.353$) or in the DR-stratified and DR-adjusted models (global $P \geq 0.251$). In a prespecified laboratory-adjusted sensitivity analysis in which the binary comorbidity indicators were replaced by continuous HbA1c, eGFR, and non-HDL-C (multiple imputation, m = 20), the association with 10-year ASCVD mortality was essentially unchanged from the primary model (HR trend, 1.47; 95% CI, 1.18 to 1.83; $P < 0.001$); the complete-laboratory subset was directionally concordant though underpowered ($n = 2,547$, 31 events; HR trend, 1.37; 95% CI, 0.95 to 1.97) (**Supplementary Table 8**).

Incremental predictive value of Dr. Noon CVD over standard clinical models

In the overall population for 10-year mortality, adding the retinal AI increased the C-index from 0.690 to 0.721 (ΔC-index, +0.030; $P = 0.001$), a significant improvement, and the reclassification analysis demonstrated a significant improvement in risk assignment,

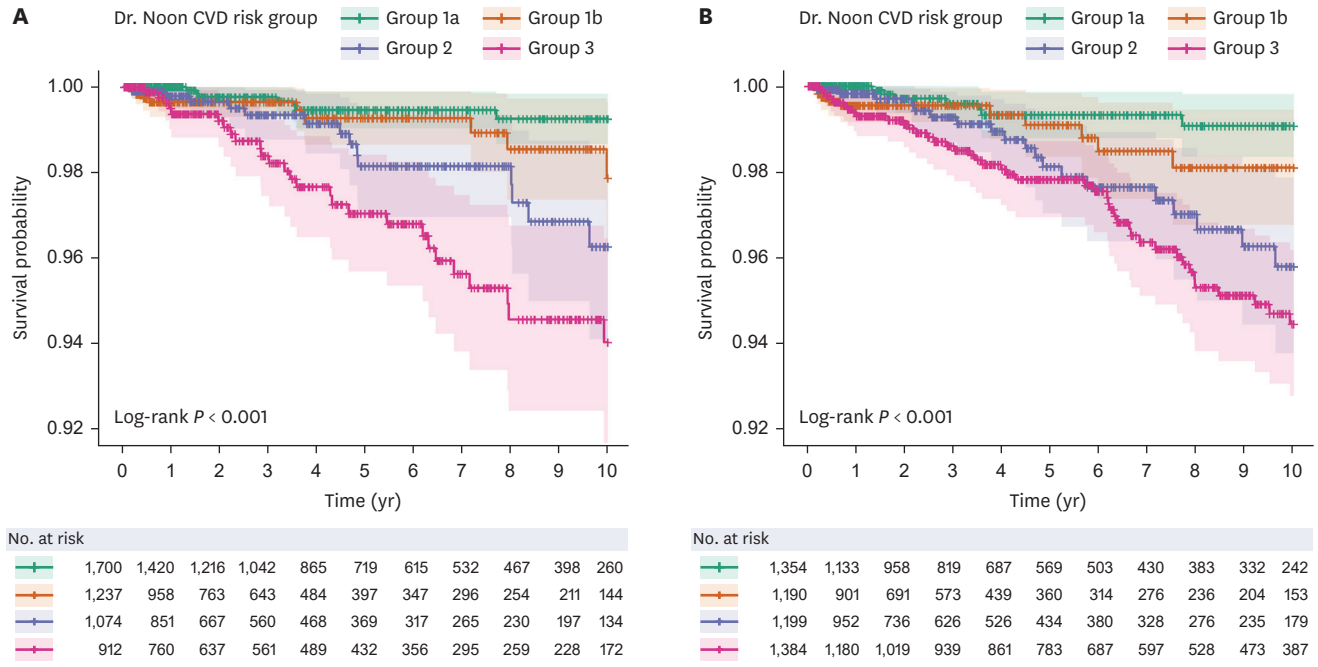


Fig. 2. Kaplan-Meier curves for 10-year atherosclerotic cardiovascular disease mortality by Dr. Noon CVD groups in hypertension and diabetes. Panels show 10-year follow-up analysis in (A) hypertension and (B) diabetes subgroups. Survival trajectories are stratified by the 4-tier risk classification system (Group 1a, 1b, 2, and 3). Shaded bands represent 95% confidence intervals. Differences in survival distributions were assessed using the log-rank test.

with a total NRI of 0.484 (95% CI, 0.233 to 0.666) (**Table 4**). For the overall 5-year model, the C-index increased from 0.683 to 0.710 (ΔC-index, +0.027; $P = 0.037$), and the total NRI was 0.395 (95% CI, 0.108 to 0.632) (**Table 4**).

Subgroup analyses revealed distinct baseline predictive performances. In the hypertension subgroup, the baseline 10-year C-index (0.691) improved to 0.723 upon adding Dr. Noon CVD, a significant gain in discrimination (ΔC-index, +0.032; $P = 0.024$), with a total NRI of 0.413 (95% CI, 0.078 to 0.710) (**Supplementary Table 9**). In the 5-year analysis of the hypertension subgroup, the C-index increased from 0.693 to 0.720 (ΔC-index, +0.027; $P = 0.056$), and the total NRI was 0.400 (95% CI, 0.046 to 0.729) (**Supplementary Table 9**).

In the diabetes subgroup, baseline clinical models showed notably lower predictive power compared to the overall and hypertension cohorts. For 10-year mortality, adding the AI increased the baseline C-index from 0.659 to 0.685 (ΔC-index, +0.026; $P = 0.040$) and yielded a significant total NRI of 0.481 (95% CI, 0.230 to 0.665) (**Supplementary Table 10**). In the 5-year analysis, the increment was attenuated (C-index, 0.660 to 0.676; ΔC-index, +0.016, $P = 0.220$), and the total NRI did not reach statistical significance (0.296; 95% CI, −0.007 to 0.597) (**Supplementary Table 10**).

DISCUSSION

This study establishes the independent prognostic value of the Dr. Noon CVD score for predicting long-term ASCVD mortality in a rigorously defined primary prevention cohort of patients with cardiometabolic disease. By utilizing a comprehensive 10-year follow up horizon, the algorithm successfully stratified mortality risk across the overall population

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Table 4. Incremental predictive value of Dr. Noon CVD for 5- and 10-year ASCVD mortality

Variable	Model 1[a]		Model 2[b]		Model 3[c]	
	aHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value
Stratified by 4-tier Dr. Noon CVD risk group (10-yr ASCVD mortality)						
Age	**1.06 (1.04, 1.09)**	**< 0.001**	**1.06 (1.04, 1.09)**	**< 0.001**	**1.05 (1.02, 1.07)**	**< 0.001**
Sex	**1.71 (1.14, 2.56)**	**0.009**	**1.68 (1.12, 2.51)**	**0.012**	1.48 (0.98, 2.22)	0.059
Hypertension	1.11 (0.71, 1.73)	0.653	1.04 (0.66, 1.64)	0.854	1.09 (0.69, 1.72)	0.706
Diabetes	**1.91 (1.11, 3.27)**	**0.019**	**1.84 (1.07, 3.17)**	**0.027**	1.52 (0.88, 2.64)	0.136
CKD	-		1.90 (0.98, 3.71)	0.059	1.83 (0.93, 3.58)	0.078
Dr. Noon CVD group[d]						
Group 1a	-		-		1.00 (Reference)	
Group 1b	-		-		1.81 (0.78, 4.21)	0.171
Group 2	-		-		**2.52 (1.13, 5.63)**	**0.024**
Group 3	-		-		**3.66 (1.69, 7.89)**	**< 0.001**
HR trend (per 1-tier increase)	-		-		**1.49 (1.21, 1.85)**	**< 0.001**
Model performance[e]						
C-index	0.683 (0.629, 0.744)		0.690 (0.635, 0.755)		0.721 (0.670, 0.783)	
Incremental improvement[e]			(Model 2 vs. Model 1)		(Model 3 vs. Model 2)	
ΔC-index	-		+0.007 (−0.001, 0.029)	0.183	**+0.030 (0.006, 0.065)**	**0.001**
NRI	-		0.093 (−0.078, 0.224)[f]	0.408	**0.484 (0.233, 0.666)**	**< 0.001**
Event NRI	-		−0.716 (−0.879, 0.837)[f]	0.121	**0.225 (0.028, 0.376)**	**0.017**
Non-event NRI	-		0.808 (−0.809, 0.855)[f]	0.121	**0.259 (0.176, 0.334)**	**< 0.001**
Stratified by 3-tier Dr. Noon CVD risk group (5-yr ASCVD mortality)						
Age	**1.05 (1.02, 1.08)**	**< 0.001**	**1.05 (1.02, 1.08)**	**< 0.001**	**1.04 (1.01, 1.06)**	**0.010**
Sex	1.61 (0.96, 2.68)	0.070	1.56 (0.93, 2.61)	0.089	1.42 (0.85, 2.39)	0.185
Hypertension	1.63 (0.92, 2.88)	0.096	1.46 (0.82, 2.63)	0.202	1.52 (0.84, 2.74)	0.164
Diabetes	**2.34 (1.20, 4.54)**	**0.012**	**2.21 (1.13, 4.30)**	**0.020**	1.89 (0.96, 3.72)	0.066
CKD	-		**2.23 (1.07, 4.61)**	**0.031**	**2.14 (1.03, 4.44)**	**0.041**
Dr. Noon CVD group[d]						
Group 1	-		-		1.00 (Reference)	
Group 2	-		-		1.65 (0.80, 3.39)	0.174
Group 3	-		-		**2.41 (1.25, 4.66)**	**0.009**
HR trend (per 1-tier increase)	-		-		**1.55 (1.12, 2.14)**	**0.008**
Model performance[e]						
C-index	0.670 (0.618, 0.745)		0.683 (0.624, 0.759)		0.710 (0.652, 0.785)	
Incremental improvement[e]			(Model 2 vs. Model 1)		(Model 3 vs. Model 2)	
ΔC-index	-		+0.013 (−0.002, 0.041)	0.210	**+0.027 (0.001, 0.068)**	**0.037**
NRI	-		0.145 (−0.025, 0.346)[f]	0.110	**0.395 (0.108, 0.632)**	**0.012**
Event NRI	-		−0.679 (−0.829, 0.831)[f]	0.080	0.124 (−0.086, 0.303)	0.253
Non-event NRI	-		0.824 (−0.801, 0.856)[f]	0.080	**0.272 (0.186, 0.353)**	**0.015**

Bold values indicate statistical significance at *P*-value < 0.05.
ASCVD, atherosclerotic cardiovascular disease; aHR, adjusted hazard ratio; CI, confidence interval; CKD, chronic kidney disease; NRI, net reclassification improvement.
[a]Model 1 was adjusted for age, sex, hypertension, and diabetes; [b]Model 2 included all variables in Model 1 plus CKD; [c]Model 3 included all variables in Model 2 plus the Dr. Noon CVD risk group.
[d]Dr. Noon CVD risk group was categorized into 3 groups for the 5-year analysis and 4 groups for the 10-year analysis.
[e]C-index, ΔC-index, NRI, event NRI, non-event NRI, and 95% CI were derived from 2,000 bootstrap replicates.
[f]For the Model 2-versus-Model 1 comparison, the wide event and non-event NRI confidence intervals reflect two bootstrap clusters arising from sign variation in the single added binary CKD coefficient.

and within distinct hypertension and diabetes subgroups. Importantly, the predictive power of the retinal AI remained robust even after adjustment for the available clinical risk factors (age, sex, hypertension, and diabetes) and renal function, validating its utility as an independent biomarker.

Our study benefits from the rigorous validation utilizing real-world data derived from a tertiary hospital cardiometabolic cohort. While predicting 10-year hard endpoints such as mortality is inherently more challenging than estimating intermediate or composite events, the retinal AI demonstrated stable and consistent prognostic capabilities. Furthermore,

the algorithm exhibited robust structural flexibility, successfully categorizing cardiovascular risk into both a granular 4-tier system for the 10-year horizon and an established 3-tier system for the 5-year horizon. This dual validation not only supports the tool's scalability and reliability across variable clinical follow-up periods but also confirms that the 10-year 4-tier model effectively captures granular risk gradients, which aligns with and extends the clinical applicability of the previously validated 5-year 3-tier categorization [11,13].

In patients with hypertension, the high-risk group (Group 3) exhibited a more than 3-fold increased risk of 10-year ASCVD mortality compared with the lowest-risk tier (adjusted HR, 3.15). This finding aligns with recent evidence demonstrating that the Dr. Noon CVD score progressively increases with the severity of HTR, capturing risk gradients that conventional cardiovascular risk calculators often overlook [14]. This suggests that the DL algorithm effectively captures hypertensive retinal vascular changes—such as arteriolar narrowing, arteriovenous nicking, and widening of the arteriolar light reflex—which are established markers of systemic vascular damage [18]. Given that high inter-observer variability [19,20] and the transient nature of acute retinal signs [21] limit the utility of manual assessment in routine primary prevention [19], the DL algorithm overcomes these traditional barriers by providing a standardized and reproducible quantification of hypertensive vascular damage [14,15,17].

The Dr. Noon CVD score was particularly valuable in the diabetes subgroup, where conventional clinical risk factors were least discriminating. Despite this lower baseline discrimination, the score retained a significant graded association with 10-year ASCVD mortality (HR trend, 1.42) and independently identified high-risk diabetic patients beyond their traditional risk profiles. Furthermore, the reclassification benefit in this subgroup (NRI, 0.481) was comparable to that in the overall cohort and greater than in the hypertension subgroup (NRI, 0.481 vs. 0.413). This suggests that the retinal AI provides a fully automated readout of nascent microvascular signals—such as arteriolar narrowing, venular dilation, and reduced fractal dimension, which prior studies have linked to cardiovascular outcomes [7,8]—that reflect the cumulative cardiometabolic burden in diabetes yet are missed by traditional clinical models, less discriminating in this subgroup (C-index 0.659), and would otherwise require labor-intensive manual grading. This predictive independence from classical retinopathy features aligns with the broader oculomics literature, in which fundus-based DL models capture systemic vascular risk beyond features detectable by human graders [9,10,12,22].

Consistent with this, the score's prognostic value was retained regardless of DR status: it stratified 10-year ASCVD mortality in the majority of patients without ICD-coded DR (full-adjusted HR trend, 1.47) and persisted after direct adjustment for DR (HR trend, 1.41), despite only a weak correlation with it (Spearman rho = 0.28). This indicates that the retinal AI captures pathological alterations extending well beyond the binary presence of retinopathy. Given the algorithm's training to predict the probability of CAC, its strong association with ASCVD mortality likely reflects a synergy between subclinical macrovascular burden [11,12] and direct retinal-microvascular signals [7,8,21,23-25]. Although the lack of concurrent CAC measurements in this cohort precludes the formal partitioning of these pathways, this combined signal enables the algorithm to refine cardiovascular risk stratification far beyond the limitations of conventional DR grading.

We also examined whether the retinal AI provides prognostic value independent of renal function, given the shared microvascular pathology of the reno-retinal axis [16]. After

adjusting for CKD status, the Dr. Noon CVD score remained an independent predictor in both hypertension (adjusted HR, 1.48) and diabetes (HR trend, 1.42), demonstrating prognostic independence across both high-risk populations. Although the eye and kidney share microvascular characteristics [26], retinal imaging appears to offer additive information not fully captured by renal assessment alone. The retinal microvasculature allows direct visualization of the systemic microcirculation, potentially reflecting cerebral or coronary vascular health more directly than renal filtration markers [27].

The reclassification analysis provides strong evidence for the clinical utility of the Dr. Noon CVD score. Over the 10-year horizon, the total NRI was 0.484 overall, with a comparable value of 0.481 in the diabetes subgroup. Previous literature has reported NRI values of 0.079 for high-sensitivity C-reactive protein and 0.659 for CAC scoring [28]. While CAC is a highly established predictor, its requirement for radiation and dedicated imaging facilities restricts its accessibility in routine primary care. In contrast, retinal imaging provides a non-invasive, radiation-free alternative that can be performed during routine eye exams. By enabling automated, specialist-independent cardiovascular screening during mandatory DR exams, Dr. Noon CVD acts as a practical opportunistic screening tool. It allows primary care physicians and diabetes specialists to identify high-risk individuals who would otherwise be overlooked by standard clinical models, facilitating early preventive intervention without increasing the patient's diagnostic burden.

The primary methodological strength of this study lies in its rigorous cohort definition; by executing a comprehensive review of ICD-10 codes, we excluded patients with any history of CVD prior to baseline to establish a true primary prevention cohort. Furthermore, the utilization of a 10-year follow-up horizon with mortality ascertainment through a highly reliable national death registry provided definitive, hard endpoints.

Our study has limitations inherent to its retrospective, electronic health record-based design. Certain clinical variables, including quantitative laboratory data, systolic blood pressure, and smoking status, were incompletely recorded. While we addressed missing laboratory values through multiple imputation, the absence of blood pressure and smoking data precluded direct comparisons with standard risk equations like the PCE or PREVENT. Notably, however, prior UK Biobank studies have already established that this retinal biomarker provides incremental predictive value over these conventional tools [12,13]. Furthermore, because the longitudinal use of cardioprotective medications (e.g., statins, renin–angiotensin system blockers, and sodium–glucose cotransporter-2 inhibitors) was not modelled, residual confounding from differential treatment cannot be excluded.

Another limitation is the lack of clinical severity grading for specific retinopathies. DR was ascertained via ICD-10 codes that also capture diabetic cataract (H28.0), so this indicator reflects coded diabetic eye disease rather than graded retinopathy and likely under-captures milder disease; standardized severity grades for both DR and HTR are rarely documented in routine practice [20,21].

The study's generalizability may also be influenced by its single-center, predominantly Korean tertiary-care cohort, the 17-year study period during which medical guidelines evolved, and the use of diverse fundus cameras. Despite the varying hardware, the algorithm maintained robust performance, supporting its real-world applicability [17].

Finally, several co-authors are affiliated with the developer of the Dr. Noon CVD algorithm. To minimize potential bias, the model was applied as a fixed, commercially deployed tool without any retraining or tuning on the present cohort, and all statistical analyses were independently verified by an unaffiliated co-author. Nonetheless, residual bias cannot be fully excluded, highlighting the need for independent, multicenter external validation.

CONCLUSIONS

The DL-based retinal cardiovascular assessment is a robust, independent predictor of 10-year ASCVD mortality in patients with hypertension and diabetes. The algorithm provides significant prognostic value beyond the available clinical risk factors and renal function in a strictly defined primary prevention cohort. The reclassification benefit was greater in the diabetes subgroup than in hypertension, consistent with the poorer discrimination of conventional risk factors in diabetes. The ability to identify high-risk individuals currently missed by standard models supports the use of this tool for opportunistic cardiovascular screening within routine primary care and specialized diabetes clinics.

ACKNOWLEDGEMENTS

Not applicable.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Underlying causes of cardiovascular death

Supplementary Table 2
Sensitivity analysis of the Dr. Noon CVD score for overall circulatory mortality (ICD-10 I00–I99)

Supplementary Table 3
Baseline characteristics of patients with hypertension stratified by Dr. Noon CVD risk

Supplementary Table 4
Baseline characteristics of patients with diabetes stratified by Dr. Noon CVD risk

Supplementary Table 5
Dr. Noon CVD risk scores and 5-year ASCVD mortality in hypertension and diabetes subgroups

Supplementary Table 6
Dr. Noon CVD score by DR status

Supplementary Table 7
Risk of 10-year ASCVD mortality based on the Dr. Noon CVD score and DR subgroups

Supplementary Table 8

Impact of laboratory-based adjustments on the prognostic value of the Dr. Noon CVD score for ASCVD mortality

Supplementary Table 9

Incremental predictive value of Dr. Noon CVD in patients with hypertension for ASCVD mortality

Supplementary Table 10

Incremental predictive value of Dr. Noon CVD in patients with diabetes for ASCVD mortality

Supplementary Fig. 1

Study flow diagram illustrating the selection of the study population. A total of 36,735 patients with cardiometabolic disease (hypertension or diabetes) were screened. After excluding patients without available digital fundus photography, with ungradable images, without a baseline diagnosis of hypertension or diabetes, with a history of cardiovascular disease, or those outside the age criteria, 7,832 patients were included in the final analysis. The final cohort was further stratified into hypertension and diabetes subgroups.

Supplementary Fig. 2

Five-year cardiovascular survival by Dr. Noon CVD groups in (A) hypertension and (B) diabetes subgroups. Survival trajectories are stratified by the 3-tier risk classification system (Group 1, 2, and 3). Shaded bands represent the 95% confidence intervals. Differences in survival distributions were assessed using the log-rank test.

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