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Short Report

Artificial intelligence based retinal imaging for cardiovascular risk and statin guidance in retinal vein occlusion

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1. Introduction

Retinal vein occlusion (RVO) affects approximately 28 million individuals worldwide and is increasingly recognized as a retinal indicator of systemic vascular dysfunction [1]. Although RVO is associated with elevated cardiovascular disease (CVD) risk [2,3], and statin therapy may reduce cardiovascular events in these patients [4], no standardized framework exists for their cardiovascular evaluation. Traditional tools like the Pooled Cohort Equations (PCE) often underestimate risk in Asian populations and do not account for retinal microvascular signs [5,6]. Consequently, a clinical gap remains in risk stratification and management for patients with RVO [2].

Recent advances in deep learning enable automated cardiovascular risk prediction from retinal images. Dr. Noon CVD (Mediwhale Inc., Seoul, South Korea) is an artificial intelligence (AI)-based medical device that estimates 5-year cardiovascular risk by predicting coronary artery calcium (CAC) probability [7]. While its performance is comparable to CAC scoring in general populations, it remains unclear whether this model accurately captures cardiovascular risk in patients with RVO, where retinal architectural changes (e.g., hemorrhages, venous engorgement) might confound AI predictions.

This study aimed to (1) investigate whether the AI-estimated cardiovascular risk is elevated in patients with RVO compared to propensity-matched controls, assessing if the magnitude of this risk aligns with known epidemiological data; and (2) evaluate the potential utility of this AI score as a decision-support tool for statin initiation, particularly in intermediate risk groups where clinical discretion is required.

2. Materials/subjects and methods

2.1. Study design and datasets

This retrospective study included participants aged 40–79 years from Hanyang University Guri Hospital (HUGH, South Korea) between 2018 and 2024. The study adhered to the Declaration of Helsinki (IRB No. GURI 2024–12–007–001). Participants with prior CVD, other retinal disorders, or missing/out-of-range parameters required for valid PCE calculation (high-density lipoprotein cholesterol [HDL-C] 20–100 mg/dL, systolic blood pressure [SBP] 90–200 mmHg, total cholesterol [TC] 130–320 mg/dL) were excluded. Two retinal specialists (Y.U.S. and S.H.) independently reviewed all fundus images to confirm the RVO diagnosis and subtype classification (branch [BRVO] or central [CRVO]) [2], with excellent agreement (intraclass correlation coefficient [ICC]> 0.9). To assess external generalizability, we analyzed the publicly available Brazilian Multilabel Ophthalmological Dataset (BRSET) [8], comprising 16,266 macula-centered fundus images from 8524 patients recruited during ophthalmological campaigns in São Paulo, Brazil.

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2.2. Cardiovascular risk and statin eligibility assessment

Cardiovascular risk was assessed using the AI-based Dr. Noon CVD software and PCE. Dr. Noon CVD estimates 5-year cardiovascular risk by predicting the probability of CAC from retinal images. Based on the score, individuals are stratified into low (<31), moderate (31–40), and high (≥41) risk categories, which correspond to CAC score groups of 0, 1–100, and >100, respectively (Figure S1) [7]. The software has demonstrated high repeatability and reproducibility (ICC>0.99) in prior validation studies [9]. The PCE calculates the 10-year risk of a first atherosclerotic CVD event using standard clinical variables [6]. Statin eligibility was defined based on established thresholds: (1) PCE risk ≥5 % [6], or (2) Dr. Noon CVD score ≥31 (moderate-to-high risk) [7].

2.3. Retinal image acquisition and statistical analysis

Fundus images were acquired using a Topcon DRI OCT Triton System (Topcon Corporation, Tokyo, Japan) at HUGH or Canon CR-2 (Canon Inc., Tokyo, Japan) and Topcon TRC—NW800 (Topcon Corporation) for BRSET. Images with insufficient quality for AI analysis were excluded. Statistical analyses were performed using R version 4.4.3 (The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were compared using the Wilcoxon rank-sum test, and categorical variables using Fisher's exact test to derive odds ratios (ORs). Longitudinal changes were assessed via the Wilcoxon signed-rank test. Receiver operating characteristic (ROC) curves were compared using DeLong's test, and model agreement was quantified using Cohen's kappa and the Z-test. To compare our cross-sectional findings with established longitudinal epidemiological data [3], we calculated the risk ratio using a weighted mean of the AI-predicted event probabilities. The detailed mathematical derivation for this weighted risk ratio is provided in Text S1. A two-sided p-value<0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

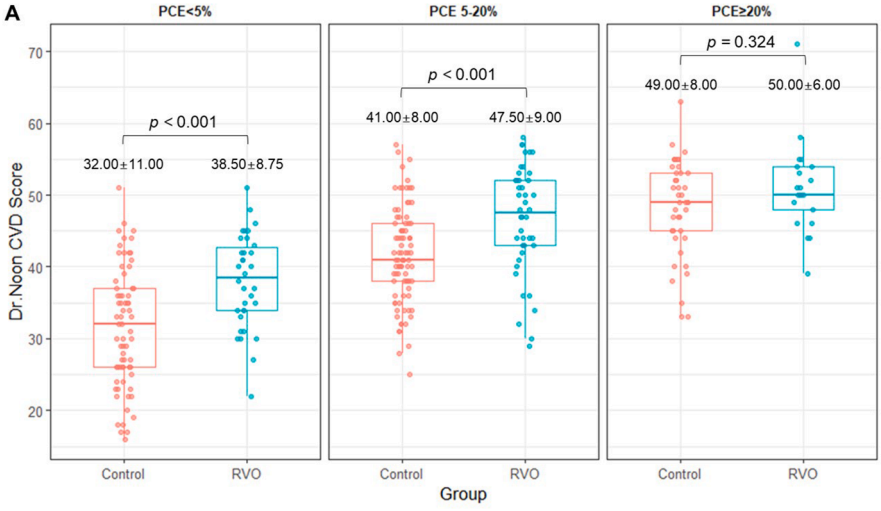
Among 1481 eligible participants, 99 with RVO and 403 controls were identified. Before matching, the RVO group was older and had higher SBP compared to controls ($p < 0.05$). After 1:2 PSM, 99 RVO patients and 198 controls were selected (Figure S2). All matching covariates achieved optimal balance (SMD<0.1) (Figure S3). Despite balanced traditional risk factors, the median Dr. Noon CVD score remained significantly higher in the RVO group compared to controls ($p < 0.001$), whereas PCE scores showed a smaller marginal difference (Table S1). This trend was consistently observed in the external BRSET dataset (Table S2).

3.2. Enhanced cardiovascular risk stratification and statin eligibility

Dr. Noon CVD demonstrated greater sensitivity in detecting cardiovascular risk among RVO patients compared to PCE. When stratified by PCE risk levels, Dr. Noon CVD scores were significantly elevated in the RVO group within the low (<5 %) and intermediate (5–20 %) PCE categories ($p < 0.001$) (Fig. 1A). The agreement between PCE and Dr. Noon CVD risk categories was significantly weaker in the RVO group compared to controls (Cohen's kappa=0.143 vs. 0.512, $p = 0.003$), suggesting that PCE underestimates risk in this population (Table S3).

Regarding statin eligibility, PCE failed to distinguish RVO patients from controls (OR 1.02 [95 % CI 0.60–1.76], $p = 1.000$). In contrast, Dr. Noon CVD identified a significantly higher proportion of RVO patients as eligible for statin therapy, yielding an odds ratio of 2.91 (95 % CI 1.21–8.07; $p = 0.014$) (Fig. 1B).

A



B

Cardiovascular risk scores	Group	Statin eligible, n (%)	Odds ratio (95% CI)	*p*-value
PCE	Control	129 (65.2%)	Reference	1.000
	RVO	**65 (65.7%)**	**1.02** (0.60–1.76)	
Dr. Noon CVD	Control	162 (81.8%)	Reference	**0.014**
	RVO	**92 (92.9%)**	**2.91** (1.21–8.07)	

Fig. 1. Comparison of Dr.Noon CVD Score Between RVO and Control Groups Across PCE Risk Categories Box plots show Dr.Noon CVD scores stratified by PCE risk categories (<5%, 5–20%, ≥20%). Median ± interquartile range values are presented above each group. p-values were calculated using the Wilcoxon rank-sum test to compare RVO and control groups within each PCE risk category. Notably, the difference between RVO and control was more pronounced in low-to-intermediate PCE risk (<20%), suggesting that RVO patients exhibited consistently higher Dr.Noon CVD scores even when traditional PCE-based risk was not elevated. PCE = Pooled Cohort Equation 10-year atherosclerotic cardiovascular risk; RVO = retinal vein occlusion.

3.3. Stability of Dr.Noon CVD score over time

Among 47 RVO participants with follow-up imaging (180–365 days), Dr. Noon CVD scores remained stable in the overall RVO group (p = 0.165) and across subtypes (BRVO p = 0.432; CRVO p = 0.250) (Fig. 2A). A representative case showed that the Dr. Noon CVD score remained constant (58 at both time points) despite the resolution of retinal hemorrhage (Fig. 2B). For PCE scores, a subgroup analysis was performed on 10 participants with available follow-up data. In this limited subset, PCE scores showed a marginal trend toward change over the same period (p = 0.058) (Figure S4), in contrast to the stability observed in Dr. Noon CVD scores.

4. Discussion

This study demonstrates that the AI-based Dr. Noon CVD model identifies elevated cardiovascular risk in patients with RVO that is largely overlooked by conventional risk estimators such as PCE. A primary concern regarding retinal AI is the potential for risk score volatility, where predictions might be driven by transient local artifacts (e.g., hemorrhages) rather than underlying systemic vascular architecture. Our findings indicate that Dr. Noon CVD is not confounded by these local artifacts. Dr. Noon CVD scores remained stable even after significant resolution of retinal hemorrhage (p = 0.165), suggesting the model captures chronic systemic vascular burden rather than acute ocular pathology.

This interpretation is supported by established epidemiological evidence. Although the cross-sectional design precludes direct determination of incident risk, our weighted analysis yielded a risk ratio of 1.17 (RVO vs. controls), consistent with the adjusted hazard ratio of approximately 1.2 reported in large-scale cohort studies [3,7]. This suggests that Dr. Noon CVD captures the magnitude of excess cardiovascular risk associated with RVO that has been documented in prospective studies.

This excess risk was reflected in statin eligibility assessment. Dr. Noon CVD identified a significantly higher proportion of RVO patients as statin-eligible compared to controls (OR 2.91), whereas PCE showed no significant distinction (OR 1.02). This discrepancy likely arises because PCE relies on standard risk factors that are often well-controlled or balanced in RVO populations, failing to capture the microvascular burden detectable through retinal imaging. Comparable findings were reported in hypertensive retinopathy, where traditional risk scores failed to discriminate patients by retinopathy severity, whereas Dr. Noon CVD showed significant differentiation and improved classification upon integration with conventional models [10]. The longitudinal analysis further demonstrated that while PCE scores tended to fluctuate with dynamic clinical variables (p = 0.058), Dr. Noon CVD scores remained stable, supporting its potential as a long-term marker for vascular aging and a more consistent baseline for therapeutic decision-making.

Our study has limitations. First, as a validated 10-year cardiovascular risk equation specific to the Korean population is currently unavailable, we employed the PCE. While PCE is known to underestimate risk in Asian populations, it remains the international standard for comparison. Second, while the cross-sectional design limits the determination of actual incident cardiovascular risk by precluding the assessment of incident events, the consistency between our estimated risk ratios and previously reported hazard ratios supports the model's robustness and clinical applicability. Finally, the sample size for longitudinal PCE analysis was small (n = 10), warranting cautious interpretation of the contrast between the dynamic nature of PCE and the stability of the AI model.

In conclusion, AI-based retinal imaging with Dr. Noon CVD identifies cardiovascular risk in RVO patients that is often underestimated by conventional risk scores, consistent with established epidemiological evidence. By providing a stable risk assessment that is not confounded by acute retinal changes, this AI tool may be of clinical value for guiding statin therapy and CVD prevention in this population.

Data availability

Sunjin Hwang had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical statement

This study was approved by the Institutional Review Board of Hanyang University Guri Hospital (IRB No. GURI 2024–12–007), and the study adhered to the tenets of the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of the study.

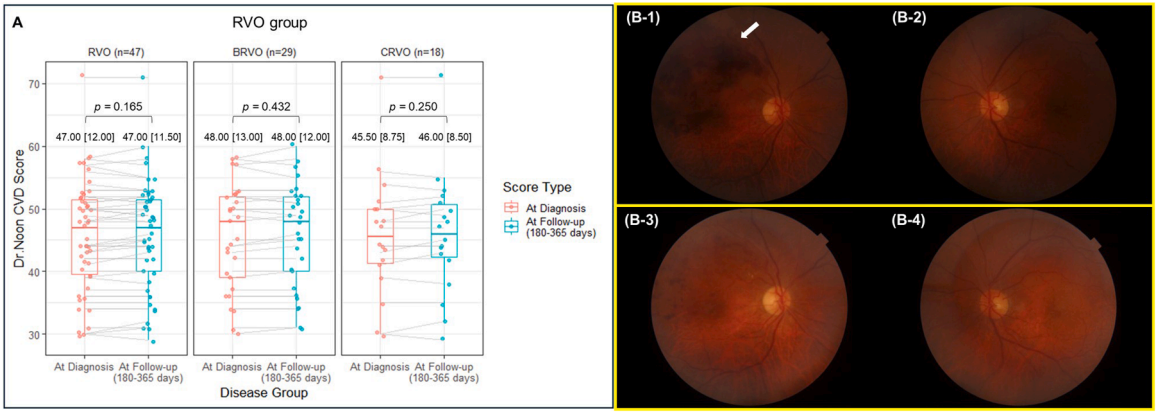


Fig. 2. Comparison of Dr.Noon CVD Scores at Diagnosis and Follow-up in RVO groups (overall RVO, BRVO, and CRVO) and a Representative Case of Dr. Noon CVD score change in RVO groups (A) Box plots of Dr.Noon CVD scores at diagnosis and follow-up (180-365 days later) by RVO subtype: overall RVO, BRVO, and CRVO. Paired comparisons were performed using the Wilcoxon signed-rank test. (B) Representative fundus photographs from a participant with BRVO. Panels B-1 and B-2 show the study and fellow eye, respectively, at diagnosis; panels B-3 and B-4 show the same eyes at follow-up. Acute-phase retinal hemorrhage is observed in the study eye (B-1, white arrow), which resolves in the chronic phase (B-3). Despite marked changes in retinal appearance, Dr.Noon CVD score remained unchanged: 58 and 57 at diagnosis, and 58 and 57 at follow-up, for the study and fellow eyes, respectively. BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; RVO = retinal vein occlusion.

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CRediT authorship contribution statement

Dongjin Nam: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yong-Hwan Jang:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **So Jung Ryu:** Writing – review & editing, Validation, Investigation, Formal analysis, Data curation. **Sahil Thakur:** Writing – review & editing, Validation, Investigation, Formal analysis, Data curation. **Simon Nusinovici:** Writing – review & editing, Validation, Investigation, Formal analysis, Data curation. **Junseok Park:** Writing – review & editing, Validation, Investigation, Formal analysis, Data curation. **Moonsu Kim:** Writing – review & editing, Validation, Investigation, Formal analysis, Data curation. **Sunjin Hwang:** Writing – review & editing, Writing – original draft, Validation, Resources, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Sunjin Hwang reports financial support was provided by KMEDIhub. Dongjin Nam reports a relationship with Mediwhale Inc that includes: employment. Yong-Hwan Jang reports a relationship with Mediwhale Inc that includes: employment. Sahil Thakur reports a relationship with Mediwhale Inc that includes: employment. Simon Nusinovici reports a relationship with Mediwhale Inc that includes: employment. Junseok Park reports a relationship with Mediwhale Inc that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2026.101427.

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