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HbA1c and the stage of diabetic retinopathy: a two-country analysis of national survey data from the United States and South Korea

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Article

Keywords:

Posted Date: November 26th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11847630/v1

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Additional Declarations: There is no conflict of interest

HbA1c and the stage of diabetic retinopathy: a two-country analysis of national survey data from the United States and South Korea

Running head: HbA1c and diabetic retinopathy stage

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Word count: abstract 246 words; main text 3212 words (excluding abstract, tables, figure legends, and references)

Tables: 3; **Figures:** 2; **Supplementary material:** Supplementary Tables S1–S14, Supplementary Figure S1, and analysis code

Competing interests: The authors declare no competing interests.

Abstract

Background/Objectives: We examined whether glycated hemoglobin (HbA1c) reliably reflects diabetic retinopathy (DR) stage in individual patients, and how much referable or vision-threatening disease would be missed if unscreened patients were prioritized by HbA1c.

Subjects/Methods: Adults aged ≥40 years with diagnosed diabetes and graded fundus photographs in the US National Health and Nutrition Examination Survey 2005–2008 (n = 842) and the Korea National Health and Nutrition Examination Survey 2008–2012 (n = 1,749) were staged on the International Clinical Diabetic Retinopathy scale. We estimated survey-weighted HbA1c by stage, compared models based on HbA1c, diabetes duration, and clinical history, and applied US models in Korea.

Results: Each 1-percentage-point higher HbA1c raised the odds of a more advanced stage (adjusted odds ratio 1.51, 95% CI 1.34–1.71, in the US; 1.45, 1.31–1.61, in Korea), but the stages overlapped widely. Among participants with HbA1c below 7%, 10.2% in both countries (US 6.2–14.2; Korea 7.4–13.0) had referable DR. HbA1c ranked stage worse than duration alone in the US (C-index 0.69 vs 0.75; difference −0.059, −0.105 to −0.013) but not in Korea (0.70 vs 0.68). No model agreed well with graded stage (weighted kappa 0.22–0.43). Prioritizing unscreened patients with HbA1c ≥7% would have missed 28.6% (19.6–37.5) of referable DR in the US and 25.4% (19.2–31.5) in Korea, and 34.4% (19.9–48.8) and 19.3% (9.8–28.8) of vision-threatening DR.

Conclusions: Although HbA1c tracks retinopathy severity at the population level, it cannot reliably stage individual patients. Prioritizing unscreened patients by HbA1c misses substantial sight-threatening disease and performs no better than duration-based triage.

Keywords: diabetic retinopathy; glycated hemoglobin; screening; NHANES; KNHANES; prediction model

Summary

What was known before

- Higher HbA1c is associated with the presence and progression of diabetic retinopathy.
- Clinical guidelines already use glycemic control alongside prior examination findings to set retinal screening intervals.

What this study adds

- In nationally representative US and South Korean data, HbA1c levels overlapped widely across retinopathy stages and could not indicate disease severity in individual patients.
- Roughly one-quarter of referable retinopathy and up to one-third of vision-threatening retinopathy occurred in adults with HbA1c below 7%.
- Prioritizing unscreened patients by HbA1c misses substantial sight-threatening disease and performs no better than triaging by diabetes duration.

Introduction

Diabetic retinopathy (DR) affects approximately one in five people with diabetes worldwide, and its burden is predicted to grow to around 160 million adults by 2045.[1] Because early DR

causes no symptoms, guidelines recommend a retinal examination at the diagnosis of type 2 diabetes and regular follow-ups. The American Diabetes Association (ADA) allows the interval to be extended to every one to two years when previous examinations show no retinopathy and glycemic indicators are within the goal range,[2] meaning glycemic control already helps guide screening frequency after a normal baseline exam.

Intensive glucose control reduced the development and progression of retinopathy in both the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study (UKPDS), underpinning the glycated hemoglobin (HbA1c) target of below 7% recommended for most adults.[3,4] The diagnostic threshold of 6.5% was chosen partly because retinopathy becomes more common above this level,[5] whereas UKPDS observational data showed that each 1% reduction in HbA1c was associated with a 37% lower risk of microvascular complications, with no threshold below which risk disappeared.[6] Alongside glycemic exposure, diabetes duration has been recognized as a primary risk factor since the Wisconsin Epidemiologic Study of Diabetic Retinopathy,[7] and data from the US National Health and Nutrition Examination Survey (NHANES) confirm that HbA1c, duration, and insulin use are each independently associated with retinopathy.[8]

In practice, the question is rarely only whether a patient has retinopathy, but how advanced it is, because stage decides what happens next: re-screening for no or mild disease, referral for moderate non-proliferative DR (NPDR), and consideration of treatment for severe NPDR, proliferative DR (PDR), or macular edema.[2,9,10] Most studies of HbA1c, including earlier analyses of the US and Korean national surveys,[8,11] have modeled it against the presence of retinopathy or against vision-threatening retinopathy as a single outcome. A few small single-center studies have compared HbA1c across stages, with inconsistent results.[12–14] HbA1c is

also one input to risk-based models that set the next screening interval after a baseline examination,[15,16] but these predict future risk, not the current stage.

No guideline uses HbA1c to stage retinopathy, and staging requires retinal imaging. The question matters before that imaging takes place. Many people with diabetes have never had a retinal examination, and where screening capacity is limited, unscreened patients may be prioritized by what is already known about them, such as their glycemic control. Patients, too, may take a "good" HbA1c as reassurance that their eyes are unaffected. Whether a current HbA1c can stand in for the stage of the retina in a patient who has not yet been examined has not been tested in population-representative data.

Using graded retinal photographs from national surveys in the United States and South Korea, we aimed to describe HbA1c at each stage of DR, compare how well HbA1c, diabetes duration, and clinical history predict an individual's stage, test whether models built in one country hold in the other, and estimate how much referable and vision-threatening retinopathy would be missed if unscreened patients were prioritized by HbA1c.

Methods

Data sources

We used public data from the 2005–2006 and 2007–2008 cycles of NHANES, a nationally representative survey of the non-institutionalized US population run by the National Center for Health Statistics. Participants aged 40 years and older were offered two 45° non-mydriatic digital photographs of each eye, graded centrally with a modification of the Airlie House classification.[17] For replication and external testing, we used the 2008–2012 cycles of the Korea National Health and Nutrition Examination Survey (KNHANES), which has a similar

design,[18] its non-mydriatic fundus photographs were graded for individual DR lesions.[11] Both surveys were approved by their agencies' ethics review boards, and participants gave written informed consent. This analysis used only de-identified public data and did not require further ethics approval.

Study population

Of 7,081 NHANES participants aged 40 years or older, 1,174 reported that a doctor had told them they had diabetes. Of these, 255 had no retinal photographs, 35 had photographs that could not be graded in either eye, and 42 had no HbA1c result, leaving 842 participants. In KNHANES, 2,276 of 20,419 participants aged 40 years or older with eye examination data reported a physician diagnosis of diabetes; after excluding 313 without a gradable photograph, 23 with DR but no recorded lesion, and 191 without HbA1c, 1,749 remained.

Retinopathy stage

We staged the worse eye on the International Clinical Diabetic Retinopathy (ICDR) scale:[9] no DR; mild NPDR (microaneurysms only); moderate NPDR; severe NPDR; and PDR. In NHANES, stages were derived from the graded severity level (10–15, no DR; 20, mild; 31–41, moderate; 51, severe; 60 or higher, PDR). In KNHANES, stages were assigned from lesions: microaneurysms only, mild; dot hemorrhages, hard exudates, or cotton-wool spots, moderate; venous beading or intraretinal microvascular abnormalities in any quadrant, severe; and new vessels, vitreous or preretinal hemorrhage, fibrous proliferation, tractional detachment, or laser scars, PDR. Clinically significant macular edema (CSME), graded from non-stereoscopic photographs, was recorded separately in both surveys.

For modeling, we used three stages: no DR, mild NPDR, and moderate NPDR or worse, with CSME at any stage counted in the last group. We call this group referable retinopathy, because the ADA recommends referral for moderate or worse NPDR or any macular edema[2]. Because some programs refer at a higher threshold, we also report vision-threatening DR (severe NPDR, PDR, or CSME).

Clinical variables

HbA1c was measured in whole blood. Diabetes duration was age minus age at diagnosis. Self-reported variables were insulin use, oral glucose-lowering medication, diagnosed hypertension, current smoking, and previous myocardial infarction; obesity (body mass index ≥ 30 kg/m^2) and systolic blood pressure were measured. These variables are routinely available in clinical practice and were recorded in both surveys.

Statistical analysis

Descriptive and association analyses used the survey weights, strata, and primary sampling units, with Taylor series variance estimation and each stage treated as a domain. In KNHANES, the 2008 eye examination ran only in the second half of the year, so we used the second-half examination weight for 2008. We fitted survey-weighted proportional odds models of stage on HbA1c, crude and adjusted for duration and age, and estimated the sensitivity and specificity of HbA1c cut-offs of 7%, 8%, and 9%.

To test prediction of stage, we fitted five proportional odds models: duration alone (D); clinical history without HbA1c (S0: duration, age, sex, insulin, oral medication, hypertension, systolic blood pressure, obesity, smoking, and myocardial infarction); HbA1c alone (S1); HbA1c and duration (S2); and HbA1c with all S0 variables (S3). Because duration is the

best-established single predictor,[7] the main comparisons were HbA1c alone and HbA1c with duration against duration alone. Performance was corrected for optimism with 300 bootstrap samples,[19] which also gave confidence intervals and paired differences. The main measures were the ordinal C-index and calibration slope; as a secondary measure, we classified participants with Youden-index cut-offs and report the weighted kappa. For external testing, models trained on all NHANES participants were applied unchanged to KNHANES. We also fitted logistic models for vision-threatening DR. Prediction models were unweighted, because they estimate risk for an individual patient rather than a population quantity. Reporting follows the TRIPOD statement.[20]

To show what HbA1c-based prioritization would mean, we estimated the weighted proportion of referable and vision-threatening DR in participants with HbA1c below 7%, and compared this with prioritizing the same proportion of participants by predicted risk from D, S0, and S3. We also used decision curve analysis[21] over threshold probabilities of 1% to 25%, and estimated population totals with the survey weights.

Sensitivity analyses used the original NHANES grading, in which level 31 is mild NPDR; excluded probable type 1 diabetes, insulin users, KNHANES participants classed as PDR from laser scars alone, and the 2009 KNHANES cycle; added race and ethnicity, albuminuria, and estimated glomerular filtration rate[22] in NHANES; restricted NHANES to participants not told that diabetes had affected their eyes; reweighted for missing photographs or HbA1c by inverse probability of inclusion; and added participants with undiagnosed diabetes. Analyses were done in Python 3 with our own maximum-likelihood code; the code is provided as supplementary material.

Results

Participants

Korean participants had a shorter duration of diabetes than US participants (median 6 vs 8 years), used insulin less often (8.0% vs 26.2%), and were much less often obese (5.8% vs 60.6%) (Table 1). Any DR was present in 30.2% (95% CI 26.0–34.3) of US and 21.3% (18.7–23.8) of Korean participants, referable retinopathy in 19.8% (16.5–23.2) and 19.2% (16.8–21.6), and vision-threatening DR in 5.5% (3.8–7.1) and 5.4% (4.1–6.7). Mild NPDR was much less common in Korea (28 vs 84 participants), recorded prevalence was lower in the 2009 KNHANES cycle than in other years, and 37 of 66 Korean PDR cases were recorded only as laser scars (Supplementary Tables S8 and S11).

HbA1c across stages

Mean HbA1c rose from no DR to moderate NPDR (US 6.81% to 7.99%; Korea 7.13% to 7.95%) and was 8.21% and 8.46% in PDR (Table 2, Figure 1). Each 1 percentage-point higher HbA1c increased the odds of a more advanced stage by about half (adjusted OR 1.51, 95% CI 1.34–1.71, in the US; 1.45, 1.31–1.61, in Korea), with similar odds ratios at every cut-point, including PDR (Supplementary Table S1).

The stages nevertheless overlapped widely (Figure 1). Among participants with HbA1c below 7%, 16.9% (12.5–21.3) in the US and 11.8% (8.7–14.9) in Korea had DR, and 10.2% in both countries (US 6.2–14.2; Korea 7.4–13.0) had referable retinopathy. Among those with HbA1c of 9% or higher, 44.1% (29.3–58.9) and 57.1% (48.9–65.4) had no DR. HbA1c distinguished any DR with an AUC of 0.70 in both countries; a 7% cut-off identified 71.4%

(US) and 74.6% (Korea) of referable retinopathy, with a specificities of 62.4% and 53.4% (Supplementary Table S2).

Predicting stage

Duration alone ranked participants by stage better than HbA1c alone in the US (ordinal C-index 0.75 vs 0.69; difference −0.059, 95% CI −0.105 to −0.013) and similarly in Korea (0.68 vs 0.70; difference 0.015, −0.027 to 0.053) (Table 3). Adding HbA1c to duration improved ranking slightly in the US (0.77) and more in Korea (0.73; difference 0.055, 0.035 to 0.076). The best model combined HbA1c with clinical history (0.78 and 0.75), but agreement between predicted and graded stage was poor to moderate for every model (weighted kappa 0.32–0.43 in the US and 0.22–0.30 in Korea).

Applied unchanged in Korea, the US models ranked stage about as well as models fitted locally (C-index 0.68–0.74). For referable retinopathy, the clinical and combined models were well calibrated in Korea (slopes 0.88 and 0.98), whereas HbA1c alone was not (slope 1.27, 1.05–1.50) (Supplementary Figure S1); all models overestimated any DR in Korea. For vision-threatening DR, HbA1c alone had an AUC of 0.68 (US) and 0.72 (Korea), against 0.76 and 0.77 for duration alone. When applied to the Korean cohort, the simpler models retained their discrimination (duration 0.77; HbA1c with duration 0.82), whereas the clinical and combined models dropped substantially (0.63 and 0.68) (Supplementary Table S12).

HbA1c-based prioritization

Prioritizing only participants with HbA1c of 7% or higher (44.3% of the US sample) would have left 28.6% (19.6–37.5) of referable and 34.4% (19.9–48.8) of vision-threatening DR unprioritized. At the same workload, prioritizing by duration alone would have left 14.6%

(7.7–21.4) and 8.4% (2.7–14.0) (Supplementary Table S3). In Korea, all approaches performed similarly, leaving 24.9% to 30.6% of referable and 15.7% to 21.5% of vision-threatening DR unprioritized. In decision curve analysis, no model added net benefit over examining everyone at thresholds below about 5% in the US and 7% in Korea (Figure 2). Weighted to the national populations, an estimated 692,000 US adults (441,000–942,000) and 83,000 Korean adults (58,000–107,000) had HbA1c below 7% and referable retinopathy, including 231,000 and 18,000 with vision-threatening DR (Supplementary Tables S4 and S9).

Sensitivity analyses

With the original NHANES grading, 5.8% (2.3–9.2) of US participants with HbA1c below 7% had referable retinopathy, but an HbA1c rule still missed 28.8% of these cases (Supplementary Table S9). The association persisted after excluding probable type 1 diabetes, laser-only PDR, or the 2009 KNHANES cycle, and after adjustment for race and ethnicity, albuminuria, and kidney function (adjusted OR 1.44–1.53); HbA1c alone ranked stage with a C-index of 0.69–0.70 in every analysis (Supplementary Tables S10 and S13). US participants with referable retinopathy, who had been told that diabetes affected their eyes, had a lower mean HbA1c than those who had not (7.70% vs 8.23%). Excluding them, or excluding insulin users, strengthened the US odds ratio to about 1.6. Among the 654 US participants not told about their eyes, HbA1c still ranked stage poorly (C-index 0.70; duration alone 0.73), and 27.1% (18.0–36.1) of their referable retinopathy occurred at HbA1c below 7%. Re-weighting for missing photographs and adding participants with undiagnosed diabetes changed the results little (Supplementary Table S14).

Discussion

In national samples of adults with diabetes from two countries, HbA1c rose stepwise across the stages of DR, yet it could not place individual patients in the right stage. The HbA1c ranges of adjacent stages overlapped widely, no fixed cut-off separated one stage from the next, HbA1c alone ranked stage no better than diabetes duration alone, and between one in five and one in three people with vision-threatening retinopathy had HbA1c below 7%. No model we built, with or without HbA1c, agreed closely enough with the graded stage to definitively stand in place of a retinal examination.

The association itself agrees with earlier work: our odds ratio is close to the 1.45 reported for any retinopathy in the same NHANES cycles[8] and the 1.52 reported in KNHANES.[11] What an odds ratio does not show, however, is overlap. In NHANES, the middle half of HbA1c values was 6.0–7.4% without DR and 6.3–8.5% with mild NPDR, and the median HbA1c in PDR (8.2%) fell inside the middle half of moderate NPDR (6.9–9.0%). An odds ratio of 1.5 per percentage point shifts the whole distribution only slightly, so at any given HbA1c a patient could be at almost any stage. HbA1c marks the line between better and worse glycemic exposure, not between stages.

Because the design is cross-sectional, the HbA1c we measured is the value at the time of the survey, not the exposure that produced the retinopathy. Patients told that they had advanced retinopathy may have had treatment intensified, lowering HbA1c in the stages in which it should be highest, and rapid lowering can itself be followed by early worsening of retinopathy.[23,24] Our data show a modest effect of this kind in the US, where excluding participants who knew about their eyes, or insulin users, strengthened the association. In Korea, excluding insulin users or laser-treated participants changed nothing. More

importantly, participants who had not been told about their eyes are the closest our data came to an unscreened population, and in them HbA1c still ranked stage poorly and missed more than a quarter of referable disease below 7%. A measurement that can change within months in response to treatment cannot show how much damage years of exposure have already done.

The Korean replication strengthens these conclusions. Korean participants had shorter duration, used less insulin, and were graded with a different, lesion-based protocol, yet the association, the overlap between stages, and the discrimination of HbA1c (AUC 0.70) were remarkably similar. The gap between population-level association and individual-level staging therefore appears to be a general feature of HbA1c. The Korean grading has weaknesses: recorded prevalence was unusually low in 2009, severe NPDR was defined more broadly than the ICDR rule, more than half of PDR was recorded only as laser scars, and mild NPDR was almost never recorded. None of these changed our findings in sensitivity analyses, but the Korean analysis is better described as a test of how the models transfer across populations and grading protocols than as a clean external validation. Because pairs involving mild NPDR made up 37% of the comparisons behind the US C-index but only 10% in Korea, the Korean results say little about mild NPDR, the stage at which tighter systemic control may matter most (Supplementary Table S7).

Misjudging stage has direct consequences, because stage sets the urgency of referral. A rule that prioritized only patients whose HbA1c was above goal would have missed about a quarter of referable retinopathy and up to a third of vision-threatening retinopathy. Prioritizing by duration missed fewer cases in the US but not in Korea, and at the low risk thresholds appropriate for sight-threatening disease, examining everyone was as good as any

model. Our findings are consistent with the ADA rule that allows longer intervals after normal examinations when glycemic indicators are within goal.[2] In ACCORD, no participant with no retinopathy at baseline and mean HbA1c below 7% developed vision-threatening retinopathy over four years,[25] and in a Danish program that sets intervals from retinal lesions, HbA1c added little to the risk of unexpected progression.[26] Both concern patients whose retina has already been examined. Our data concern the step before that: in a patient who has not yet been examined, a good HbA1c does not show the stage of the retina.

These findings do not question HbA1c as a treatment target; lowering it over years prevents retinopathy and slows its progression.[3,4] HbA1c is the right number to treat, but not a reliable number to stage by. Duration alone ranked stage better than HbA1c in the US and about as well in Korea, and in the US the other clinical variables added almost nothing to it, so our comparison is largely one of duration against HbA1c. Duration probably does better because it reflects cumulative exposure over many years, consistent with the Wisconsin study[7], while HbA1c reflects only the previous two to three months. When transferred to Korea, the simple models held their discrimination, whereas the ten-variable model did not, probably because variables such as obesity and blood pressure relate differently to retinopathy between the two populations. Glucagon-like peptide-1 receptor agonists, now widely used, can lower HbA1c substantially within months, which is likely to loosen the link between a current HbA1c and stage further.

This study has strengths. Both surveys are nationally representative, photographs were graded centrally, descriptive analyses accounted for the survey designs, models were compared with optimism-corrected measures, and the findings were replicated in a second country and tested across a broad set of sensitivity analyses. It also has limitations. The design is cross-sectional,

so we cannot say whether HbA1c predicts progression, and HbA1c was measured once. Diagnosis, duration, and treatment were self-reported. Non-mydriatic photographs of a limited field can miss peripheral lesions. The two surveys graded retinopathy differently, as discussed above. The data predate the wide use of newer glucose-lowering drugs, only 27 NHANES participants had PDR, and race, albuminuria, and kidney function were available only in NHANES. The prioritization analysis describes prevalent disease and cannot show whether any strategy would improve outcomes. Finally, the prediction models were unweighted, so their performance describes the survey samples rather than the national populations.

Conclusion

In national survey data from two countries, HbA1c was clearly associated with DR stage across the population but was a poor indicator of stage for an individual patient. Diabetes duration ranked patients better than HbA1c in the US and comparably in Korea, and no model based on HbA1c or clinical history agreed closely enough with the graded stage to replace retinal examination. Screening priority should not rest on HbA1c: triage using a threshold of 7% would miss a substantial share of sight-threatening disease.

Declarations

Ethics statement: NHANES protocols were approved by the National Center for Health Statistics Research Ethics Review Board, and KNHANES was approved by the Institutional Review Board of the Korea Disease Control and Prevention Agency. Both surveys were conducted in accordance with the Declaration of Helsinki, and all participants gave written

informed consent. This secondary analysis used only de-identified public data and did not require further ethics approval.

Author contributions: SJ conceived and designed the study, obtained and analyzed the data, interpreted the results, and wrote the manuscript. MVP supervised the work and critically reviewed the manuscript for important intellectual content. Both authors approved the final version and agree to be accountable for all aspects of the work.

Funding: This research received no external funding.

Data availability: NHANES data are publicly available from the US Centers for Disease Control and Prevention (https://wwwn.cdc.gov/nchs/nhanes/). KNHANES data are available from the Korea Disease Control and Prevention Agency (https://knhanes.kdca.go.kr) after acceptance of the data-use agreement. The analysis code is provided as supplementary material.

Use of generative AI: The authors used Claude (Anthropic) to help edit the analysis code and for language editing. The authors reviewed and verified all code, results, and text, and take full responsibility for the content of this article.

Acknowledgements: None.

Competing interests: The authors declare no competing interests.

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Figure legends

Figure 1. HbA1c by diabetic retinopathy stage in the worse eye, US (NHANES 2005–2008, n = 842) and Korea (KNHANES 2008–2012, n = 1,749). Boxes show the median and interquartile range; whiskers extend to 1.5 times the interquartile range; dots are individual participants. The dotted line marks HbA1c 7%. NHANES: National Health and Nutrition Examination Survey; KNHANES: Korea National Health and Nutrition Examination Survey; HbA1c: glycated hemoglobin.

Figure 2. Decision curves for identifying moderate non-proliferative diabetic retinopathy or worse, or clinically significant macular edema. Net benefit of prioritizing patients by HbA1c alone (S1, dashed), clinical history without HbA1c (S0, dash-dotted), and both (S3, solid), compared with prioritizing everyone (dotted line) or no one (horizontal line at zero). US curves use 10-fold cross-validated predictions; Korean curves use the US-trained models applied unchanged. The faint vertical line marks a threshold of 10%. HbA1c: glycated hemoglobin.

Table 1. Characteristics of adults aged 40 years or older with diagnosed diabetes (survey-weighted)

Characteristic	US (NHANES 2005–2008)	Korea (KNHANES 2008–2012)
Participants, n	842	1,749
Age, y, mean (95% CI)	61.2 (60.3–62.2)	61.1 (60.5–61.8)
Women, %	52.8 (47.1–58.5)	47.0 (44.1–49.9)
HbA1c, %, mean (95% CI)	7.12 (6.98–7.26)	7.32 (7.23–7.40)
HbA1c below 7%, %	55.7 (50.7–60.8)	48.0 (44.9–51.1)
Diabetes duration, y, median (IQR)	8 (3–15)	6 (3–11)
Insulin, %	26.2 (22.3–30.0)	8.0 (6.4–9.7)
Oral glucose-lowering medication, %	74.9 (69.1–80.8)	84.8 (82.3–87.3)
Diagnosed hypertension, %	67.8 (62.9–72.6)	55.5 (52.6–58.5)
Systolic blood pressure, mmHg, mean	131	128
Obesity (BMI ≥30 kg/m²), %	60.6 (56.0–65.2)	5.8 (4.4–7.1)
Current smoking, %	15.6 (12.3–18.9)	31.6 (28.9–34.3)
Previous myocardial infarction, %	13.1 (9.8–16.5)	2.3 (1.6–3.1)
Any DR, %	30.2 (26.0–34.3)	21.3 (18.7–23.8)
Moderate NPDR or worse, or CSME, %	19.8 (16.5–23.2)	19.2 (16.8–21.6)

Percentages are survey-weighted, with 95% CIs in parentheses. NHANES: National Health and Nutrition Examination Survey; KNHANES: Korea National Health and Nutrition Examination Survey; HbA1c: glycated hemoglobin; BMI: body mass index; DR: diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; CSME: clinically significant macular edema; CI: confidence interval; IQR: interquartile range

Table 2. HbA1c and diabetes duration by retinopathy stage (worse eye, ICDR-aligned)

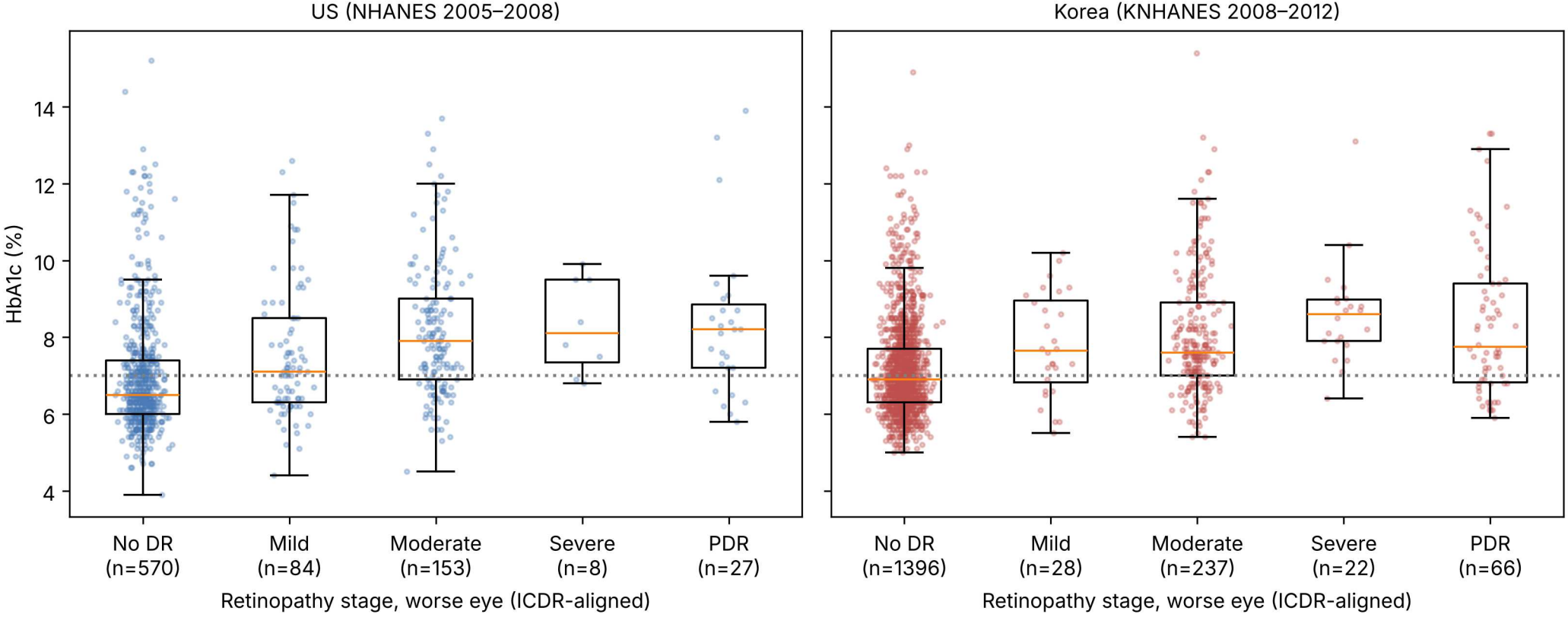
Stage	US: n	US: HbA1c, weighted mean % (95% CI)	US: HbA1c, median % (IQR)	Korea: n	Korea: HbA1c, weighted mean % (95% CI)	Korea: HbA1c, median % (IQR)
No DR	570	6.81 (6.67–6.95)	6.5 (6.0–7.4)	1,396	7.13 (7.04–7.21)	6.9 (6.3–7.7)
Mild NPDR	84	7.54 (7.08–8.00)	7.1 (6.3–8.5)	28	7.62 (7.04–8.21)	7.7 (6.8–8.9)
Moderate NPDR	153	7.99 (7.65–8.34)	7.9 (6.9–9.0)	237	7.95 (7.70–8.19)	7.6 (7.0–8.9)
Severe NPDR	8	7.97 (7.27–8.68)	8.1 (7.3–9.5)	22	8.46 (8.02–8.89)	8.6 (7.9–9.0)
PDR	27	8.21 (7.14–9.28)	8.2 (7.2–8.8)	66	8.46 (7.88–9.04)	7.8 (6.8–9.4)
CSME (any stage)	34	7.72 (7.11–8.34)	8.0 (6.8–8.8)	29	8.97 (8.23–9.70)	8.7 (8.2–9.8)

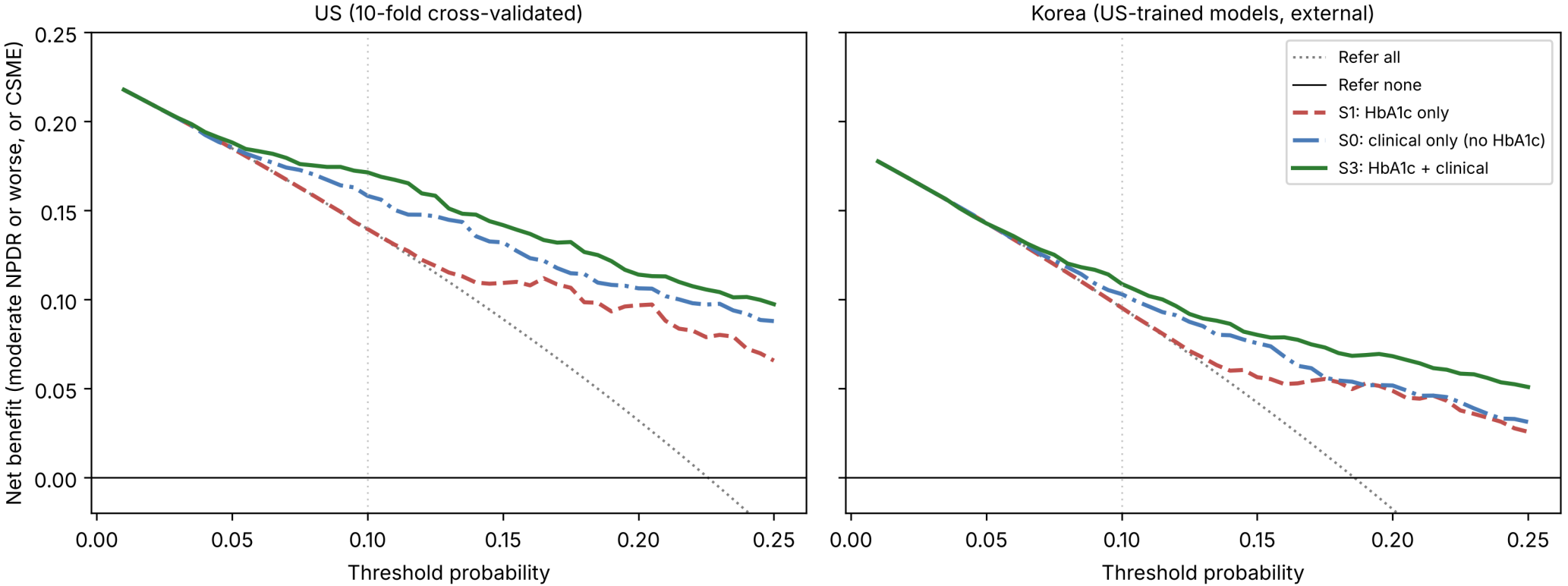
Two US participants graded as having CSME without retinopathy are counted as no DR in this table and as moderate NPDR or worse in the models. Stages follow the ICDR scale: mild NPDR, microaneurysms only; moderate NPDR, more than microaneurysms but less than severe; severe NPDR, venous beading or intraretinal microvascular abnormalities; PDR, new vessels, vitreous or preretinal hemorrhage, fibrous proliferation, tractional detachment, or previous laser treatment. ICDR: International Clinical Diabetic Retinopathy scale; DR: diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; CSME: clinically significant macular edema; HbA1c: glycated hemoglobin; CI: confidence interval; IQR: interquartile range

Table 3. Discrimination (ordinal C-index, 95% CI), calibration, and agreement of the stage prediction models

Model	US, internal	Korea, internal	US-trained, tested in Korea	Calibration slope in Korea, moderate+	Calibration-in-the-large in Korea, any DR	Weighted kappa, US / Korea
D: duration only	0.75 (0.72–0.78)	0.68 (0.65–0.71)	0.68 (0.65–0.71)	1.09 (0.86–1.33)	−0.52 (−0.64 to −0.40)	0.43 / 0.22
S1: HbA1c only	0.69 (0.66–0.73)	0.70 (0.66–0.73)	0.70 (0.66–0.72)	1.27 (1.05–1.50)	−0.69 (−0.80 to −0.59)	0.32 / 0.22
S2: HbA1c + duration	0.77 (0.74–0.80)	0.73 (0.70–0.76)	0.73 (0.71–0.76)	1.13 (0.99–1.31)	−0.56 (−0.68 to −0.45)	0.40 / 0.27
S0: clinical history, no HbA1c	0.76 (0.73–0.79)	0.71 (0.68–0.74)	0.70 (0.67–0.73)	0.88 (0.72–1.07)	−0.44 (−0.56 to −0.32)	0.38 / 0.25
S3: HbA1c + clinical history	0.78 (0.75–0.80)	0.75 (0.72–0.78)	0.74 (0.71–0.77)	0.98 (0.85–1.13)	−0.44 (−0.57 to −0.29)	0.37 / 0.30

Internal estimates and weighted kappa are corrected for optimism with 300 bootstrap samples. Clinical history: diabetes duration, age, sex, insulin, oral glucose-lowering medication, diagnosed hypertension, measured systolic blood pressure, obesity, current smoking, and previous myocardial infarction. A calibration slope of 1 indicates ideal calibration; a calibration-in-the-large below 0 indicates that the model predicted more disease than was observed. Moderate+: moderate NPDR or worse, or CSME. DR: diabetic retinopathy; HbA1c: glycated hemoglobin; NPDR: non-proliferative diabetic retinopathy; CSME: clinically significant macular edema; CI: confidence interval


US (NHANES 2005–2008)
Korea (KNHANES 2008–2012)
HbA1c (%)
14
12
10
8
6
4
No DR (n=570)
Mild (n=84)
Moderate (n=153)
Severe (n=8)
PDR (n=27)
No DR (n=1396)
Mild (n=28)
Moderate (n=237)
Severe (n=22)
PDR (n=66)
Retinopathy stage, worse eye (ICDR-aligned)
Retinopathy stage, worse eye (ICDR-aligned)


US (10-fold cross-validated)
Korea (US-trained models, external)
Net benefit (moderate NPDR or worse, or CSME)
0.25
0.20
0.15
0.10
0.05
0.00
0.00
0.05
0.10
0.15
0.20
0.25
Threshold probability
Refer all
Refer none
S1: HbA1c only
S0: clinical only (no HbA1c)
S3: HbA1c + clinical

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- HbA1cDRsupplementarymaterial.docx
- HbA1cDRstagecodeandresults.zip