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8  
1 **Composite metabolic indices are associated with severity of proliferative diabetic**  
2 **retinopathy in type 2 diabetes: a three-centre cross-sectional study**

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51  
17 **Background:** Proliferative diabetic retinopathy (PDR) is an advanced complication of type  
18 2 diabetes and an important cause of visual impairment. Routinely available metabolic  
19 measures may provide complementary information on advanced disease severity and  
20 support timely ophthalmic assessment, particularly where access to specialist services is  
21 limited. Here, this research examined whether five composite metabolic indices—  
22 triglyceride-glucose (TyG), triglyceride glucose-body mass index (TyG-BMI), atherogenic  
23 index of plasma (AIP), metabolic score for insulin resistance (METS-IR), and cholesterol,

24 high-density lipoprotein, and glucose (CHG) index—could differentiate stage 6 PDR from  
25 stages 4/5.

26 **Methods:** This three-center cross-sectional study included 484 patients with type 2  
27 diabetes mellitus and PDR stages 4–6 between January 2021 and December 2025. The  
28 primary analysis compared stage 6 with combined stages 4/5. Multivariable logistic  
29 regression estimated odds ratios (ORs) per 1-standard deviation (SD) increase in each  
30 index after adjustment for demographic, clinical, and center-level factors. Firth bias-  
31 reduced regression was used to assess sparse-data sensitivity, while ordered-stage, quartile,  
32 and component-excluded models were employed for secondary analyses.

33 **Results:** The primary comparison included 347 patients with stage 4 or 5 PDR and 137  
34 with stage 6 PDR. All five indices were positively associated with stage 6 PDR, with  
35 adjusted ORs per 1-SD increase of 18.75 (95% confidence interval [CI]: 10.10–34.79) for  
36 TyG, 647.94 (95% CI: 163.35–2570.06) for TyG-BMI, 12.25 (95% CI: 7.41–20.25) for  
37 AIP, 15.40 (95% CI: 7.83–30.27) for METS-IR, and 10.61 (95% CI: 6.06–18.59) for CHG  
38 (all  $P < 0.001$ ). Firth estimates remained positive, and secondary ordered-stage and quartile  
39 analyses showed broadly consistent severity gradients. However, models that excluded  
40 fasting plasma glucose, BMI, or both produced substantially weaker associations for those  
41 indices; for TyG-BMI, the OR for stages 5 and 6 *versus* stage 4 decreased to 1.23 (95% CI:  
42 0.91–1.67).

43 **Conclusions:** Higher composite metabolic indices were associated with more advanced  
44 PDR among patients with type 2 diabetes mellitus. These indices may offer a practical,  
45 low-cost adjunct to retinal assessment and enable coordinated metabolic and ophthalmic

care, particularly in resource-limited settings. Their integration into diabetes management could support timely ophthalmic management and reduce avoidable vision loss.

**Keywords:** diabetic retinopathy; diabetes mellitus, type 2; triglyceride-glucose index; atherogenic index of plasma; metabolic score for insulin resistance; cholesterol, high-density lipoprotein, and glucose index; metabolic syndrome

## 1. Introduction

Diabetic retinopathy (DR) is a major microvascular complication of diabetes and a leading cause of preventable visual impairment. In 2020, an estimated 22.27% of people with diabetes had DR and 6.17% had vision-threatening disease, corresponding to approximately 103 million and 29 million adults worldwide; both disease burdens are projected to increase substantially by 2045 [1]. Proliferative diabetic retinopathy (PDR) is an advanced stage of DR marked by retinal ischemia and pathological neovascularization, which can progress to fibrovascular proliferation, vitreoretinal traction, and tractional retinal detachment [2]. Although glycemic exposure, diabetes duration, and blood pressure are established determinants of DR [3, 4], they do not fully account for the variation in advanced retinal disease manifestations.

Insulin resistance and atherogenic dyslipidemia may help explain this residual heterogeneity. These metabolic abnormalities can contribute to retinal injury by promoting endothelial dysfunction, oxidative stress, inflammation, and altered lipid handling. Several composite indices can be derived from routine clinical measurements. The triglyceride-glucose (TyG) index reflects insulin resistance [5, 6]; the TyG-body mass index (TyG-BMI) additionally incorporates adiposity; and the atherogenic index of plasma (AIP), based on the triglyceride (TG)-to-high-density lipoprotein cholesterol (HDL-C) ratio, can

1 69 identify an adverse lipid profile [7]. The metabolic score for insulin resistance (METS-IR)  
2 70 integrates glucose, TG, HDL-C, and BMI [8], whereas the cholesterol, high-density  
71 lipoprotein, and glucose (CHG) index combines glycemic status with cholesterol balance  
72 [9]. These indices may therefore capture complementary dimensions of metabolic  
73 dysfunction not fully reflected by individual glycemic or lipid metrics.

74 Clinical evidence has increasingly linked composite metabolic indices with DR.

6 75 Meta-analyses have reported that higher TyG values are positively associated with DR in  
76 type 2 diabetes, despite variation in effect sizes and substantial inter-study heterogeneity

1 77 [10-12]. In a cross-sectional study of 2,211 patients with type 2 diabetes, METS-IR, TyG-  
6 78 BMI, and the triglyceride-to-HDL-C ratio were associated with the presence of DR, while  
79 insulin resistance indices were related to DR severity [13]. Recent work has also linked

6 80 AIP, CHG, and remnant cholesterol with the presence or severity of DR [9, 14, 15].  
81 However, most studies have compared DR with non-DR controls or used broad retinopathy  
82 categories, leaving it unclear whether these metabolic indices can differentiate among  
83 stages of established PDR, particularly those characterized by neovascularization,  
84 fibrovascular proliferation, and tractional retinal detachment.

85 This study examined whether routinely derived composite metabolic indices—

7 86 specifically TyG, TyG-BMI, AIP, METS-IR, and CHG—are associated with PDR severity  
61 87 across stages 4, 5, and 6 in a three-center sample of patients with type 2 diabetes. By  
88 focusing on distinctions within established PDR rather than broad DR categories, the  
89 hypothesis was that higher index values would be associated with more advanced PDR  
90 after adjustment for demographic, clinical, and center-level factors.

91

## 2. Methods

### 2.1 Study design and patient sampling

This three-center, cross-sectional study evaluated patient records from January 2021 to December 2025 to determine the associations between composite metabolic indicators and PDR severity. Eligible records were restricted to one eye per patient with type 2 diabetes mellitus and PDR stage 4, 5, or 6. Stage 4 denoted retinal neovascularization; stage 5, fibrovascular proliferation; and stage 6, tractional retinal detachment. For the primary analysis, stages 4 and 5 were combined as the reference group, with stage 6 serving as the binary outcome. The original ordered three-stage variable was retained for secondary analyses. Records were retrospectively identified from the ophthalmology databases of three hospitals using admission date, diabetes diagnosis, and PDR stage. All records meeting the database query criteria were screened without sampling following identification. The initial query yielded 507 potentially eligible records: 129 from Hebei General Hospital, 196 from Shijiazhuang People's Hospital, and 182 from Shijiazhuang Second Hospital. The exclusion of 12 duplicate records and 11 records from patients with type 1 diabetes resulted in a final analytic sample of 484 unique patient records. Because the study period and PDR stage criteria were applied during initial database identification, no additional records were excluded based on date or stage, nor did missing laboratory values result in participant exclusion (Fig. 1A; Table S1). The patient cluster identifier field was evaluated for repeated patient records; no duplicate cluster identifiers were detected in the final dataset. The recorded PDR stage corresponded strictly to the included study eye (right or left) rather than a worse-eye, treated-eye, or bilateral

114 patient-level classification; therefore, adjustment for within-patient bilateral correlation  
115 was not required.

116

## 117 2.2 Data collection

118 PDR stage assignment followed the late-stage PDR framework in the 2022 Chinese  
119 DR guidelines and was consistent with established clinical research grading standards [16,  
120 17]. Stage assignment was abstracted from source ophthalmology records using routine  
121 specialist fundus examination and retinal images available at each center. Two attending  
122 ophthalmologists independently assigned a PDR stage to each eye. When ratings differed,  
123 the case was adjudicated by a senior retinal specialist, whose decision defined the final  
124 analytic PDR stage; when ratings agreed, the concordant stage was retained. The grading  
125 file contained study identifiers, hospital, admission date, and PDR stage fields, but no  
126 laboratory measurements or derived metabolic indices, ensuring that grading was masked  
127 to study exposures.

128 To ensure temporal alignment between metabolic measurements and retinal status,  
129 the ophthalmic examination used to assign PDR stage was defined as the index assessment.

130 Fasting plasma glucose (FPG), glycated hemoglobin A1c (HbA1c), total cholesterol (TC),  
131 TG, HDL-C, low-density lipoprotein cholesterol (LDL-C), and serum creatinine were  
132 measured as part of the same index hospitalization and within 3 calendar days before or  
133 after retinal staging. Fasting plasma glucose and lipid measurements were obtained after  
134 an overnight fast. When repeated eligible measurements were available within this  
135 window, the result closest to the index assessment was retained. All laboratory components  
136 used to calculate a given composite metabolic index were required to originate from the

19

137 same laboratory assessment. Treatment status was abstracted for the index hospitalization;  
138 however, the exact timing of treatment initiation or modification relative to blood sampling  
139 and retinal staging was not available.

140 Demographic, clinical, and laboratory variables were abstracted from source  
141 hospital records and harmonized into a common data dictionary. Variables included age,  
142 sex, BMI, smoking status, alcohol consumption, diabetes duration, hypertension, systolic  
143 blood pressure, hyperlipidemia, statin or lipid-lowering treatment, insulin or oral  
144 antidiabetic drug use, HbA1c, FPG, TC, TG, HDL-C, LDL-C, serum creatinine, and  
145 estimated glomerular filtration rate (eGFR). FPG and lipid measurements were reported in  
146 mmol/L across centers; assay, analyzer, calibration, and quality control details were  
147 unavailable. Key categorical covariates were harmonized from source medical records  
148 using recorded diagnoses, documented history, relevant contemporaneous clinical or  
149 laboratory criteria, and medication use. Hypertension and hyperlipidemia were coded as  
150 present when supported by the combined source record rather than a single study-defined  
151 numerical threshold. Current smoking and alcohol consumption denoted active use  
152 documented in admission or social history. Statin or other lipid-lowering therapy and  
153 antidiabetic medication use (insulin or oral agents) were coded from active medication  
154 records during the index hospitalization. Derived lipid fractions and ratios included non-  
155 HDL-C, remnant cholesterol, TG/HDL-C, TC/HDL-C, and LDL-C/HDL-C. Composite  
156 metabolic indicators were calculated using published equations [5-9], with a structured  
157 summary of formulas, input units, and unit conversions provided in Table S2.

158 Missing data were restricted to continuous variables: BMI (14/484, 2.9%), FPG  
159 (12/484, 2.5%), and eGFR (11/484, 2.3%); PDR stage and all categorical variables were

complete. To ensure reproducibility, data quality was verified by applying broad hard range plausibility limits to continuous variables and prespecified code checks to categorical variables (Table S1). For the primary analysis, missing values were imputed using single median imputation. Missing BMI, FPG, or eGFR values were imputed using the median of observed values within the same hospital and PDR-stage stratum, defaulting sequentially to hospital-specific and overall sample medians. Imputation was performed prior to calculating the composite indices, which were subsequently derived from the completed component variables. Missing values are reported in Table 1, and findings were evaluated for robustness using complete-case and multiple-imputation sensitivity analyses.

## 2.3 Data analysis

The normality of continuous variables was evaluated using the Kolmogorov-Smirnov test (sample size  $n \geq 50$ ) or the Shapiro-Wilk test ( $n < 50$ ). Normally distributed continuous variables are reported as means  $\pm$  standard deviation (SD), whereas non-normally distributed continuous variables are presented as medians (25th and 75th percentiles). Categorical variables are summarized as counts and percentages. Baseline characteristics were compared across ordered PDR stages using tests for linear trend. The primary exposure set comprised the TyG index, TyG-BMI, AIP, METS-IR, and CHG index. Secondary exploratory indicators included TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, non-HDL-C, and remnant cholesterol. Each indicator was transformed into a  $z$ -score using the full imputed dataset and modeled individually to prevent multicollinearity among composite indices. Cross-index comparisons of regression coefficients or odds ratio (OR) magnitudes were not performed because  $z$ -score standardization does not eliminate

183 differences in distributional shape, component composition and overlap, mathematical  
184 coupling with covariates, model specification, or sparse outcome structures. Correlations  
185 among indicators were summarized graphically.

186 Primary associations were evaluated using multivariable binary logistic regression,  
187 with stage 6 as the outcome and combined stages 4 and 5 as the reference group. ORs were  
188 reported per 1-standard-deviation (SD) increase in each metabolic indicator. The primary  
189 adjustment set included age, sex, BMI, hypertension, HbA1c, FPG, diabetes duration,  
190 smoking status, alcohol consumption, and hospital fixed effects (Model C). Each metabolic  
191 indicator was modeled separately. To evaluate sparse-data sensitivity, the stage 6 *versus*  
192 stages 4 and 5 contrast was refit using Firth bias-reduced logistic regression with penalized  
193 likelihood 95% confidence intervals (CIs), alongside evaluation of separation and  
194 influence diagnostics. For secondary ordered-stage analyses, a partial proportional-odds  
195 cumulative logit model was used, in which the exposure coefficient was allowed to differ  
196 across cutoffs (stages 5 and 6 *vs.* stage 4 and stage 6 *vs.* stages 4 and 5), while adjustment  
197 covariate slopes were constrained to be equal. A likelihood-ratio test with 1 degree of  
198 freedom was used to assess exposure nonparallelism. Four conventional proportional-odds  
199 models were also retained as secondary summaries: Model A was unadjusted; Model B  
200 adjusted for age, sex, and BMI; Model C further adjusted for hypertension, HbA1c, FPG,  
201 diabetes duration, smoking status, alcohol consumption, and hospital fixed effects; and  
202 Model D additionally adjusted for statin or other lipid-lowering treatment and  
203 hyperlipidemia. Variance inflation factors were calculated for each Model C specification.  
204 A multinomial logistic model with stage 4 as the reference category was constructed as a  
205 sensitivity analysis.

206 In secondary proportional-odds summaries, dose-response relationships were  
207 evaluated by modeling quartiles of the five primary indicators, using the lowest quartile as  
208 the reference, and testing for a linear trend across quartiles. Sensitivity analyses of the  
209 ordered-stage models were conducted by applying the proportional-odds Model C  
210 specification to complete cases, after 1st and 99th percentile winsorization, with additional  
211 adjustment for lipid-lowering treatment and hyperlipidemia, excluding users of statin or  
212 lipid-lowering medications, restricting the sample to records with eGFR  $\geq 60$  mL/min/1.73  
213 m<sup>2</sup>, and excluding Shijiazhuang People's Hospital. Additionally, a binary logistic  
214 regression model comparing stages 5 and 6 with stage 4 was constructed to evaluate the  
215 lower cumulative stage contrast. Exploratory effect modification was evaluated by  
216 stratifying analyses according to sex, age (<60 vs.  $\geq 60$  years), hypertension status, HbA1c  
217 level (<8% vs.  $\geq 8\%$ ), and hospital. Exposure-by-subgroup interaction terms were  
218 incorporated into ordered logistic models, with the stratification covariate omitted from the  
219 corresponding model. Hospital interaction was evaluated using a joint Wald test. All  
220 statistical tests were two-sided, and no adjustment for multiplicity was applied to  
221 exploratory subgroup or sensitivity analyses. To assess post hoc model stability, center and  
222 exposure quartiles were cross-tabulated by PDR stage, exact complete or quasi-complete  
223 separation was evaluated using linear programming, and Cook's distance and exposure  
224 difference in fitted betas (DFBETAs) were calculated for both cumulative binary contrasts.  
225 In addition, the secondary partial proportional-odds model was re-estimated after  
226 sequentially excluding each center. These diagnostics were performed to assess the  
227 robustness of association direction rather than clinically calibrated effect sizes. To evaluate  
228 center-related confounding in the ordered-stage model, the partial proportional-odds model

was compared with an otherwise identical model that omitted hospital fixed effects. The same clinical model was fit separately within the two centers with sufficient stage 4 overlap for exploratory analysis (39 and 13 stage 4 records, respectively), using the full-sample exposure SD. A separate ordered-stage within-center model was not fit for Shijiazhuang People's Hospital because it contained only one stage 4 record. The association between center and PDR stages was assessed using a chi-square test and Cramér's  $V$ . To assess mathematical coupling between each composite exposure and its covariates, component-excluded sensitivity models were constructed: FPG was omitted from the TyG and CHG models, and BMI and FPG were omitted from the TyG-BMI and METS-IR models; the AIP adjustment set remained unchanged. All other Model C covariates, including hospital fixed effects, were retained. For the primary binary outcome, the association between center and outcome group was quantified using a chi-square test and Cramér's  $V$ . Hospital-related robustness was evaluated through comparisons between models with and without hospital fixed effects, leave-one-center-out sensitivity analyses, and within-center analyses where sufficient stage overlap was available.

For the multiple-imputation sensitivity analysis, missing BMI, FPG, and eGFR values were imputed using chained equations with predictive mean matching across 20 imputed datasets. The imputation model included hospital center, age, sex, smoking status, alcohol consumption, diabetes duration, hypertension, systolic blood pressure, HbA1c, TC, TG, HDL-C, LDL-C, serum creatinine, hyperlipidemia, statin or other lipid-lowering treatment, and insulin or oral antidiabetic drug use, alongside other incomplete continuous variables; PDR stage was excluded from the imputation model. Composite indices were recalculated within each imputed dataset, the secondary partial proportional-odds Model C

252 was refit, and estimates were combined using Rubin's rules (Table S3). In an additional  
253 sensitivity analysis, an aggregate indicator for insulin or oral antidiabetic drug use was  
254 added to the secondary partial proportional-odds Model C; specific glucose-lowering  
255 medication classes could not be entered separately (Table S4).

### 257 3. Results

#### 258 3.1 Baseline characteristics

259 From the source datasets, 507 potentially eligible records were identified; after  
260 excluding 12 duplicates and 11 records from patients with type 1 diabetes, the final dataset  
261 comprised 484 unique patient records, including 53 for stage 4 (11.0%), 294 for stage 5  
262 (60.7%), and 137 for stage 6 (28.3%) (Fig. 1A and 1B; Table 1, Table S1). The two  
263 attending ophthalmologists agreed on 455 of 484 records (94.0%), yielding an unweighted  
264 kappa of 0.889 and a quadratic-weighted kappa of 0.918. All 29 disagreements involved  
265 adjacent stages and were adjudicated by a senior retinal specialist, whose final  
266 classification aligned with attending ophthalmologist 1 in all 29 cases (Table S5). A unit-  
267 of-analysis audit confirmed 484 unique patient cluster IDs, with no repeated or bilateral  
268 patient contributions (Table S6). Stage composition varied across centers: Hebei General  
269 Hospital included 123 records, Shijiazhuang People's Hospital included 188 records, and  
270 Shijiazhuang Second Hospital included 173 records (Fig. 1B). The association between  
271 center and stage distribution was substantial ( $\chi^2 = 107.75$ ,  $df = 4$ ,  $P < 0.001$ ; Cramér's  $V =$   
272 0.334), with Shijiazhuang People's Hospital including only one stage 4 record (Table S7).  
273 After combining stages 4 and 5 for the primary outcome, the counts for combined stages 4  
274 and 5 *versus* stage 6 were 76 *versus* 47 at Hebei General Hospital, 128 *versus* 60 at

Shijiazhuang People's Hospital, and 143 *versus* 30 at Shijiazhuang Second Hospital. Thus, each center was represented in both primary outcome groups. The association with center was weaker for the primary binary outcome than for the original three-stage classification but remained statistically significant ( $\chi^2 = 17.40$ ,  $df = 2$ ,  $P < 0.001$ ; Cramér's  $V = 0.190$ ).

The mean age was  $55.66 \pm 11.18$  years, and 207 records (42.8%) were from female patients. Hypertension was documented in 281 records (58.1%), hyperlipidemia in 97 (20.0%), and statin or lipid-lowering treatment in 90 (18.6%). Several lipid variables differed across PDR stages: TG increased from a median of 1.42 mmol/L in stage 4 to 2.38 mmol/L in stage 6; HDL-C decreased from  $1.76 \pm 0.25$  mmol/L in stage 4 to a median of 1.13 mmol/L in stage 6; and LDL-C increased from a median of 1.82 mmol/L in stage 4 to 2.94 mmol/L in stage 6 (all  $P_{\text{trend}} < 0.001$ ). Composite indicators showed similar gradients across stages: TyG increased from  $8.94 \pm 0.56$  in stage 4 to  $9.57 \pm 0.50$  in stage 6; AIP increased from -0.11 (-0.25, -0.01) to 0.33 (0.23, 0.42); METS-IR increased from 34.99 (33.54, 39.05) to 41.31 (37.25, 46.55); and the CHG index increased from 5.10 (4.87, 5.35) to  $5.69 \pm 0.42$  (all  $P_{\text{trend}} < 0.001$ ; Table 1). Current smoking and alcohol consumption were less frequent in patients with higher PDR stages (both  $P_{\text{trend}} < 0.001$ ; Table 1). A combined indicator of insulin or oral antidiabetic drug use was documented in 470 records (97.1%), and in similar proportions across PDR stages ( $P_{\text{trend}} = 0.520$ ; Table 1).

**Table 1.** Baseline characteristics by proliferative diabetic retinopathy stage.

| Characteristic | Overall           | Stage 4           | Stage 5           | Stage 6           | Missing before imputation | <i>P</i> for trend |
|----------------|-------------------|-------------------|-------------------|-------------------|---------------------------|--------------------|
| <i>N</i>       | 484               | 53                | 294               | 137               | 0 (0.0%)                  |                    |
| Age, years     | $55.66 \pm 11.18$ | $57.36 \pm 12.73$ | $55.90 \pm 10.85$ | $54.49 \pm 11.23$ | 0 (0.0%)                  | 0.087              |

33

|                                |                     |                      |                     |                      |           |       |
|--------------------------------|---------------------|----------------------|---------------------|----------------------|-----------|-------|
| BMI, kg/m <sup>2</sup>         | 25.34 ± 3.59        | 25.28 ± 3.22         | 25.37 ± 3.58        | 25.31 [22.66, 27.04] | 14 (2.9%) | 0.974 |
| Diabetes duration, years       | 10.00 [7.00, 20.00] | 15.00 [10.00, 20.00] | 10.00 [6.00, 20.00] | 10.00 [7.00, 20.00]  | 0 (0.0%)  | 0.630 |
| HbA1c, %                       | 7.90 [7.40, 9.09]   | 8.51 ± 1.48          | 7.90 [7.31, 9.12]   | 7.81 [7.50, 8.70]    | 0 (0.0%)  | 0.214 |
| Fasting plasma glucose, mmol/L | 7.54 [6.16, 9.52]   | 7.50 [6.40, 9.50]    | 7.70 [5.95, 9.76]   | 7.30 [6.30, 9.00]    | 12 (2.5%) | 0.290 |

24

|                                 |                         |                         |                         |                         |           |        |
|---------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-----------|--------|
| Systolic blood pressure, mmHg   | 141.07 ± 19.85          | 140.25 ± 19.23          | 140.22 ± 19.62          | 143.22 ± 20.54          | 0 (0.0%)  | 0.179  |
| Total cholesterol, mmol/L       | 4.51 ± 1.02             | 4.37 [3.72, 4.62]       | 4.39 ± 0.95             | 4.60 [4.13, 5.60]       | 0 (0.0%)  | <0.001 |
| Triglycerides, mmol/L           | 1.65 [1.26, 2.21]       | 1.42 [1.02, 1.63]       | 1.42 [1.10, 1.93]       | 2.38 [1.89, 2.72]       | 0 (0.0%)  | <0.001 |
| HDL-C, mmol/L                   | 1.14 [1.00, 1.37]       | 1.76 ± 0.25             | 1.16 ± 0.27             | 1.13 [0.96, 1.21]       | 0 (0.0%)  | <0.001 |
| LDL-C, mmol/L                   | 2.65 ± 0.80             | 1.82 [1.57, 2.02]       | 2.62 ± 0.68             | 2.94 [2.44, 3.48]       | 0 (0.0%)  | <0.001 |
| eGFR, mL/min/1.73m <sup>2</sup> | 87.55 ± 35.27           | 83.32 ± 33.51           | 90.66 ± 35.40           | 82.52 ± 35.15           | 11 (2.3%) | 0.245  |
| TyG index                       | 9.21 ± 0.63             | 8.94 ± 0.56             | 9.08 ± 0.62             | 9.57 ± 0.50             | 12 (2.5%) | <0.001 |
| TyG-BMI                         | 230.59 [205.57, 257.42] | 224.74 [202.79, 250.26] | 228.64 [203.33, 255.93] | 238.40 [217.70, 261.19] | 25 (5.2%) | 0.001  |
| AIP                             | 0.14 ± 0.25             | -0.11 [-0.25, -0.01]    | 0.09 ± 0.22             | 0.33 [0.23, 0.42]       | 0 (0.0%)  | <0.001 |

|                                                        |                            |                            |                            |                            |           |        |
|--------------------------------------------------------|----------------------------|----------------------------|----------------------------|----------------------------|-----------|--------|
| METS-IR                                                | 40.10<br>[35.61,<br>45.19] | 34.99<br>[33.54,<br>39.05] | 40.36<br>[35.75,<br>45.58] | 41.31<br>[37.25,<br>46.55] | 25 (5.2%) | <0.001 |
| CHG index                                              | 5.56 ±<br>0.45             | 5.10<br>[4.87,<br>5.35]    | 5.59 ±<br>0.42             | 5.69 ±<br>0.42             | 12 (2.5%) | <0.001 |
| Female sex                                             | 207<br>(42.8%)             | 26<br>(49.1%)              | 120<br>(40.8%)             | 61<br>(44.5%)              | 0 (0.0%)  | 0.964  |
| Hypertension                                           | 281<br>(58.1%)             | 31<br>(58.5%)              | 168<br>(57.1%)             | 82<br>(59.9%)              | 0 (0.0%)  | 0.709  |
| Current<br>smoking                                     | 89<br>(18.4%)              | 16<br>(30.2%)              | 59<br>(20.1%)              | 14<br>(10.2%)              | 0 (0.0%)  | <0.001 |
| Current<br>drinking                                    | 73<br>(15.1%)              | 18<br>(34.0%)              | 42<br>(14.3%)              | 13 (9.5%)                  | 0 (0.0%)  | <0.001 |
| Hyperlipidemia                                         | 97<br>(20.0%)              | 8<br>(15.1%)               | 59<br>(20.1%)              | 30<br>(21.9%)              | 0 (0.0%)  | 0.349  |
| Statin/lipid-<br>lowering<br>treatment                 | 90<br>(18.6%)              | 14<br>(26.4%)              | 49<br>(16.7%)              | 27<br>(19.7%)              | 0 (0.0%)  | 0.702  |
| Use of insulin<br>and/or oral<br>antidiabetic<br>drugs | 470<br>(97.1%)             | 51<br>(96.2%)              | 285<br>(96.9%)             | 134<br>(97.8%)             | 0 (0.0%)  | 0.520  |

294

### 295 3.2. Associations between composite metabolic indicators and stage 6 PDR

296 In the clinically adjusted primary binary logistic models, all five prespecified  
 297 composite indicators were positively associated with higher odds of stage 6 PDR compared  
 298 with combined stages 4 and 5 (Table 2; Fig. 2). The ORs per 1-SD increase were 18.75  
 299 (95% CI: 10.10–34.79) for TyG, 647.94 (95% CI: 163.35–2570.06) for TyG-BMI, 12.25  
 300 (95% CI: 7.41–20.25) for AIP, 15.40 (95% CI: 7.83–30.27) for METS-IR, and 10.61 (95%  
 301 CI: 6.06–18.59) for the CHG index (all  $P < 0.001$ ). Firth bias-reduced estimates for the  
 302 same contrast remained positive at 16.46 (95% CI: 9.34–31.08), 464.57 (95% CI: 132.11–

1890.74), 10.96 (95% CI: 6.93–18.37), 13.44 (95% CI: 7.19–26.58), and 9.68 (95% CI: 5.75–17.22), respectively. Exact complete or quasi-complete separation was not detected in the fitted binary designs, although the large TyG-BMI estimate and influence diagnostics indicated that numerical magnitude remained sensitive to sparse data structure and covariate specification (Table S7).

Secondary ordered-stage analyses were directionally consistent with the primary binary comparison. In the partial proportional-odds model, higher values for all five indices were positively associated with advanced PDR across both stage thresholds (stage 5 or 6 vs. stage 4, and stage 6 vs. stages 4 and 5) (Table S8). The magnitude of the association varied across stage thresholds for the TyG index, AIP, METS-IR, and the CHG index, whereas the effect of TyG-BMI remained constant across thresholds. Standard ordinal models assuming a common odds ratio across stage thresholds (Models A–D) were presented as secondary summary measures (Table 3 and Table S9). Exposure VIFs were 1.80 for the TyG index, 10.21 for TyG-BMI, 1.13 for AIP, 5.70 for METS-IR, and 2.87 for the CHG index; corresponding maximum VIFs within each Model C specification were 2.00, 10.21, 1.95, 5.70, and 2.89 (Table S10). In the multinomial sensitivity analysis, all five indices remained positively associated with stage 6 relative to stage 4. However, because stage 4 contained few observations as the reference category, estimates for TyG-BMI, METS-IR, and the CHG index were markedly elevated and imprecise, requiring cautious interpretation (Table 5 and Table S11).

Excluding index-specific components from the composite indicators substantially altered the magnitude of several ordered-stage associations. After omitting FPG from the TyG and CHG models and omitting BMI and FPG from the TyG-BMI and METS-IR

models, the ORs for stage 5 or 6 *versus* stage 4 and stage 6 *versus* stages 4 and 5 were 1.87 (95% CI: 1.39–2.50) and 3.47 (95% CI: 2.60–4.63) for the TyG index, 1.23 (95% CI: 0.91–1.67) and 1.45 (95% CI: 1.17–1.80) for TyG-BMI, 2.51 (95% CI: 1.74–3.61) and 1.45 (95% CI: 1.17–1.79) for METS-IR, and 6.60 (95% CI: 4.15–10.50) and 2.06 (95% CI: 1.62–2.64) for the CHG index, respectively. AIP model estimates were unchanged because neither FPG nor BMI is a component of the index. Thus, in contrast to the large estimates observed in the primary models, excluding embedded components attenuated risk estimates across the four remaining indices, such that the TyG-BMI association for stage 5 or 6 *versus* stage 4 was no longer statistically significant (Table S7).

Secondary proportional-odds quartile analyses showed that severity gradients were monotonic for all five primary indicators (Table 4, Table S12, and Table S13; Fig. 3).

36 Compared with the lowest quartile, the highest quartile was associated with higher odds of advanced PDR for the TyG index (OR: 40.51, 95% CI: 18.80–87.30), TyG-BMI (OR: 15.54, 95% CI: 5.23–46.15), AIP (OR: 132.44, 95% CI: 56.43–310.81), METS-IR (OR: 79.30, 95% CI: 27.82–226.02), and the CHG index (OR: 116.05, 95% CI: 45.24–297.72) (all  $P_{\text{trend}} < 0.001$ . Correlation analyses showed that related indices clustered as expected,

17 with strong correlations observed between TyG-BMI and METS-IR and between TC/HDL-C and LDL/HDL-C (Fig. 4), supporting the decision to model composite indicators separately. Because these quartile models impose common proportional odds across stages, they reflect an overall dose-response pattern but do not replace the primary binary estimates. Stage-by-quartile cross-tabulations showed three empty cells for AIP; minimum cell counts were 1 for METS-IR and the CHG index and 3 for the TyG index, whereas the minimum cell count for TyG-BMI was 11 (Table S7).

349 **Table 2.** Primary binary logistic regression comparing stage 6 with stages 4 and 5, Model  
 350 C.

| Exposure  | Primary binary odds<br>ratios (95% CI) | Firth sensitivity odds<br>ratios (95% CI) | <i>P</i> -value | <i>N</i> |
|-----------|----------------------------------------|-------------------------------------------|-----------------|----------|
| TyG index | 18.75 (10.10–34.79)                    | 16.46 (9.34–31.08)                        | <0.001          | 484      |
| TyG-BMI   | 647.94 (163.35–<br>2570.06)            | 464.57 (132.11–<br>1890.74)               | <0.001          | 484      |
| AIP       | 12.25 (7.41–20.25)                     | 10.96 (6.93–18.37)                        | <0.001          | 484      |
| METS-IR   | 15.40 (7.83–30.27)                     | 13.44 (7.19–26.58)                        | <0.001          | 484      |
| CHG index | 10.61 (6.06–18.59)                     | 9.68 (5.75–17.22)                         | <0.001          | 484      |

351 Note: Stage 6 ( $n = 137$ ) was coded as the outcome, and stages 4 and 5 were combined as  
 352 the reference group ( $n = 347$ ). Primary odds ratios are per 1-SD increase from standard  
 353 logistic Model C, adjusted for age, sex, body mass index, hypertension, glycated  
 354 hemoglobin A1c, fasting plasma glucose, diabetes duration, smoking status, alcohol  
 355 consumption, and hospital fixed effects. The Firth column reports bias-reduced estimates  
 356 for the same contrast with penalized-likelihood 95% CIs ( $P < 0.001$  for all primary  
 357 exposure tests). Because 1-SD units are sample-dependent, odds ratio magnitudes do not  
 358 represent calibrated clinical effect sizes and should not be used to rank indices. Ordered  
 359 three-stage analyses are presented as secondary analyses in Table S8; additional stability  
 360 diagnostics are provided in Table S7.

361 **Table 3.** Secondary proportional-odds estimates across sequential adjustment models for  
 362 primary indices.

| Exposure  | Model A                       | Model B                        | Model C                          | Model D                          |
|-----------|-------------------------------|--------------------------------|----------------------------------|----------------------------------|
| TyG index | 2.13 (1.75–2.58); $P < 0.001$ | 2.14 (1.76–2.61); $P < 0.001$  | 4.97 (3.65–6.75); $P < 0.001$    | 5.00 (3.67–6.80); $P < 0.001$    |
| TyG-BMI   | 1.34 (1.12–1.60); $P = 0.001$ | 6.18 (3.84–9.94); $P < 0.001$  | 42.60 (20.63–87.98); $P < 0.001$ | 43.24 (20.88–89.56); $P < 0.001$ |
| AIP       | 5.49 (4.15–7.26); $P < 0.001$ | 6.01 (4.49–8.05); $P < 0.001$  | 6.68 (4.89–9.13); $P < 0.001$    | 6.71 (4.90–9.18); $P < 0.001$    |
| METS-IR   | 1.54 (1.28–1.85); $P < 0.001$ | 8.77 (5.61–13.70); $P < 0.001$ | 27.50 (15.02–50.32); $P < 0.001$ | 27.94 (15.20–51.36); $P < 0.001$ |
| CHG index | 1.97 (1.62–2.39); $P < 0.001$ | 1.95 (1.60–2.38); $P < 0.001$  | 13.54 (8.62–21.28); $P < 0.001$  | 14.05 (8.91–22.17); $P < 0.001$  |

Note: Values are common odds ratios (95% CIs) per 1-SD increase from proportional-odds models and are retained as secondary ordered-stage summaries; the primary binary stage 6 *versus* stage 4/5 results are shown in Table 2. Model A was unadjusted; Model B was adjusted for age, sex, and body mass index (BMI); Model C was additionally adjusted for hypertension, glycated hemoglobin A1c, fasting plasma glucose, diabetes duration, smoking status, alcohol consumption, and hospital fixed effects; and Model D was additionally adjusted for statin or lipid-lowering treatment and hyperlipidaemia.

**Table 4.** Secondary proportional-odds quartile summaries for primary indices.

| Exposure | Q2 vs. Q1           | Q3 vs. Q1           | Q4 vs. Q1            | P for trend |
|----------|---------------------|---------------------|----------------------|-------------|
| TyG      | 2.97 (1.67–         | 8.49 (4.60–         | 40.51 (18.80–        | <0.001      |
| index    | 5.28); $P < 0.001$  | 15.66); $P < 0.001$ | 87.30); $P < 0.001$  |             |
| TyG-     | 2.64 (1.44–         | 6.12 (2.86–         | 15.54 (5.23–         | <0.001      |
| BMI      | 4.86); $P = 0.002$  | 13.09); $P < 0.001$ | 46.15); $P < 0.001$  |             |
| AIP      | 4.65 (2.33–         | 39.51 (17.61–       | 132.44 (56.43–       | <0.001      |
|          | 9.28); $P < 0.001$  | 88.65); $P < 0.001$ | 310.81); $P < 0.001$ |             |
| METS-    | 5.23 (2.81–         | 15.98 (7.39–        | 79.30 (27.82–        | <0.001      |
| IR       | 9.75); $P < 0.001$  | 34.54); $P < 0.001$ | 226.02); $P < 0.001$ |             |
| CHG      | 7.41 (3.92–         | 21.55 (10.71–       | 116.05 (45.24–       | <0.001      |
| index    | 13.99); $P < 0.001$ | 43.33); $P < 0.001$ | 297.72); $P < 0.001$ |             |

**Note:** Values are common odds ratios (95% CIs) from proportional-odds Model C with quartile 1 (Q1) as the reference; The  $P$  for trend treats quartiles as an ordinal variable. Because the primary analysis compares stage 6 with combined stages 4 and 5, these ordered-stage results serve only as secondary dose-response summaries. Because several stage-by-quartile cells were sparse or empty (Table S7), the resulting very large quartile estimates should not be interpreted as precise clinical effect sizes.

**Table 5.** Multinomial logistic regression sensitivity analysis.

| Exposure  | Stage 5 vs. 4 OR (95% CI)               | Stage 6 vs. 4 OR (95% CI)                  | N   |
|-----------|-----------------------------------------|--------------------------------------------|-----|
| TyG index | 1.49 (0.88–2.51); $P = 0.135$           | 26.44 (12.22–57.21); $P < 0.001$           | 484 |
| TyG-BMI   | 2.70 (0.78–9.35); $P = 0.117$           | 1546.15 (264.24–9047.12); $P < 0.001$      | 484 |
| AIP       | 4.50 (2.53–8.00); $P < 0.001$           | 48.56 (22.75–103.66); $P < 0.001$          | 484 |
| METS-IR   | 5829.05 (281.80–120576.27); $P < 0.001$ | 58552.46 (2641.75–1297772.86); $P < 0.001$ | 484 |
| CHG index | 152.82 (28.35–823.81); $P < 0.001$      | 1216.51 (206.61–7162.90); $P < 0.001$      | 484 |

Note: Stage 4 ( $n = 53$ ) is the reference category, and all models apply the Model C adjustment set. Because of the small size of the stage 4 group, centre-stage imbalance, cell sparsity, and potential quasi-separation, very large estimates and wide confidence intervals should be interpreted as unstable sensitivity results, rather than precise biological effect sizes or evidence for ranking indices. Corresponding Firth, separation, and influence diagnostics for the cumulative contrasts are shown in Table S7.

### 3.3 Subgroup analysis

In exploratory stratified analyses, the positive direction of association was maintained across sex, age groups, hypertension status, HbA1c categories, and hospital sites for all five primary indicators (Table S14; Fig. 5). For the TyG index, interactions with sex, age, hypertension, and HbA1c category were non-significant, whereas the interaction with hospital site was statistically significant ( $P_{\text{interaction}} < 0.001$ ), with the largest point estimate observed at Shijiazhuang People's Hospital and the smallest at

Shijiazhuang Second Hospital (Table S14; Fig. 5A). For TyG-BMI, interaction signals were observed for sex ( $P_{\text{interaction}} = 0.025$ ) and hospital site ( $P_{\text{interaction}} = 0.001$ ), although associations remained positive across both male and female strata (Table S14; Fig. 5B).

For AIP, interactions were detected for HbA1c category and hospital site (both  $P_{\text{interaction}} < 0.001$ ), with larger point estimates among participants with HbA1c  $\geq 8\%$  than among those with HbA1c  $< 8\%$  (Table S14; Fig. 5C). For METS-IR, interactions were observed for sex, HbA1c category, and hospital site (all  $P_{\text{interaction}} < 0.001$ ), with associations being numerically stronger among female participants and individuals with HbA1c  $\geq 8\%$  (Table S14; Fig. 5D). For the CHG index, interaction signals were observed for HbA1c category and hospital site (both  $P_{\text{interaction}} < 0.001$ ; Table S14; Fig. 5E). Across all exploratory subgroup analyses, statistically significant interactions included TyG by hospital site ( $P_{\text{interaction}} < 0.001$ ); TyG-BMI by sex ( $P_{\text{interaction}} = 0.025$ ) and hospital site ( $P_{\text{interaction}} = 0.001$ ); AIP by HbA1c category ( $P_{\text{interaction}} < 0.001$ ) and hospital site ( $P_{\text{interaction}} < 0.001$ ); METS-IR by sex ( $P_{\text{interaction}} < 0.001$ ), HbA1c category ( $P_{\text{interaction}} < 0.001$ ), and hospital site ( $P_{\text{interaction}} < 0.001$ ); and CHG index by HbA1c category ( $P_{\text{interaction}} < 0.001$ ) and hospital site ( $P_{\text{interaction}} < 0.001$ ).

### 3.4 Sensitivity analysis

Sparse-data diagnostics for the primary stage 6 *versus* stage 4/5 contrast were consistent with the direction of association rather than precise numerical calibration (Table 2 and Table S7). Firth estimates were finite and positive for all five indices, and linear-programming checks detected no complete or quasi-complete separation. No observation yielded a Cook's distance  $\geq 1$ , although multiple observations exceeded  $4/n$ , and DFBETA

415 diagnostics for the exposure term indicated that individual observations exerted moderate  
416 influence. These findings supported the rationale for using the combined binary outcome.

417 Secondary ordered-stage summaries remained positive across complete-case,  
418 winsorized, Model D, lipid-lowering treatment exclusion,  $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$ , and  
419 center-exclusion analyses (Table S15 and Table S16; Fig. 6). In the multiple-imputation  
420 analysis that excluded the PDR stage from the imputation predictors, all five indices  
421 remained positively associated with both cumulative stage contrasts, and threshold-specific  
422 complete-case models showed the same direction of effect (Table S3). The separate stage  
423 5/6 *versus* stage 4 binary contrast was also positive across all five indices but remained  
424 particularly unstable for METS-IR and the CHG index because it relied on the small stage  
425 4 group (Table S17 and Table S7).

426 Hospital sensitivity analyses indicated that the direction of association remained  
427 positive across all evaluable centers, whereas numerical magnitudes varied materially  
428 (Table S7). Adding hospital fixed effects changed the stage 5/6 *versus* stage 4 ORs by 0.97-  
429 to 1.38-fold and the stage 6 *versus* stage 4/5 ORs by 1.09- to 1.22-fold; the largest change  
430 occurred for the CHG index at the lower threshold, shifting from 29.31 to 40.47. All 15  
431 leave-one-center-out model refits converged and yielded positive associations. Across  
432 center exclusions, OR ranges for stage 5/6 *versus* stage 4 and stage 6 *versus* stage 4/5,  
433 respectively, were 2.81 to 3.79 and 4.54 to 13.03 for the TyG index, 19.52 to 71.02 and  
434 24.69 to 101.29 for TyG-BMI, 3.04 to 6.68 and 8.65 to 10.72 for AIP, 41.66 to 85.54 and  
435 22.85 to 33.04 for METS-IR, and 20.02 to 138.37 and 10.97 to 18.25 for the CHG index.  
436 Within-center models at Hebei General Hospital and Shijiazhuang Second Hospital also  
437 showed positive associations across all five indices, although point estimates varied and

several CIs were wide. Shijiazhuang People's Hospital did not support a separate ordered-stage fit because only one stage 4 participant was included.

Additional adjustment for the aggregate insulin and/or oral antidiabetic drug-use indicator produced threshold-specific estimates close to the secondary partial proportional-odds Model C results. For stage 5/6 *versus* stage 4 and stage 6 *versus* stage 4/5, the respective ORs were 3.55 and 7.18 for the TyG index, 36.81 and 48.98 for TyG-BMI, 4.95 and 9.48 for AIP, 57.33 and 25.32 for METS-IR, and 40.31 and 10.92 for the CHG index (Table S4).

446

## 4. Discussion

### 4.1 Key results

In this three-center cross-sectional study of 484 patients with type 2 diabetes and established PDR, higher values for the TyG index, TyG-BMI, AIP, METS-IR, and CHG index were consistently associated with higher odds of stage 6 PDR relative to stages 4 and 5. Secondary ordered-stage and quartile analyses demonstrated concordant severity gradients, and the positive direction of association was generally preserved across sensitivity analyses. However, the magnitude of several estimates, particularly for indices incorporating BMI or FPG, was sensitive to sparse-data structure and covariate specification, showing substantial attenuation in component-excluded models. Taken together, these findings indicated that adverse composite metabolic profiles are associated with more advanced PDR within established disease; however, these effect estimates should not be interpreted as calibrated risk estimates, causal effects, or evidence of superiority of one index over another.

461

462 **4.2 Interpretation**

463 The present findings are directionally consistent with the expanding literature on

464 routinely calculated metabolic indices and DR. A 2023 meta-analysis of 10 observational

465 studies involving 13,716 patients with type 2 diabetes reported that higher TyG index

466 values were associated with DR in both categorical and continuous analyses [10].

467 Subsequent syntheses reached similar conclusions while highlighting between-study

468 heterogeneity and sensitivity to small-study effects in categorical analyses [11, 12]. Xu et

469 al. reported that 1-SD increases in METS-IR and TyG-BMI were associated with the

470 presence of DR among 2,211 patients with type 2 diabetes, yielding ORs of 1.97 and 1.94,

471 respectively [13]. For lipid-focused markers, Shan et al. reported that remnant cholesterol

472 was linked to DR presence and severity [14], while Zhang et al. observed that the odds of

473 DR were greater in the highest AIP quartile than in the lowest quartile [15]. Similarly, a

474 2026 cross-sectional study of 1,909 adults with diabetes found that higher values for the

475 CHG index were independently associated with DR and demonstrated modest

476 discrimination for DR status [9]. The larger effect estimates observed in the present study

477 may reflect several methodological factors: the restriction of the cohort to patients with

478 established PDR, the late-stage comparison of stage 6 *versus* stages 4 and 5, mathematical

479 coupling, and dataset-specific sparsity or near-separation. The primary finding remains the

480 cross-sectional association between these metabolic indices and PDR stage among patients

481 with established disease, rather than a clinical threshold or definitive ranking of the indices.

482 Furthermore, component-excluded analyses indicated that covariate-exposure

483 mathematical coupling contributed materially to the unusually large, uniformly adjusted

estimates for indices containing BMI or FPG. Accordingly, the magnitude of these uniformly adjusted estimates does not provide reliable evidence for an independent biological effect of comparable size.

Several biological pathways may underlie the observed associations. Insulin resistance can promote hyperglycaemia, TG-rich lipoprotein accumulation, lipotoxicity, oxidative stress, and low-grade inflammation [18-20]. The pattern of higher triglycerides and lower HDL-C captured by AIP and related ratios may indicate that reverse cholesterol transport is impaired, and that the anti-inflammatory, antioxidant, and endothelial-protective capacity is reduced [21, 22]. Furthermore, lipid dysregulation in DR extends beyond changes in circulating lipid concentrations. Experimental and clinical data indicate that altered retinal fatty-acid metabolism, disrupted cholesterol homeostasis, and ceramide imbalances contribute directly to blood-retinal barrier dysfunction and inflammatory injury [23]. In the ischaemic retina, these disturbances may interact with the angiogenic signaling and fibrovascular responses that characterize advanced PDR. Indices incorporating BMI, particularly TyG-BMI and METS-IR, may additionally capture adiposity-related metabolic stress, suggesting that this burden also contributes to the observed associations. Evidence

from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye clinical trials indicates that fenofibrate-based strategies can reduce the need for retinopathy-related laser treatment or slow DR progression in selected patients with type 2 diabetes [24, 25]. However, these trial findings do not establish any single composite index as a therapeutic target in established PDR. The effects of fenofibrate on the retina may not be mediated solely through changes

506 in conventional circulating lipid concentrations. Moreover, the observational design of the  
507 present study precludes evaluating treatment efficacy.

508

### 509 4.3 Generalisability

510 The findings pertain to patients with type 2 diabetes and established PDR treated at  
511 three participating tertiary hospitals in China. Consequently, these results should not be  
512 directly extrapolated to community screening, individuals with type 1 diabetes, or patients  
513 without DR or with non-proliferative DR. Nor do they necessarily apply to other ethnic  
514 groups, different healthcare settings, or longitudinal prognosis and treatment response.  
515 Additionally, because the study included only three centres with limited overlap in stage  
516 distribution, the data cannot support reliable centre-level random effects or cluster-robust  
517 inference. Validation in a larger number of centres with balanced stage representation is  
518 needed. While the indices are inexpensive to calculate and rely on routine measurements,  
519 this study did not assess discrimination, calibration, incremental predictive value, or  
520 clinical decision thresholds. Prospective multi-regional studies with standardised retinal  
521 grading, repeated metabolic measurements, and adequate representation of each disease  
522 stage are needed to establish temporal relationships and external validity. Future research  
523 should also determine whether composite indices provide clinically meaningful  
524 information beyond established risk factors, supporting rather than replacing  
525 comprehensive ophthalmic assessment.

526

527 **4.4 Study strengths and limitations**

528 This study has several strengths. It included 484 eye-specific records from three  
529 centers and evaluated five composite metabolic indices derived from routinely available  
530 measurements. The prespecified primary comparison of stage 6 with combined stages 4/5  
531 reduced dependence on the sparse stage 4 category and ensured representation of both  
532 outcome groups across centers. PDR stage was independently assessed by two graders  
533 masked to the metabolic exposures, and inter-grader agreement was high. Missing data  
534 were uncommon, and the consistency of the association direction was examined using  
535 multiple complementary sensitivity analyses, including Firth penalisation, alternative  
536 missing-data approaches, center-restricted analyses, component-excluded models, and  
537 additional treatment adjustment.

538 Several limitations should also be considered. First, the cross-sectional design  
539 precludes the assessment of temporality or causality. The observed metabolic  
540 abnormalities may contribute to advanced PDR, accompany disease progression, or be  
541 influenced by behavioural or treatment changes once severe ocular disease develops.  
542 Restriction to patients with established PDR treated at three tertiary hospitals also  
543 introduces potential referral and selection bias, including collider bias, and limits inference  
544 beyond this clinical population [26]. In addition, differences in stage distribution, case mix,  
545 referral patterns, and ascertainment across the three centers could not be fully addressed by  
546 hospital adjustment or center-specific sensitivity analyses, and laboratory comparability  
547 across centers was not independently verified.

548 Second, the three-stage distribution was imbalanced, with a relatively small stage  
549 4 group and limited center-stage overlap. Although combining stages 4 and 5 reduced this  
550 dependence in the primary analysis and formal diagnostics did not identify complete or  
551 quasi-complete separation, the large estimates and their attenuation with Firth penalization  
552 indicate that the findings were vulnerable to sparse data and influential observations. For  
553 indices incorporating BMI or FPG, particularly TyG-BMI and METS-IR, collinearity and  
554 mathematical coupling with adjustment covariates may also have inflated or destabilized  
555 effect estimates, as suggested by the component-excluded analyses. The secondary three-  
556 stage analyses should therefore be interpreted cautiously.

557 Third, although missingness was limited, single imputation did not account for  
558 imputation uncertainty; the concordant multiple-imputation and complete-case analyses  
559 reduce but do not eliminate this concern. Residual confounding also remains possible  
560 because longitudinal glycemic exposure, detailed glucose-lowering therapy, dietary  
561 factors, acute illness, and ocular treatment history were incompletely captured. Metabolic  
562 indices were based on a single fasting assessment and may therefore not reflect long-term  
563 metabolic status, while the timing of treatment changes relative to laboratory  
564 measurements was unavailable. PDR grading was retrospective and was not based on  
565 standardized central image acquisition, and fellow-eye stage was unavailable, precluding  
566 assessment of bilateral discordance or worse-eye classification. Insulin and oral therapy  
567 could not be separated, and information on individual agents, dose, duration, adherence,  
568 recent treatment changes, GLP-1 receptor agonists, SGLT2 inhibitors, and other drug  
569 classes was unavailable. Finally, the exploratory subgroup analyses and evaluation of  
570 multiple correlated indices increase the possibility of chance findings.

44 Taken together, these limitations mean that the results should be interpreted as  
572 hypothesis-generating evidence of eye-specific cross-sectional associations with PDR  
573 severity rather than as causal effects, clinically calibrated thresholds, treatment  
574 recommendations, or evidence for comparative superiority among the indices.

#### 576 4.5 Clinical implementation

577 The findings indicate that the five composite metabolic indices evaluated here  
578 (TyG, TyG-BMI, AIP, METS-IR, and CHG) may serve as low-cost adjunctive tools for  
579 identifying patients with type 2 diabetes and established PDR who are at increased risk of  
580 advanced proliferative disease. Markedly elevated values may imply that patients face a  
581 higher probability of stage 6 disease, supporting closer ophthalmic surveillance, timely  
582 retinal imaging, and earlier referral to retinal specialists. Because these indices are derived  
583 from routinely available fasting laboratory and anthropometric data, they can be  
584 automatically calculated within electronic health record systems without additional testing.  
585 This enables risk-based alerts and more efficient prioritization of ophthalmic care,  
586 particularly in settings with limited specialist resources. Integration into existing diabetes  
587 management pathways may therefore offer a practical approach to combined metabolic and  
588 ophthalmic risk assessment. However, these indices should complement rather than replace  
589 established ophthalmological evaluation, and prospective studies are needed to define  
590 clinically meaningful thresholds and determine whether index-guided management  
591 improves outcomes without increasing unnecessary intervention or patient anxiety.

## 593 5. Conclusion

594 This three-center study showed that higher TyG, TyG-BMI, AIP, METS-IR, and  
595 CHG index values were consistently associated with higher odds of stage 6 PDR relative  
596 to stages 4/5 in patients with type 2 diabetes and established proliferative disease. These  
597 severity-related associations suggest that composite metabolic indices may provide useful  
598 adjunctive information for identifying patients who require closer retinal assessment.  
599 Because they are derived entirely from routinely available fasting laboratory and  
600 anthropometric measurements, these indices offer a practical and low-cost approach that  
601 could be integrated into existing diabetes care pathways without additional testing. Their  
602 use may be particularly relevant in settings with limited access to retinal imaging or other  
603 specialist ophthalmic services, where better prioritization could support timely surveillance,  
604 coordinated metabolic and eye care, and broader access to interventions aimed at  
605 preventing avoidable vision loss. These indices should complement, rather than replace,  
606 comprehensive ophthalmological evaluation. Prospective multicenter studies are needed to  
607 validate their incremental clinical value, establish meaningful thresholds, and determine  
608 whether their use can improve patient outcomes and the efficient delivery of ophthalmic  
609 care.

610

## 611 Declarations

### 612 Ethics approval and consent to participate

613 The Ethics Committees of Shijiazhuang People's Hospital (No. 2025-205), Shijiazhuang  
614 Second Hospital (No. SEY-KYLLLL-2026002), and Hebei General Hospital (No. 2026-  
615 LW-43) approved this study. All procedures were conducted following the Declaration of

4 616 Helsinki. Because this was a retrospective study using anonymized data, the requirement  
617 for patient informed consent was waived.

618 **Consent for publication**

619 Not applicable.

9 620 **Data availability**

621 All data supporting the findings of this study are available within the paper and its  
622 Supplementary Information.

623 **Competing interests**

624 The authors declare no competing interests.

4 625 **Funding**

626 This study received no specific funding from any funding agency.

627 **Authors' contributions**

628 Y. L., and J.H. analyzed the data and wrote the manuscript. M.X., L.L., X.H., D.W., and  
43 629 H.W. collected the data. Q.R. designed and supervised the study. All authors reviewed the  
630 manuscript.

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634  
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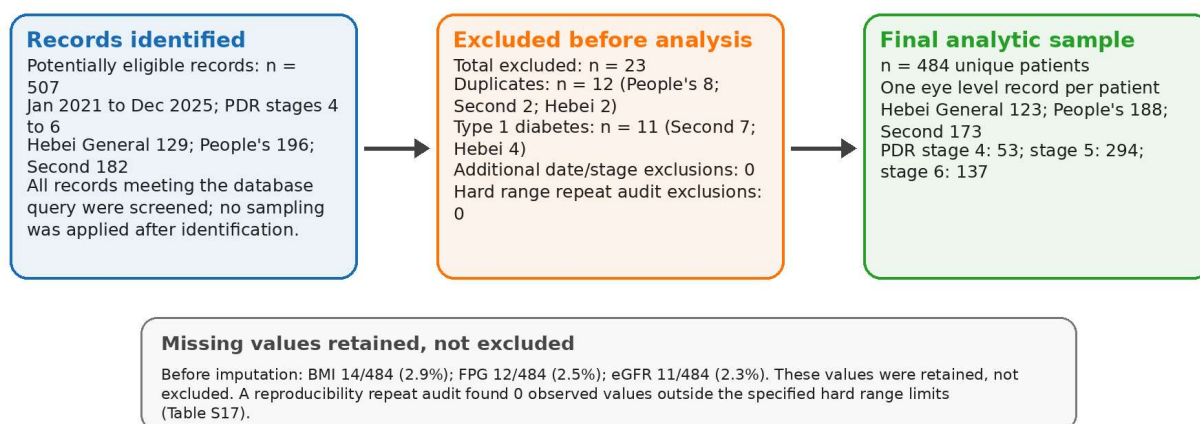
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## Figures

## A. Participant flow



## B. PDR stage distribution

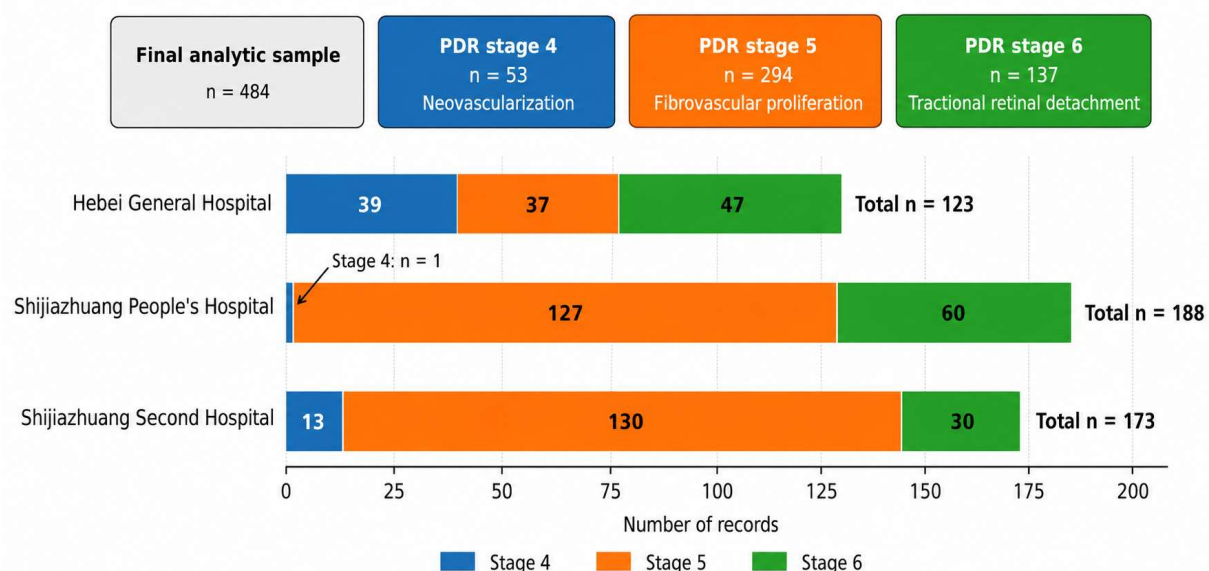
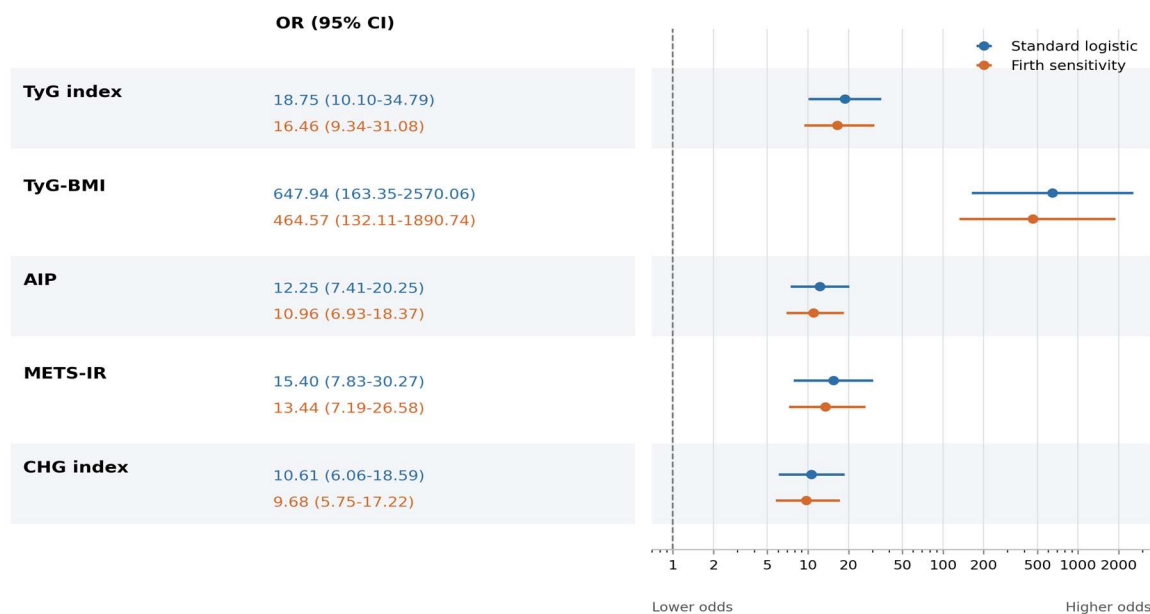


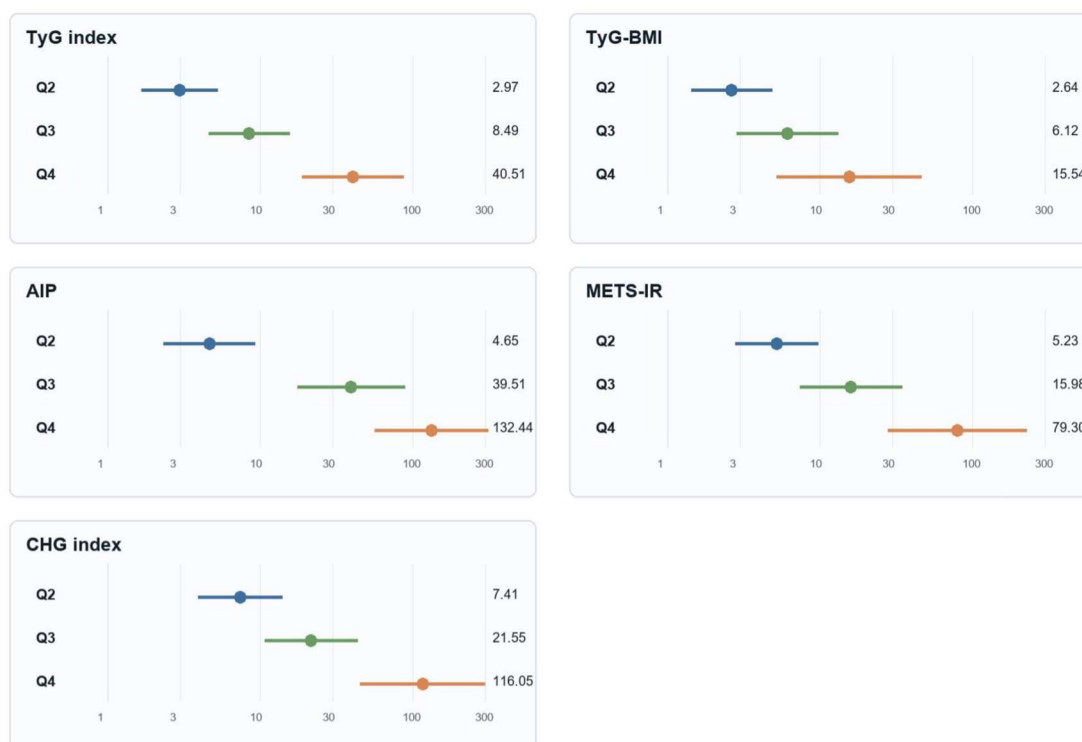
**Fig. 1.** Analytical sample construction and proliferative diabetic retinopathy (PDR) stage distribution. (A) Strengthening the Reporting of Observational studies in Epidemiology (STROBE)-style participant flow from database identification to the final analytic sample. (B) PDR stage distribution by center in the final analytic sample.

712



713

714 **Fig. 2.** Adjusted odds ratios for stage 6 proliferative diabetic retinopathy (PDR) *versus*  
715 stages 4 and 5. Estimates in blue are from the primary standard logistic Model C; estimates  
716 in orange are Firth bias-reduced sensitivity estimates.



717

718 **Fig. 3.** Secondary proportional-odds quartile analyses for primary metabolic indices.

719 Sparse or empty stage-by-quartile cross-tabulations are detailed in Table S7. The numerical

720 magnitude should not be interpreted as calibrated clinical effect sizes.

|                     | TyG  | TyG-BMI | AIP  | METS-IR | CHG  | TG/HDL-C | TC/HDL-C | LDL/HDL-C | non-HDL-C | Remnant-C |
|---------------------|------|---------|------|---------|------|----------|----------|-----------|-----------|-----------|
| TyG index           | 1.00 | 0.50    | 0.72 | 0.38    | 0.72 | 0.64     | 0.31     | 0.28      | 0.34      | 0.29      |
| TyG-BMI             | 0.50 | 1.00    | 0.41 | 0.91    | 0.33 | 0.35     | 0.17     | 0.14      | 0.15      | 0.18      |
| AIP                 | 0.72 | 0.41    | 1.00 | 0.48    | 0.44 | 0.90     | 0.61     | 0.59      | 0.31      | 0.16      |
| METS-IR             | 0.38 | 0.91    | 0.48 | 1.00    | 0.38 | 0.43     | 0.32     | 0.32      | 0.05      | 0.01      |
| CHG index           | 0.72 | 0.33    | 0.44 | 0.38    | 1.00 | 0.36     | 0.59     | 0.57      | 0.49      | 0.27      |
| TG/HDL-C ratio      | 0.64 | 0.35    | 0.90 | 0.43    | 0.36 | 1.00     | 0.55     | 0.53      | 0.26      | 0.14      |
| TC/HDL-C ratio      | 0.31 | 0.17    | 0.61 | 0.32    | 0.59 | 0.55     | 1.00     | 0.98      | 0.74      | 0.38      |
| LDL/HDL-C ratio     | 0.28 | 0.14    | 0.59 | 0.32    | 0.57 | 0.53     | 0.98     | 1.00      | 0.70      | 0.24      |
| non-HDL-C           | 0.34 | 0.15    | 0.31 | 0.05    | 0.49 | 0.26     | 0.74     | 0.70      | 1.00      | 0.70      |
| Remnant cholesterol | 0.29 | 0.18    | 0.16 | 0.01    | 0.27 | 0.14     | 0.38     | 0.24      | 0.70      | 1.00      |

721

722 **Fig. 4.** Correlation matrix for composite metabolic indicators.

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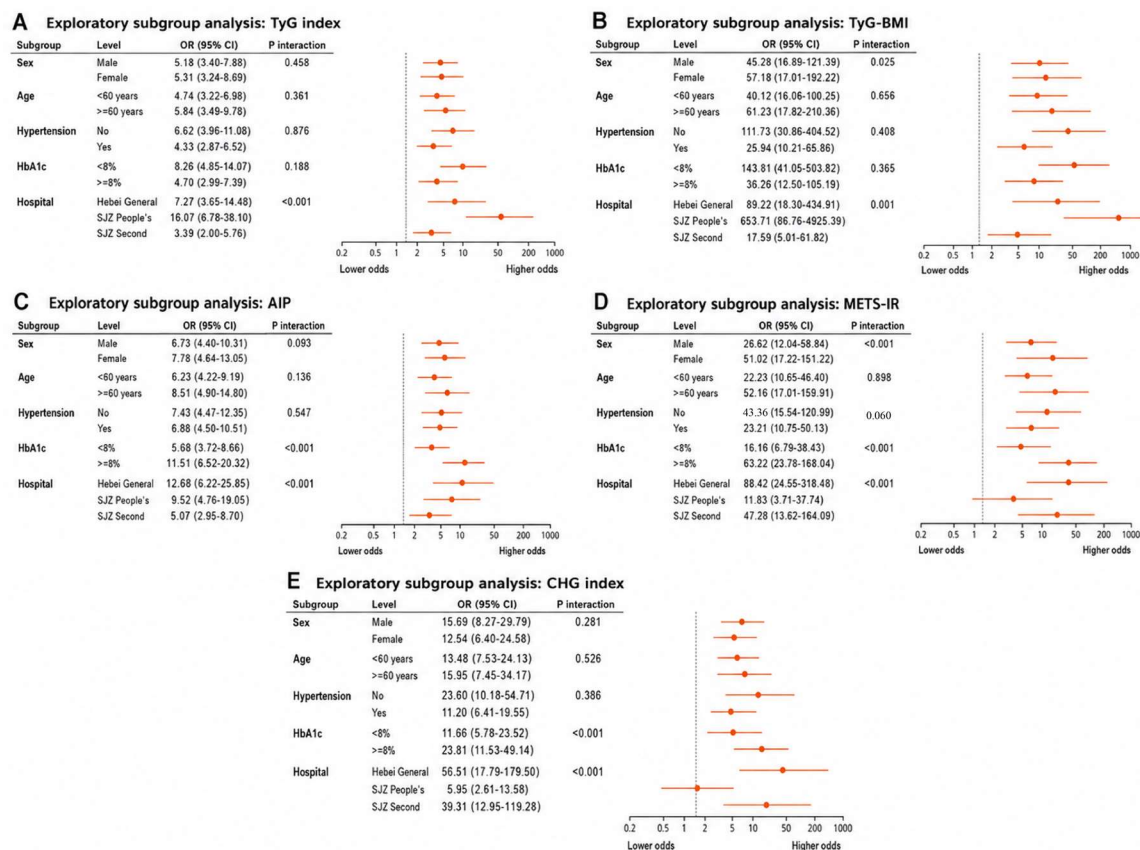
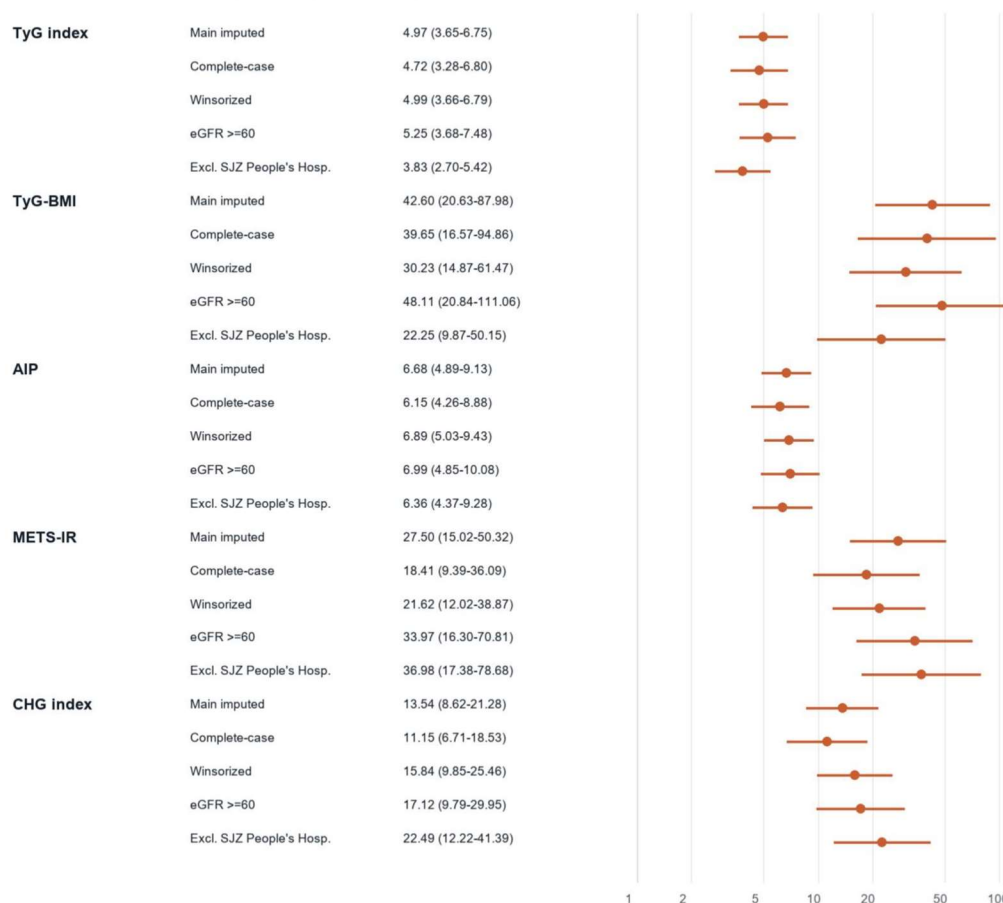


**Fig. 5.** Subgroup forest plots.



727

728 **Fig. 6.** Secondary proportional-odds sensitivity analyses for selected primary indices.729 Concordance of direction, rather than similarity of OR magnitude, served as the primary  
730 robustness criterion.

731

732