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Original Article

Predictive efficacy assessment of serum β_2-microglobulin combined with urinary albumin-to-creatinine ratio for renal function deterioration in type 2 diabetic patients with kidney disease

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Abstract: Objective: To assess the value of serum β_2-microglobulin (β_2MG) and urinary albumin-to-creatinine ratio (UACR) in predicting short-term renal function decline in patients with type 2 diabetic kidney disease (DKD). Methods: We retrospectively analyzed 356 patients with diabetic kidney disease who received standard care combined with SGLT-2 inhibitors and were followed for six months at Baoji People's Hospital and Hanzhong People's Hospital. Renal deterioration was defined as a ≥30% decline in estimated glomerular filtration rate (eGFR). Clinical and biochemical indicators were assessed using multivariate logistic regression. Model discrimination and calibration were examined through ROC analysis, Akaike information criterion (AIC), and DeLong testing. An additional cohort of 145 patients was used for external validation. Results: Among all participants, 78 (21.9%) experienced renal function decline. Seven variables were independently associated with deterioration: contrast agent exposure, systolic blood pressure, fasting glucose, HbA1c, cystatin C, UACR, and β_2-microglobulin. UACR had the strongest individual performance (AUC=0.891; cutoff =174.8 mg/g). The complete seven-factor model demonstrated excellent discrimination (AUC=0.994) and maintained high accuracy in external validation (AUC=0.949; sensitivity 90.6%; specificity 93.8%). Conclusion: β_2-microglobulin and UACR emerged as robust early predictors of renal deterioration in DKD. A combined model integrating these and related indicators provides precise short-term risk assessment and may assist clinicians in tailoring management strategies.

Keywords: Type 2 diabetes, diabetic kidney disease, β_2-microglobulin, urinary albumin-to-creatinine ratio, cystatin C, renal function deterioration, prediction model

Introduction

Type 2 diabetes mellitus (T2DM) is rising worldwide, with earlier onset increasingly recognized as a distinct and burdensome trend [1]. Diabetic kidney disease (DKD) remains a leading pathway to end-stage renal disease (ESRD) and excess cardiovascular risk, despite advances in glucose-lowering and cardiorenal therapies [2]. Kidney histology can forecast who will reach ESRD, yet it does not fully account for how quickly renal function declines - pointing to a gap between structural assessment and dynamic risk [3]. As machine-learning work begins to translate into explainable tools for DKD prediction [4], there is a parallel need to define near-term outcomes that are clinically actionable.

Traditional markers - estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR) - anchor DKD staging and prognosis [5], but both have blind spots. eGFR equations vary in performance across subgroups; in elderly Chinese patients, creatinine-, cystatin C-, and combined equations showed notable differences by diabetes and hypertension status [6]. Early hyperfiltration may conceal injury behind apparently preserved eGFR [7], and a non-albuminuric DKD phenotype with

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progressive loss of function despite normoalbuminuria is increasingly reported [8]. Even within "normal" albumin ranges, higher ACR tertiles tracked later microalbuminuria and cardiovascular risk in adolescents with diabetes (AdDIT) [9]. Beyond filtration and albuminuria, inflammation, oxidative stress, and tubular injury biomarkers are under active study for earlier detection and better risk stratification [7, 10-12].

Therapeutically, sodium-glucose cotransporter-2 (SGLT-2) inhibitors and GLP-1 receptor agonists now shape cardiorenal care in diabetes, with accumulating evidence for kidney protection across risk strata [2]. Yet clinicians still lack practical tools to flag which patients on contemporary regimens are at imminent risk of meaningful decline.

Against this background, we studied DKD patients receiving standardized care that included SGLT-2 inhibitors. We retrospectively profiled clinical and biochemical features, compared patients with versus without short-term deterioration, and built multivariable prediction models using routinely available markers. Motivated by prior work linking eGFR change with hard outcomes [5] and proposals to operationalize rapid decline over a 6-12-month window [12], we defined the endpoint as a ≥30% eGFR reduction within six months. Our aim was to develop and externally test a concise, clinic-ready model for near-term risk identification in a Chinese DKD population, while situating performance alongside existing literature on biomarker-based and machine-learning approaches.

Materials and methods

Sample size calculation

We planned sample size around events per variable, not a single-proportion formula. With seven predictors and a 6-month endpoint, we targeted about 10-12 events per predictor. Using an expected event rate near 20% (from Roumeliotis et al. [12], 18.7% over 6-12 months), this implies roughly 350-420 patients (~70-84 events). Our internal cohort had 356 patients and 21.9% events (about 78), which gives ~11 EPV. We then set aside a separate cohort for external testing (n=145). Note: the $Z^2P(1-P)/E^2$ formula (P=0.1868, E=0.05) only tells you how many patients you need to estimate an event rate within ±5%; it does not ensure a stable multivariable model.

Study population

We assembled two consecutive cohorts at a single tertiary center. The development cohort included 356 adults with type 2 diabetes and diabetic kidney disease seen from January 2019 to March 2022 at Baoji People's Hospital and Hanzhong People's Hospital; all were managed with routine care that included an SGLT-2 inhibitor. The external cohort comprised 145 patients seen from April 2022 to January 2024. The index date was the first visit with complete baseline labs after starting the regimen. Follow-up was 6 months. The primary endpoint was a ≥30% drop in eGFR from baseline within that window. This study, conducted at Baoji People's Hospital, was approved by Hanzhong People's Hospital Ethics Committee, and all patient data were de-identified prior to analysis.

Inclusion and exclusion criteria

Inclusion criteria: (1) diagnosis of T2DM according to WHO criteria; (2) confirmed DKD with established clinical staging based on UACR and eGFR; (3) age ≥18 years; (4) received standardized treatment including SGLT-2 inhibitors with ≥6 months follow-up; (5) complete clinical and laboratory data.

Exclusion criteria: (1) primary or secondary kidney diseases (e.g., IgA nephropathy, lupus nephritis, polycystic kidney disease); (2) recent major cardiovascular or cerebrovascular events (within 6 months); (3) active liver disease, malignancy, or severe infection; (4) pregnancy or lactation; (5) treatment discontinuation or missing key data.

Treatment protocol

All participants underwent six months of standardized therapy. Dapagliflozin (10 mg once daily) and linagliptin (5 mg once daily) were used as part of the SGLT-2 inhibitor-based regimen. To optimize glycemic and renal control, patients also received gliclazide MR (30-120 mg once daily) and metformin ER (500 mg once

to three times daily). Doses were titrated individually based on glucose readings, tolerance, and renal function.

Data collection

Clinical and biochemical data were abstracted from the electronic record around a prespecified index date (the first visit with complete baseline labs after treatment initiation) and from routine follow-up within 6 months. We recorded demographics and history (age, sex, BMI, smoking and alcohol use, hypertension, coronary heart disease, and iodinated contrast exposure during follow-up), hemodynamic and metabolic measures (clinic systolic/diastolic blood pressure, fasting glucose, HbA1c, total cholesterol, triglycerides, LDL-C), and renal markers (serum creatinine, eGFR by CKD-EPI 2021 creatinine-cystatin C, urea, uric acid, cystatin C). Additional variables included homocysteine, HOMA-IR, urinary albumin-to-creatinine ratio from a first-morning spot urine, and β_2-microglobulin. Renal deterioration was defined a priori as a ≥30% fall in eGFR from baseline within 6 months. Two investigators independently verified all entries against source files, with discrepancies adjudicated by consensus; missing baseline covariates were handled using prespecified rules (complete-case analysis or multiple imputation, as applicable).

Laboratory measurements

All tests were performed in the hospital's central laboratory on fasting venous blood and first-morning midstream urine. Serum creatinine, urea, uric acid, glucose, total cholesterol, triglycerides, LDL-C, and β_2-microglobulin were measured on automated chemistry analyzers; HbA1c by high-performance liquid chromatography; cystatin C by immunoturbidimetry; and fasting insulin by chemiluminescence. eGFR was calculated with the modified MDRD equation: eGFR [mL/(min·1.73 m^2)] = 175 × (Scr/88.4)^-1.234 × (Age)^-0.179 × 0.79 (if female). HOMA-IR was computed as [FPG (mmol/L) × fasting insulin (μU/mL)]/22.5. UACR was derived as urinary albumin (mg/L) divided by urinary creatinine (g/L) and expressed as mg/g. All assays followed standardized internal quality-control procedures to ensure analytical reliability.

Outcomes

The primary endpoint was a ≥30% fall in eGFR from baseline within 6 months of the index date. Secondary endpoints were pre-to-post changes in clinical and laboratory measures over the same window (absolute and relative change from baseline).

Statistical analysis

Analyses used R 4.3.3 (two-sided α=0.05). Continuous variables were inspected by Q-Q plots and the Kolmogorov-Smirnov test. Results are reported as mean ± SD or median (IQR) as appropriate, and categorical data as n (%). Between-group differences used Welch's t test or the Wilcoxon rank-sum test, while χ^2 or Fisher's exact test was applied to categorical comparisons depending on expected counts. Correlations used Pearson's r when approximately normal and Spearman's ρ otherwise. Candidate predictors were selected a priori (clinical relevance) and if P<0.10 in univariable tests, then entered into multivariable logistic regression; multicollinearity was checked with VIF (flagged at >5). Discrimination was summarized by ROC AUC with 95% CIs (bootstrap, 1,000 resamples) and compared by DeLong's test. Model parsimony used AIC. Calibration was assessed by calibration plots and by reporting the intercept and slope. We derived the Youden index to illustrate one operating point. Internal performance was optimism-corrected by bootstrap; external performance was evaluated in the independent cohort using the same metrics. Missing baseline covariates were handled per a prespecified plan (complete-case if <5% missing; otherwise multiple imputation).

Results

Changes in clinical indicators before and after treatment

After 6 months, diastolic blood pressure fell (P<0.001). Fasting plasma glucose and HbA1c improved (both P<0.001). Total cholesterol, triglycerides, and LDL-C decreased (all P<0.001). eGFR increased (P<0.001), while creatinine and uric acid declined (both P<0.001); cystatin C showed a modest reduction (P=0.001). Hcy and HOMA-IR decreased (both P<0.001).

Table 1. Assessment of changes in clinical indicators before and after treatment

Variable	Pre-treatment (n=356)	Post-treatment (n=356)	t/Z value	*P* value
Systolic blood pressure (mmHg)	135 [125, 145]	123.5 [84, 177]	0.835	0.403
Diastolic blood pressure (mmHg)	80.5 [73, 87]	76 [72, 79]	7.369	<0.001
Fasting blood glucose (mmol/L)	9.4 [8.5, 10.3]	7.3 [6.4, 8.1]	14.739	<0.001
HbA1c (%)	9.24±1.63	7.9±1.02	13.134	<0.001
Total cholesterol (mmol/L)	5.19 [4.4375, 5.9725]	3.975 [3.26, 4.67]	12.316	<0.001
Triglycerides (mmol/L)	2.465 [2.1575, 2.94]	1.945 [1.55, 2.3525]	10.954	<0.001
LDL-C (mmol/L)	3.19±0.59	2.37±0.65	16.721	<0.001
eGFR [ml/(min·1.73 m^2)]	60.91 [57.4325, 64.465]	78.68 [72.375, 85.5925]	10.204	<0.001
Creatinine (μmol/L)	109.7 [96.175, 117.225]	90.2 [78.1, 101.65]	7.717	<0.001
Urea (mmol/L)	6.09±1.41	5.94±1.11	1.611	0.108
Uric acid (μmol/L)	373.47±72.85	311.56±67.46	11.406	<0.001
Cystatin C (mg/L)	1.75±0.74	1.59±0.58	3.299	0.001
Hcy (μmol/L)	13.26±3.21	11.68±2.62	7.191	<0.001
HOMA-IR	4.82±1.49	3.56±1.18	12.79	<0.001
UACR (mg/g)	115.12 [78.19, 158.93]	91.255 [58.945, 125.635]	5.366	<0.001
β2-MG (mg/L)	6.065 [3.675, 8.345]	4.04 [3.2075, 5.015]	9.337	<0.001

Note: HbA1c: Glycated hemoglobin, LDL-C: Low-density lipoprotein cholesterol, eGFR: Estimated glomerular filtration rate, Hcy: Homocysteine, HOMA-IR: Homeostatic model assessment of insulin resistance, UACR: Urinary albumin-to-creatinine ratio, β2-MG: Beta-2 microglobulin.

UACR and β2-MG also declined (both P< 0.001). Systolic blood pressure and urea did not change significantly (both P>0.05) (**Table 1**).

Baseline characteristics: deterioration vs. normal

Age, sex, smoking/alcohol history, hypertension, and coronary heart disease were similar between the groups (all P>0.05). The deterioration group had higher BMI (P<0.001) and a higher rate of contrast use (P=0.021) (**Table 2**).

Pre-treatment clinical indicators by outcome

Before treatment, the deterioration group had higher systolic blood pressure, fasting glucose, and HbA1c (all P<0.001). It also had higher eGFR (P<0.001), lower creatinine (P<0.001), and higher cystatin C (P<0.001). UACR and β2-MG were higher (both P<0.001), whereas HOMA-IR was lower (P=0.024). Diastolic blood pressure, lipids, urea, uric acid, and Hcy did not differ (all P>0.05) (**Table 3**).

Correlation with eGFR

Among 10 candidate variables (BMI, contrast use, systolic blood pressure, fasting glucose, HbA1c, creatinine, cystatin C, HOMA-IR, UACR, β2-MG), UACR, creatinine, and cystatin C showed the strongest correlations with eGFR (**Figure 1**). Because eGFR defined the outcome and incorporates creatinine, both were excluded from regression to avoid reverse causation and collinearity.

Risk factor analyses

Nine variables entered modeling (BMI, contrast use, systolic blood pressure, fasting glucose, HbA1c, cystatin C, HOMA-IR, UACR, β2-MG); all had VIF<5 (**Table 4**).

Univariate results: Contrast use was protective (OR=0.538, P=0.022). Risk increased with systolic blood pressure (OR=1.069), fasting glucose (OR=4.475), HbA1c (OR=2.113), cystatin C (OR=15.577), UACR (OR=1.041), and β_2-MG (OR=1.788) (all P<0.001). HOMA-IR was inversely associated with the risk (OR=0.819, P=0.023) (**Table 5**).

Multivariate results: Independent predictors were: contrast use (OR=0.051, P=0.008), systolic blood pressure (OR=1.106, P=0.001), fasting glucose (OR=5.329, P<0.001), HbA1c (OR=4.242, P<0.001), cystatin C (OR=16.540, P<0.001), UACR (OR=1.073, P<0.001), and

Table 2. Assessment of baseline characteristics between renal function deterioration and normal groups

Variable	Total	Deterioration Group (n=78)	Normal Group (n=278)	Statistical Value	*P* value
Age	56.18±6.05	55.67±6.43	56.32±5.95	0.847	0.398
Gender				0.188	0.665
Male	240 (67.42%)	51 (65.38%)	189 (67.99%)		
Female	116 (32.58%)	27 (34.62%)	89 (32.01%)	6.52	<0.001
BMI	23.18 [22.25, 24.24]	24.76 [23.20, 25.98]	22.95 [22.16, 23.84]		
Smoking History				0.139	0.709
No	248 (69.66%)	53 (67.95%)	195 (70.14%)		
Yes	108 (30.34%)	25 (32.05%)	83 (29.86%)		
Alcohol Consumption History				0.321	0.571
No	133 (37.36%)	27 (34.62%)	106 (38.13%)		
Yes	223 (62.64%)	51 (65.38%)	172 (61.87%)		
Hypertension History				0.472	0.492
No	103 (28.93%)	25 (32.05%)	78 (28.06%)		
Yes	253 (71.07%)	53 (67.95%)	200 (71.94%)		
Coronary Heart Disease History				0.304	0.581
No	86 (24.16%)	17 (21.79%)	69 (24.82%)		
Yes	270 (75.84%)	61 (78.21%)	209 (75.18%)		
Contrast Agent Usage				5.319	0.021
No	100 (28.09%)	30 (38.46%)	70 (25.18%)		
Yes	256 (71.91%)	48 (61.54%)	208 (74.82%)		

Note: BMI: Body Mass Index.

Table 3. Assessment of pre-treatment clinical indicators between renal function deterioration and normal groups

Variable	Total	Deterioration Group (n=78)	Normal Group (n=278)	t/Z value	*P* value
Systolic blood pressure (mmHg)	135.00 [125.00, 145.00]	152.00 [137.00, 157.75]	133.00 [125.00, 143.00]	6.824	<0.001
Diastolic blood pressure (mmHg)	80.32±9.60	79.18±8.84	80.64±9.79	1.262	0.209
Fasting blood glucose (mmol/L)	9.40 [8.50, 10.30]	10.80 [10.35, 11.30]	9.00 [8.30, 10.00]	9.837	<0.001
HbA1c (%)	9.35 [8.20, 10.40]	10.95 [8.83, 11.60]	9.10 [8.00, 10.00]	6.903	<0.001
Total cholesterol (mmol/L)	5.22±1.15	5.12±1.23	5.25±1.13	0.809	0.42
Triglycerides (mmol/L)	2.51±0.59	2.45±0.56	2.53±0.59	1.147	0.254
LDL-C (mmol/L)	3.19±0.59	3.18±0.61	3.19±0.59	0.101	0.92
eGFR [ml/(min·1.73 m^2)]	60.91 [57.43, 64.47]	67.77 [66.42, 69.49]	59.55 [56.10, 61.95]	13.445	<0.001
Creatinine (μmol/L)	109.70 [96.18, 117.22]	99.45 [86.25, 106.80]	113.35 [101.50, 119.30]	7.813	<0.001
Urea (mmol/L)	6.09±1.41	6.11±1.55	6.09±1.37	0.107	0.915
Uric acid (μmol/L)	373.47±72.85	373.92±65.17	373.34±74.97	0.068	0.946
Cystatin C (mg/L)	1.73 [1.23, 2.26]	2.63 [2.38, 2.99]	1.53 [1.14, 1.96]	10.338	<0.001
Hcy (μmol/L)	13.26±3.21	13.46±3.04	13.21±3.26	0.626	0.533
HOMA-IR	4.82±1.49	4.48±1.50	4.91±1.47	2.278	0.024
UACR (mg/g)	115.12 [78.19, 158.93]	194.27 [166.29, 215.08]	101.81 [67.61, 134.38]	10.556	<0.001
β2-MG (mg/L)	6.06 [3.68, 8.34]	10.02 [8.96, 11.19]	5.45 [3.06, 7.10]	10.19	<0.001

Note: HbA1c: Glycated hemoglobin, LDL-C: Low-density lipoprotein cholesterol, eGFR: Estimated glomerular filtration rate, Hcy: Homocysteine, HOMA-IR: Homeostatic model assessment of insulin resistance, UACR: Urinary albumin-to-creatinine ratio, β2-MG: Beta-2 microglobulin. All indicators above were measured before treatment.

β2-MG (OR=2.557, P<0.001). BMI (P=0.086) and HOMA-IR (P=0.128) were not significant (**Table 6**).

Single-marker ROC performance

UACR yielded the highest AUC (0.891; 95% CI 0.839-0.943) with specificity 98.20%, sensitivity 73.08%, and an optimal cutoff of 174.825 mg/g. Other AUCs ranged 0.566-0.883 (**Table 7**; **Figure 2**).

Model selection by AIC

Across 120 models derived from the seven variables, AIC ranged 69.6-324.5. The five best

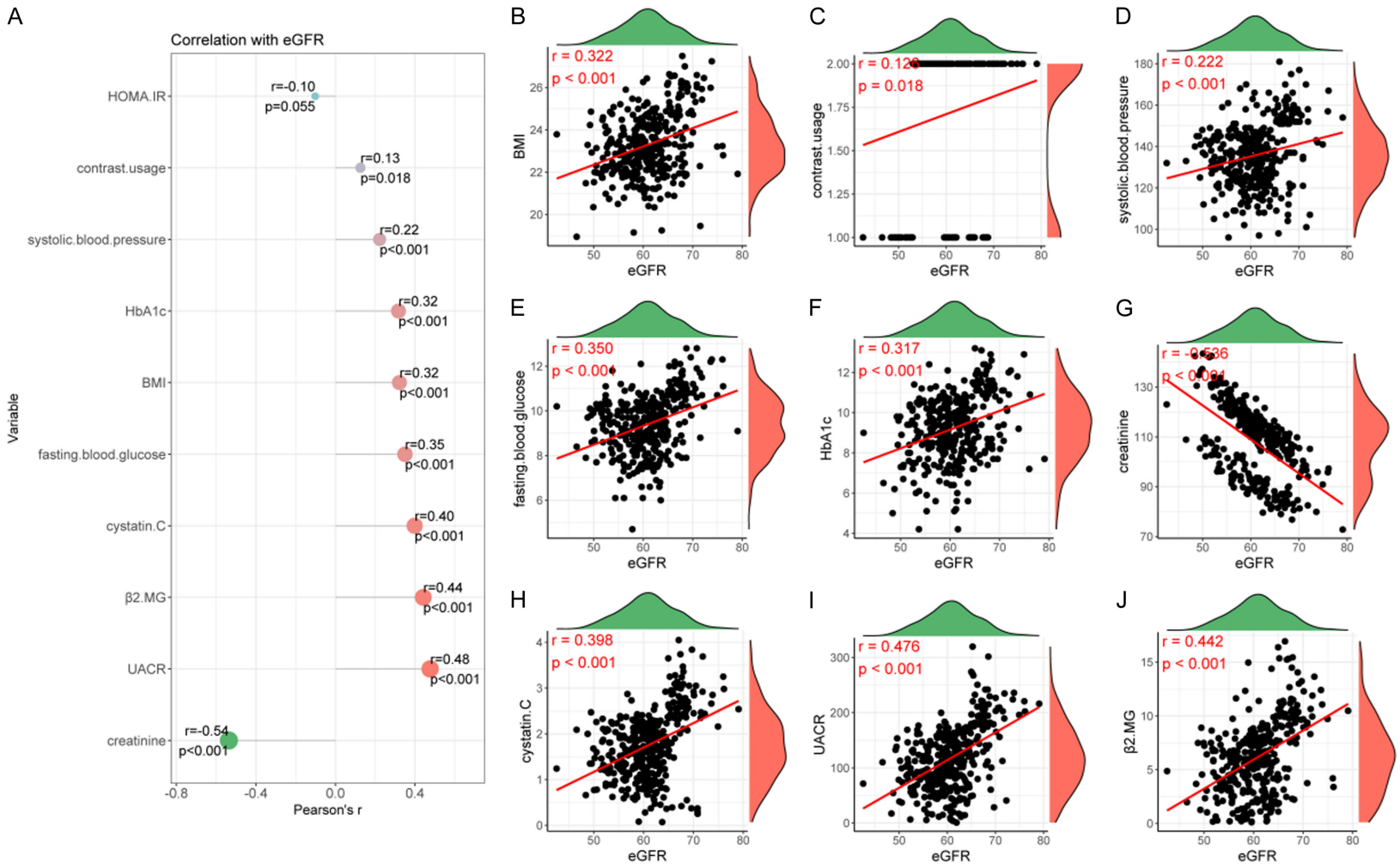

Figure 1. Correlation analysis between eGFR and various indicators. A. Lollipop chart displaying correlations between eGFR and 10 variables. B. Scatter plot of correlation between eGFR and BMI. C. Scatter plot of correlation between eGFR and contrast usage. D. Scatter plot of correlation between eGFR and systolic blood pressure. E. Scatter plot of correlation between eGFR and fasting blood glucose. F. Scatter plot of correlation between eGFR and HbA1c. G. Scatter plot of correlation between eGFR and creatinine. H. Scatter plot of correlation between eGFR and cystatin C. I. Scatter plot of correlation between eGFR and HOMA-IR. J. Scatter plot of correlation between eGFR and UACR. Note: BMI: Body Mass Index, HbA1c: Glycated hemoglobin, eGFR: Estimated glomerular filtration rate, Hcy: Homocysteine, HOMA-IR: Homeostatic model assessment of insulin resistance, UACR: Urinary albumin-to-creatinine ratio, β2-MG: Beta-2 microglobulin. All indicators above were measured before treatment.

Table 4. Variance inflation factor (VIF) values and variable assignment for screening variables

Variable	VIF	Interpretation	Assignment
BMI	1.19	Low multicollinearity	Original data
Contrast usage	2.082	Low multicollinearity	Yes =1, No =2
Systolic blood pressure	1.962	Low multicollinearity	Original data
Fasting blood glucose	2.167	Low multicollinearity	Original data
HbA1c	2.459	Low multicollinearity	Original data
Cystatin C	2.56	Low multicollinearity	Original data
HOMA-IR	1.312	Low multicollinearity	Original data
UACR	4.032	Low multicollinearity	Original data
β2-MG	3.318	Low multicollinearity	Original data
Deterioration status			Deterioration =1, Normal =0

Note: BMI: Body Mass Index, HbA1c: Glycated hemoglobin, HOMA-IR: Homeostatic model assessment of insulin resistance, UACR: Urinary albumin-to-creatinine ratio, β2-MG: Beta-2 microglobulin. All indicators were measured before treatment.

Table 5. Univariate analysis of renal function deterioration

Variable	Estimate	Std Error	*P* Value	OR	Lower	Upper
BMI	0.734	0.106	<0.001	2.082	1.693	2.562
Contrast usage	-0.619	0.271	0.022	0.538	0.317	0.915
Systolic blood pressure	0.067	0.011	<0.001	1.069	1.047	1.092
Fasting blood glucose	1.499	0.186	<0.001	4.475	3.108	6.444
HbA1c	0.748	0.110	<0.001	2.113	1.703	2.622
Cystatin C	2.746	0.332	<0.001	15.577	8.120	29.882
HOMA-IR	-0.200	0.088	0.023	0.819	0.689	0.973
UACR	0.041	0.005	<0.001	1.041	1.032	1.051
β2-MG	0.581	0.071	<0.001	1.788	1.555	2.055

Note: BMI: Body Mass Index, HbA1c: Glycated hemoglobin, HOMA-IR: Homeostatic model assessment of insulin resistance, UACR: Urinary albumin-to-creatinine ratio, β2-MG: Beta-2 microglobulin, OR: Odds Ratio, Lower and Upper represent 95% confidence intervals. All indicators were measured before treatment.

Table 6. Multivariate analysis of renal function deterioration

Variable	Estimate	Std Error	*P* Value	OR	Lower	Upper
BMI	0.430	0.250	0.086	1.537	0.96	2.628
Contrast usage	-2.982	1.117	0.008	0.051	0.004	0.351
Systolic blood pressure	0.100	0.031	0.001	1.106	1.048	1.185
Fasting blood glucose	1.673	0.454	<0.001	5.329	2.453	15.326
HbA1c	1.445	0.405	<0.001	4.242	2.112	10.744
Cystatin C	2.806	0.788	<0.001	16.54	4.437	105.813
HOMA-IR	-0.492	0.324	0.128	0.611	0.296	1.092
UACR	0.071	0.018	<0.001	1.073	1.042	1.121
β2-MG	0.939	0.235	<0.001	2.557	1.734	4.447

Note: BMI: Body Mass Index, HbA1c: Glycated hemoglobin, HOMA-IR: Homeostatic model assessment of insulin resistance, UACR: Urinary albumin-to-creatinine ratio, β2-MG: Beta-2 microglobulin, OR: Odds Ratio, Lower and Upper represent 95% confidence intervals. All indicators were measured before treatment.

models had AICs well below the overall range; the seven-variable model (Top 1) had the lowest AIC (69.6). Coefficients were largest for cystatin C and fasting glucose in most top models (**Table 8**; **Figure 3**).

AUC comparison and DeLong tests

Discrimination was highest for Top 1 (AUC= 0.994), followed by Top 2 and Top 3 (AUC= 0.990), and Top 4/Top 5 (AUC=0.988). DeLong

Table 7. ROC curve analysis results for renal function deterioration-related indicators

Marker	AUC	95% CI	Specificity	Sensitivity	Youden Index	Cut-off	Accuracy	Precision	F1 Score
Contrast usage	0.566	0.506-0.626	74.82%	38.46%	13.28%	-1.5	66.85%	38.46%	33.71%
Systolic blood pressure	0.753	0.675-0.830	95.32%	64.10%	59.43%	150	88.48%	64.10%	70.92%
Fasting blood glucose	0.864	0.810-0.919	93.53%	74.36%	67.88%	10.45	89.33%	74.36%	75.32%
HbA1c	0.756	0.686-0.825	95.32%	56.41%	51.73%	10.85	86.80%	56.41%	65.19%
Cystatin C	0.883	0.820-0.946	95.68%	80.77%	76.45%	2.345	92.42%	80.77%	82.35%
UACR	0.891	0.839-0.943	98.20%	73.08%	71.28%	174.825	92.70%	73.08%	81.43%
β2-MG	0.878	0.823-0.932	95.32%	76.92%	72.25%	8.935	91.29%	76.92%	79.47%

Note: UACR: Urinary albumin-to-creatinine ratio, HbA1c: Glycated hemoglobin, β2-MG: Beta-2 microglobulin, AUC: Area Under the Curve, CI: Confidence Interval. All indicators were measured before treatment.

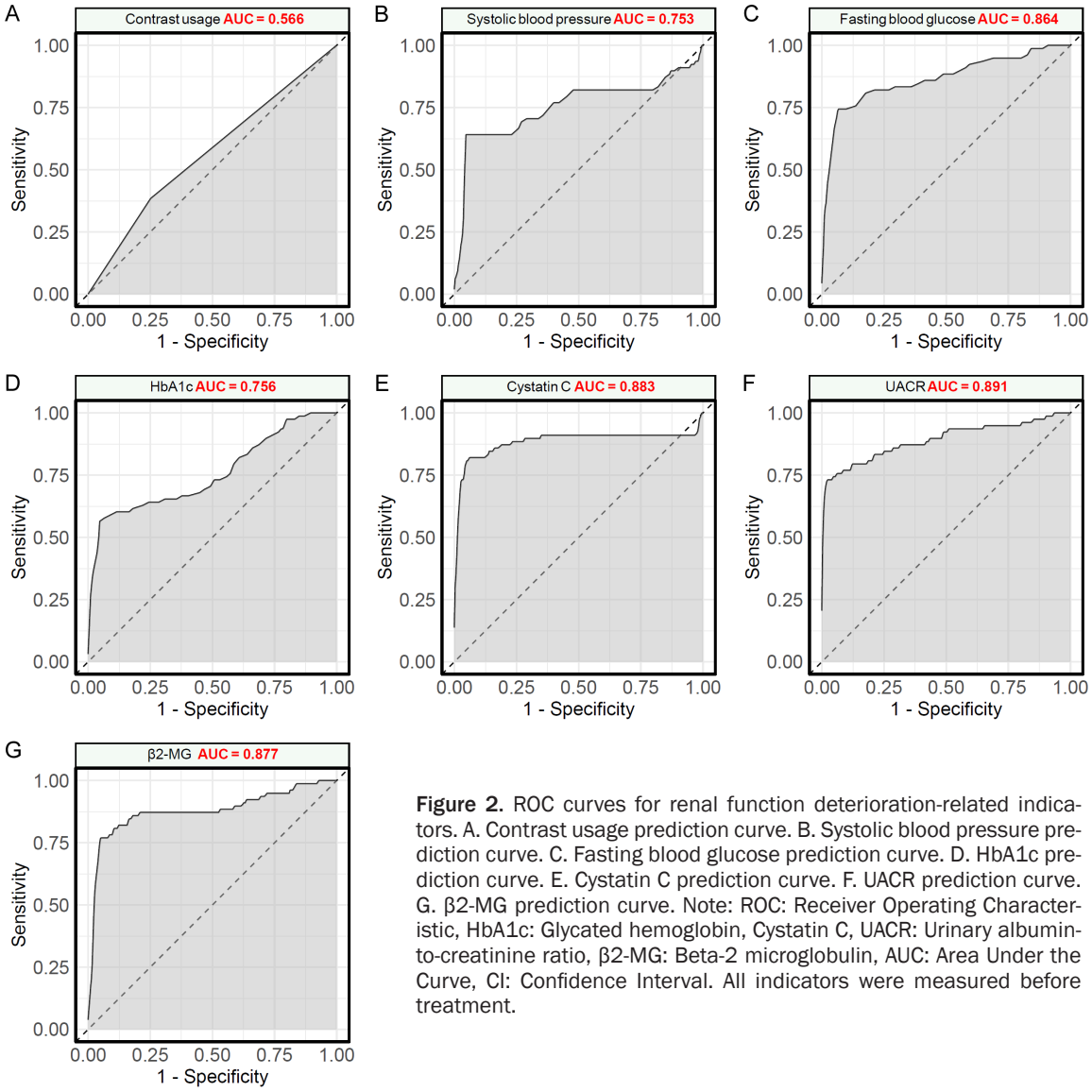

Figure 2. ROC curves for renal function deterioration-related indicators. A. Contrast usage prediction curve. B. Systolic blood pressure prediction curve. C. Fasting blood glucose prediction curve. D. HbA1c prediction curve. E. Cystatin C prediction curve. F. UACR prediction curve. G. β2-MG prediction curve. Note: ROC: Receiver Operating Characteristic, HbA1c: Glycated hemoglobin, Cystatin C, UACR: Urinary albumin-to-creatinine ratio, β2-MG: Beta-2 microglobulin, AUC: Area Under the Curve, CI: Confidence Interval. All indicators were measured before treatment.

tests showed small but significant differences between Top 1 and Top 4 (P=0.033; ΔAUC= 0.006, 95% CI 0.000-0.011) and between Top 1 and Top 5 (P=0.031; ΔAUC=0.006, 95% CI 0.001-0.012); other pairwise comparisons were not significant (P>0.05) (**Figure 4**; **Table 9**).

Table 8. Construction of renal function deterioration prediction models

Model	Formula
Contrast usage, Systolic blood pressure, Fasting blood glucose, HbA1c, Cystatin C, UACR, β2-MG (Top 1)	Logit(y) = -2.5712 × Contrast usage + 0.0887 × Systolic blood pressure + 1.5598 × Fasting blood glucose + 1.2608 × HbA1c + 2.4714 × Cystatin C + 0.0612 × UACR + 0.8960 × β2-MG + (-56.3186)
Systolic blood pressure, Fasting blood glucose, HbA1c, Cystatin C, UACR, β2-MG (Top 2)	Logit(y) = 0.0665 × Systolic blood pressure + 1.3049 × Fasting blood glucose + 0.9222 × HbA1c + 2.0071 × Cystatin C + 0.0461 × UACR + 0.6941 × β2-MG + (-47.2625)
Contrast usage, Fasting blood glucose, HbA1c, Cystatin C, UACR, β2-MG (Top 3)	Logit(y) = -1.5866 × Contrast usage + 1.1403 × Fasting blood glucose + 0.8896 × HbA1c + 1.8942 × Cystatin C + 0.0451 × UACR + 0.6815 × β2-MG + (-33.3315)
Fasting blood glucose, HbA1c, Cystatin C, UACR, β2-MG (Top 4)	Logit(y) = 1.0958 × Fasting blood glucose + 0.7734 × HbA1c + 1.9063 × Cystatin C + 0.0412 × UACR + 0.6009 × β2-MG + (-33.2850)
Contrast usage, Systolic blood pressure, Fasting blood glucose, Cystatin C, UACR, β2-MG (Top 5)	Logit(y) = -1.4316 × Contrast usage + 0.0613 × Systolic blood pressure + 1.3607 × Fasting blood glucose + 2.1264 × Cystatin C + 0.0399 × UACR + 0.5797 × β2-MG + (-34.4418)

Note: HbA1c: Glycated hemoglobin, Cystatin C, UACR: Urinary albumin-to-creatinine ratio, β2-MG: Beta-2 microglobulin, AIC: Akaike Information Criterion. All indicators were measured before treatment.

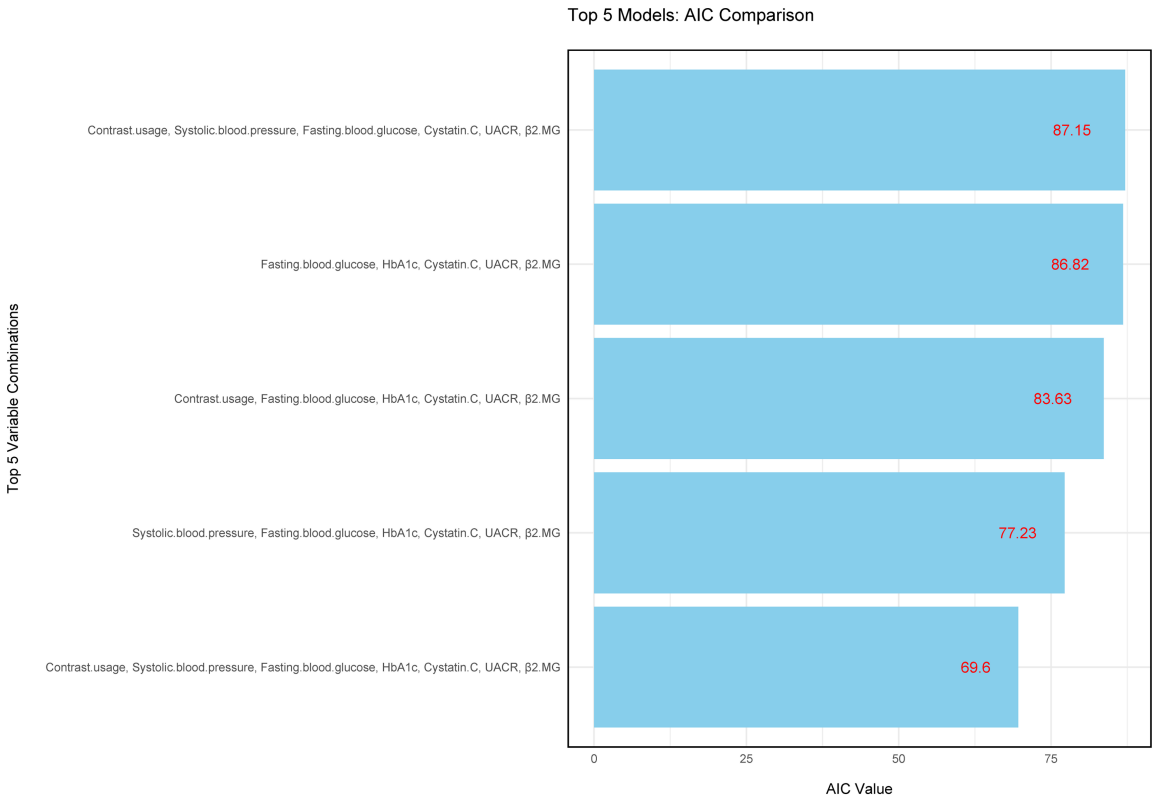

Figure 3. AIC comparison of Top 5 models. Note: HbA1c: Glycated hemoglobin, Cystatin C, UACR: Urinary albumin-to-creatinine ratio, β2-MG: Beta-2 microglobulin, AIC: Akaike Information Criterion. All indicators were measured before treatment.

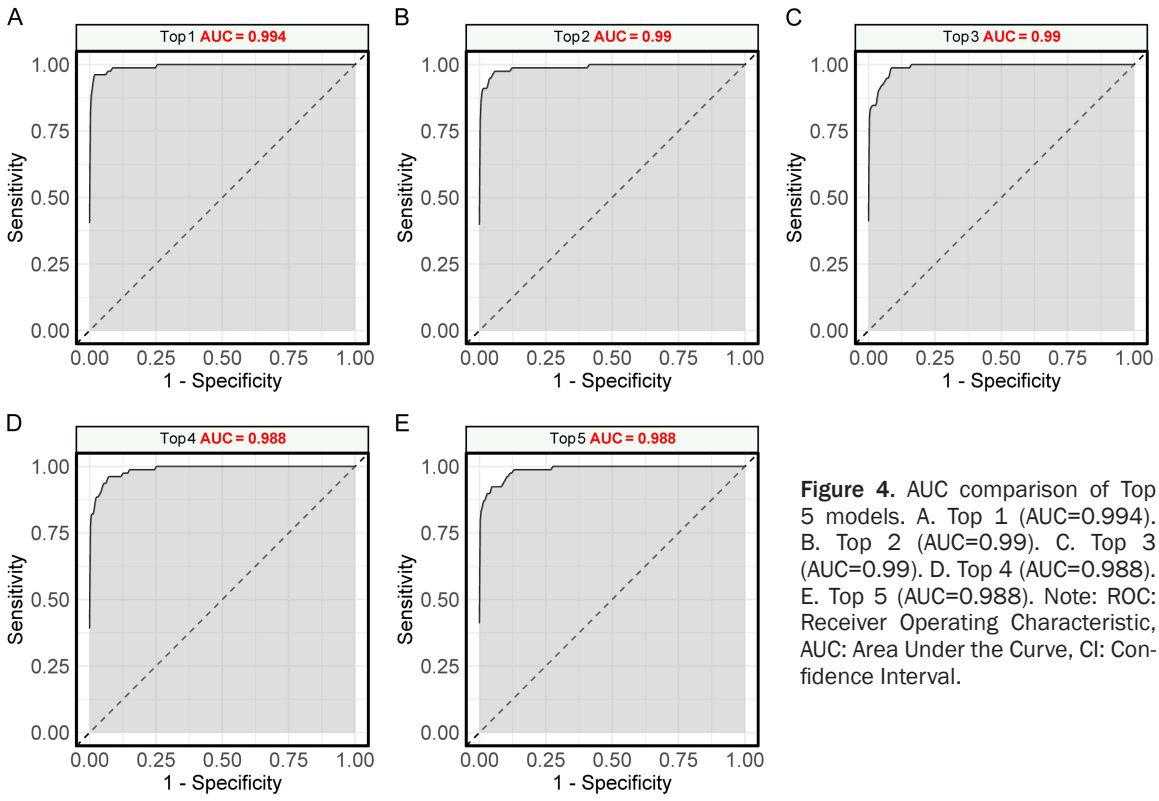

Figure 4. AUC comparison of Top 5 models. A. Top 1 (AUC=0.994). B. Top 2 (AUC=0.99). C. Top 3 (AUC=0.99). D. Top 4 (AUC=0.988). E. Top 5 (AUC=0.988). Note: ROC: Receiver Operating Characteristic, AUC: Area Under the Curve, CI: Confidence Interval.

Table 9. DeLong test results between Top 5 models

Model 1	Model 2	Z value	*P* value	AUC Difference	95% CI
Top 1	Top 2	1.531	0.126	0.004	-0.01
Top 1	Top 3	1.372	0.170	0.003	-0.009
Top 1	Top 4	2.129	0.033	0.006	0.000-0.011
Top 1	Top 5	2.160	0.031	0.006	0.001-0.012
Top 2	Top 3	-0.107	0.915	0	-0.015
Top 2	Top 4	0.651	0.515	0.002	-0.012
Top 2	Top 5	0.694	0.488	0.002	-0.013
Top 3	Top 4	1.268	0.205	0.002	-0.007
Top 3	Top 5	0.878	0.38	0.003	-0.012
Top 4	Top 5	0.144	0.885	0	-0.011

Note: AUC: Area Under the Curve, CI: Confidence Interval.

Cohort comparability

The external cohort (n=145) and internal cohort (n=356) were comparable for outcome incidence (22.07% vs. 21.91%; χ^2=0.002, P=0.969) and for key baseline variables (all P>0.05) (Table S1).

External validation

All five models retained high performance in the external cohort. Top 1 achieved AUC=0.949 (95% CI 0.895-1.000), sensitivity 90.62%, specificity 93.81%, and accuracy 93.10%. AUCs for Top 2-Top 5 were 0.943, 0.939, 0.933, and 0.933, respectively; none differed significantly from Top 1 by DeLong testing (all P>0.05) (Figure S1; Tables S2, S3). Simplified models therefore offer similar discrimination with fewer variables and greater practicality.

Discussion

T2DM is a major chronic metabolic disease worldwide, and its prevalence continues to rise with population aging [1]. Approximately 30-40% of patients eventually develop DKD, which has become a leading cause of ESRD and a major contributor to cardiovascular morbidity and mortality [13]. A meta-analysis including 27.5 million individuals by Grams et al. [14] confirmed that both lower eGFR and higher albuminuria were strongly associated with increased risks of renal failure, cardiovascular events, and hospitalization. UACR exhibits substantial within-person variability in type 2 diabetes (coefficient of varia-

tion ~50% [15]), which limits its reliability for serial monitoring and risk stratification. We therefore examined short-term kidney function decline - defined a priori as a ≥30% decrease in eGFR within 6 months - and developed a multivariable prediction model incorporating seven routinely available variables, including β_2-microglobulin (β2-MG), UACR, and cystatin C (CysC). The intent was early identification of patients at high risk of diabetic kidney disease (DKD) progression under contemporary care with SGLT-2 inhibitors. In internal evaluation, the model showed very high discrimination (AUC 0.994), and performance remained strong in an external cohort (AUC 0.949). These results suggest that the approach can flag short-term risk with high accuracy. Nevertheless, because near-perfect AUCs may reflect optimism or data leakage, we report separate internal validation results and an independent validation sample, and we assess calibration alongside discrimination. If confirmed prospectively, such a tool could support timely intensification of renoprotective therapy and closer monitoring in clinical practice.

Our study identified β2-MG, UACR, and cystatin C as independent markers associated with short-term renal function decline in DKD. β2-MG, a low-molecular-weight protein freely filtered by the glomerulus and reabsorbed by proximal tubules, increases when tubular reabsorption is impaired [16]. Consistent with Li et al. [17], who showed that urinary β2-MG and retinol-binding protein correlate with UACR and renal function in Chinese patients with T2DM, our findings support β2-MG as an early indicator of tubular injury that often precedes glomerular damage. UACR remains the standard marker of glomerular barrier injury, and prior work has proposed screening cut-offs such as eGFR ≤84.8 mL/min/1.73 m^2 or UACR ≥15.5 mg/g for DKD risk stratification [18]. In our cohort, UACR showed the highest single-marker discrimination for short-term decline (AUC 0.891), consistent with its direct capture of albumin leakage. Cystatin C - less dependent on muscle mass than creatinine - was strongly associated with risk (OR 16.540) and had an AUC of 0.883, suggesting good ability to detect early filtration changes. In line with Wang et al. [20] and Akpınar et al. [19], higher CysC levels and trajectories were linked to DKD progression in our data as well. Taken together, β_2-microglobulin, UACR, and cystatin C index complementary domains of injury (tubular and glomerular), when combined, provide a more complete picture of near-term renal deterioration risk.

In our cohort, patients who declined had higher baseline eGFR than those who remained stable. Two factors likely drive this. One is biology: early DKD can present with glomerular hyperfiltration, a response to intraglomerular hypertension that can hide injury behind normal or even high eGFR [21]. The other is arithmetic: with a threshold defined as a ≥30% drop, people starting higher have more room to fall and are mathematically more likely to cross that cut-point, independent of disease biology. Consistent with this, Wen et al. reported faster eGFR decline among T2DM patients with hyperfiltration versus those with normal filtration [22], and a recent analysis described a U-shaped association between stress hyperglycemia and ESRD risk [23]. Second, our endpoint (≥30% eGFR decline within 6 months) mathematically favors larger relative drops among individuals starting from higher eGFR, which can amplify the observed association independent of biology. These points reinforce interpreting eGFR alongside complementary biomarkers such as UACR and β2-MG to better gauge risk. We observed an inverse association between contrast exposure and short-term decline (OR=0.051, P=0.008). Given the retrospective design, this likely reflects confounding by indication or selection (e.g., patients with better baseline kidney function or lower clinical concern were more likely to receive contrast) rather than a protective effect; causal inferences are not warranted. Higher systolic blood pressure, fasting glucose, and HbA1c were associated with deterioration, aligning with the established contribution of hemodynamic and metabolic stress via oxidative and inflammatory pathways [24]. Prospective analyses using slope-based outcomes and careful adjustment for baseline eGFR and imaging indications would help disentangle biological effects from threshold and selection biases.

Our seven-predictor model (contrast exposure, systolic BP, fasting glucose, HbA1c, cystatin C, UACR, β2-MG) showed high discrimination in

the development cohort (AUC 0.994; AIC 69.6) with calibration that tracked observed risk. External validation remained strong (AUC 0.949), and at a prespecified threshold both sensitivity and specificity exceeded 90%. Pairwise AUC comparisons (DeLong) showed little change when contrast exposure or systolic BP were removed (AUC≈0.99; P>0.05), indicating limited added value from these variables. Comparable performance has been reported with different feature sets, for example, Wang et al. reported an AUC of 0.960 using eGFR, glycated albumin, uric acid, HbA1c, and zinc [25]. Although the full model ranked highest numerically, the gap versus simpler four- or five-variable versions (AUC≈0.988) was small; the four-marker model (fasting glucose, HbA1c, cystatin C, UACR, β2-MG) may therefore be the more practical choice for routine use.

Multiple studies indicate that β_2-microglobulin (β2-MG), UACR, and cystatin C are informative for DKD risk. He et al. showed that mismatch between cystatin C- and creatinine-based eGFR independently predicted mortality and cardiovascular events in diabetes [26], suggesting that these filtration markers capture different facets of risk. In our data, β2-MG - an early tubular injury marker - had an AUC of 0.878 for short-term decline. UACR, the routine staging marker, had a similar AUC (0.891) and was directionally in line with DCCT/EDIC. Cystatin C showed the strongest association with our endpoint (OR 16.540) and an AUC of 0.883; it is less dependent on muscle mass than creatinine, though it can vary with inflammation and thyroid status. Large cohorts reported similar patterns: in 12,190 Chinese adults, Zou et al. identified cystatin C as a key risk indicator with a LightGBM model [27], and Korean T2DM cohorts validated ML and logistic models with AUCs of 0.811-0.827 [28]. In our analysis, combining β2-MG, UACR, and cystatin C improved discrimination over any single marker, likely because they index both glomerular and tubular injury. Unlike most work focused on 1-5-year outcomes, we used a 6-month window (≥30% eGFR drop) to capture near-term risk; an event rate of 21.9% suggests clinical relevance for monitoring and treatment adjustment. Similar to the CREDENCE-derived approach described by Januzzi et al. [29], our results support integrating multiple routinely available biomarkers to update DKD risk and guide individualized intervention. That said, differences in populations, endpoints, and follow-up length across studies warrant cautious comparison, and prospective validation with calibration reporting will be important for clinical adoption.

Our cohort received background therapy with SGLT-2 inhibitors. Over follow-up, HbA1c, UACR, β2-MG, and cystatin C declined, consistent with the known hemodynamic and metabolic effects of this class (lower intraglomerular pressure, improved glycemic control, and anti-inflammatory signaling). Trials of agents such as dapagliflozin have shown slower DKD progression [30], and the biomarker trajectories we observed are directionally aligned with those data. Even so, a subset of patients met the endpoint of ≥30% eGFR decline, indicating heterogeneity of response under contemporary care and a need for risk stratification beyond glycemic metrics alone. External evidence also points to broader determinants of risk. In histology-confirmed DKD, Zou et al. identified cystatin C, serum albumin, and hemoglobin as major predictors of ESRD using a random-forest model [31], highlighting potential roles for filtration status, nutritional reserve, and anemia. Together with our findings, this supports incorporating routinely available markers - filtration (cystatin C), UACR, β2-MG, and general health indices - into pragmatic tools to flag patients who may require closer monitoring or treatment intensification despite SGLT-2 inhibitor therapy.

Our study has several limitations. The retrospective, single-center design and the 6-month horizon limit inference about long-term kidney outcomes and generalizability. Although discrimination was very high in both the development (AUC 0.994) and external cohorts (AUC 0.949), near-perfect AUCs raise the possibility of optimism or subtle leakage; future work should report optimism-corrected performance and detailed calibration (slope/intercept, Brier score) and include decision-curve analysis. Residual confounding is likely because lifestyle factors, genetics, and several emerging biomarkers were unavailable, and treatment exposures (e.g., renin-angiotensin system inhibitors, SGLT-2 inhibitor dose/adherence) were not fully characterized. Our endpoint (≥30% eGFR decline within 6 months) can mathematically couple risk with higher baseline eGFR, which should be addressed with slope-based outcomes in longer follow-up. We also did not

systematically evaluate therapy interactions. Future studies will extend follow-up, incorporate additional biomarkers (e.g., NGAL, KIM-1), predefine thresholds, and prospectively test the model in multicenter settings to assess transportability across diverse patient groups.

Conclusion

We developed a seven-variable model with very high discrimination for short-term DKD decline (AUC 0.994 internally; 0.949 externally); a simpler four-marker version (glucose, HbA1c, cystatin C, UACR, β2-MG) achieved ~0.988 and is likely more practical. Higher baseline eGFR in decliners likely reflects early hyperfiltration and threshold coupling, so multibiomarker assessment is warranted; prospective multicenter validation with full calibration/utility analyses is still needed.

Disclosure of conflict of interest

None.

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Table S1. Baseline characteristics of external validation cohort and internal modeling cohort

Variable	Total	External Cohort (n=145)	Internal Cohort (n=356)	Statistical Value	*P* value
Deterioration Status				0.002	0.969
Deterioration	110 (21.96%)	32 (22.07%)	78 (21.91%)		
Normal	391 (78.04%)	113 (77.93%)	278 (78.09%)		
Contrast Agent Usage				0.434	0.51
Yes	145 (28.94%)	45 (31.03%)	100 (28.09%)		
No	356 (71.06%)	100 (68.97%)	256 (71.91%)		
Pre-treatment systolic blood pressure	135.75±15.24	135.70±15.48	135.77±15.16	-0.049	0.961
Pre-treatment fasting blood glucose	9.39±1.33	9.36±1.34	9.40±1.32	-0.317	0.751
Pre-treatment HbA1c	9.27±1.60	9.34±1.54	9.24±1.63	0.638	0.524
Pre-treatment eGFR	61.06±5.66	61.46±5.93	60.90±5.54	0.993	0.321
Pre-treatment creatinine	109.60 (21.80)	109.60 (22.10)	109.70 (21.05)	0.804	0.422
Pre-treatment cystatin C	1.75±0.74	1.76±0.74	1.75±0.74	0.156	0.876
Pre-treatment HOMA-IR	4.83±1.52	4.85±1.59	4.82±1.49	0.248	0.804
Pre-treatment UACR	117.09 (82.25)	119.96 (86.18)	115.12 (80.74)	0.333	0.739
Pre-treatment β2-MG	6.24 (4.74)	6.52 (4.71)	6.06 (4.67)	1.088	0.277

Note: HbA1c: Glycated hemoglobin, HOMA-IR: Homeostatic model assessment of insulin resistance, UACR: Urinary albumin-to-creatinine ratio, β2-MG: Beta-2 microglobulin, OR: Odds Ratio, Lower and Upper represent 95% confidence intervals. All indicators were measured before treatment.

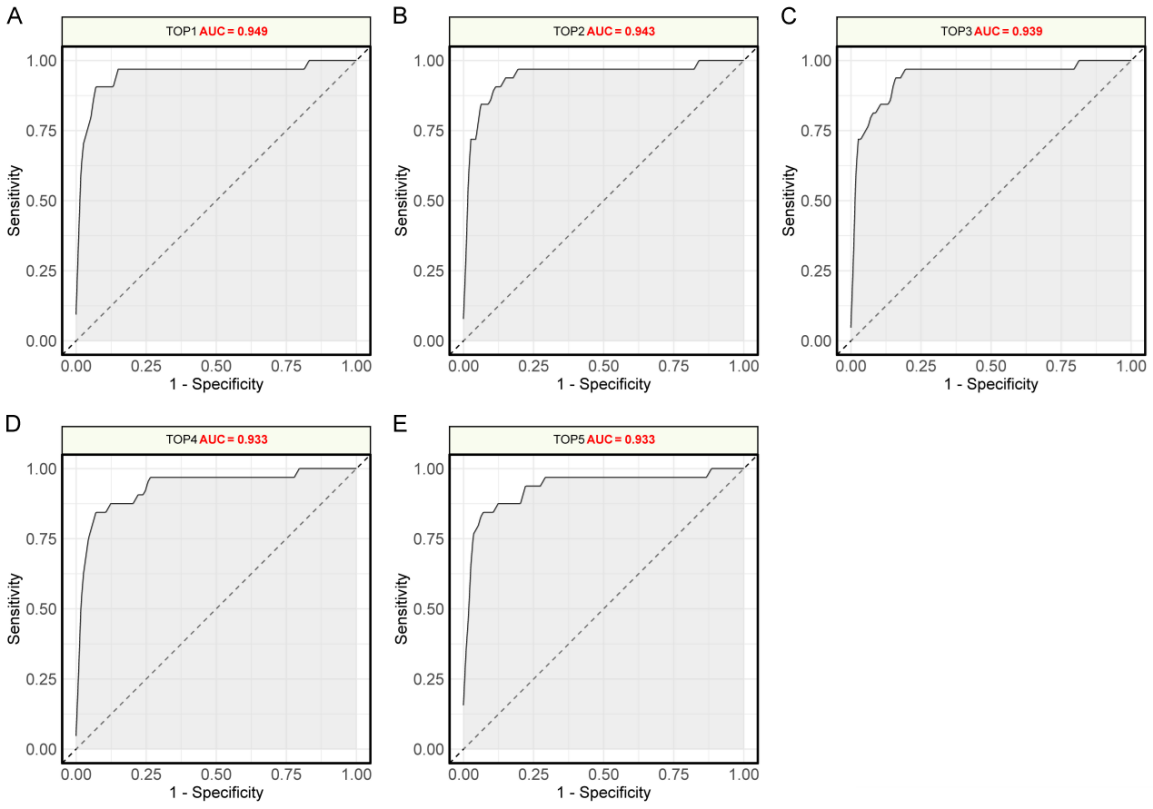

Figure S1. ROC curves of Top 5 prediction models in the external validation cohort. A. Top 1 (AUC=0.949). B. Top 2 (AUC=0.943). C. Top 3 (AUC=0.939). D. Top 4 (AUC=0.933). E. Top 5 (AUC=0.933). Note: ROC: Receiver Operating Characteristic, AUC: Area Under the Curve, CI: Confidence Interval.

Table S2. ROC curve analysis of Top 5 prediction models in the external validation cohort

Marker	95% CI	Specificity	Sensitivity	Youden index	Cut off	Accuracy	Precision	F1 Score
TOP 1	0.895-1.000	93.81%	90.62%	84.43%	-0.445	93.10%	90.62%	85.29%
TOP 2	0.888-0.998	89.38%	90.62%	80.01%	-1.022	89.66%	90.62%	79.45%
TOP 3	0.884-0.993	84.96%	93.75%	78.71%	-1.917	86.90%	93.75%	75.95%
TOP 4	0.877-0.989	93.81%	84.38%	78.18%	-0.348	91.72%	84.38%	81.82%
TOP 5	0.874-0.993	93.81%	84.38%	78.18%	-0.782	91.72%	84.38%	81.82%

Note: Abbreviations: AUC, Area Under the Curve; CI, Confidence Interval.

Table S3. Pairwise delong test for AUC comparison of Top 5 prediction models

Marker1	Marker2	Z_value	*P*_value	AUC_difference	CI_lower_upper
TOP 1	TOP 2	1.224	0.221	0.006	-0.003-0.014
TOP 1	TOP 3	1.288	0.198	0.01	-0.005-0.025
TOP 1	TOP 4	1.457	0.145	0.016	-0.005-0.037
TOP 1	TOP 5	1.603	0.109	0.015	-0.003-0.034
TOP 2	TOP 3	0.73	0.466	0.004	-0.007-0.016
TOP 2	TOP 4	1.373	0.17	0.01	-0.004-0.025
TOP 2	TOP 5	0.978	0.328	0.01	-0.010-0.030
TOP 3	TOP 4	1.045	0.296	0.006	-0.005-0.017
TOP 3	TOP 5	0.478	0.633	0.006	-0.017-0.028
TOP 4	TOP 5	-0.021	0.983	0	-0.026-0.025

Note: Abbreviations: AUC, Area Under the Curve; CI, Confidence Interval.