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Predictive model of declining glomerular filtration rate in type 2 diabetes mellitus with poorly glycemic control: Integration of RAAS and TGFB polymorphisms with clinical risk factors in the Jambi Malay population

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Abstract

Background: Diabetic kidney disease (DKD) is a major complication of type 2 diabetes mellitus (T2DM) and a leading cause of end-stage renal disease worldwide. Despite optimal glycemic and blood pressure control, many patients experience renal decline, suggesting a role for genetic factors. **Objective:** To develop a predictive model integrating clinical and genetic parameters to identify individuals at risk of declining glomerular filtration rate (GFR) among Malay Jambi patients with poorly controlled T2DM. **Methods:** A cross-sectional study of 62 patients was conducted using *ACE* rs4343 and *TGFB1* rs1800470 genotyping by Tetra-ARMS PCR. Declining renal function was defined as eGFR <60 mL/min/1.73 m² (KDIGO 2024). Logistic regression and ROC analyses assessed model performance. **Results:** Older age and higher blood pressure were associated with reduced GFR. The *TGFB1* rs1800470 TT and *ACE* rs4343 AG genotypes significantly increased the risk of renal decline (adjusted OR 7.79 and 5.98, respectively; $p < 0.05$). The integrated clinical–genetic model achieved the highest discrimination (AUC = 0.859; sensitivity 78.9%; specificity 88.4%). **Conclusion:** Integrating *ACE* and *TGFB1* genotypes with clinical factors enhances DKD risk prediction and supports early genotype-informed interventions. This approach strengthens population-specific precision nephrology in Indonesia and provides a foundation for future polygenic risk model development.

Keywords: Type 2 diabetes mellitus; diabetic kidney diseases; declining GFR; RAAS; TGFB; genetic polymorphism; poorly glycemic control; Malay population

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INTRODUCTION

Diabetic kidney disease (DKD), also referred to as diabetic nephropathy (DN), remains one of the most severe complications of type 2 diabetes mellitus (T2DM) and a leading cause of end-stage renal disease (ESRD) worldwide. The Global Burden of Disease 2021 report revealed a marked rise in disability-adjusted life years (DALYs) attributable to DKD, reflecting its escalating impact on global health (1). In Indonesia, diabetes-related morbidity and mortality are projected to increase substantially by 2045 if current prevention and control measures remain inadequate (2). National data from the Indonesian Renal Registry (IRR) confirm that diabetes is the predominant cause of ESRD requiring dialysis (3). Similarly, global estimates suggest that approximately 30–40% of diabetic individuals will develop renal impairment (4), highlighting the urgent need for early detection and stratification of individuals at risk.

Despite achieving optimal glycemic and blood pressure control, many patients continue to experience progressive renal decline, suggesting that conventional management strategies alone are insufficient to prevent DKD. Persistent metabolic memory, oxidative stress, and endothelial dysfunction contribute to sustained renal injury even after glucose normalization (5–7). Beyond these metabolic factors, genetic susceptibility has emerged as a major determinant of individual vulnerability to renal function decline. Several loci have been shown to modulate kidney function differently in diabetic compared with non-diabetic populations (8,9). Among these, the renin–angiotensin–aldosterone system (RAAS) and transforming growth factor-β (TGF-β) signaling pathways play pivotal roles in the development and progression of DKD. Angiotensin II stimulates TGF-β1 expression, driving extracellular matrix accumulation and tubulointerstitial fibrosis, while sustained TGF-β1 activation amplifies RAAS-induced injury (10–14). Genetic variants such as ACE rs4343 and TGFB1 rs1800470 may alter enzyme activity or cytokine expression, thereby influencing individual susceptibility to DKD across populations (9, 15–16).

In Indonesia, population-specific genomic data are still limited, yet existing studies have demonstrated marked allele frequency variations among Javanese, Sundanese, and Malay groups. The Malay Jambi population, characterized by Austronesian and proto-Malay admixture, exhibits a high prevalence of hypertension and poorly controlled T2DM (17–20). Previous studies by our research group identified significant associations between ACE rs4343 and TGFB1 rs1800470 variants and reduced renal function in local diabetic cohorts (20,21). Building upon these findings, the present study aimed to develop and validate an integrated predictive model that combines genetic polymorphisms and clinical risk factors to estimate declining glomerular filtration rate (GFR) among patients with poorly controlled T2DM in the Malay Jambi population. This work not only strengthens the understanding of gene–environment interactions in DKD but also lays the groundwork for developing polygenic and machine-learning–based risk models, aligning with Indonesia's roadmap toward population-specific precision nephrology.

METHODS

Study design and participants

This study design was cross-sectional. The sample of DNA get from DNA biobank of the previous study conduct by Elfiani et al. Participants were adults aged 35–75 years with a confirmed diagnosis of T2DM according to the PERKENI (Perkumpulan Endokrinologi Indonesia) 2021 guideline (22). Subjects were included if they had uncontrolled blood glucose, defined as fasting plasma glucose (FPG) ≥130 mg/dL and/or 2-hour postprandial glucose ≥180 mg/dL, or uncontrolled blood pressure

≥130/90 mmHg, based on the same guideline. Exclusion criteria were type 1 diabetes, CKD of non-diabetic origin, acute infection, liver failure, pregnancy, or use of nephrotoxic drugs. A total of *62* subjects were enrolled consecutively. Written informed consent was obtained. The study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Jambi (Ethical Clearance No. 2082/UN21.8/PT.01.04/2025) and conducted under the principles of the Declaration of Helsinki (2013).

Clinical and laboratory assessments

Demographic and clinical characteristics including age, sex, and blood pressure were recorded. Blood pressure was measured twice after 5 minutes of rest using a calibrated sphygmomanometer; the average was used for analysis. Venous blood samples were obtained after overnight fasting for plasma glucose and creatinine assessment using standard enzymatic methods. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI 2021 equation, which provides improved accuracy in Asian populations. Declining GFR was defined as eGFR <60 mL/min/1.73 m² according to KDIGO 2024 (23).

Genotyping of ACE rs4343 and TGFB1 rs1800470

Genomic DNA was extracted from whole blood using the QIAamp DNA Mini Kit (Qiagen, Germany). Genotyping for *ACE* rs4343 and *TGFB1* rs1800470 was performed using the Tetra-Primer Amplification Refractory Mutation System PCR (T-ARMS PCR), optimized in this research group's previous studies (20, 21). PCR conditions included an initial denaturation at 95°C for 5 min, followed by 35 cycles at 94°C for 30 s, annealing (60°C for *ACE*, 62°C for *TGFB1*) for 30 s, and extension at 72°C for 45 s, with final extension for 5 min. PCR products were visualized on 2% agarose gel stained with ethidium bromide. Genotype and allele frequencies were obtained by direct counting. Then Hardy–Weinberg equilibrium (HWE) was tested using the chi-square test ($p > 0.05$).

Statistical analysis

Data were analyzed using SPSS v26.0 (IBM Corp.) and MedCalc v22.0. Continuous variables were presented as mean ± SD or median (IQR), and categorical variables as counts and percentages. Between-group comparisons (declining vs. preserved GFR) used the independent *t*-test or Mann–Whitney U test, and Chi-square for categorical data. Associations between genetic variants and GFR decline were analyzed using binary logistic regression, adjusted for age, sex, and blood pressure, under dominant, recessive, and additive models. Three prediction models were constructed; Model 1 (Clinical): age, sex, blood pressure, Model 2 (Integrated): clinical + genetic variables (*ACE* rs4343, *TGFB1* rs1800470) and Model 3 (Genetic-only): *ACE* and *TGFB1* variants only. Discrimination was assessed by ROC curve analysis and comparison of AUCs using the DeLong test. Model calibration was verified with the Hosmer–Lemeshow test. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical and demographic characteristics

A total of 62 Malay patients with type 2 diabetes mellitus and poorly controlled blood glucose were included in this study, consisting of 19 subjects with declining GFR (<60 ml/min/1.73m²) and 43 subjects with preserved renal function. As shown in Table 1, subjects with declining GFR were significantly older (mean age 55 ± 5.01 vs. 49.33 ±

8.24 years, p = 0.002) and had higher systolic and diastolic blood pressure compared to those with preserved renal function (p < 0.001 and p = 0.036, respectively).

Table 1. Baseline subject sample

Characteristic	Decline GFR (n= 19)	Not Decline GFR (n= 43)	p-value
Age, years old	55 ±5.01	49.33 ±8.24	0.002
GFR,	38.39 ±14.21	94.63 ±20.17	< 0.001
Gender			0.710
Female, n	12	25	
Male, n	7	18	
Blood Pressure			
Systolic blood pressure, mmHg	150.00 (110.00-170.00)	120.00 (100.00-170.00)	<0.001
Diastolic blood pressure, mmHg	80.00 (70.00-100.00)	80.00 (60.00-100.00)	0.036
Uncontrolled Blood pressure	8	4	0.005
Controlled Blood pressure	11	39	
Fasting plasma glucose, mg/dL	171.00 (80.00-247.00)	143.00 (76.00-277.00)	0.546
2 hours post prandial plasma glucose, mg/dL	227.00 (180.00-350.00)	234.00 (168.00-456.00)	0.945

Remarks: GFR=glomerular filtration rate calculated based on KDIGO online calculator

The proportion of patients with uncontrolled blood pressure was also higher in the declining GFR group (p = 0.005). In contrast, fasting and postprandial glucose levels did not differ significantly between groups, indicating that all participants met the criteria for persistent poor glycemic control. These findings suggest that factors beyond glycemia such as aging and hemodynamic stress may play a pivotal role in renal decline among T2DM patients with uncontrolled blood sugar.

Genotype distribution and Hardy–Weinberg Equilibrium

Both TGFB1 rs1800470 and ACE rs4343 polymorphisms conformed to Hardy–Weinberg equilibrium (p > 0.05), confirming genotyping reliability and the absence of major population stratification (Table 2). The minor allele frequencies (MAF) observed in this Malay Jambi cohort were 0.326–0.474 for TGFB1 rs1800470 and approximately 0.454 for ACE rs4343.

Genetic association with renal function decline

As presented in Table 3, individuals carrying the TT genotype of TGFB1 rs1800470 showed a significantly higher risk of GFR decline under a recessive model (adjusted OR = 7.79; 95% CI, 1.20–50.68; p = 0.032). Similarly, carriers of the AG genotype at ACE rs4343 exhibited increased odds of renal impairment compared with AA homozygotes (adjusted OR = 5.98; 95% CI, 1.13–31.65; p = 0.035). These associations remained significant after adjusting for age, sex, and blood pressure, indicating an independent contribution of genetic variation to renal vulnerability.

Predictive model performance

To evaluate predictive accuracy, three models were compared: (1) a clinical model including age, sex, and blood pressure; (2) a genetic-only model incorporating ACE rs4343 and TGFB1 rs1800470; and (3) an integrated clinical–genetic model combining

both domains. As summarized in Table 4 and Figure 1, the integrated model achieved the highest discrimination (AUC = 0.859) compared with the clinical-only model (AUC = 0.777) and the genetic-only model (AUC = 0.710). The integrated model also yielded optimal sensitivity (78.9%) and specificity (88.4%) with a Youden Index of 0.459, suggesting superior balance between true-positive and false-positive classifications.

This finding indicates that the inclusion of genetic parameters significantly enhances the predictive performance for identifying individuals at risk of renal function decline. Such improvement supports the translational potential of genotype-informed screening tools in diabetic kidney disease (DKD) prevention, especially in resource-constrained settings where prioritizing high-risk patients is essential. Taken together, these results demonstrate that both clinical and genetic factors contribute meaningfully to renal vulnerability among T2DM patients with poor glycemic control in the Malay Jambi population. The following discussion explores the biological and translational implications of these findings in the broader context of diabetic kidney disease pathogenesis and precision nephrology.

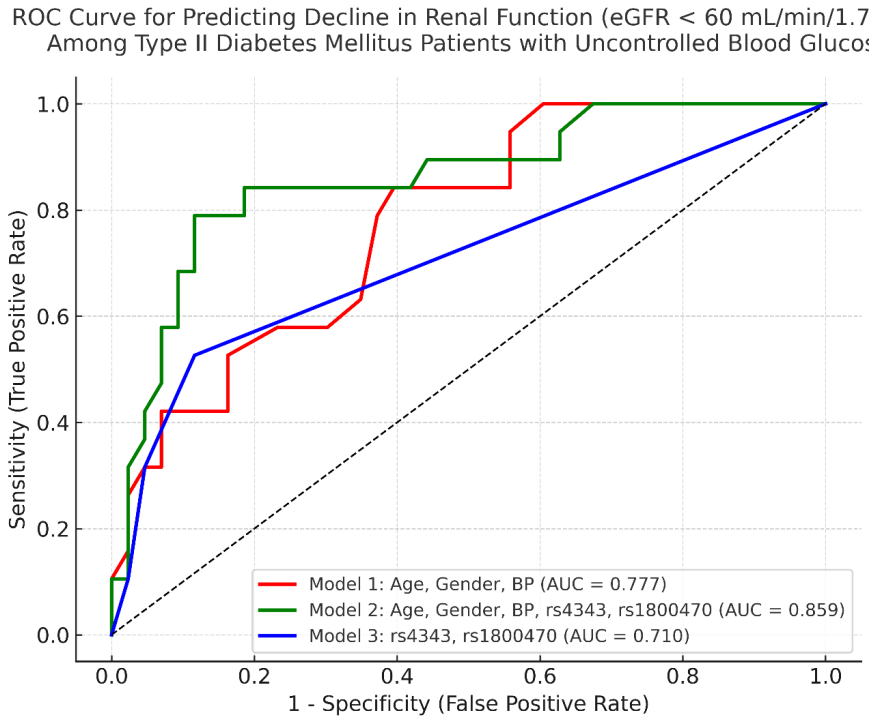

Figure 1. Roc curve of 3 models for predicting decline renal function in Type II diabetes mellitus patients with uncontrolled blood glucose

DISCUSSION

The present study investigated clinical and genetic determinants of renal function decline in patients with type 2 diabetes mellitus (T2DM) and poorly controlled glycemia within the Malay Jambi population. In this cohort, subjects with decreased estimated glomerular filtration rate (eGFR) were significantly older and exhibited higher systolic and diastolic blood pressure compared to those with preserved renal function, whereas fasting and postprandial glucose levels were not significantly different. This finding suggests that, among individuals with persistent hyperglycemia, renal impairment is more strongly driven by hemodynamic and age-related factors than by short-term glycemic fluctuations. Such observation reinforces the notion that the pathogenesis of diabetic kidney disease (DKD) extends beyond metabolic control

Table 2. Hardy Weinberg Equilibrium Estimation

Genotype	Decline GFR					Not Decline GFR				
	Observed value	Expected value	Chi-square	p-value	MAF	Observed value	Expected value	Chi-square	p-value	MAF
TGF-B rs1800470										
TT	6	5				2	4			
TC	8	9	0.460	0.498	0.474	24	19	3.157	0.076	0.326
CC	5	5				17	20			
ACEI rs4343										
AA	13	14	0.668	0.413		39	39	0.102	0.750	0.454
AG	6	5				4	4			

MAF= minor allele frequency; p-value calculated with degree of freedom= 1

Table 3. Association of genetic and diabetic nephropathy

Genotype	Decline GFR	Not Decline GFR	p-value	OR (95% CI)	Adjusted p-value	Adjusted OR (95% CI)
TGF-B rs1800470 (recessive model)						
TCCC	13	41	ref			
TT	6	2	0.008	9.46 (1.70-52.71)	0.032	7.79 (1.20-50.68)
ACEI rs4343 (codominant model)						
AA			ref			
AG	6	4	0.038	4.5 (1.20-18.47)	0.035	5.98 (1.13-31.65)

Remarks: Bivariate analysis performed with Fisher exact test. Adjusted for age, gender and blood pressure

Tabel 4. ROC curve model for predict decline renal function in Type II diabetes mellitus patients with uncontrolled blood glucose

Model	AUC	Sensitivity	Specificity	Cutoff Youden Index	p-value
Model 1: Age, Gender, BP	0.777	0.842	0.605	0.247	0.0
Model 2: Age, Gender, BP, rs4343, rs1800470	0.859	0.789	0.884	0.459	0.0
Model 3: rs4343, rs1800470	0.710	0.526	0.884	0.48	0.0026

alone, with vascular stress and neurohormonal activation, particularly the renin angiotensin aldosterone system (RAAS) which playing critical roles in disease progression (5–7).

Both TGFB1 rs1800470 and ACE rs4343 polymorphisms in this study conformed to Hardy–Weinberg equilibrium, with minor allele frequencies (MAF) within the global reference range yet showing population-specific variations. The MAF of TGFB1 rs1800470 (0.326–0.474) was slightly lower than that reported in East Asian cohorts, while the MAF of ACE rs4343 (≈0.454) was relatively higher, consistent with the known genetic admixture among Malay subpopulations (24,25). These allele distributions highlight the importance of population-tailored genetic studies, as local ancestry may influence linkage disequilibrium patterns and the expression of kidney-related traits.

Genotype–phenotype analysis demonstrated that the TGFB1 rs1800470 TT genotype was significantly associated with a higher risk of declining GFR under a recessive model, while carriers of the AG genotype at ACE rs4343 had greater odds of renal impairment than AA homozygotes. These associations remained robust after adjustment for age, sex, and blood pressure, indicating that genetic predisposition exerts an independent effect beyond conventional clinical risk factors. The biological plausibility of these findings is well established: angiotensin II induces TGFB1 expression, promoting mesangial expansion and extracellular matrix accumulation, while TGF-β1 in turn amplifies RAAS-induced fibrosis through profibrotic gene activation and epithelial to mesenchymal transition (6,7). Thus, concurrent risk alleles in ACE and TGFB1 may act synergistically to accelerate nephron loss under conditions of chronic hypertension and hyperglycemia as dual-axis mechanism that bridges hemodynamic and molecular injury in DKD.

To evaluate predictive performance, three models were compared: a clinical-only model, a genetic-only model, and an integrated clinical–genetic model. The integrated model demonstrated superior discrimination (AUC = 0.859; sensitivity 78.9%; specificity 88.4%) compared to either domain alone, confirming that incorporating genetic markers meaningfully improves risk classification. This aligns with previous reports showing that the addition of genetic variants or polygenic risk scores enhances DKD prediction accuracy in Asian populations (26–28). Importantly, the model's high specificity suggests potential clinical utility in resource-limited settings such as Indonesia, where efficient identification of high-risk patients is essential for targeted intervention.

The findings underscore that integrating genotype information specifically ACE rs4343 and TGFB1 rs1800470 into clinical risk assessment can enhance early recognition of renal vulnerability among patients with T2DM and uncontrolled glycemia. Such integration may inform precision strategies, including earlier RAAS blockade, stricter blood pressure management, and personalized renal monitoring. Beyond its clinical value, this study contributes novel population-based genetic data for the Malay Jambi group, an underrepresented Southeast Asian cohort, thereby enriching regional genomic databases and supporting the development of future polygenic risk models within the Universitas Jambi precision medicine roadmap.

Several limitations merit consideration. The modest sample size restricts statistical power, particularly for detecting small genetic effects. The cross-sectional design limits inference regarding causality or longitudinal GFR trajectories. Moreover, potential confounders such as medication adherence, dietary salt intake, or diabetes duration were not fully captured. Future prospective, multi-ethnic studies with larger samples are needed to validate these findings and refine model calibration across

diverse Indonesian populations. Despite these limitations, the present study represents an early but crucial step toward the application of genotype-informed prediction for DKD in Indonesia. By integrating clinical and genetic parameters, it provides a feasible framework for personalized risk stratification and aligns with national efforts to incorporate genetic data into chronic disease prevention strategies.

CONCLUSIONS

This study identifies significant associations between ACE rs4343 and TGFB1 rs1800470 polymorphisms and renal function decline in patients with poorly controlled type 2 diabetes mellitus within the Malay Jambi population. Integrating these genetic variants with clinical parameters including age, sex, and blood pressure produced the most accurate predictive model (AUC 0.859), outperforming clinical- or genetic-only approaches. These results underscore the interplay of hemodynamic and genetic factors in DKD pathogenesis through RAAS and TGF-β–mediated profibrotic pathways. The integrated model demonstrates strong potential for early identification of individuals at high risk of DKD, supporting genotype-informed clinical decisions in resource-limited settings. Beyond its clinical relevance, this study contributes the first population-based genetic data for the Malay Jambi group and provides a foundation for future development of polygenic and machine-learning–based predictive tools to advance precision nephrology in Indonesia.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

FUNDING

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DECLARATION OF ARTIFICIAL INTELLIGENCE USE

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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