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Higher eGFRdiff Is Associated With Increased Risk of Rapid Kidney Function Decline in Hypertensive Individuals

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Abstract

Background

Hypertensive nephropathy is the second contributing factor to end-stage renal disease, while the relationship between the difference between estimated glomerular filtration rates (eGFRdiff) and rapid kidney function decline (RKFD) in hypertensive patients remains unclear.

Methods

This study included 2,230 hypertensive patients from the China Health and Retirement Longitudinal Study (CHARLS, 2011–2015). Multivariable logistic regression and restrictive cubic spline analysis were used to evaluate the association between eGFRdiff and the risk of RKFD. The area under the curve (AUC) of receiver operating characteristic (ROC) was calculated to assess the predictive ability of eGFRdiff.

Results

In both the crude model and adjusted models, eGFRdiff showed a significant positive correlation with the risk of RKFD. In Model 3, when compared to quantile 1 (Q1) of eGFRabdiff, the odds ratios (ORs) across the Q2, Q3, Q4 were: 1.82 (95% CI 0.82–4.06), 1.47 (95% CI 0.63–3.45), and 3.88 (95% CI 1.82–8.25), respectively (*P* for trend = 0.01). Similarly, compared to quantile 1 (Q1) of eGFRrediff, the ORs across the Q2, Q3, Q4 were: 1.99 (95% CI 0.92–4.31), 1.46 (95% CI 0.63–3.40), and 3.44 (95% CI 1.62–7.30), respectively (*P* for trend = 0.002). The ROC analysis indicated that the discriminative power of eGFRabdiff and eGFRrediff for predicting RKFD risk was 0.633 and 0.610, respectively.

Conclusion

There was a significant positive correlation between eGFRabdiff or eGFRrediff and the risk of RKFD in hypertensive individuals.

Introduction

Hypertension remains one of the most prevalent chronic diseases worldwide, posing a considerable threat to public health due to its strong association with life-threatening illnesses. This condition considerably increases the risk of cardiovascular disease, stroke, and kidney disease.[1,2] The latest report from the World Health Organization highlights a troubling rise in the global prevalence of hypertension, and a particularly concerning aspect of the report is the stark variation in the effectiveness of prevention and treatment efforts across different regions, with notable disparities even within the same geographical area.[3] The number of people aged 30–79 with hypertension worldwide had reached 1,278 million in 2019, indicating a significant increase since 648 million in 1990.[3] Hypertension is recognized as the second leading cause of end-stage renal disease among patients with chronic kidney disease (CKD), underscoring its critical role in

renal pathology. Furthermore, analyses from the United States National Health and Nutrition Examination Survey (NHANES) revealed that the age-standardized prevalence of stage 1 CKD gradually increased from 4.9% in 2003 to 2006 to 7% in 2015 to 2018 among US adults with hypertension, signaling an expanding public health burden associated with hypertension-related kidney damage.[4] Hypertensive nephropathy is fundamentally a chronic inflammatory disease. Persistent hypertension contributes to renal arteriopathy, secondary ischemic renal parenchymal injury, glomerulosclerosis, renal tubular atrophy and interstitial fibrosis.[5–7] Hypertension serves not only as a pivotal driver of renal deterioration but also as a major complication of CKD. This gives rise to a vicious cycle in which elevated blood pressure results in glomerular hypertension and damage to renal units, and the deteriorating kidney function, in turn, further exacerbates hypertension.[8] Such bidirectional interactions make monitoring changes in renal function crucial for managing the health of hypertensive patients.

Rapid kidney function decline (RKFD) typically refers to a substantial short-term decrease in the glomerular filtration rate (GFR) that surpasses the age-related natural decline. The current international consensus, as outlined by Kidney Disease: Improving Global Outcomes in 2012 (KDIGO 2012), recommends that an annual estimated glomerular filtration rate (eGFR) decline of ≥ 5 ml/min/1.73m² be utilized as a threshold for identifying patients at high risk of CKD progression.[9] In hypertensive patients, a rapid decline in eGFR is most strongly associated with the highest risk of all-cause mortality.[10] Moreover, the risk of heart failure increased by 1.4 times in individuals with RKFD.[11] The decline of renal function not only directly leads to the increased need for renal replacement therapy, but also independently correlates with the increased risk of cardiovascular events,[12] highlighting its clinical importance as a hub of multiple system diseases.

The current classification system for CKD mainly relies on biomarkers reflecting glomerular function, specifically the eGFR, and markers of renal injury, such as the urine albumin-to-creatinine ratio (UACR). At present, the 2021 updated Chronic Kidney Disease Epidemiology Collaboration creatinine equation, which excludes race-based coefficients (2021 CKD-EPI), is the recommended standard for evaluating eGFR.[13] However, serum creatinine is highly sensitive to numerous confounding factors. Dietary habits, especially high animal protein consumption, may cause temporary elevations of creatinine.[14] Muscle mass significantly influences serum creatinine concentrations as well, since creatinine is a waste product generated by muscle metabolism.[15] Moreover, serum creatinine levels often remain within the normal range during the early stages of kidney injury, leading to a false sense of injury regarding renal health.[16] Considering the limitations of the 2021 creatinine-based GFR estimation formula (eGFRcr) in assessing renal function, the 2021 CKD-EPI guidelines recommend adding cystatin C as a replacement or supplementary biomarker for creatinine, particularly when creatinine estimation is imprecise. Combined with creatinine, cystatin C provides more accurate GFR estimation, especially in high-risk populations.[17] On the other hand, regarding markers of renal injury, UACR ≥ 30 mg/g is the core standard for CKD diagnosis and staging, and an independent predictor of decreased renal function.[18,19] However, substantial variability limits the reliability of a single UACR measurement. Additionally, UACR lacks specificity in predicting the rate of GFR decline and does not adequately reflect tubular interstitial injury,[20] which is a critical pathway in the progression of CKD. As a result, the evaluation of novel biomarkers for assessing the decline in renal

function continues to attract considerable scientific interest. Neutrophil gelatinase-associated lipocalin (NGAL) has been identified as a predictive marker for renal function impairment in patients with hypertension.[21] However, NGAL mainly serves as an excellent biomarker for detecting acute kidney injury,[22] yet it is not an ideal long-distance runner in the context of chronic kidney disease. Its primary value lies in providing early warning of acute risks in CKD patients, rather than replacing traditional indicators such as eGFR and UACR for defining and tracking the long-term, gradual progression of CKD, and it may be affected by non-renal factors such as infection or inflammation.[23] A recent study has highlighted a significant association between soluble urokinase plasminogen activator receptor (suPAR) levels and rapid kidney function decline.[24] The principal limitation of suPAR in predicting chronic renal function decline is its non-specificity, as it serves as a broad marker of inflammation and various disease states rather than being kidney-specific.[25] Additionally, unlike creatinine—which relies on established eGFR calculation formulas—suPAR currently lacks clear and unified clinical decision thresholds. There is no widely accepted cutoff value to guide clinical decision-making, further restricting its practical application in kidney disease prognosis. Other potential biomarkers, such as epidermal growth factor (EGF) and circular RNAs (circRNAs),[26,27] all have limitations in the standardization of their detection. Therefore, the development of precise methods or biomarkers to identify high-risk patients for RKFD among hypertensive individuals is of critical importance.

eGFRdiff is a novel clinical parameter that represents the difference between eGFR calculated using creatinine-based and cystatin C-based equations. Traditionally, creatinine-based eGFR (eGFRcr) is the most common method due to its low cost and widespread availability. However, eGFRcr can be influenced by factors unrelated to kidney function. The 2012 cystatin C-based GFR estimation formula (eGFRcys) provides an alternative estimation that is less affected by these non-renal factors, as cystatin C production is relatively constant across individuals. The eGFRdiff is calculated by subtracting eGFRcr from eGFRcys (eGFRcys - eGFRcr). It helps clinicians interpret kidney function tests more accurately, especially in complex cases where non-renal influences on creatinine or cystatin C are suspected. By highlighting these discrepancies, eGFRdiff can guide decisions on whether additional tests are needed or whether cystatin C-based assessment should be prioritized for a more reliable evaluation of GFR. Furthermore, a population-based cohort study has reported that the large eGFRdiff was independently associated with risk of diabetic microvascular complications among adults with diabetes.[28] Additionally, a meta-analysis from the Chronic Kidney Disease Prognosis Consortium demonstrated that in outpatient settings, the presence of eGFRcys at least 30% lower than eGFRcr was associated with significantly higher rates of all-cause mortality, cardiovascular events, and kidney failure.[29] Another study comparing serum creatinine- and cystatin C-based eGFR at baseline found that serum cystatin C may help detect early kidney dysfunction in individuals with type 1 diabetes, even before indicators such as albuminuria or reduced creatinine-based eGFR become apparent.[30] These findings above collectively indicated that eGFRdiff plays an important role in the progression of kidney failure.

In this study, we aimed to evaluate the association of eGFRdiff and RKFD among hypertensive individuals, to better interpret the clinical significance of discrepancies between eGFRcys and eGFRcr in this population. A clearer understanding of this discordance may contribute to improved management and monitoring of renal

function among individuals with hypertension, thus enhancing long-term renal outcomes in hypertensive patients.

Methods

Study population

The study initially included 6,600 hypertensive participants from the CHARLS 2011 cohort. After eliminating cases with missing creatinine and cystatin C data from both 2011 and 2015, the final study cohort consisted of 2,230 participants (Fig. 1). The CHARLS survey project was approved by the Biomedical Ethics Committee of Peking University (No. IRB00001052-11015), and all participants were required to sign informed consent.

Ascertainment of hypertension and RKFD

The diagnosis of hypertension is established based on multiple blood pressure readings obtained during at least two separate visits, utilizing a threshold of 140/90 mmHg, or if the individual has been diagnosed with hypertension by a physician.[31]

A reduction of eGFR by 30% or more from baseline to follow-up was defined as RKFD,[32] with the use of a based creatinine-cystatin C equation to estimate GFR without considering racial factors.

Calculation of eGFRabdiff/eGFRrediff

The 2012 CKD-EPI cystatin C equation and 2021 race-free CKD-EPI equations were used to calculate eGFRcys, eGFRcr, and the 2021 creatinine and cystatin C based GFR estimation formula (eGFRcr-cys), respectively.[13,33] The two key metrics we focused on were the absolute difference between estimated glomerular filtration rates (eGFRabdiff, calculated as eGFRcys minus eGFRcr) and the relative difference between estimated glomerular filtration rates (eGFRrediff, calculated as eGFRcys divided by eGFRcr).[34,35]

Covariates

The following covariates were evaluated: sociodemographic factors such as age, sex, education level, marital status, and place of residence; lifestyle factors including smoking status and alcohol consumption; anthropometric measurements like body mass index (BMI) and waist circumference; medical history comprising hypertension and type 2 diabetes mellitus (T2DM); and laboratory indicators, specifically glycated hemoglobin (HbA1c), serum creatinine, serum cystatin C, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL).

Statistical analysis

The participants were divided into two groups based on whether or not they experienced RKFD. Continuous variables are presented as the mean ± standard deviation (SD) compared using an independent samples t-test. Categorical variables are presented as frequencies (percentages). Additionally, we divided the variables into four groups according to the quartiles of eGFRabdiff and eGFRrediff to comprehensively elucidate the relationship between eGFRabdiff/eGFRrediff and the risk of RKFD in patients with hypertension. Multivariable logistic regression based on restricted cubic splines (RCS) were used to evaluate the association of eGFRabdiff/eGFRrediff and the risk of RKFD. Model discrimination was assessed using receiver operating characteristic (ROC) curve analysis, with performance summarized by the area under the curve (AUC). In addition, we conducted subgroup and interaction analyses. Analyses were conducted using R statistical software (version 4.4.1).

Results

Basic characteristics of study population

As shown in Table 1, the study included 2,230 hypertensive patients, with 92 (4.13%) having RKFD and 2,138 (95.87%) without RKFD. The median age of the RKFD group was 65.17 years, which was significantly higher than the median age of the non-RKFD group at 61.79 years. No significant differences were observed between the two groups in terms of gender, residence place, TC, BMI, education level, smoking status, and alcohol consumption habits. The RKFD group showed a higher prevalence of T2DM and a higher proportion of individuals living alone. At baseline, RKFD patients exhibited higher TG levels, waist circumference, and HbA1c levels, while LDL and HDL levels were significantly lower than those in the non-RKFD group. The average eGFRcr was also notably reduced in the RKFD group. However, values for eGFRcr-cys and eGFRcys were significantly higher in RKFD patients, with statistical significance ($P < 0.01$). Additionally, both eGFRabdiff and eGFRrediff measurements were elevated in the RKFD cohort relative to the non-RKFD group. These findings suggested distinct metabolic and renal function profiles associated with RKFD.

Associations of eGFRabdiff/eGFRrediff with the risk of RKFD

During a 4-year follow-up period, it was observed that 92 (4.13%) participants developed RKFD. To evaluate the association between eGFRabdiff/eGFRrediff and the risk of RKFD, the multivariable logistic regression analysis was conducted using RCS. As shown in Figs. 2-3, the RCS demonstrated a significant positive relationship between eGFRabdiff/eGFRrediff and the risk of RKFD in all models (P for overall < 0.05, P for nonlinear > 0.05). To further validate these findings, we categorized the eGFRabdiff and eGFRrediff into quartiles, with the lowest quartile (Q1) group serving as the reference group. As shown in Table 2, in the unadjusted model, the odds ratios (ORs) of RKFD for Q2, Q3, and Q4 groups compared to the Q1 were 1.76 (95% CI 0.83-3.73), 1.28 (95% CI 0.58-2.85), and 3.74 (95% CI 1.89-7.37), respectively (P for trend < 0.001). In the age and marital status adjusted model (Model 1), the ORs of RKFD for Q2, Q3, and Q4 groups were 1.82 (95% CI 0.85-3.87), 1.45 (95% CI 0.65-3.24), and 4.44 (95% CI 2.22-8.89), respectively (P for trend < 0.001). After further adjusting for TG, LDL, HDL, HbA1c, and waist circumference (Model 2), the corresponding ORs for Q2, Q3, Q4 groups were 1.82 (95% CI 0.82-4.05), 1.49 (95% CI 0.63-3.48), and 3.97 (95% CI 1.87-8.45), respectively (P for trend = 0.01). When further adjusting for T2DM (Model 3), the ORs

remained similar across groups: 1.82 (95% CI 0.82-4.06), 1.47 (95% CI 0.63-3.45), and 3.88 (95% CI 1.82-8.25) (*P* for trend = 0.01).

In the analysis of eGFRrediff and the risk of RKFD, we observed similar results. In the crude model, the OR for Q4 group was 2.90 (95% CI 1.52-5.53) compared to Q1. In model 1 adjusted for age and marital status, the OR for Q4 group was 3.83 (95% CI 1.95-7.52). In model 2 further adjusted for TG, LDL, HDL, HbA1c, and waist circumference, the OR for Q4 group was 3.54 (95% CI 1.67-7.51). In model 3 further adjusted for T2DM, the OR for Q4 group was 3.44 (95% CI 1.62-7.30). All models showed a linear trend (*P* for trend < 0.05) (Table 3). Based on these findings, we concluded that the eGFRabdiff and eGFRrediff were positively associated with the risk of RKFD.

In the Supplementary Figs. 1-2 and Supplementary Tables 1-2, the application of the same analytical methods as previously used to assess the relationship between eGFRabdiff/eGFRrediff and RKFD yielded consistent conclusions when employing the eGFRcys to confirm the decline of GFR. However, when utilizing eGFRcr to evaluate the decline of GFR, the results were completely opposite as shown in Supplementary Figs. 3-4 and Supplementary Tables 3-4. Both eGFRabdiff and eGFRrediff exhibited a significant negative correlation with developing RKFD. This phenomenon may be explained by patients with hypertension often exhibiting advanced age and reduced muscle mass—factors that influence creatinine test results. The eGFR based on creatinine levels may overestimate renal function, resulting in significantly lower eGFRcys compared to eGFRcr. When actual renal function declines, eGFRcr also decreases. However, because its baseline is artificially elevated, the slope of decline may appear less steep and could even be partially masked by concurrent muscle mass reduction resulting in lower creatinine production. As a result, reliance on eGFRcr assessment may miss the true rapid decline in kidney function and fail to classify it as such.

Stratified analysis

To evaluate whether there are differences in the association between eGFRabdiff/eGFRrediff and the risk of RKFD across subgroups, we used stratified analyses according to age (<60 or ≥60 years), marital status (married or unmarried), TG (<150 or ≥150 mg/dL), LDL (<130 or ≥130 mg/dL), HDL (<40 or ≥40 mg/dL), HbA1C (<6 or ≥6%), WC (<85 or ≥85 cm), and presence of T2DM. As illustrated in Figs. 4-5, the positive association between eGFRabdiff/eGFRrediff and RKFD appeared in each subgroup, indicating the robustness of our findings.

Predictive efficacy of eGFRabdiff and eGFRrediff for the risk of RKFD

Fig. 6 presented the ROC curve analysis to evaluate the discriminative power of eGFRabdiff and eGFRrediff in predicting the risk of RKFD. The area under the curve (AUC) of eGFRabdiff and eGFRrediff was 0.633 and 0.610, respectively. The optimal threshold for eGFRabdiff was -10 ml/min/1.73m², with a sensitivity of 0.554 and specificity of 0.701. For eGFRrediff, the optimal threshold was 0.897, yielding a sensitivity of 0.506 and specificity of 0.710. These results suggested that eGFRabdiff and eGFRrediff demonstrate predictive capability for the risk of RKFD.

Discussion

This study firstly investigated the relationship between eGFRdiff (including eGFRabdiff and eGFRrediff) and the risk of RKFD in hypertensive patients. Results demonstrated that both eGFRabdiff and eGFRrediff are positively associated with RKFD in hypertensive patients. This suggested the monitoring of eGFRabdiff and eGFRrediff may play a critical role in the management of RKFD in hypertensive patients. The findings offer potential clinical utility for the early detection and monitoring of RKFD in hypertensive individuals.

In our study, three distinct eGFR formulas were employed to estimate RKFD in order to assess whether the choice of formula influences the ascertainment of RKFD risk. Interestingly, when RKFD was estimated by eGFRcr-cys or eGFRcys, eGFRdiff showed a significant positive correlation with the risk of RKFD among hypertensive patients. In contrast, when traditional creatinine-based GFR was used to evaluate RKFD, eGFRdiff exhibited a significant negative correlation with the risk of RKFD. This contradictory phenomenon highlighted the importance of method selection in forecasting RKFD. Previous study has reported that the combined eGFRcr-cys performs best across all patient types for predicting measured GFR.[36] Cystatin C, less affected by muscle mass, gender, or diet, is more effective in assessing renal function than creatinine may underestimate.[37,38] When creatinine levels are combined with cystatin C (eGFRcr-cys), this approach shows superior predictive power for GFR compared to creatinine alone,[17,39] while drawbacks of relying solely on eGFRcr for assessing RKFD are obvious. A primary concern is that creatinine levels are affected by muscle mass. Meta-analytical evidence has linked sarcopenia—age-related muscle loss—to hypertension in older adults.[40] In patients with muscle mass loss related diseases, reliance on eGFRcr may lead to an overestimation of renal function, potentially delaying the identification of renal impairment.[41] Consequently, eGFRcr shows low sensitivity in the early detection of renal function decline. This highlighted the importance of the selection of different formulas for estimating the risk of RKFD amog hypertensive individuals.

A potential explanation for the observed relationship between a higher eGFRdiff and increased risk of RKFD in hypertensive patients may lie in the distinct biological characteristics and clinical implications of these two filtration markers. Cystatin C, a low-molecular-weight protein produced at a constant rate by nucleated cells, is freely filtered by the glomeruli.[42] Cystatin C is neither secreted nor reabsorbed by the renal tubules, and is almost entirely metabolized by the proximal tubular cells.[43] Its levels may remain relatively stable unless there is significant reduction in glomerular filtration. In contrast, creatinine is derived from muscle metabolism and is both filtered by glomerulus and secreted by the renal tubules.[44] A positive eGFRdiff, or a larger gap between eGFRcys and eGFRcr, might signify early tubular dysfunction rather than pure glomerular impairment that affects serum creatinine. In hypertensive individuals, hypertensive nephrosclerosis often involves tubular injury and interstitial inflammation,[5] which can impair the proximal tubule's secretory function for creatinine, thereby raising serum creatinine and lowering eGFRcr, while the effect on cystatin C may be relatively minor. Furthermore, the production of the anti-inflammatory cytokine interleukin-10 (IL-10), which plays a significant role in hypertension and vascular remodeling, may lead to a reduction in the generation of cystatin C,[45–47] thus resulting in a relatively higher eGFRcys. Thus, eGFRdiff may serve as an integrative marker of underlying pathological processes—such as glomerular hyperfiltration, tubular injury, or vascular impairment—that predispose to RKFD. A larger eGFRdiff (whether positive or negative) has been confirmed by multiple studies to be associated with an increased risk of cardiovascular disease, all-cause

mortality, and end-stage renal disease.[48–50] This reflects a "dysregulation" in the metabolic pathways of the two biomarkers, and such dysregulation itself is a manifestation of pathological conditions. The positive association between eGFRdiff and risk of RKFD suggested that eGFRdiff may capture aspects of renal vulnerability beyond conventional GFR estimates, highlighting the utility of eGFRdiff in refining risk stratification of RKFD in hypertensive individuals.

In conclusion, this study initially revealed the positive association between eGFRabdiff/eGFRrediff and the risk of RKFD in hypertensive patients. Future research should validate this observation across diverse populations. In addition, elucidating the underlying mechanisms linking eGFRabdiff or eGFRrediff to RKFD would facilitate a clearer understanding of the pathological processes involved in RKFD development.

Limitation

The limitations of this study must be thoroughly considered. Firstly, the retrospective design introduces selection bias and information bias, requiring caution in causal inference. Secondly, the study population was primarily drawn from a single center specializing in older adults, resulting in limited sample representativeness and necessitating further validation of the results generalizability. Thirdly, despite adjusting for multiple confounding factors, unmeasured variables such as patient lifestyle, medication adherence, and genetic background may still influence the outcomes. Future multicenter, large-sample prospective studies will help validate the robustness of these findings. Additionally, cystatin C testing remains expensive and has low adoption, with many medical institutions still relying on creatinine as the primary marker,[51] which may complicate its future clinical application.

Conclusion

In this prospective cohort study, we observed a significant positive correlation between eGFRdiff and the risk of RKFD estimated from eGFRcr-cys and eGFRcys. These findings offer meaningful insights for evaluating the risk of RKFD in hypertensive individuals.

Declarations

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Author Contributions

Lu Zhang and Qian-Qian Wang conducted the statistical analyses, interpreted the data, and drafted the manuscript. Chao-Fei Shen contributed to discussion of the results and reviewed the final manuscript. Le

Zhang and Jun Wu conceived and designed the study, interpreted the data, and critically revised the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Availability of data and materials

The data used in this study are available in the CHARLS database.

Clinical Trial Number

Not applicable.

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Tables

Table 1. Basic characteristics of study population

Variable	RKFD (n=92)	Non-RKFD (n=2138)	*P*-value
Age, years	65.17 ± 10.26	61.79 ± 9.22	<0.001
Sex			0.95
Female	52(56.52%)	1189(55.61%)	
Male	40(43.48%)	949(44.39%)	
South North			0.69
North	43(46.74%)	1057(49.44%)	
South	49(53.26%)	1081(50.56%)	
Residence place			0.11
Rural	50(54.35%)	1350(63.14%)	
Urban	42(45.65%)	788(36.86%)	
TG, mg.dL	188.35 ± 125.33	146.79 ± 112.84	<0.01
TC, mg.dL	194.69 ± 35.18	197.55 ± 40.33	0.45
LDL, mg.dL	107.70 ± 39.02	119.25 ± 37.39	<0.01
HDL, mg.dL	41.55 ± 13.10	49.37 ± 14.87	<0.0001
HbA1c, %	5.71 ± 1.45	5.33 ± 0.86	0.02
BMI, kg/m^2	25.24 ± 3.42	24.57 ± 4.02	0.09
Waist circumference, cm	91.91 ± 11.66	87.50 ± 12.82	<0.01
eGFRcr, mL/min/1.73 m^2	87.38 ± 20.57	92.89 ± 14.63	0.01
eGFRcys, mL/min/1.73 m^2	88.91 ± 27.47	75.16 ± 20.56	<0.0001
eGFRcr-cys, mL/min/1.73 m^2	93.04 ± 24.65	86.12 ± 18.08	<0.01
eGFRabdiff, mL/min/1.73 m^2	1.52 ± 20.88	-17.73 ± 16.58	<0.0001
eGFRrediff	1.02 ± 0.28	0.81 ± 0.18	<0.0001
Smoke			0.54
Ever smoke, don't known whether smoke now	10(10.99%)	203(9.50%)	
Former, now quit	60(65.93%)	1317(61.66%)	
Never smoke	21(23.08%)	592(27.72%)	
Still smoke	0(0.00%)	24(1.12%)	

Drink frequency in the past			0.54
<1/month	7(9.21%)	155(9.37%)	
>1/month	11(14.47%)	173(10.45%)	
No	58(76.32%)	1327(80.18%)	
Education			0.50
<= 9, years	82(89.13%)	1960(91.80%)	
>9 and <=12, years	9(9.78%)	143(6.70%)	
>12, years	1(1.09%)	32(1.50%)	
Marriage status			<0.001
Married	64(69.57%)	1800(84.19%)	
Non-married	28(30.43%)	338(15.81%)	
T2DM			<0.001
No	58(63.04%)	1715(80.22%)	
Yes	34(36.96%)	423(19.78%)	

Abbreviations: BMI, body mass index; eGFRabdiff, absolute difference between estimated glomerular filtration rates; eGFRrediff, relative difference between estimated glomerular filtration rates; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; eGFRcr-cys, creatinine and cystatin C based estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; RKFD, rapid kidney function decline; TC, total cholesterol; TG, triglyceride; T2DM, type 2 diabetes mellitus.

Table 2 Associations between eGFRabdiff and the risk of RKFD based on eGFRcr-cys

RKFD	Crude Model		Model 1		Model 2		Model 3	
	95% CI	*P*	95% CI	*P*	95% CI	*P*	95% CI	*P*
Q1	reference		reference		reference		reference	
Q2	1.76 (0.83,3.73)	0.14	1.82 (0.85,3.87)	0.12	1.82 (0.82,4.05)	0.14	1.82 (0.82,4.06)	0.14
Q3	1.28 (0.58,2.85)	0.54	1.45 (0.65,3.24)	0.37	1.49 (0.63,3.48)	0.36	1.47 (0.63,3.45)	0.37
Q4	3.74 (1.89,7.37)	<0.001	4.44 (2.22,8.89)	<0.0001	3.97 (1.87,8.45)	<0.001	3.88 (1.82,8.25)	<0.001
***P* for trend**		<0.001		<0.001		0.01		0.01

Abbreviations: CI, Confidence Interval; eGFRabdiff, absolute difference between estimated glomerular filtration rates; eGFRcr-cys, the 2021 creatinine and crystatin C based GFR estimation formula; Q, quantile; RKFD, rapid kidney function decline.

Crude model: unadjusted;

Model 1: adjusted by age and marital status;

Model 2: adjusted by age, marital status, triglyceride (TG), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), glycosylated hemoglobin (HbA1c) and waist circumference;

Model 3: adjusted by age, marital status, TG, LDL, HDL, HbA1c, waist circumference and presence of type 2 diabetes mellitus (T2DM).

Table 3 Associations between eGFRrediff and the risk of RKFD based on eGFRcr-cys

RKFD	Crude Model		Model 1		Model 2		Model 3	
	95%CI	*P*	95%CI	*P*	95%CI	*P*	95%CI	*P*
Q1	reference		reference		reference		reference	
Q2	1.58 (0.78,3.20)	0.21	1.82 (0.89,3.74)	0.10	2.01 (0.93,4.35)	0.08	1.99 (0.92,4.31)	0.08
Q3	1.08 (0.50,2.33)	0.84	1.41 (0.64,3.10)	0.39	1.48 (0.64,3.44)	0.36	1.46 (0.63,3.40)	0.37
Q4	2.90 (1.52,5.53)	0.001	3.83 (1.95,7.52)	<0.0001	3.54 (1.67,7.51)	<0.001	3.44 (1.62,7.30)	0.001
***P* for trend**		0.002		<0.001		0.002		0.002

Abbreviations: CI, Confidence Interval; eGFRrediff, relative difference between estimated glomerular filtration rates; eGFRcr-cys, the 2021 creatinine and crystatin C based GFR estimation formula; Q, quantile; RKFD, rapid kidney function decline.

Crude model: unadjusted;

Model 1: adjusted by age and marital status;

Model 2: adjusted by age, marital status, triglyceride (TG), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), glycosylated hemoglobin (HbA1c) and waist circumference;

Model 3: adjusted by age, marital status, TG, LDL, HDL, HbA1c, waist circumference and presence of type 2 diabetes mellitus (T2DM).

Figures

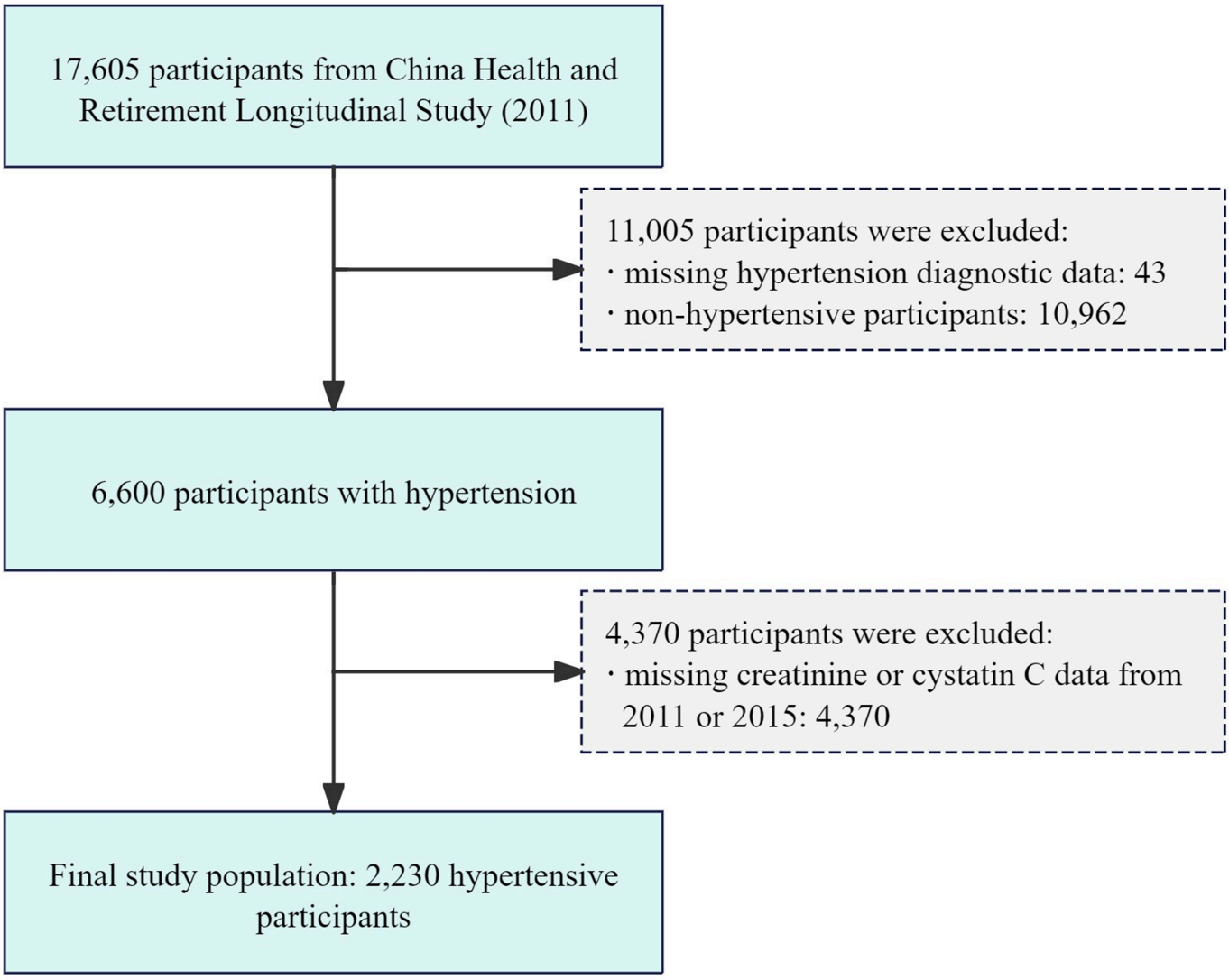


Figure 1

Flow chart of the study population.

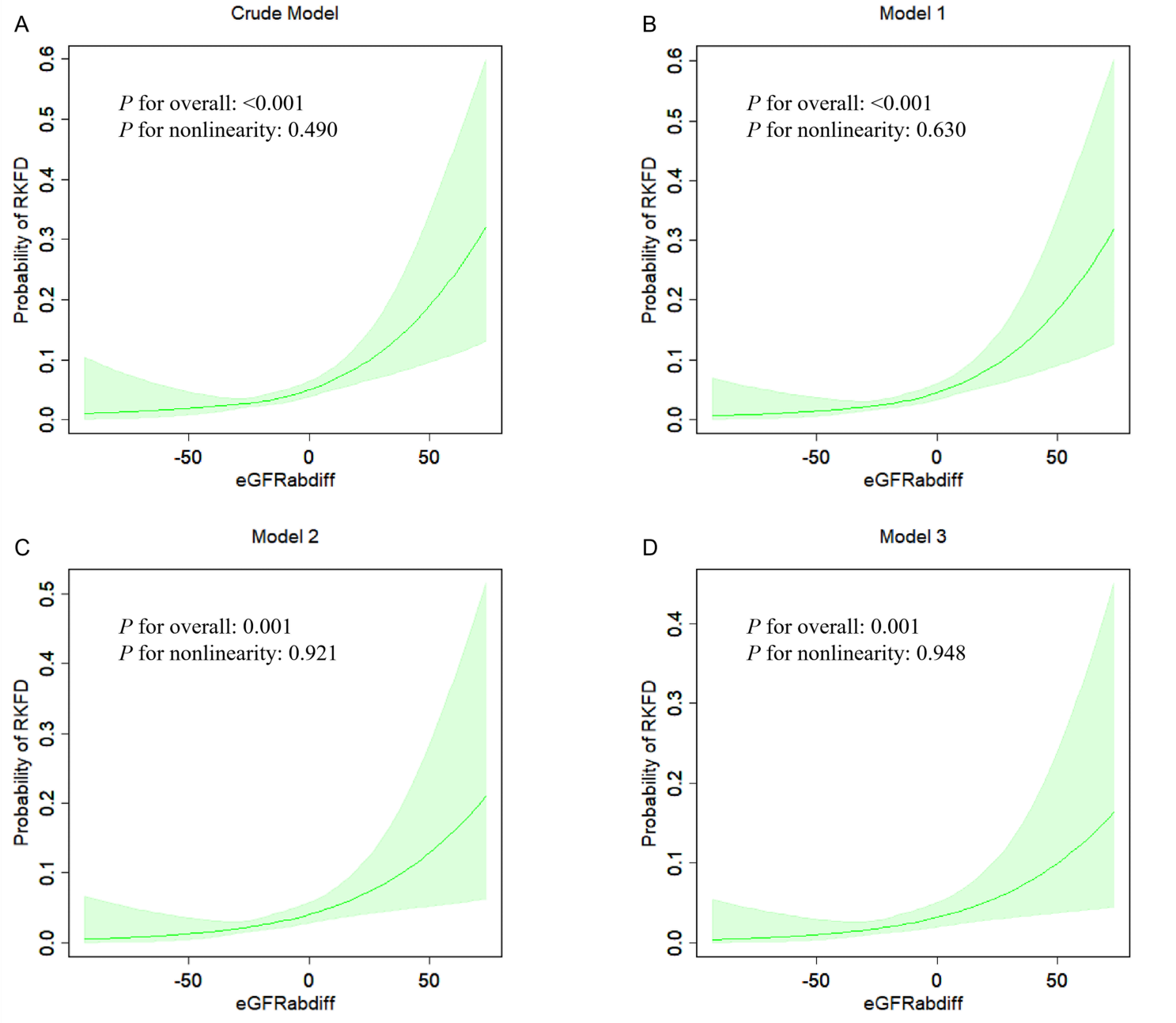


Figure 2

Association of eGFRabdiff and the risk of rapid kidney function decline (RKFD) according to the 2021 creatinine and cystatin C based GFR estimation formula (eGFRcr-cys). A) Crude model: unadjusted; **B)** Model 1: adjusted by age and marital status; **C)**Model 2: adjusted by age, marital status, triglyceride (TG), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), glycosylated hemoglobin (HbA1c) and waist circumference; **D)** Model 3: adjusted by age, marital status, TG, LDL, HDL, HbA1c, waist circumference and presence of type 2 diabetes mellitus (T2DM).

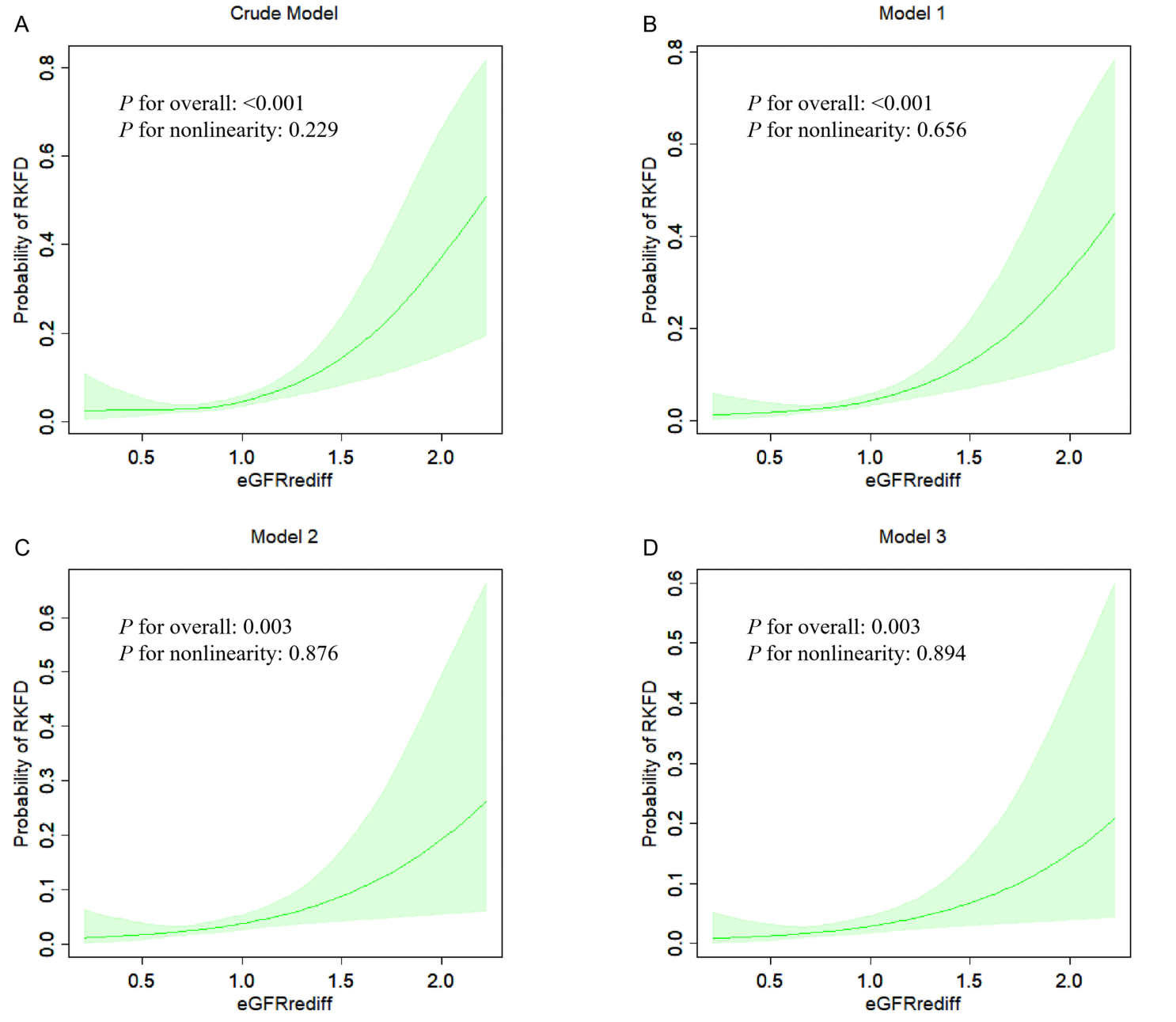


Figure 3

Association of eGFRrediff and the risk of rapid kidney function decline (RKFD) according to the 2021 creatinine and cystatin C based GFR estimation formula (eGFRcr-cys). A) Crude model: unadjusted; **B)** Model 1: adjusted by age and marital status; **C)** Model 2: adjusted by age, marital status, triglyceride (TG), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), glycosylated hemoglobin (HbA1c) and waist circumference; **D)** Model 3: adjusted by age, marital status, TG, LDL, HDL, HbA1c, waist circumference and presence of type 2 diabetes mellitus (T2DM).

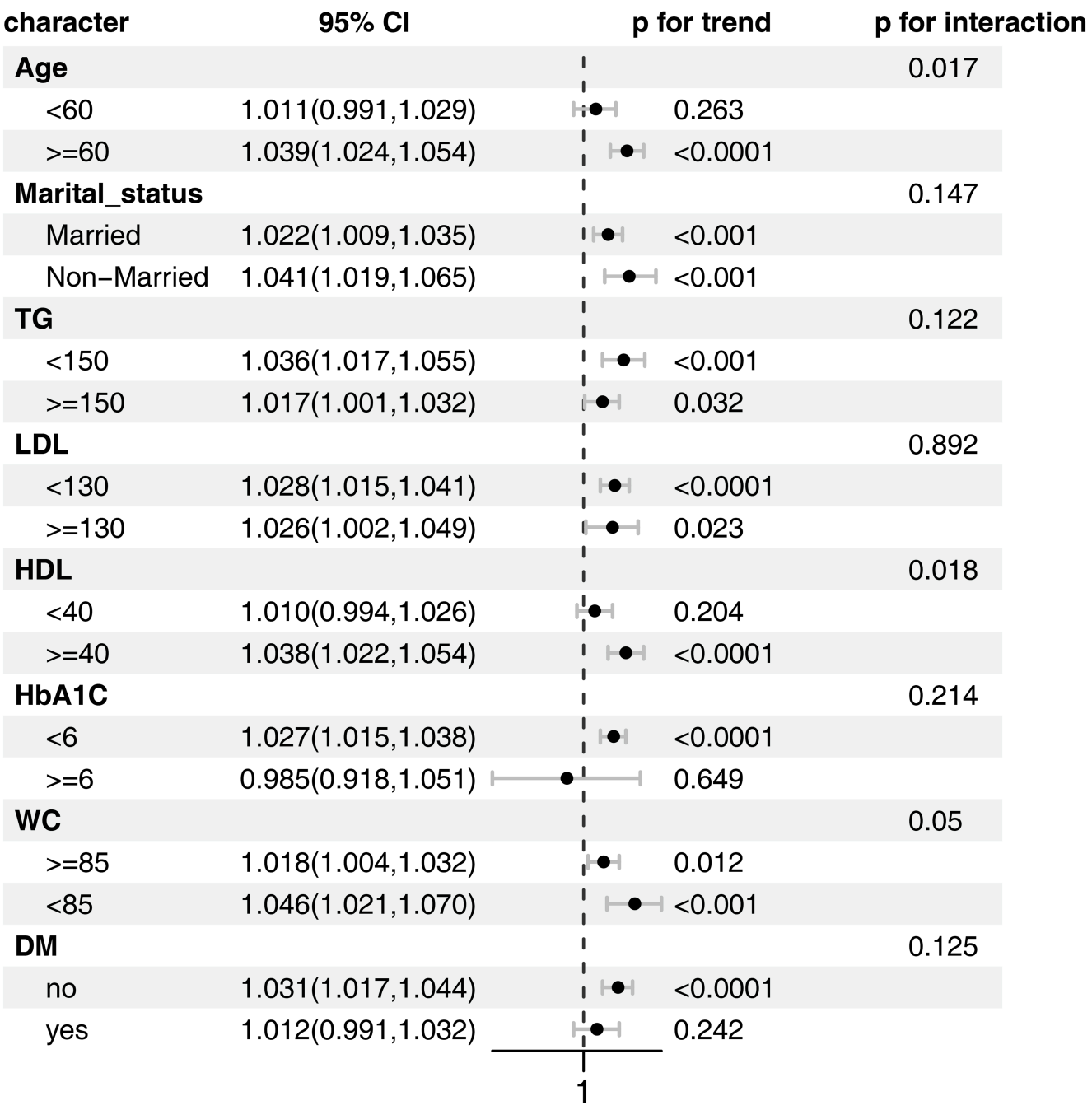


Figure 4

Association of eGFRabdiff and the risk of rapid kidney function decline (RKFD) in different subgroups. DM, type 2 diabetes mellitus; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglyceride; WC, waist circumference.

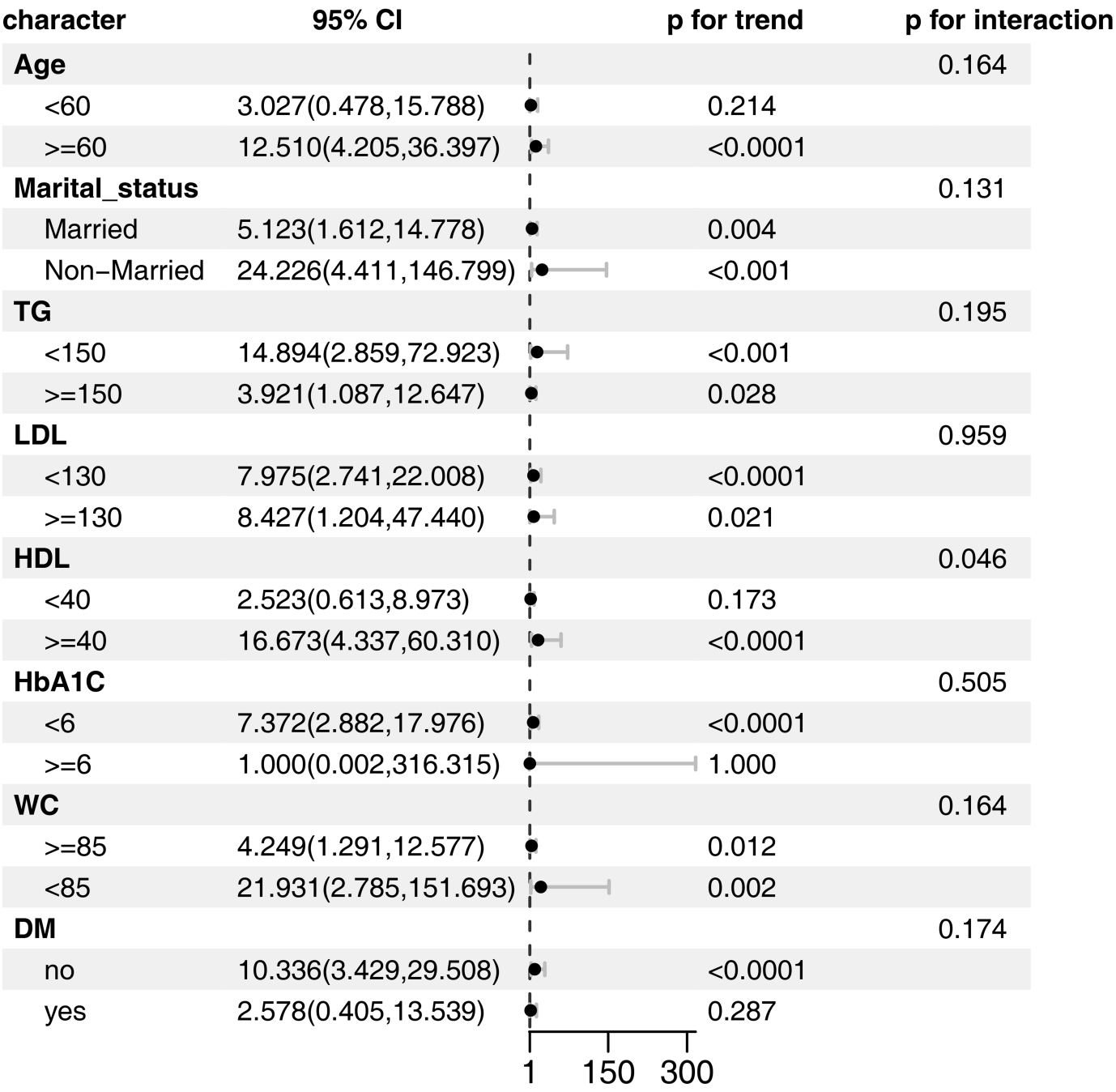


Figure 5

Association of eGFRrediff and the risk of rapid kidney function decline (RKFD) in different subgroups. DM, type 2 diabetes mellitus; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglyceride; WC, waist circumference.

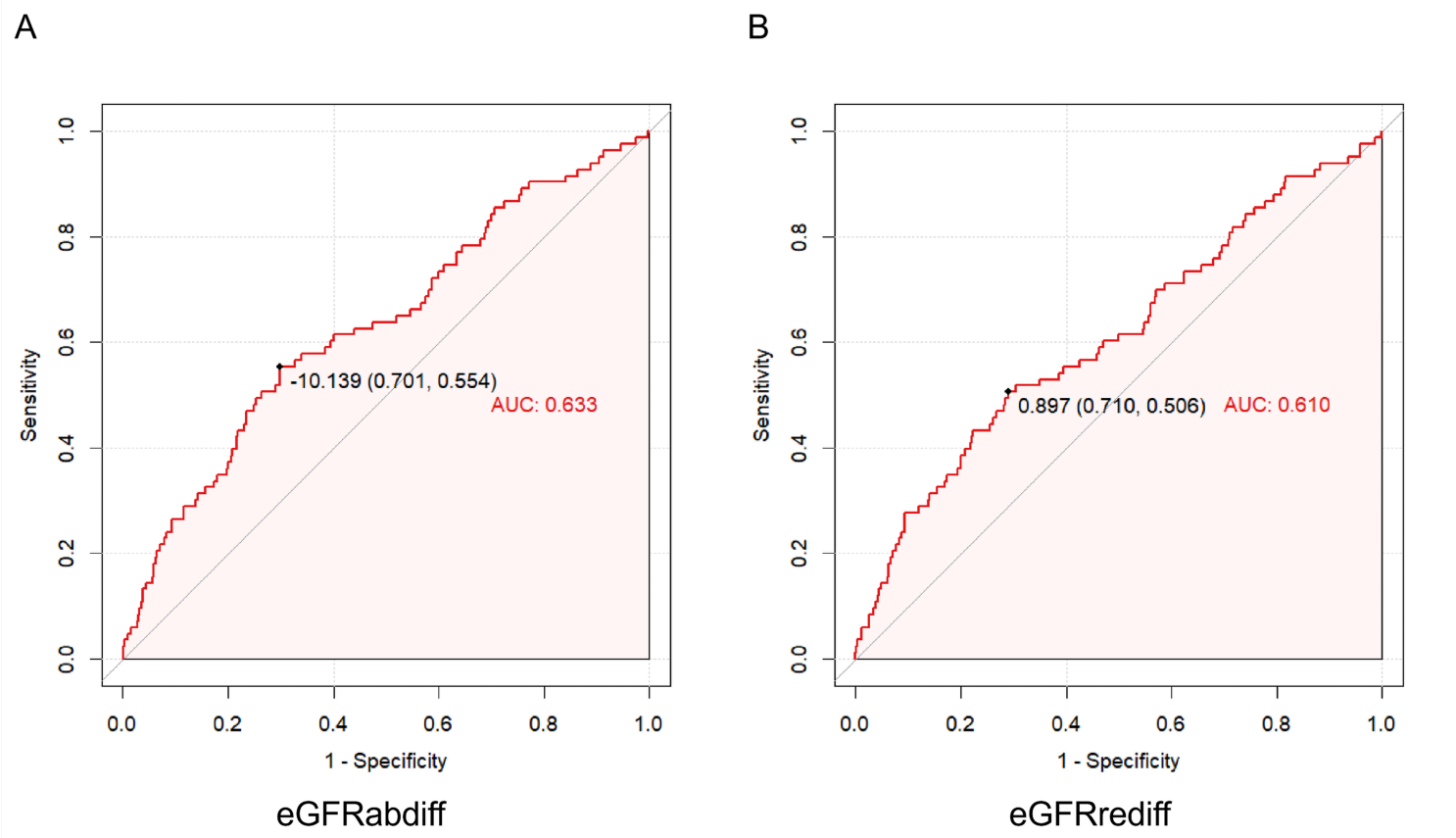


Figure 6

Performance of the eGFRabdiff/eGFRrediff for predicting rapid kidney function decline (RKFD). A) The receiver operating characteristic curve (ROC) analyses for eGFRabdiff in predicting RKFD. **B)** The ROC analyses for eGFRrediff in predicting RKFD.

Supplementary Files

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