Diabetology & Metabolic Syndrome

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Comparison of the correlation of creatinine- and cystatin C–Based estimated GFR and their differences with new-onset heart failure in a community-based population with type 2 diabetes

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Abstract

Aims This study aimed to investigate the impact of different estimated glomerular filtration rate (eGFR) values like cystatin C-based eGFR (eGFRcys), creatinine-based eGFR (eGFRcr), and their difference (eGFRdiff; eGFRcys -eGFRcr), on the incidence of heart failure (HF) in patients with type 2 diabetes(T2D).

Methods Being a prospective cohort study, it included 7,967 patients with T2D who underwent serum creatinine and cystatin C tests as part of the Kailuan Group's 6th annual health examination (2016). Subsequently, eGFRcys, eGFRcr, and eGFRdiff were calculated. Patients were categorized into three groups: negative (<-15 mL/min/1.73 m^2), midrange (-15 to 15 mL/min/1.73 m^2), and positive (> 15 mL/min/1.73 m^2) eGFRdiff groups, respectively. Furthermore, the relationship between the various eGFR measurements and new-onset HF were studied using Cox proportional hazards regression, and the potential improvement in predictive capability was evaluated by adding these eGFR metrics to established HF risk models.

Results Among 7967 participants with mean age of 60.51 years, there were 20.92% women and 79.08% men. At baseline, eGFRcys and eGFRcr values differed by more than 15 mL/min/1.73m^2 in 41.3% of participants. During a median follow-up period of 3.76 years, there were 172 (2.16%) new HF cases and 517 (6.49%) all-cause deaths. The cumulative incidence of HF in the midrange, negative, and positive eGFRdiff groups was 1.74%, 4.10%, and 0.61%, respectively ($p < 0.001$). In multivariable adjusted models, participants in the negative eGFRdiff group had higher risk of HF compared with the midrange eGFRdiff group (HR, 2.15; 95% CI, 1.57–2.94). Conversely, participants in the positive eGFRdiff group had lower risk for HF (HR, 0.40; 95% CI, 0.17–0.93). And each 15 mL/min/ 1.73 m^2 higher

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eGFRdiff was associated with 34% (HR, 0.66; 95% CI, 0.58 – 0.47)lower risk of incident HF. The predictive capacity for HF risk in diabetic individuals was enhanced by adding eGFRcys or eGFRdiff to established HF risk models, with eGFRcys showing more significant additional predictive value.

Conclusion These findings suggest that large differences between eGFRcys and eGFRcr were common in community-based population with T2D. Different eGFR metrics can independently predict HF incidence in patients with T2D. Additionally, metrics like eGFRcys and eGFRdiff provide significant predictive value for HF risks beyond traditional risk factors, with eGFRcys showing more pronounced benefits in such cases.

Keywords Stimated glomerular filtration rate, Heart failure, Type 2 diabetes, Serum creatinine, Cystatin C

Introduction

Heart failure (HF) is the terminal stage of several cardiovascular diseases. The incidence of HF is rising annually due to an aging population and the ongoing prevalence of metabolic risk factors like hypertension and diabetes [1]. In developed countries, the adult HF prevalence is approximately 1–2%, which can escalate up to 10% in those>70 years [2, 3]. In China, the adult HF prevalence increased from 0.9 to 1.3% in 2003 and 2012–2015, with approximately 5 million additional cases during this period [4, 5].Despite significant advances in HF treatment, its prognosis remains poor, with an approximately 50% 5-year mortality rate [6]. This underscores the importance of accurately identifying the high-risk populations for providing early targeted interventions to effectively prevent HF onset.

The glomerular filtration rate estimated by serum creatinine (eGFRcr) is the most accurate indicator for assessing renal function. Moreover, a decline in eGFRcr is an independent risk factor for predicting the onset, progression, and poor prognosis of HF [7–9]. Compared to serum creatinine, cystatin C remains unaffected by muscle mass, age, and gender [10, 11]. Therefore, a stronger and more linear association has been observed between eGFRcys decline and the risks of HF, cardiovascular disease, and mortality [12, 13]. However, discrepancies between eGFRcr and eGFRcys are common. The difference between eGFRcys and eGFRcr (eGFRdiff), a novel variable, has significant predictive value for incident HF in the general population and chronic kidney disease patients (CKD) [14, 15].

However, existing research has mainly focused on the general population and CKD individuals. The predictive value of different eGFR metrics based on cystatin C and serum creatinine for HF incidence in diabetic patients at high risk for HF and CKD has not yet been assessed. Therefore, we investigated the predictive value of different eGFR metrics for HF incidence in the population with type 2 diabetes(T2D) by using the Kailuan study data.

Materials and methods

Study cohort

Being a prospective cohort study, health examinations for active and retired Kailuan Group personnel were conducted every two years from June 2006 to October 2007 in 11 hospitals, including Kailuan General Hospital and its affiliated hospitals. Follow-up assessments included incident HF and mortality. In the 6th health examination in 2016, cystatin C was investigated in T2D patients. We selected T2D patients who participated in this health examination and underwent cystatin C investigations as our study subjects. The inclusion criteria were: (1) Those who participated in the 2016 annual health examination and met the diagnostic criteria for T2D; (2) Patients with the availability of primary research data, including cystatin C and serum creatinine, and (3) Those willing to participate and provide informed consent. The exclusion criteria were: (1) Patients with a history of HF before the health examination and (2) Those having valvular and congenital heart diseases, respectively.

Collection of general clinical data and laboratory investigations

Patient data like age, gender, personal history, disease history, and medication usage were obtained through face-to-face interviews. We measured height, weight, blood pressure, heart rate, and relevant biochemical indicators by following previously published methods [16]. Smoking was defined as averaging at least one cigarette per day>1 year or having quit smoking<1 year ago. Additionally, body mass index (BMI) was calculated as weight / height^2 (kg/m^2).

Calculation and grouping of eGFRcr and eGFRcys

We used the 2012 CKD Epidemiology Collaboration (CKD-EPI) cystatin C equation and 2021 race-free CKD-EPI equations to calculate eGFRcys and eGFRcr, respectively [10, 17], and eGFRdiff=eGFRcys- eGFRcr.

The subjects were divided into 3 groups according to eGFRdiff level: negative eGFRdiff group: lower than −15 mL/min/1.73 m^2, with eGFRcys lower than eGFRcr; mid-range eGFRdiff group: -15 to 15 mL/min/1.73 m^2, with eGFRcys similar to eGFRcr; positive eGFRdiff group: 15

mL/min/1.73 m^2 or greater, with eGFRcys higher than eGFRcr.

Diagnostic criteria.

T2D: The American Diabetes Association (ADA) Criteria for Diagnosis of Diabetes (2010) was referred [18].

1) History of T2D;

Or 2) Fasting blood glucose (FBG) ≥ 7.0 mmol/L;

Or 3) Two-hour blood glucose of ≥ 11.1 mmol/L in random plasma glucose test or oral glucose tolerance test;

Or 4) Hemoglobin A1c (HbA1c) ≥ 6.5%(47.5 mmol/mol).

HF: Chinese Guidelines for the Diagnosis and Treatment of Chronic Heart Failure (2018) was referred [19].

1) Symptoms and signs of HF, manifested as shortness of breath, fatigue, palpitations, fluid retention, as well as New York Heart Association (NYHA) heart function grade II and above;
2) Modified Simpson's method: the left ventricular ejection fraction < 50% measured by echocardiography;
3) Plasma N-terminal pro-B-type natriuretic peptide ≥ 125 ng/L.

The diagnosis must meet conditions (1) as well as at least one of conditions (2) and (3).

Follow-up and endpoint events

After the completion of the 6th health examination, that is, the starting point of follow-up, trained medical staff reviewed the inpatient diagnosis and recorded the endpoint events of the participants in the Affiliated Hospitals of Kailuan Group and the Designated Hospitals for Medical and Health Insurance of China every year. The end-point events ware defined as HF during the follow-up. The time of the first event was considered as the endpoint for those with >2 events, and the final follow-up date for those without HF was December 31, 2020. All diagnoses were confirmed by professional physicians according to the inpatient medical records.

Statistical analysis

Normally distributed measurement data were expressed as mean+sd. Multiple pairwise-comparison between different groups was conducted using a one-way analysis of variance. The least significant difference (LSD) test and Dunnett's T3 test were used for evaluating the homogeneity of variance and heterogeneity of variance, respectively. Non-normally distributed data were presented as median and centiles (25th and 75th), while the comparison between the groups was performed using the Kruskal-Wallis rank sum test. Enumeration data were presented as frequency and percentage (n, %), and comparisons between groups were performed by the chi-square test. The Kaplan-Meier method was used to calculate the incidence of HF events in each group and the overall population, and a log-rank test was adopted to compare the difference in the incidence of HF.

eGFRcys and eGFRcr were categorized into the following four groups (ml/min/1.73m^2): ≥90, 60–89, 45–59, ≤45.The eGFRdiff was assessed as a categorical and continuous variable. The effect of different eGFR groups and each 15 increases in eGFR on new-onset HF was studied using a multivariate Cox stepwise regression model. Model 1 unadjusted. Model 2 was adjusted for age and sex. Model 3 was further adjusted for SBP, BMI, TC, HbA1c, hemoglobin, smoking, anti-diabetic treatment, antihypertensive treatment, MI, and atrial fibrillation.

In addition, based on Model 1(age, sex), Model 2 (ARIC-sans-BNP model: age, sex, HR, BMI, SBP, HbA1c, hypertension and MI), C-Statistic, net reclassification index (NRI), and integrated discrimination improvement (IDI) were used to assess the ability of different eGFR to improve HF prediction models, respectively.

In order to avoid the influence of MI and hypertension on HF, sensitivity analysis was performed after excluding the above population.

SAS version 9.4 was used for the analysis (SAS Institute, Cary, NC, USA). All statistical analyses were double-tailed, with statistical significance set at $P<0.05$.

Results

We included 7,967 participants who met the diagnostic criteria for T2D and underwent the 6th health examination as well as cystatin C and serum creatinine investigations.

Baseline characteristics

At baseline, the participants' average age was 60.51±10.03 years, with 6,300 (79.08%) males. The average systolic blood pressure (SBP) and HbA1c were 147.27±20.58 mmHg and 7.57±1.66%, respectively. The eGFRcys, eGFRcr, and eGFRdiff were 88.77±22.73 mL/min*1.73 m^2, 93.41±15.43 mL/min*1.73 m^2, and −4.59±18.72 mL/min*1.73 m^2, respectively. The eGFR evaluated by serum creatinine and cystatin C showed inconsistent results, with eGFRcys values generally being lower than eGFRcr.

More than half of participants had a baseline eGFRdiff between −15 and 15 mL/min/1.73 m^2 (4679 participants [58.7%]; midrange eGFRdiff); 2280 participants (28.6%) had an eGFRdiff less than −15 mL/min/1.73 m^2 (negative eGFRdiff), and 1008 participants (12.6%) had an eGFRdiff of 15 mL/min/1.73 m^2 or greater (positive eGFRdiff). Compared with the other 2 eGFRdiff groups, participants in the negative eGFRdiff group were older, more often female, with higher baseline SBP, BMI, uACR and more

anti-diabetic and antihypertensive treatment (Table 1; Fig. 1).

Cumulative incidence of HF events by eGFRdiff groups

Following a median follow-up time of 3.76±0.72 years, 172 patients (2.16%) developed HF, and 517 patients (6.49%) died of all-cause mortality, respectively. The cumulative HF incidence in the midrange, negative, and positive eGFRdiff groups was 1.74%, 4.10%, and 0.61%, respectively. A log-rank test showed a significant difference in the cumulative incidence between the three groups (Fig. 2).

Multivariate cox regression analysis of the relationship between eGFR and new-onset HF

Using HF occurrence and grouping by different eGFR measures as the dependent and independent variables, the multivariate Cox regression analysis made adjustments for all traditional cardiovascular disease risk factors. The results showed that compared to the normal eGFRcr group, the HF risk increased progressively with reducing eGFRcr (HR values 1.84–3.61, all $p<0.05$). Similarly, the HF risk increased progressively with decreasing eGFRcys, compared to the normal eGFRcys group (HR values 3.21–10.84, all $p<0.05$). Moreover, the negative eGFRdiff group displayed a significantly increased risk of HF (HR 2.15; 95% CI: 1.57–2.94), while the positive eGFRdiff group had a significantly reduced HF risk when compared to the midrange eGFRdiff group (HR 0.40; 95% CI: 0.17–0.93). And each 15 mL/min/ 1.73 m^2 higher eGFRdiff was associated with 34% (HR, 0.66; 95% CI, 0.58−0.47)lower risk of incident HF.

Table 1 Baseline characteristics overall and by eGFRdiff categories in participants

	overall 7967	<-15 ml/min/1.73m^2 2280	-15 ~ 15 ml/min/1.73m^2 4679	≥ 15 ml/min/1.73m^2 1008	*P* value
Male, n (%)	6300(79.08)	1728(75.79)	3723(79.57)	849(84.23)	< 0.001
Age, years	60.51 ± 10.03	62.44 ± 10.06	59.61 ± 10.12	60.31 ± 8.88	< 0.001
eGFRcr, ml/min/1.73m^2	93.41 ± 15.43	93.63 ± 14.92	94.84 ± 15.66	86.26 ± 13.45	< 0.001
eGFRcys, ml/min/1.73m^2	88.77 ± 22.73	67.96 ± 16.92	93.69 ± 17.74	113.03 ± 17.15	< 0.001
SBP, mmHg	147.27 ± 20.58	149.47 ± 21.34	146.51 ± 20.21	145.81 ± 20.19	< 0.001
DBP, mmHg	82.53 ± 10.81	82.52 ± 11.35	82.56 ± 10.64	82.40 ± 10.49	0.928
HR, bpm	79.33 ± 12.74	80.05 ± 13.26	79.09 ± 12.43	78.38 ± 12.74	0.040
BMI, kg/mm^2	25.83 ± 3.47	26.13 ± 3.57	25.79 ± 3.42	25.28 ± 3.36	< 0.001
Waist circumference, cm	88.11 ± 7.16	88.60 ± 7.38	87.98 ± 7.04	87.55 ± 7.15	0.093
TC, mmol/L	5.52 ± 1.15	5.56 ± 1.14	5.52 ± 1.14	5.44 ± 1.20	0.026
HDL-C*, mmol/L	1.39(1.19 ~ 1.63)	1.36(1.15 ~ 1.60)	1.40(1.21 ~ 1.65)	1.40(1.21 ~ 1.68)	0.091
LDL-C, mmol/L	3.25 ± 0.96	3.16 ± 0.88	3.24 ± 0.95	3.48 ± 1.11	< 0.001
FBG, mmol/L	9.08 ± 3.18	9.06 ± 3.15	9.07 ± 3.15	9.03 ± 3.30	0.776
HbA1c, %	7.57 ± 1.66	7.60 ± 1.60	7.56 ± 1.68	7.50 ± 1.67	0.231
Hemoglobin, g/L	151.27 ± 63.57	150.20 ± 52.45	151.31 ± 69.22	153.57 ± 59.04	0.381
hsCRP *, mg/L	1.14(0.39 ~ 2.81)	1.60(0.59 ~ 3.79)	1.03(0.35 ~ 2.57)	0.83(0.30 ~ 2.18)	0.264
Smoking, n (%)	1361(17.08)	412(18.07)	820(17.53)	129(12.80)	0.001
Hypertension, n (%)	4116(51.66)	2399(51.27)	1191(52.24)	526(52.18)	0.706
Atrial fibrillation, n (%)	93(1.46)	31(1.81)	54(1.42)	8(0.93)	0.023
MI, n (%)	168(2.38)	48(2.11)	96(2.05)	24(2.38)	0.804
uACR, mg/mmol					< 0.001
< 3	5270(66.15)	1341(58.82)	3176(67.88)	753(74.70)	
3–30	2207(27.70)	720(31.58)	1257(26.86)	230(22.82)	
≥ 30	490(6.15)	219(9.61)	246(5.26)	25(2.48)	
Anti-diabetic treatment, n (%)	3283(41.21)	1008(44.21)	1901(40.63)	374(37.10)	0.003
Insulin, n (%)	1349(16.93)	445(19.52)	751(16.05)	153(15.18)	< 0.001
Oral medicine, n (%)	2321(29.13)	688(30.18)	1358(29.07)	275(27.28)	0.234
Antihypertensive treatment, n (%)	1100(13.81)	181(7.94)	248(5.3)	33(3.27)	< 0.001
ACEI/ARB	120(1.51)	46(2.02)	69(1.47)	5(0.05)	< 0.001
Beta-blocker, n (%)	86(1.08)	25(1.10)	55(1.18)	8(1.44)	0.721
Calcium channel blocker, n (%)	309(3.88)	14(3.37)	163(3.48)	30(8.50)	< 0.001
Diuretic, n (%)	69(0.87)	48(0.78)	43(1.65)	7(1.26)	0.001

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; TC: Total cholesterol; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; FBG: Fasting blood glucose; HbA1c: Hemoglobin A1c; hs-CRP: High sensitivity C-reactive protein; MI: Myocardial infarction; uACR: urine albumin-to-urine creatinine ratio; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; * expressed in M(Q1 ~ Q3)

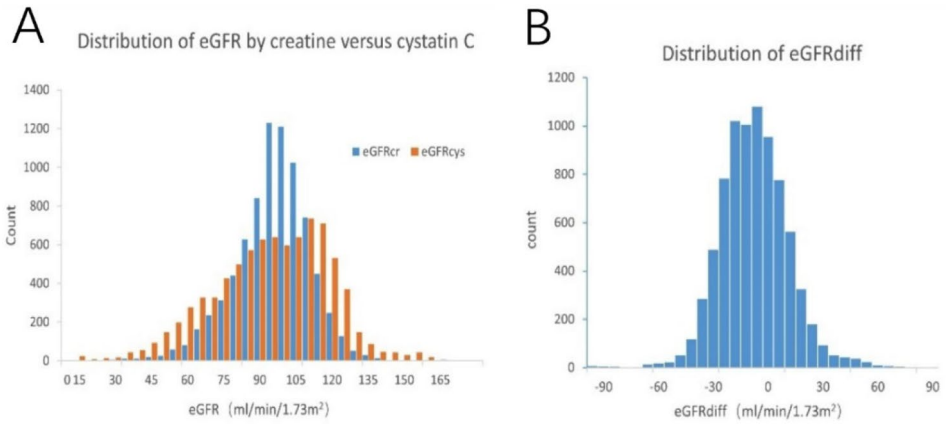


Fig. 1 **A**: Distribution of eGFRcr and eGFRcys in the total population; **B**: Distribution of eGFRdiff in the total population

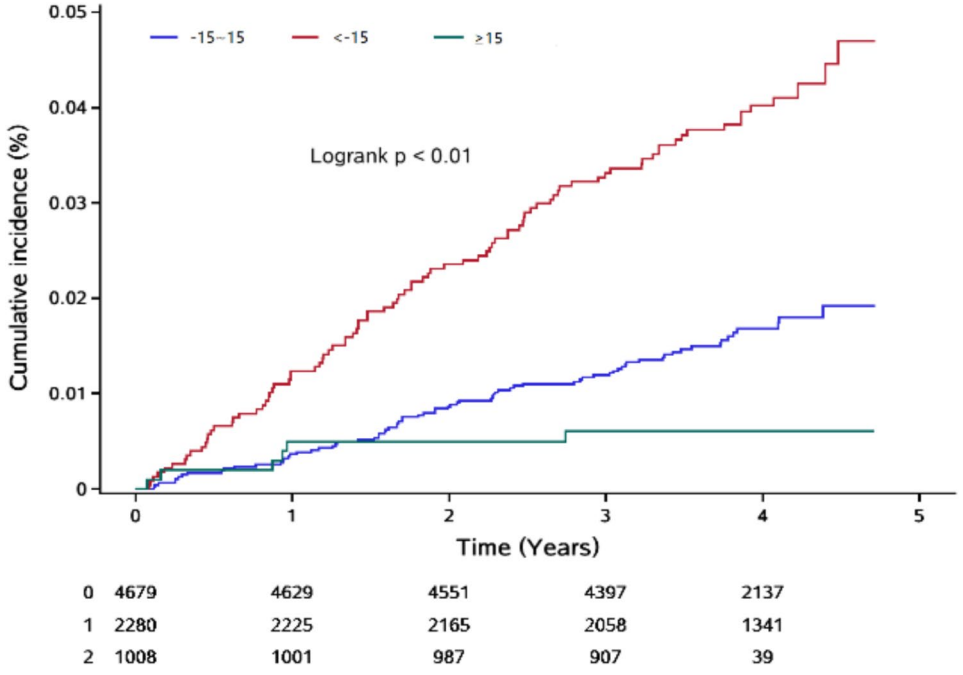


Fig. 2 Incidence of heart failure by eGFRdiff category: lower than – 15 mL/min/1.73 m^2, -15 to 15 mL/min/1.73 m^2, 15 mL/min/1.73 m^2 or greater. $p < 0.01$ for differences among curves using the log-rank test

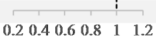
Additional predictive value of eGFR for established HF risk models

In order to explore whether adding different eGFR measures to established HF risk models could improve predictive performance, we added continuous eGFRcr, eGFRcys, and eGFRdiff variables as well as grouped eGFRdiff to model 1 (age and sex) and model 2 (ARIC-sans-BNP model [20]), respectively. Addition of eGFRcr to the ARIC-sans-BNP model led to negligible improvement, eGFRcys and eGFRdiff outperformed eGFRcr in HF prediction beyond conventional risk factors, and the best model was the addition of eGFRcys to ARIC-sans-BNP model (Table 3).

Subgroup analysis

No significant interactions were observed between eGFRdiff groups and age, sex, SBP, HbA1c, BMI, uACR, hypertension, or MI status on the impact of HF ($p > 0.05$). Subgroup analysis results showed that HF risk decreased as eGFRdiff increased in all subgroups, consistent with the overall population results.

Subgroup	NO.	Events	Incidence Rate	eGFRdiff(mean±sd)	HR(95%CI)	*P* for interaction
Age						0.765
<65 Years	5547	89	4.19	-4.15±18.83		
>65 Years	2420	83	9.45	-5.75±18.56		
Sex						0.598
Male	6300	137	5.75	-3.78±18.91		
Female	1667	35	5.66	-7.87±17.84		
SBP						0.582
<140 mmHg	3009	44	3.83	-3.78±19.15		
>140 mmHg	4958	128	6.91	-5.15±18.51		
HbA1c						0.27
<7%	3454	53	4.08	-4.21±19.13		
>7%	4513	119	6.99	-4.96±18.47		
BMI						0.701
<24 kg/m^2	2351	45	5.16	-3.07±19.31		
24~28 kg/m^2	3809	74	5.1	-4.70±18.44		
>28 kg/m^2	1807	53	7.82	-6.55±18.55		
uACR						0.307
<3 mg/mmol	5270	52	2.58	-3.06±18.87		
3~30 mg/mmol	2207	66	8.06	-6.76±17.91		
>30 mg/mmol	490	54	31.56	-12.01±18.64		
Hypertension						0.115
Yes	4116	98	6.36	-4.48±18.23		
No	3851	74	5.07	-4.80±19.31		
MI						0.675
Yes	168	156	26.88	-5.23±18.75		
No	7799	16	5.3	-4.62±19.30		



Sensitivity analysis

In the primary study, the participants were divided into three groups based on eGFRdiff (in mL/min/1.73 m^2). The result display that eGFRdiff was still significantly associated with incident HF when the participants were divided into quartiles of eGFRdiff in the further study (Additional file 1:Table S1). Even after excluding individuals with hypertension or MI at baseline, the relationship persisted(Additional file 1:Table S2).

Discussion

This study found that both eGFRcr and eGFRcys can independently predict HF incidence in individuals with T2D; however, common discrepancies have been observed between these two measures. Additionally, eGFRdiff, defined as eGFRcys−eGFRcr, is also an independent predictor of incident HF. Our results showed that the negative eGFRdiff group displayed a significantly increased HF risk, while the positive eGFRdiff group had a lower HF risk, compared to the midrange eGFRdiff group. However, eGFRcys exhibits superior additional predictive value for incident HF compared to eGFRdiff and eGFRcr in population with T2D, beyond traditional heart failure risk factors.

Our population with T2D revealed poorly managed metabolic indicators like blood pressure, blood glucose, and BMI. Many patients with T2D showed significant discrepancies between eGFRcr and eGFRcys, consistent with previous studies. Subsequently, our study also confirmed the independent predictive value of both these measures for incident HF, i.e., HF risk gradually increases as eGFRcr and eGFRcys decrease. For the same degree of decline in eGFRcys and eGFRcr, the risk of GFRcys-predicted incident HF was higher than that predicted by eGFRcr. This finding corroborates the results of Chen et al. [21] in the general population. Since cystatin C is less influenced by other factors compared to creatinine, we suggest that eGFRcys might more accurately reflect glomerular filtration rate and can identify high-risk individuals for incident HF better than eGFRcr.

Due to individual discrepancies between eGFRcys and eGFRcr, recent studies have confirmed the associations of eGFRdiff with cognitive decline [22], kidney failure [23], atrial fibrillation [24], and all-cause mortality [25]. In many studies on the general population [21], hypertensive population [26], and CKD patients [27], 23.8%, 29%, and 34% of subjects had an absolute eGFRdiff>15, respectively. Moreover, in our type 2 diabetes population, the proportion of patients with an absolute eGFRdiff>15 was higher (41.2%), suggesting more significant discrepancies between eGFRcys and eGFRcr in Chinese patients with T2D. However, further research is needed to confirm the distribution and potential clinical significance of individual eGFRdiff in this cohort due to the paucity of relevant data.

After adjusting for relevant influencing factors, regression analysis results showed that compared to the midrange eGFRdiff group, the negative eGFRdiff group displayed a 115% increased HF risk (HR=2.15; 95% CI: 1.57–2.94), while the positive eGFRdiff group revealed a 60% decreased HF risk (HR=2.15;95%CI:1.57–2.94). Thus, for every 15 mL/min/1.73 m^2 eGFRdiff increase, the HF risk was reduced by 34%. In the CRIC baseline study [27], the increased and decreased risk of HF in the

Table 2 Hazard ratios (HR) and 95% confidence intervals of different eGFR for HF

	No.	Median Follow-up (years)	Incident Heart Failure(%)	incidence Rate (/1000 person-years)	Model1	Model 2	Model 3[#]
eGFRcr							
> 90	5133	4.05	66(1.29)	3.29	1	1	1
60–90	2618	3.66	85(3.25)	9.19	2.83(2.05, 3.92)	1.88(1.31, 2.71)	1.84(1.18, 2.81)
45 ~ 60	165	3.45	14(8.48)	26.34	8.11(4.55, 14.47)	4.26(2.25, 8.06)	1.67(0.67, 4.18)
< 45	51	3.26	7(13.73)	48.56	14.91(6.83, 32.54)	9.41(4.21, 21.06)	3.61(1.27, 10.31)
eGFRcys							
> 90	4005	3.80	27(0.67)	1.77	1	1	1
60–90	3088	3.97	81(2.62)	6.91	3.89(2.52, 6.02)	3.18(2.03, 4.99)	3.21(1.89, 5.45)
45 ~ 60	620	3.76	35(5.65)	15.75	8.88(2.52, 6.02)	6.14(3.56, 10.59)	5.39(2.83, 10.28)
< 45	254	3.74	29(11.42)	34.30	19.32(11.43, 32.64)	13.20(7.45, 23.38)	10.84(5.32, 22.07)
eGFRdiff							
<-15	4703	4.11	76(3.22)	10.35	2.45(1.81, 3.34)	2.07(1.52, 2.83)	2.15(1.57, 2.94)
-15 ~ 15	2159	3.85	90(1.18)	4.22	1	1	1
≥ 15	1015	3.47	6(10.79)	1.74	0.41(0.18, 0.94)	0.40(0.18, 0.92)	0.40(0.17, 0.93)
eGFRdiff Per + 15	7967	3.83	172(2.13)	5.73	0.67(0.60, 0.75)	0.61(0.53, 0.71)	0.66(0.58, 0.74)

Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: in the eGFRcr and eGFRcys models, adjusted for age, sex, SBP, BMI, TC, HbA1c, hemoglobin, smoking, anti-diabetic treatment, antihypertensive treatment, MI and atrial fibrillation, eGFRdiff models adjusted for baseline eGFRcr based on the above influencing factors. eGFR in mL/min/1.73 m^2

negative and positive eGFRdiff groups was not statistically significant, compared to the midrange eGFRdiff group. However, in time-updated analyses, the negative eGFRdiff group showed enhanced HF risk (HR = 1.99; 95% CI: 1.39–2.86), and the positive eGFRdiff group displayed reduced lower HF risk (HR = 0.67; 95% CI: 0.49–0.91) compared to midrange eGFRdiff. Due to such consistent results, the impact of the discrepancy between eGFRcys and eGFRcr on new-onset HF in the diabetic population was more pronounced than in the CKD population. This may be related to the baseline differences in eGFRcr and eGFRcys levels between the two populations; however, further research is needed to verify this finding.

Because 15 mL/min/1.73 m^2 represents a clinically meaningful difference in eGFR that also distinguishes CKD stages, eGFRdiff was categorized based on a cut-off point of 15. In the sensitivity analysis, our results (Supplemental Table S1), which are in line with the conclusions of Carrero et al. [14], were identical even after grouping participants into eGFRdiff-based quartiles and repeating the Cox analysis with each additional standard deviation. Since hypertension and myocardial infarction are two major causes of HF, we performed a sensitivity analysis excluding these two groups to minimize their impact. Nevertheless, the results remained consistent (Supplementary Table S1). Due to gender imbalance and poor metabolic control in this population, we repeated Cox regression in different subgroups and obtained consistent results across all subgroups.

We not only confirmed that different eGFR measures can independently predict HF risk in type 2 diabetes patients, but also found that adding eGFRcr, eGFRcys, and eGFRdiff to established HF risk prediction models improves their predictive ability; however, eGFRcys provides superior additional predictive value compared to eGFRdiff. To our knowledge, this is the first study to evaluate how various eGFR measures in a type 2 diabetes population can improve traditional HF prediction models. To date, only Lees et al. [25] have confirmed that eGFRcys greatly improves cardiovascular disease prediction models than eGFRdiff in the general population.

No conclusive evidence is available regarding the mechanism underlying the association between eGFRdiff and incident HF. A possible explanation suggests the presence of "Pore Shrinkage Syndrome," in which the glomerular basement membrane's pore size decreases. Due to the larger molecular weight of cystatin C than creatinine, glomerular filtration of cystatin C decreases while creatinine filtration is unaffected. As a result, serum cystatin C levels increase and creatinine levels remain unchanged, thereby causing reduced eGFRcys compared to eGFRcr [28]. Subsequently, elevated pro-atherogenic protein levels in such patients could lead to the occurrence and development of cardiovascular diseases [29].

Table 3 The additional predictive value of different eGFR for HF

	C-Statistic	*P*-value	NRI	*P*-value	IDI	*P*-value
Model 1	0.746(0.708, 0.783)	-	ref	-	ref	-
Model 1 + eGFRcr	0.755(0.719, 0.792)	0.211	0.152(0.003, 0.195)	< 0.001	0.004(-0.001, 0.013)	0.364
Model 1 + eGFRcys	0.784(0.749, 0.820)	0.002	0.171(0.014, 0.288)	< 0.001	0.012(0.001, 0.036)	< 0.001
Model 1 + eGFRdiff	0.773(0.737, 0.810)	0.010	0.147(-0.025, 0.269)	0.182	0.008(0.001, 0.015)	< 0.001
Model 1 + eGFRdiff group	0.747(0.709, 0.784)	0.750	0.162(-0.075, 0.209)	0.182	0.001(0.000, 0.002)	< 0.001
Model 2	0.725(0.680, 0.771)	-	ref	-	ref	-
Model 2 + eGFRcr	0.742(0.696, 0.789)	0.209	0.197(0.030, 0.292)	< 0.001	0.005(0.001, 0.009)	< 0.001
Model 2 + eGFRcys	0.783(0.735, 0.831)	0.005	0.200(0.023, 0.213)	< 0.001	0.012(0.001, 0.019)	< 0.001
Model 2 + eGFRdiff	0.766(0.719, 0.813)	0.010	0.084(-0.010, 0.182)	0.364	0.005(-0.001, 0.009)	0.182
Model 2 + eGFRdiff group	0.725(0.679, 0.771)	0.730	0.162(-0.129, 0.233)	0.364	0.000(0.000, 0.001)	0.182

Model 1: age, sex; Model 2 (ARIC-sans-BNP model): age, sex, HR, BMI, SBP, HbA1c, hypertension and MI. Abbreviation: NRI: net reclassification improvement; IDI: integrated discrimination improvement

Another possible explanation is "sarcopenia," as diabetic patients are more prone to sarcopenia compared to those with normal blood glucose levels [30]. Reduced muscle mass causes lower creatinine, higher eGFRcr, and significantly negative eGFRdiff values, respectively [31]. Thus, sarcopenia and HF share common pathophysiological pathways. A muscle metaboreceptor (ergoreceptor) contributes to the hemodynamic and autonomic responses to exercise by controlling the sympathetic, hypertensive, and hyperpnoic responses to exercise and may have a role in the vicious cycle of sympathetic activation, which is considered one of the central elements of HF pathogenesis [32, 33].

Our study had some limitations. Firstly, HF events were identified based on hospitalization diagnosis codes, which may vary across hospitals and exclude non-hospitalized HF patients. Secondly, our observational study design could not establish causality. Lastly, baseline serum creatinine and cystatin C measurements were taken only once and might have caused misclassification bias. However, the large sample size, a stable cohort, detailed influencing factors, and our robust results lend high credibility to our conclusions.

Conclusion

This study confirmed the independent predictive values of different eGFR metrics for HF risk in patients with T2D. Specifically, eGFRcys demonstrates greater sensitivity in predicting HF risk and can significantly enhance the predictive capability of traditional HF models. Our findings support a comprehensive use of cystatin C to estimate eGFR clinically, thereby emphasizing the need to assess eGFRcys rather than relying solely on eGFRcr or eGFRdiff values for HF risk stratification.

Additional file 1: Table S1. The effect of eGFRdiff on heart failure by quartile and each SD increase(Sensitivity analysis). Table S2. Hazard ratios (HR) and 95% Confidence intervals of different eGFRcr for heart failure (Sensitivity analysis).

Abbreviations

HF	Heart failure
T2D	Type 2 diabetes
eGFR	Estimated glomerular filtration rate
NRI	Net reclassification improvement
IDI	Integrated discrimination improvement
SD	Standard deviation
BMI	Body mass index
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
ADA	American Diabetes Association
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
HR	Heart rate
TC	Total cholesterol
HDL-C	High density lipoprotein-cholesterol
LDL-C	Low density lipoprotein-cholesterol
FBG	Fasting blood glucose
HbA1c	Hemoglobin A1c
hs-CRP	High sensitivity C-reactive protein
MI	Myocardial infarction
uACR	urine albumin-to-urine creatinine ratio
ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
WATCH-DM	Age, sex, BMI, SBP, DBP, FPG, serum creatinine, HDL cholesterol, MI

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-024-01461-2.

Supplementary Material 1

Acknowledgements

We thank all the survey teams of the Kailuan Study Group for their contribution and the study participants who contributed their information.

Author contributions

DS wrote the manuscript. DS, WS and JT conducted the data extraction and data analysis. DS, JT, GW and QZ did the statistical analyses. SW and WG reviewed and edited the manuscript. All authors read and approved the final manuscript.

Funding

No funding.

Data availability

No datasets were generated or analysed during the current study.

Declaration

Ethics approval and consent participate
The study protocol was approved by the Ethics Committee of Kailuan General Hospital. All participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 21 July 2024 / Accepted: 30 August 2024
Published online: 12 September 2024

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