Clinical and Experimental Nephrology (2022) 26:1180–1193
https://doi.org/10.1007/s10157-022-02262-5

ORIGINAL ARTICLE

Prediction of cardiovascular outcome by estimated glomerular filtration rate among high-risk patients: a Thai nationwide cohort study

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Received: 6 December 2021 / Accepted: 3 August 2022 / Published online: 23 August 2022

Abstract

Background Decline of estimated glomerular filtration rate (eGFR) is associated with increased cardiovascular (CV) morbidity and mortality, but the predictive value of different eGFR on CV outcomes is limited in Southeast Asian populations.
Aims We aimed to stratify CV outcomes according to renal function among Thai patients with high atherosclerosis risk.
Methods We performed a secondary analysis in a 5-year national cohort entitled "CORE-Thailand study." Subjects were classified in 6 groups according to baseline kidney function: group I, eGFR ≥ 90; group II, eGFR 60–89; group IIIa, eGFR 45–59; group IIIb, eGFR 30–44; group IV, eGFR 15–29; group V, eGFR < 15 ml/min/1.73 m^2 or receiving renal replacement therapy. The primary outcome was 4-point major adverse cardiovascular events (MACE). Secondary outcomes included all-cause mortality, CV mortality, hospitalization for heart failure, nonfatal myocardial infarction, and nonfatal stroke.
Results A total of 6376 subjects (3467 men and 2909 women) were categorized in 6 groups. After adjusting covariates in the Cox proportional hazards model, compared to group I, subjects in groups II–V had a 1.65-fold, 2.17-fold, 2.67-fold, 4.24-fold, and 4.87-fold risk for 4-point MACE, respectively, with statistical significance at $P < 0.05$ in all groups. Kaplan–Meier analysis illustrated stepwise lower survivals from 4-point MACE following the groups with lower baseline eGFR (log-rank test with $P < 0.001$). All secondary outcomes showed similar trends as the primary outcome, except nonfatal stroke.
Conclusion Lower baseline kidney function was independently associated with increased risk of CV events and all-cause mortality in Thai populations at high CV risk.

Keywords Glomerular filtration rate · Chronic kidney disease · Atherosclerosis · High cardiovascular risk

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Introduction

Advanced chronic kidney disease (CKD) with and without dialysis exhibits extremely high mortality rates and over one half of these deaths are attributable to cardiovascular (CV) events [1]. Early kidney disease has a major effect on global morbidity and mortality [2]. Early estimated glomerular filtration rate (eGFR) decline and albuminuria are associated with an increased risk for CV disease and are risk multipliers among patients with multiple comorbid diseases [3, 4]. Further understanding of CV risks and outcomes of patients with mild kidney impairment is necessary.

CKD is regarded as a coronary heart disease risk equivalent and CKD reveals a risk of coronary events similar to those with previous myocardial infarction [5]. Although both CKD and CV diseases share common traditional risk factors, decreased renal function is independently associated with increased CV events. This phenomenon could be seen at early stages of kidney impairment until late stages in both general and high CV risk populations [6, 7]. Further, meta-analysis in settings of heart failure confirmed that mortality worsened incrementally across the range of kidney function [8]. Conflicting evidence exists concerning whether mild to moderate kidney impairment was an independent risk factor for CV disease in the general population [9]. Several literature reports provided evidence of mild kidney impairment and the risk for subsequent CV events among patients having pre-existing vascular disease or high CV risk [10, 11]. Evidence in Southeast Asian populations with high CV risk remains limited. We analyzed data from the prospective cohort study in CORE-Thailand project to estimate the impact of GFR on CV outcomes and mortality after adjusting for other CV risk among Thai patients with high-risk CV.

Materials and methods

We performed a secondary analysis of data collected from the CORE-Thailand study, which was a multicenter prospective cohort of patients with high cardiovascular risks across Thailand. Twenty-five secondary to tertiary care centers participated in this cohort. The enrollment started from April 2011 to March 2014. The inclusion criteria were as follows: age 45 years or older, having at least three CV risk factors or documented CV diseases. The exclusion criteria were as follows: missing data on baseline serum creatinine or eGFR, having a history of CV events in the past three months, aortic aneurysm needed for surgery, participating in a blinded study, limited life expectancy less than 3 years from non-CV diseases or difficulty in obtaining follow-up appointments.

Definitions

The CV risk factors consisted of male aged 55 years or older, female aged 65 years or older, diabetes (type 1 or type 2 diabetes mellitus), impaired fasting glucose (fasting plasma glucose between 100 to 125 mg/dL), hypertension (systolic blood pressure (BP) $\geq$ 140 mmHg or diastolic BP $\geq$ 90 mmHg), dyslipidemia (total cholesterol > 200 mg/dL or low density lipoprotein (LDL) > 130 mg/dL or triglycerides > 150 mg/dL or high-density lipoprotein (HDL) < 40 mg/dL), CKD (estimated GFR 15–60 mL/min/1.73 m^2 or persistent albuminuria over past three months), currently smoking (at least one cigarette daily), or a family history of premature coronary artery disease (myocardial infarction (MI) or coronary angioplasty/coronary artery bypass surgery before 55 years of age in male first-degree relative or before 65 years of age in female first-degree relative).

Documented CV diseases included coronary artery disease (CAD), cerebrovascular disease (CVD) or peripheral artery disease (PAD). CAD consisted of one of the following: a history of chronic stable angina, unstable angina, myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery. CVD consisted of one of the following: a history of transient ischemic attack, ischemic stroke, carotid stenting or endarterectomy. PAD consisted of one of the following: a history of claudication with ankle-brachial index less than 0.9, aortic dissection, aortic surgery, peripheral artery angioplasty/stenting/bypass graft or amputation of ischemic limbs.

Data collection

Demographic data, a history of smoking and exercise, a family history of premature CAD, underlying diseases and ongoing medications were reviewed at baseline. We also collected data of physical and laboratory examination, including body mass index (BMI), waist circumference, BP, left ventricular ejection fraction (LVEF), serum creatinine, total cholesterol, HDL, LDL, triglycerides, fasting plasma glucose, hemoglobin A1c (HbA1c) and dipstick urine protein.

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate estimated GFR. Subjects were stratified in six groups according to estimated GFR: group I, eGFR at least 90 ml/min/1.73 m^2; group II, eGFR between 60 and 89 ml/min/1.73 m^2; group IIIa, eGFR between 45 and 59 ml/min/1.73 m^2; group IIIb, eGFR between 30 and 44 ml/min/1.73 m^2; group IV, eGFR between 15 and 29 ml/min/1.73 m^2; group V, eGFR less than 15 ml/min/1.73 m^2 or receiving renal replacement therapy, including hemodialysis, peritoneal dialysis or kidney transplant.

Outcomes

Cardiovascular events and mortality were prospectively recorded for five years after the enrollment. Data was collected using a standardized case record form at each hospital, then forwarded to the data management group. The data management group performed quality data assessments before data analysis. The annual site data monitoring was randomly performed. The primary and secondary outcomes were expressed as the HRs and 95% CI according to estimated GFR groups. We focused on 4-point major adverse cardiovascular events (MACE) as the primary outcome. The secondary outcomes included all-cause mortality, CV mortality, hospitalization for heart failure (HF), nonfatal MI and nonfatal stroke. The 4-point MACE is a composite of nonfatal MI, nonfatal stroke, hospitalization for heart failure or CV mortality.

Statistical analysis

Continuous and categorical data were presented in mean with standard deviation, and count with a percentage in columns, respectively. The ANOVA and Chi-square test were performed to compare mean and counts between groups, respectively. For each outcome, we compared the number of events using Chi-square test and analyzed the incidence rate with 95% confidence intervals (CI). Comparisons between groups are reported as hazard ratios (HR) with corresponding 95% CIs. Mixed-effects generalized linear model was performed for repeated data analysis in CV events and reported as risk ratios with 95% CIs. The multivariable model included factors at baseline for age, sex, BMI, diabetes, hypertension, dyslipidemia, CAD, CVD, PAD, family history of premature atherosclerosis, history of smoking, regular exercise, aspirin, ACEI/ARBs, statin, insulin and metformin. Sensitivity analysis was performed by including either LVEF or urine protein dipstick to the multivariable model. Subgroup analysis was classified regarding sex, diabetes status and BMI. Kaplan–Meier analysis and log-rank statistics were used to analyze outcomes and to compare survival and differences among the six groups according to estimated GFR levels. All tests performed were two-tailed and $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS 26.0 and STATA/MP 16.0.

Results

Baseline characteristics

A total of 6376 subjects (3467 men and 2909 women) were enrolled and categorized in six groups according to eGFR. Each group had mean eGFR for 98.84 ± 6.66, 74.31 ± 8.68, 52.65 ± 4.31, 38.35 ± 4.23, 23.76 ± 4.14 and 12.97 ± 18.02 ml/min/1.73 m^2, respectively. Among 340 subjects in group V, proportions of subjects receiving hemodialysis, peritoneal dialysis and kidney transplantation were 38.24, 17.65 and 10%, respectively. The characteristics of the different patient groups are given in Table 1. The mean age of the entire population was 66.12 ± 9.81 years. Generally, patients with impaired eGFR were more likely to be men, be hypertensive, have PAD and have higher age, systolic BP, triglyceride levels, urine protein levels, and higher percentage of CCBs, nitrates, diuretics, insulin and DPP-4 inhibitors use. In contrast, patients with impaired eGFR were more likely to present lower BMI, diastolic BP, LVEF, HDL, physical activity, family history of premature CAD, prevalence of dyslipidemia, be smokers and have lower percentage of statin, sulfonylurea and metformin use.

CV events and outcomes

For all end-points considered, impaired eGFR was highly significantly associated with CV outcomes (Table 2). Patients with impaired renal function had significantly higher incidence rate for the primary end-point (4-point MACE), all-cause mortality, CV mortality, hospitalization for heart failure and nonfatal stroke. However, the association was not significant for nonfatal MI.

Hazard ratios and 95% CIs for comparisons between groups for the 4-point MACE, all-cause mortality, CV mortality, hospitalization for heart failure, nonfatal MI and nonfatal stroke are shown in in Table 3. Compared with group I, the unadjusted hazard ratios for all CV outcomes were significantly higher among the lower eGFR groups. After adjusting for demographic variables in model 1, underlying diseases, risk factors and medications, lower eGFR was more informative as a predictor of all CV outcomes except nonfatal MI and nonfatal stroke.

Survival analysis is shown in Figs. 1, 2a–e. The impaired estimated GFR groups were associated with a worse survival from Kaplan–Meier curves. The worse outcomes were obviously seen in group V for all-cause mortality ($P < 0.001$), CV mortality ($P < 0.001$) and nonfatal MI ($P = 0.009$), but group IV exhibited the worst survival for nonfatal stroke ($P = 0.001$).

Sensitivity analysis

Sensitivity analyses were performed in model 2 with 32.79% of total subjects and in model 3 with 26.35% of total subjects by adding LVEF and urine albumin dipstick, respectively, to the adjusted model 1. After including LVEF in a multivariable model, the adjusted model 2 demonstrated similar trend

Table 1 Baseline Characteristics Stratified by eGFR Levels

Variable	Different groups of renal function according to eGFR (mL/min/1.73 m^2)						*p* value
	Group I eGFR > = 90 (*n* = 1098)	Group II eGFR 60–89 (*n* = 2517)	Group IIIa eGFR 45–59 (*n* = 1155)	Group IIIb eGFR 30–44 (*n* = 841)	Group IV eGFR 15–29 (*n* = 425)	Group V eGFR < 15 or receiving RRT (*n* = 340)	
Age (years)	58.22 ± 7.23	65.62 ± 9.17	69.25 ± 8.78	71.3 ± 9.17	70.72 ± 9.96	66.16 ± 9.56	< 0.001
Female (*N*, %)	573 (52.19%)	1091 (43.35%)	462 (40%)	398 (47.32%)	223 (52.47%)	162 (47.65%)	< 0.001
BMI (kg/m^2)	26.05 ± 4.85	25.52 ± 7.26	25.28 ± 4.13	25.35 ± 4.75	25.64 ± 4.94	24.38 ± 4.43	< 0.001
Waist circumference (cm)	89.01 ± 11.81	88.89 ± 10.74	89.24 ± 11.25	89.5 ± 11.87	90.29 ± 11.99	88.19 ± 11.76	0.132
Systolic BP (mmHg)	131.35 ± 17	132.14 ± 17.55	133.86 ± 19.28	134.38 ± 19.92	136.08 ± 20.43	137.17 ± 22.7	< 0.001
Diastolic BP (mmHg)	76.69 ± 10.42	75.05 ± 10.59	73.96 ± 11	72.66 ± 11.49	71.87 ± 12.59	72.54 ± 12.36	< 0.001
Diabetes (*N*, %)	735 (66.94%)	1356 (53.87%)	681 (58.96%)	576 (68.49%)	299 (70.35%)	224 (65.88%)	< 0.001
Hypertension (*N*, %)	1003 (91.35%)	2427 (96.42%)	1123 (97.23%)	829 (98.57%)	418 (98.35%)	332 (97.65%)	< 0.001
Dyslipidemia (*N*, %)	986 (89.8%)	2247 (89.27%)	1011 (87.53%)	739 (87.87%)	357 (84%)	267 (78.53%)	< 0.001
Exercise (*N*, %)	967 (88.07%)	2142 (85.1%)	980 (84.85%)	667 (79.31%)	297 (69.88%)	208 (61.18%)	< 0.001
History of smoking (*N*, %)	268 (24.41%)	632 (25.11%)	303 (26.23%)	196 (23.31%)	84 (19.76%)	42 (12.35%)	< 0.001
Current smoking (*N*, %)	89 (8.11%)	124 (4.93%)	42 (3.64%)	26 (3.09%)	12 (2.82%)	7 (2.06%)	< 0.001
Family history of premature CAD (*N*, %)	132 (12.02%)	214 (8.5%)	58 (5.02%)	50 (5.95%)	17 (4%)	31 (9.12%)	< 0.001
CAD (*N*, %)	400 (36.43%)	1153 (45.81%)	552 (47.79%)	390 (46.37%)	160 (37.65%)	102 (30%)	< 0.001
CVD (*N*, %)	86 (7.83%)	226 (8.98%)	89 (7.71%)	84 (9.99%)	37 (8.71%)	26 (7.65%)	0.426
PAD (*N*, %)	16 (1.46%)	53 (2.11%)	28 (2.42%)	35 (4.16%)	25 (5.88%)	20 (5.88%)	< 0.001
Renal replacement therapy (*N*, %)							< 0.001
Hemodialysis (*N*, %)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	130 (38.24%)	
Peritoneal dialysis (*N*, %)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	60 (17.65%)	
Kidney transplantation (*N*, %)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	34 (10%)	
LVEF (%)	59.37 ± 14.81	57.15 ± 16.16	55.97 ± 15.88	55.97 ± 16.13	53.47 ± 18.85	56.55 ± 17.91	0.008
Fasting plasma glucose (mg/dL)	129.67 ± 46.08	121.42 ± 41.41	124.52 ± 60.24	131.59 ± 53.39	136.59 ± 63.62	134.81 ± 70.88	< 0.001
HbA1c (%)	7.43 ± 1.72	7.04 ± 1.5	7.05 ± 1.37	7.21 ± 1.55	7.43 ± 1.93	7.12 ± 1.79	< 0.001
Total cholesterol (mg/dL)	172.93 ± 38.68	170.44 ± 41.83	165.69 ± 36.26	163.71 ± 38.6	168.01 ± 45.28	168.51 ± 40.21	< 0.001
Triglyceride (mg/dL)	136.97 ± 83.42	135.51 ± 77.18	138.12 ± 74.08	154.44 ± 114.61	155.92 ± 98.35	156.91 ± 195.06	< 0.001
HDL (mg/dL)	51.71 ± 14.68	50.39 ± 14.07	49.25 ± 15.54	46.46 ± 13.92	45.74 ± 13.32	47.63 ± 15.51	< 0.001
LDL (mg/dL)	98.45 ± 33.83	97.79 ± 35	93.19 ± 30.83	90.81 ± 30.7	95.08 ± 37.62	93.89 ± 32.75	< 0.001
Serum creatinine (mg/dL)	0.72 ± 0.13	0.96 ± 0.16	1.25 ± 0.17	1.59 ± 0.26	2.38 ± 0.47	6.59 ± 3.34	< 0.001
eGFR (mL/min/1.73 m^2)	98.84 ± 6.66	74.31 ± 8.68	52.65 ± 4.31	38.35 ± 4.23	23.76 ± 4.14	12.97 ± 18.02	< 0.001
Urine protein (*N*, %)							< 0.001
Negative	317 (82.98%)	530 (85.48%)	207 (73.93%)	154 (68.44%)	50 (39.68%)	13 (27.66%)	
1 +	46 (12.04%)	49 (7.9%)	37 (13.21%)	33 (14.67%)	25 (19.84%)	7 (14.89%)	
2 +	12 (3.14%)	30 (4.84%)	28 (10%)	23 (10.22%)	25 (19.84%)	9 (19.15%)	
3 +	6 (1.57%)	9 (1.45%)	7 (2.5%)	14 (6.22%)	20 (15.87%)	10 (21.28%)	
4 +	1 (0.26%)	2 (0.32%)	1 (0.36%)	1 (0.44%)	6 (4.76%)	8 (17.02%)	
Aspirin (*N*, %)	638 (58.11%)	1666 (66.19%)	807 (69.87%)	596 (70.87%)	300 (70.59%)	207 (60.88%)	< 0.001
ACEI/ARBs (*N*, %)	711 (64.75%)	1751 (69.57%)	866 (74.98%)	548 (65.16%)	199 (46.82%)	137 (40.29%)	< 0.001
Beta-blockers (*N*, %)	477 (43.44%)	1413 (56.14%)	682 (59.05%)	529 (62.9%)	251 (59.06%)	169 (49.71%)	< 0.001
Calcium channel blockers (*N*, %)	401 (36.52%)	960 (38.14%)	477 (41.3%)	411 (48.87%)	237 (55.76%)	171 (50.29%)	< 0.001
Nitrates (*N*, %)	135 (12.3%)	458 (18.2%)	270 (23.38%)	215 (25.56%)	107 (25.18%)	90 (26.47%)	< 0.001
Diuretics (*N*, %)	227 (20.67%)	621 (24.67%)	377 (32.64%)	333 (39.6%)	203 (47.76%)	144 (42.35%)	< 0.001
Statin (*N*, %)	980 (89.25%)	2249 (89.35%)	1021 (88.4%)	748 (88.94%)	353 (83.06%)	257 (75.59%)	< 0.001
Fibrates (*N*, %)	65 (5.92%)	165 (6.56%)	122 (10.56%)	84 (9.99%)	31 (7.29%)	19 (5.59%)	< 0.001

Table 1 (continued)

Variable	Different groups of renal function according to eGFR (mL/min/1.73 m^2)						*p* value
	Group I eGFR > = 90 (*n* = 1098)	Group II eGFR 60–89 (*n* = 2517)	Group IIIa eGFR 45–59 (*n* = 1155)	Group IIIb eGFR 30–44 (*n* = 841)	Group IV eGFR 15–29 (*n* = 425)	Group V eGFR < 15 or receiving RRT (*n* = 340)	
Insulin (*N*, %)	135 (12.3%)	184 (7.31%)	102 (8.83%)	135 (16.05%)	132 (31.06%)	109 (32.06%)	< 0.001
Sulfonylurea (*N*, %)	369 (33.61%)	591 (23.48%)	327 (28.31%)	267 (31.75%)	80 (18.82%)	26 (7.65%)	< 0.001
Metformin (*N*, %)	551 (50.18%)	916 (36.39%)	414 (35.84%)	228 (27.11%)	34 (8%)	23 (6.76%)	< 0.001
Thiazolidinedione (*N*, %)	111 (10.11%)	139 (5.52%)	86 (7.45%)	78 (9.27%)	41 (9.65%)	19 (5.59%)	< 0.001
DPP-4 inhibitors (*N*, %)	34 (3.1%)	66 (2.62%)	39 (3.38%)	60 (7.13%)	40 (9.41%)	13 (3.82%)	< 0.001

Continuous data are presented as mean ± SD while categorical data are expressed as number with percentage in column

CKD indicates chronic kidney disease, *eGFR* estimated glomerular filtration rate, *BMI* body mass index, *BP* blood pressure, *CAD* coronary artery disease, *CVD* cerebrovascular disease, *PAD* peripheral artery disease, *LVEF* left ventricular ejection fraction, *HbA1c* hemoglobinA1c, *HDL* high-density lipoprotein cholesterol, *LDL* low density lipoprotein cholesterol, *ECG* electrocardiogram, *ACEI/ARBs* angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, *CCBs* calcium-channel blockers, *DPP-4* inhibitors, dipeptidyl-peptidase 4 inhibitors. Diuretics are composites of hydrochlorothiazide, furosemide or spironolactone. CAD consisted of a history of chronic stable angina, unstable angina, myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery. CVD consisted of a history of transient ischemic attack, ischemic stroke, carotid stenting or carotid endarterectomy. PAD consisted of a history of intermittent claudication with ABI < 0.9, aortic dissection/surgery, peripheral artery angioplasty/stenting/bypass graft, amputation of ischemic limbs

as model 1 in 4-point MACE, all-cause mortality, hospitalization for heart failure and nonfatal MI. Meanwhile, the adjusted model 3 had similar trend as model 1 in 4-point MACE, all-cause mortality, hospitalization for heart failure and nonfatal stroke, after including dipstick proteinuria in the multivariable model. However, hazard ratios of group V in model 3 had disproportionately decreased in 4-point MACE and hospitalization for heart failure (Table 3).

Subgroup analysis

Stepwise increases in cardiovascular risk according to lower eGFR levels, except in group V of nonfatal stroke, were demonstrated in every subgroup. After dividing subjects by sex, diabetes status and BMI at 25 kg/m^2, trends of 4-point MACE, all-cause mortality, CV mortality and hospitalization for heart failure were still similar within each subgroup. Subjects with diabetes notably had significant hazard ratios of 4-point MACE, all-cause mortality, CV mortality and hospitalization for heart failure at earlier eGFR stages, compared with the non-diabetes group (Table 4). Subjects in male, diabetes and BMI ≥ 25 kg/m^2 subgroups commonly had significantly increased risks of nonfatal MI in eGFR group V and nonfatal stroke in eGFR group IV.

Repeated data analysis

Repeated data analysis of 4-point MACE, hospitalization for heart failure, nonfatal MI and nonfatal stroke was performed at 6, 12, 24, 36, 48 and 60 months of follow-up using mixed-effects generalized linear model. Comparisons between groups were reported as risk ratios with corresponding 95% CIs and demonstrated in Table 5. The results were similar to hazard ratios in Table 3 in both crude and adjusted models. However, the repeated measured model had narrower 95% CIs and more significant p value than the overall cox proportional hazards models.

Discussion

The prospective CORE-Thailand study recruited a total of 6376 subjects with high-risk CV from 25 centers across Thailand. The combination of a wide geographic distribution population provided an opportunity to assess the informativeness of kidney function on CV outcomes. The findings indicated that renal insufficiency was associated with an increased risk of CV events and other adverse cardiovascular events in Thai populations with high atherosclerosis risk, independent of all other measured variables. Our findings were consistent with several cohort studies [12–14].

A meta-analysis illustrated that a lower estimated GFR and a higher albuminuria were the independent risk factors for all-cause and CV mortality among high-risk patients. Both estimated GFR and albuminuria were independent of each other and independent of traditional CV risks. Although the study included 266,975 individuals from ten cohorts, the majority of the population were Caucasian [15]. A study in a Japanese population with high atherosclerosis risk also demonstrated a stepwise increase of major cardiac events according to the 5 CKD stages. Significant differences were found among subjects with CKD stages I or II, those with stages IV or V and subjects with stage III compared with

Table 2 Incidence of Cardiovascular Outcomes Stratified by eGFR Levels

Outcome	Different groups of renal function according to eGFR (mL/min/1.73 m^2)						*p* value
	Group I eGFR > = 90 (*n* = 1098)	Group II eGFR 60–89 (*n* = 2517)	Group IIIa eGFR 45–59 (*n* = 1155)	Group IIIb eGFR 30–44 (*n* = 841)	Group IV eGFR 15–29 (*n* = 425)	Group V eGFR < 15 or receiving RRT (*n* = 340)	
4-point MACE							
Events (*N*, %)	30 (2.73%)	146 (5.8%)[a]	99 (8.57%)[a,b]	98 (11.65%)[a,b]	69 (16.24%)[a,b,c]	46 (13.53%)[a,b,c]	< 0.001
Person-years at risk	3782.38	8282.6	3810.46	2607.55	1130.71	715.52	
Incidence rate per 100 person-years (95% CI)	0.79 (0.55–1.13)	1.76 (1.5–2.07)	2.6 (2.13–3.16)	3.76 (3.08–4.58)	6.19 (4.9–7.82)	6.29 (4.7–8.42)	
All-cause mortality							
Events (*N*, %)	18 (1.64%)	71 (2.82%)	61 (5.28%)[a,b]	48 (5.71%)[a,b]	63 (14.82%)[a,b,c,d]	51 (15%)[a,b,c,d]	< 0.001
Person-years at risk	3803.99	8319.37	3803.15	2612.93	1117.89	704.67	
Incidence rate per 100 person-years (95% CI)	0.47 (0.3–0.75)	0.85 (0.68–1.08)	1.6 (1.25–2.06)	1.84 (1.38–2.44)	5.64 (4.4–7.21)	7.24 (5.5–9.52)	
CV mortality							
Events (*N*, %)	3 (0.27%)	27 (1.07%)	27 (2.34%)[A]	21 (2.5%)[a]	17 (4%)[a,b]	14 (4.12%)[a,b]	< 0.001
Person-years at risk	3826.87	8478.39	3948.5	2729.75	1218.31	760.86	
Incidence rate per 100 person-years (95% CI)	0.08 (0.03–0.24)	0.32 (0.22–0.46)	0.68 (0.47–1)	0.77 (0.5–1.18)	1.4 (0.87–2.24)	1.84 (1.09–3.11)	
Hospitalization for HF							
Events (*N*, %)	9 (0.82%)	34 (1.35%)	42 (3.64%)[a,b]	47 (5.59%)[a,b]	38 (8.94%)[a,b,c,d]	22 (6.47%)[a,b]	< 0.001
Person-years at risk	3808.12	8437.9	3876.66	2659.31	1151.71	730.72	
Incidence rate per 100 person-years (95% CI)	0.18 (0.09–0.39)	0.34 (0.24–0.49)	0.98 (0.71–1.35)	1.69 (1.26–2.27)	2.52 (1.75–3.62)	2.46 (1.55–3.91)	
Nonfatal MI							
Events (*N*, %)	11 (1%)	44 (1.75%)	17 (1.47%)	15 (1.78%)	11 (2.59%)	10 (2.94%)	0.117
Person-years at risk	3810.02	8406.18	3919.86	2710.87	1200.71	754.31	
Incidence rate per 100 person-years (95% CI)	0.29 (0.16–0.52)	0.52 (0.39–0.7)	0.43 (0.27–0.7)	0.55 (0.33–0.92)	0.92 (0.51–1.65)	1.33 (0.71–2.46)	
Nonfatal stroke							
Events (*N*, %)	9 (0.82%)	50 (1.99%)	21 (1.82%)	17 (2.02%)	16 (3.76%)[A]	5 (1.47%)	0.008
Person-years at risk	3816.32	8427.67	3925.16	2716.66	1200.14	753.25	
Incidence rate per 100 person-years (95% CI)	0.24 (0.12–0.45)	0.59 (0.45–0.78)	0.54 (0.35–0.82)	0.63 (0.39–1.01)	1.33 (0.82–2.18)	0.66 (0.28–1.59)	

Number of events are presented as number with percentage

MI myocardial infarction, *HF* heart failure, *CV* mortality cardiovascular mortality, *4-point MACE* 4-point major adverse cardiovascular events, including composite of nonfatal MI, nonfatal stroke, hospitalization for HF or CV mortality

[a] < 0.05 compared with group I

[b] < 0.05 compared with group II

[c] < 0.05 compared with group IIIa

[d] < 0.05 compared with group IIIb

[e] < 0.05 compared with group IV

those in stage V. The major cardiac events were defined as cardiac mortality, nonfatal MI or unstable angina [16].

A comparison of South Asian, predominantly Indian origin, and European cohorts showed longitudinal associations between baseline eGFR and mortality or CV events. eGFR

Table 3 Hazard Ratio of Cardiovascular Outcomes Stratified by eGFR Levels

	Crude HR (95% CI)	*p* value	Adjusted HR Model 1 (95% CI)	*p* value	Adjusted HR Model 2* (95% CI)	*p* value	Adjusted HR Model 3** (95%CI)	*p* value
4-point MACE								
Group I	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Group II	2.23 (1.51–3.31)	< 0.001	1.65 (1.1–2.49)	0.017	1.91 (1.05–3.47)	0.03	1.67 (0.67–4.16)	0.27
Group IIIa	3.29 (2.19–4.95)	< 0.001	2.17 (1.4–3.36)	0.001	2.29 (1.22–4.32)	0.01	3.08 (1.2–7.89)	0.02
Group IIIb	4.8 (3.19–7.22)	< 0.001	2.67 (1.7–4.17)	< 0.001	2.64 (1.36–5.1)	< 0.001	2.57 (0.95–6.94)	0.06
Group IV	7.91 (5.15–12.15)	< 0.001	4.24 (2.63–6.83)	< 0.001	3.43 (1.66–7.09)	< 0.001	4.41 (1.59–12.23)	< 0.001
Group V	8.15 (5.14–12.93)	< 0.001	4.87 (2.95–8.04)	< 0.001	3.49 (1.57–7.72)	< 0.001	2.19 (0.59–8.14)	0.24
All-cause mortality								
Group I	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Group II	1.82 (1.08–3.05)	0.024	1.08 (0.63–1.85)	0.772	1.83 (0.71–4.74)	0.21	0.96 (0.35–2.58)	0.93
Group IIIa	3.41 (2.02–5.78)	< 0.001	1.59 (0.91–2.77)	0.104	1.78 (0.65–4.84)	0.26	2.31 (0.85–6.24)	0.10
Group IIIb	3.94 (2.29–6.78)	< 0.001	1.55 (0.87–2.77)	0.138	2.36 (0.86–6.49)	0.10	1.21 (0.4–3.71)	0.74
Group IV	12.67 (7.5–21.4)	< 0.001	4.22 (2.36–7.54)	< 0.001	4.12 (1.44–11.8)	0.01	3.87 (1.32–11.3)	0.01
Group V	16.39 (9.55–28.12)	< 0.001	6.83 (3.83–12.17)	< 0.001	7.35 (2.55–21.21)	< 0.001	3.38 (0.98–11.66)	0.05
CV mortality								
Group I	1.0 (reference)		1.0 (reference)		0 (0–2.691E + 250)****	0.966	1.0 (reference)	
Group II	4.09 (1.24–13.47)	0.021	2.27 (0.67–7.67)	0.187	1.0 (reference)***		1.3 (0.14–12.08)	0.82
Group IIIa	8.73 (2.65–28.79)	< 0.001	3.64 (1.06–12.5)	0.04	0.97 (0.45–2.09)	0.928	2.59 (0.28–23.99)	0.40
Group IIIb	9.95 (2.97–33.36)	< 0.001	3.48 (0.98–12.31)	0.053	1.14 (0.51–2.53)	0.749	0.79 (0.06–10.1)	0.86
Group IV	18.63 (5.46–63.62)	< 0.001	6.51 (1.78–23.8)	0.005	0.97 (0.33–2.86)	0.956	5.87 (0.57–60.7)	0.14
Group V	24.68 (7.07–86.09)	< 0.001	12.07 (3.29–44.28)	< 0.001	1.09 (0.24–5.02)	0.916	4.39 (0.33–58.07)	0.26
Hospitalization for heart failure								
Group I	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Group II	1.89 (0.83–4.31)	0.132	1.35 (0.58–3.14)	0.485	0.9 (0.33–2.51)	0.85	0.86 (0.14–5.36)	0.87
Group IIIa	5.37 (2.4–12.03)	< 0.001	3.54 (1.53–8.17)	0.003	2.46 (0.9–6.7)	0.08	4.57 (0.89–23.51)	0.07
Group IIIb	9.37 (4.23–20.78)	< 0.001	4.53 (1.95–10.55)	< 0.001	3.1 (1.11–8.68)	0.03	6.26 (1.17–33.64)	0.03
Group IV	13.58 (5.93–31.12)	< 0.001	5.69 (2.32–13.95)	< 0.001	3.01 (0.96–9.37)	0.06	7.78 (1.34–45.08)	0.02
Group V	14 (5.87–33.38)	< 0.001	6.54 (2.58–16.57)	< 0.001	3.78 (1.15–12.43)	0.03	3.34 (0.36–31.08)	0.29
Nonfatal MI								
Group I	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Group II	1.81 (0.93–3.5)	0.08	1.57 (0.77–3.21)	0.212	2.3 (0.78–6.79)	0.13	3.01 (0.36–25.04)	0.31
Group IIIa	1.5 (0.7–3.2)	0.295	1.25 (0.54–2.88)	0.605	2.48 (0.74–8.25)	0.14	2.74 (0.28–26.41)	0.38
Group IIIb	1.91 (0.88–4.16)	0.103	1.51 (0.63–3.64)	0.357	1.36 (0.31–5.88)	0.68	2.73 (0.26–28.39)	0.40
Group IV	3.11 (1.35–7.18)	0.008	2.52 (0.96–6.63)	0.06	5.18 (1.26–21.34)	0.02	1.01 (0.07–14.16)	1.00
Group V	4.18 (1.77–9.87)	< 0.001	3.93 (1.53–10.08)	0.004	6.82 (1.68–27.67)	0.01	2.06 (0.14–30.3)	0.60
Nonfatal stroke								
Group I	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Group II	2.53 (1.24–5.14)	0.01	1.97 (0.94–4.11)	0.071	2.09 (0.7–6.24)	0.19	1.8 (0.37–8.83)	0.47
Group IIIa	2.28 (1.05–4.98)	0.038	1.84 (0.8–4.24)	0.15	1.46 (0.4–5.35)	0.57	4.06 (0.78–21.24)	0.10
Group IIIb	2.68 (1.2–6.02)	0.017	1.96 (0.81–4.75)	0.135	1.22 (0.27–5.55)	0.79	1.81 (0.28–11.85)	0.53
Group IV	5.84 (2.58–13.23)	< 0.001	4.6 (1.84–11.49)	0.001	1.46 (0.22–9.54)	0.69	6.42 (1.01–40.64)	0.05
Group V	2.89 (0.97–8.63)	0.058	1.68 (0.49–5.73)	0.411	0.91 (0.09–9.4)	0.94	0.00 (0.00–00.00)***	0.99

MI myocardial infarction, *HF* heart failure, *CV* mortality cardiovascular mortality, *4-point MACE* 4-point major adverse cardiovascular events including composite of nonfatal MI, nonfatal stroke, hospitalization for HF or CV mortality. Multivariable analysis model 1 adjusted by age, sex, BMI, diabetes, hypertension, dyslipidemia, CAD, CVD, PAD, family history of premature atherosclerosis, history of smoking, regular exercise, aspirin, ACEI/ARBs, statin, insulin and metformin

*Adjusted model 2 was a sensitivity analysis performed with 32.79% of total subjects by adding LVEF variable to the model 1

**Adjusted model 3 was a sensitivity analysis performed with 26.35% of total subjects by adding urine protein dipstick variable to the model 1

***Abnormal results due to the number of participants and outcomes in the multivariable analyses were too small

****There were too small numbers of events or participants in the group I. The group II was selected as a reference group instead. All variables are at baseline

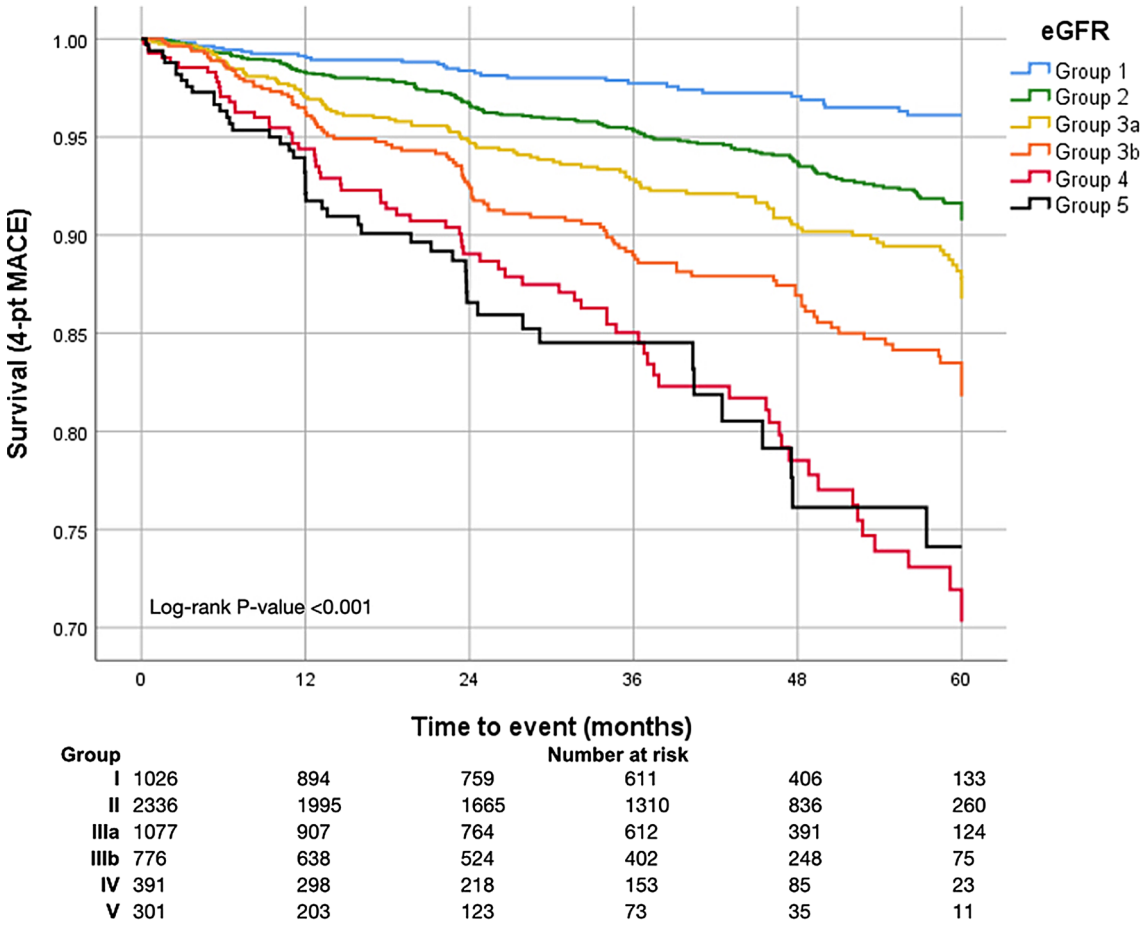

Fig. 1 Kaplan–Meier Survival Analysis of 4-point MACE Stratified by eGFR Levels. Kaplan–Meier analysis for 4-point major adverse cardiovascular events including a composite of nonfatal MI, nonfatal stroke, hospitalization for HF or CV mortality stratified by eGFR levels (log-rank test, $p < 0.001$)

calculated by the CKD-EPI-creatinine equation was significantly associated with only CV mortality in Europeans after adjusting in a multivariable model. There was no significant interaction between eGFR from the CKD-EPI-creatinine equation and mortality or CV events among South Asians [17]. Another cohort of South Asian and white individuals found a significant association between eGFR from the CKD-EPI-creatinine equation and all-cause mortality and CV events in the whole cohort. However, they did not find any association between eGFR and CV events among the South Asian subgroup [18]. In contrast, the present study found significant interactions between CKD-EPI eGFR and all CV outcomes in the Southeast Asian population. However, subjects in our study had noticeably higher CV risk at baseline than those in the South Asian and European cohorts.

Possible links between CV diseases and impaired kidney function comprise several explanations. A recent literature review by Düsing et al. provided an overview about pathophysiology between CKD and CV diseases [19]. Apart from traditional CV risk factors, accumulation of uremic toxins, chronic inflammation, endothelial dysfunction and oxidative stress were identified to act as CKD-specific alterations that increase cardiovascular risk [19]. Moreover, CKD itself is independently associated with deficiency of endogenous vasodilator nitric oxide [20, 21], valvular calcification [22], occurrence of plaque rupture and progression of calcification [23].

Interestingly, the present study demonstrated a significantly different incidence of nonfatal stroke among each group. However, subjects in group V had a lower incidence of nonfatal stroke than other groups. Patients with End-Stage Renal Disease (ESRD) have a 3–10 times higher risk of developing a stroke compared with the general population. The reason is due to the effect of both traditional cardiovascular risk factors [24, 25] and also uremic-specific risk factors (including chronic inflammation, oxidative stress, and uremic retention products), which can potentially cause

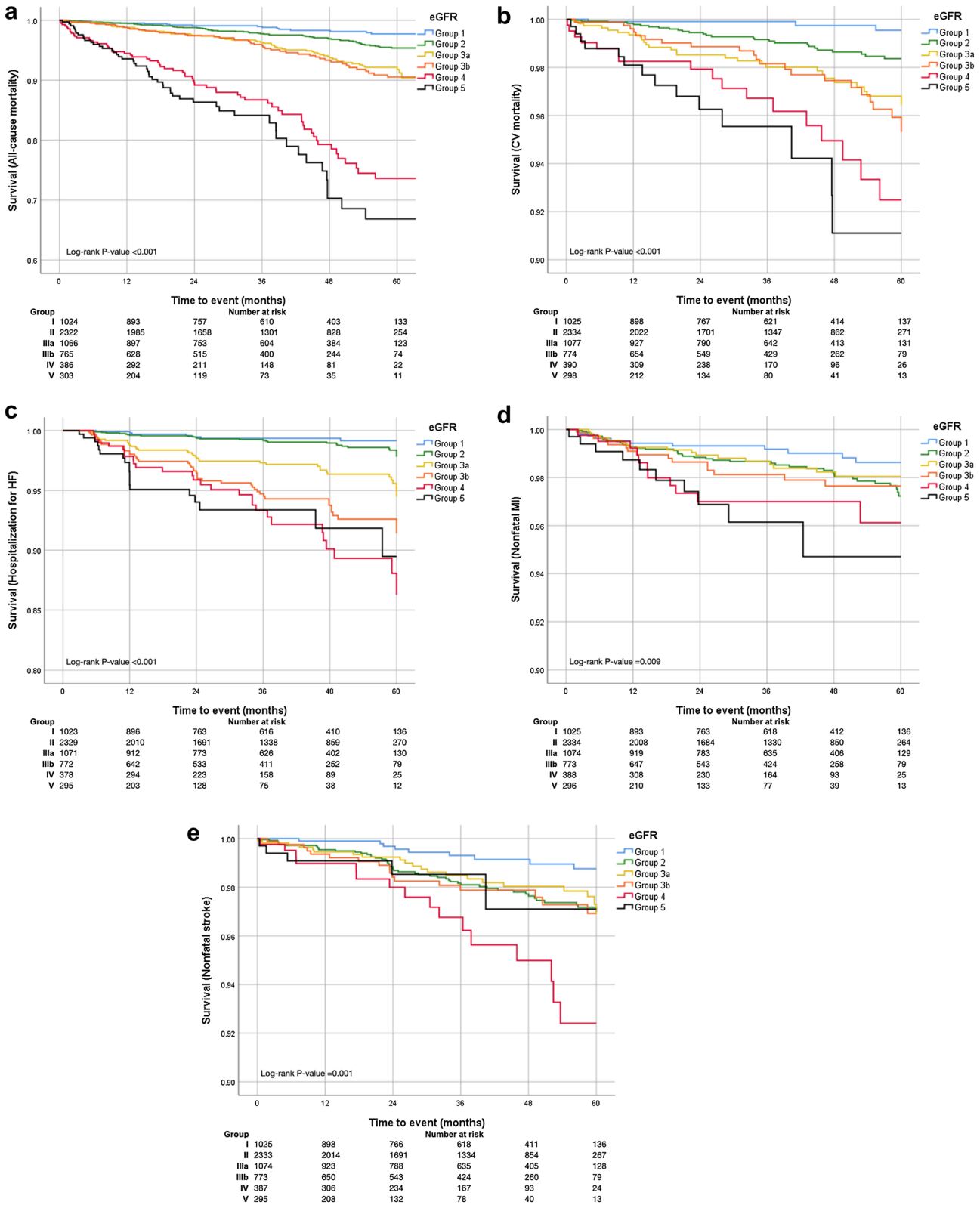

Fig. 2 Kaplan–Meier Survival Analysis of Secondary Outcomes Stratified by eGFR Levels. **a** Kaplan–Meier analysis for all-cause mortality stratified by eGFR levels (log-rank test, $p<0.001$) **b** Kaplan–Meier analysis for cardiovascular mortality stratified by eGFR levels (log-rank test, $p<0.001$) **c** Kaplan–Meier analysis for hospitalization for heart failure stratified by eGFR levels (log-rank test, $p<0.001$) **d** Kaplan–Meier analysis for nonfatal myocardial infarction stratified by eGFR levels (log-rank test, $p=0.009$) **e** Kaplan–Meier analysis for nonfatal stroke stratified by eGFR levels (log-rank test, $p=0.001$)

Table 4 Subgroup analysis according to sex, diabetes and BMI groups

Subgroup	Male ($n=3311$) Adjusted HR (95% CI)	*p* value	Female ($n=2791$) Adjusted HR (95% CI)	*p* value	DM* ($n=3736$) Adjusted HR (95% CI)	*p* value	Non-DM ($n=2367$) Adjusted HR (95% CI)	*p* value	BMI < 25 ($n=3063$) Adjusted HR (95% CI)	*p* value	BMI >= 25 ($n=3040$) Adjusted HR (95% CI)	*p* value
4-point MACE												
Group I	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Group II	1.43 (0.86–2.38)	0.164	1.91 (0.95–3.85)	0.068	1.9 (1.09–3.31)	0.023	1.29 (0.7–2.38)	0.412	1.33 (0.77–2.3)	0.304	2.11 (1.12–3.95)	0.02
Group IIIa	1.73 (1–3.01)	0.051	3.02 (1.47–6.22)	0.003	2.48 (1.39–4.45)	0.002	1.73 (0.89–3.35)	0.108	1.82 (1.02–3.25)	0.044	2.69 (1.38–5.24)	0.004
Group IIIb	2.21 (1.23–3.96)	0.008	3.37 (1.64–6.95)	0.001	3.7 (2.08–6.6)	< 0.001	1.44 (0.67–3.06)	0.35	2.56 (1.42–4.6)	0.002	2.66 (1.33–5.34)	0.006
Group IV	3.98 (2.1–7.54)	< 0.001	4.6 (2.16–9.79)	< 0.001	5.52 (2.99–10.19)	< 0.001	2.88 (1.29–6.44)	0.01	3.36 (1.75–6.44)	< 0.001	5.56 (2.72–11.34)	< 0.001
Group V	5.2 (2.75–9.82)	< 0.001	4.29 (1.87–9.8)	0.001	6.43 (3.38–12.24)	< 0.001	3.21 (1.37–7.53)	0.007	4.23 (2.21–8.1)	< 0.001	5.25 (2.36–11.67)	< 0.001
All-cause mortality												
Group I	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Group II	0.92 (0.45–1.89)	0.825	1.33 (0.59–2.99)	0.486	1.51 (0.75–3.07)	0.251	0.6 (0.26–1.38)	0.23	0.96 (0.48–1.92)	0.906	1.45 (0.62–3.37)	0.392
Group IIIa	1.09 (0.51–2.33)	0.819	2.46 (1.07–5.62)	0.034	2.09 (1–4.38)	0.049	0.91 (0.38–2.19)	0.837	1.24 (0.59–2.57)	0.574	2.5 (1.04–6)	0.04
Group IIIb	1.3 (0.59–2.86)	0.511	1.77 (0.74–4.23)	0.2	1.97 (0.93–4.19)	0.078	0.98 (0.39–2.5)	0.972	1.67 (0.8–3.49)	0.17	1.35 (0.52–3.51)	0.543
Group IV	3.34 (1.5–7.48)	0.003	5.35 (2.29–12.53)	< 0.001	5.82 (2.75–12.3)	< 0.001	2.25 (0.85–5.92)	0.102	4.54 (2.16–9.56)	< 0.001	4.16 (1.64–10.55)	0.003
Group V	6.57 (3.01–14.32)	< 0.001	7.43 (3.11–17.75)	< 0.001	9.8 (4.63–20.73)	< 0.001	3.24 (1.23–8.48)	0.017	6.56 (3.15–13.69)	< 0.001	6.42 (2.49–16.59)	< 0.001
CV mortality												
Group I	1.0 (reference)		0 (0–1.678E + 130)***	0.942	1.0 (reference)		1.0 (reference)		0 (0–1.474E+ 198)***	0.96	1.0 (reference)	
Group II	0.9 (0.25–3.31)	0.876	1.0 (reference)**		2.53 (0.57–11.24)	0.221	1.73 (0.21–14.34)	0.613	1.0 (reference)**		1.3 (0.36–4.72)	0.693
Group IIIa	1.54 (0.41–5.76)	0.522	1.51 (0.66–3.46)	0.329	3.48 (0.77–15.79)	0.106	3.68 (0.43–31.75)	0.237	1.5 (0.66–3.44)	0.337	2.26 (0.6–8.54)	0.228
Group IIIb	0.98 (0.22–4.25)	0.973	1.78 (0.82–3.88)	0.147	3.75 (0.81–17.29)	0.09	2.74 (0.27–27.59)	0.393	2.13 (0.95–4.77)	0.065	1.18 (0.27–5.07)	0.825
Group IV	3.55 (0.82–15.26)	0.089	1.89 (0.72 – 5.00)	0.198	7.55 (1.59–35.96)	0.011	4.38 (0.39–49.81)	0.234	4.87 (2.01–11.79)	< 0.001	1.85 (0.4–8.62)	0.433
Group V	9.39 (2.31–38.15)	0.002	2.86 (0.94–8.76)	0.065	15.01 (3.14 71.68)	0.001	6.61 (0.56–78.6)	0.135	4.3 (1.49–12.38)	0.007	7.66 (1.84–31.81)	0.005
Hospitalization for heart failure												
Group I	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Group II	1.64 (0.55–4.87)	0.374	0.81 (0.2–3.22)	0.764	2.07 (0.58–7.31)	0.261	0.73 (0.23–2.31)	0.593	0.92 (0.29–2.9)	0.889	1.92 (0.54–6.81)	0.312
Group IIIa	2.45 (0.79–7.6)	0.122	4.95 (1.42–17.33)	0.012	5.78 (1.67–19.99)	0.006	1.76 (0.54–5.72)	0.347	2.57 (0.84–7.89)	0.099	4.83 (1.37–17.06)	0.014
Group IIIb	3.7 (1.17–11.74)	0.026	5.34 (1.51–18.89)	0.009	9.33 (2.74–31.84)	< 0.001	1.26 (0.33–4.73)	0.735	3.97 (1.3–12.14)	0.016	4.79 (1.31–17.55)	0.018

Table 4 (continued)

Subgroup	Male ($n=3311$) Adjusted HR (95% CI)	p value	Female ($n=2791$) Adjusted HR (95% CI)	p value	DM* ($n=3736$) Adjusted HR (95% CI)	p value	Non-DM ($n=2367$) Adjusted HR (95% CI)	p value	BMI < 25 ($n=3063$) Adjusted HR (95% CI)	p value	BMI >= 25 ($n=3040$) Adjusted HR (95% CI)	p value
Group IV	3.67 (0.99–13.51)	0.051	7.56 (2.06–27.77)	0.002	10.39 (2.88–37.46)	<0.001	2.54 (0.63–10.24)	0.191	4.29 (1.27–14.42)	0.019	7.99 (2.08–30.68)	0.002
Group V	5.72 (1.61–20.34)	0.007	6.64 (1.66–26.55)	0.007	10.5 (2.79–39.57)	0.001	4.4 (1.11–17.51)	0.035	6.57 (2.03–21.31)	0.002	2.94 (0.47–18.52)	0.252
Nonfatal MI												
Group I	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Group II	1.41 (0.6–3.3)	0.43	1.95 (0.53–7.26)	0.678	1.91 (0.69–5.25)	0.211	1.27 (0.46–3.47)	0.642	1.36 (0.53–3.5)	0.525	1.96 (0.65–5.91)	0.232
Group IIIa	1.03 (0.37–2.89)	0.95	1.77 (0.41–7.68)	0.318	1.47 (0.46–4.76)	0.517	1.06 (0.32–3.55)	0.92	1.3 (0.44–3.84)	0.637	1.19 (0.31–4.51)	0.803
Group IIIb	1.51 (0.51–4.5)	0.461	1.62 (0.35–7.52)	0.445	2.39 (0.76–7.56)	0.137	0.77 (0.17–3.58)	0.743	1.25 (0.38–4.1)	0.717	1.8 (0.48–6.77)	0.382
Group IV	2.52 (0.74–8.6)	0.141	2.51 (0.49–12.86)	0.537	2.85 (0.76–10.7)	0.122	2.76 (0.66–11.58)	0.166	2.06 (0.54–7.86)	0.288	2.85 (0.68–12.04)	0.154
Group V	3.93 (1.22–12.66)	0.022	3.97 (0.77–20.44)	0.269	7.62 (2.26–25.69)	0.001	1.11 (0.12–9.94)	0.925	2.93 (0.85–10.13)	0.09	4.98 (1.14–21.78)	0.033
Nonfatal stroke												
Group I	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Group II	1.95 (0.74–5.13)	0.178	1.75 (0.56–5.49)	0.531	1.67 (0.66–4.28)	0.282	2.28 (0.67–7.73)	0.188	1.38 (0.57–3.35)	0.47	3.49 (0.8–15.23)	0.097
Group IIIa	2.6 (0.91–7.43)	0.075	0.7 (0.15–3.37)	0.341	1.55 (0.53–4.56)	0.423	2.17 (0.56–8.42)	0.261	1.37 (0.49–3.77)	0.548	3.07 (0.62–15.18)	0.168
Group IIIb	2.91 (0.93–9.17)	0.067	0.9 (0.21–3.82)	0.656	1.74 (0.58–5.2)	0.322	2.21 (0.48–10.09)	0.307	1.36 (0.46–4.03)	0.583	3.17 (0.59–16.93)	0.178
Group IV	7.5 (2.24–25.08)	0.001	1.87 (0.43–8.04)	0.891	4.83 (1.59–14.67)	0.005	2.27 (0.35–14.7)	0.392	1.09 (0.25–4.79)	0.906	14.61 (2.89–73.87)	0.001
Group V	3.48 (0.88–13.72)	0.075	0 (0–1.036E + 249)***	0.403	1.12 (0.21–6.08)	0.895	2.5 (0.4–15.65)	0.329	1.56 (0.37–6.59)	0.543	2.24 (0.19–26.31)	0.52

DM diabetes mellitus, *MI* myocardial infarction, *HF* heart failure, *CV* mortality cardiovascular mortality, *4-point MACE* 4-point major adverse cardiovascular events including composite of nonfatal MI, nonfatal stroke, hospitalization for HF or CV mortality. Multivariable analysis adjusted by age, sex, BMI, diabetes, hypertension, dyslipidemia, CAD, CVD, PAD, family history of premature atherosclerosis, history of smoking, regular exercise, aspirin, ACEI/ARBs, statin, insulin and metformin

*Subjects in the DM subgroup included those with type 1 or 2 diabetes

**There were too small numbers of events or participants in the group I. The group II was selected as a reference group instead

***Abnormal results due to the number of participants and outcomes in the multivariable analyses were too small. All variables are at baseline

Table 5 Repeated data analysis of Cardiovascular Events Stratified by eGFR Levels

	Crude risk ratio (95% CI)	*p* value	Adjusted risk ratio (95% CI)	*p* value
4-point MACE				
Group I	1.0 (reference)		1.0 (reference)	
Group II	1.92 (1.57–2.35)	< 0.001	1.48 (1.20–1.83)	0.001
Group IIIa	2.91 (2.37–3.58)	< 0.001	1.99 (1.59–2.48)	< 0.001
Group IIIb	4.21 (3.42–5.17)	< 0.001	2.43 (1.94–3.06)	< 0.001
Group IV	6.09 (4.90–7.57)	< 0.001	3.39 (2.66–4.33)	< 0.001
Group V	6.41 (5.10–8.05)	< 0.001	3.83 (2.97–4.92)	< 0.001
Hospitalization for heart failure				
Group I	1.0 (reference)		1.0 (reference)	
Group II	1.41 (0.99–2.00)	0.054	1.24 (0.85–1.82)	0.266
Group IIIa	3.65 (2.59–5.14)	< 0.001	2.75 (1.88–5.99)	< 0.001
Group IIIb	6.11 (4.36–8.57)	< 0.001	3.42 (2.32–5.03)	< 0.001
Group IV	10.29 (7.29–14.54)	< 0.001	4.74 (3.18–7.09)	< 0.001
Group V	9.36 (6.50–13.46)	< 0.001	4.78 (3.15–7.25)	< 0.001
Nonfatal MI				
Group I	1.0 (reference)		1.0 (reference)	
Group II	1.53 (1.11–2.11)	0.009	1.37 (0.96–1.94)	0.082
Group IIIa	1.47 (1.02–2.12)	0.036	1.26 (0.84–1.89)	0.255
Group IIIb	1.93 (1.34–2.80)	< 0.001	1.58 (1.04–2.42)	0.033
Group IV	2.73 (1.82–4.09)	< 0.001	2.59 (1.62–4.13)	< 0.001
Group V	3.71 (2.47–5.57)	< 0.001	4.10 (2.61–6.46)	< 0.001
Nonfatal stroke				
Group I	1.0 (reference)		1.0 (reference)	
Group II	2.80 (1.89–4.14)	< 0.001	2.42 (1.51–3.39)	< 0.001
Group IIIa	2.66 (1.74–4.07)	< 0.001	2.07 (1.38–3.40)	0.001
Group IIIb	3.19 (2.07–4.93)	< 0.001	2.15 (1.46–3.75)	< 0.001
Group IV	5.89 (3.78–9.17)	< 0.001	4.04 (2.99–7.96)	< 0.001
Group V	3.44 (2.02–5.88)	< 0.001	2.01 (1.10–3.71)	0.023

Repeated data analysis was performed at 6, 12, 24, 36, 48 and 60 months of follow-up using mixed-effects generalized linear model

MI myocardial infarction, *HF* heart failure, *4-point MACE* 4-point major adverse cardiovascular events including composite of nonfatal MI nonfatal stroke, hospitalization for HF or CV mortality. Multivariable analysis adjusted by age, sex, BMI, diabetes, hypertension, dyslipidemia, CAD, CVD, PAD, family history of premature atherosclerosis, history of smoking, regular exercise, aspirin, ACEI/ARBs, statin, insulin and metformin

endothelial dysfunction, platelet aggregation, and vascular calcification that contribute to cerebrovascular disease risks [26, 27]. Other possible risks of developing ischemic stroke in patients with ESRD include erythropoietin-induced thromboembolic events, arteriovenous shunt-related steal-like influence, and hypotensive effect during the ultra-filtration stage of hemodialysis [27, 28]. In addition, there are possible risks of developing hemorrhagic stroke including major bleeding due to using anticoagulation therapy in patients with hemodialysis [29] and polycystic kidney disease [30]. A previous case–control study showed that patients with ESRD had an almost three-fold and two-fold risk of stroke mortality compared to patients with chronic kidney disease and propensity-matched controls, respectively. Stroke mortality was higher in patients with ESRD who had hypertension, anemia, diabetes, ischemic heart disease, mental disorder, chronic obstructive pulmonary disease, hyperlipidemia, or liver cirrhosis [31]. Another cohort study conducted on the Australian and New Zealand ESRD population found that most factors of stroke mortality were non-modifiable, including older age, female, year of ESRD, and cause of ESRD [32]. The high risk of stroke mortality and CV mortality in patients with ESRD could be important factors that caused the decreased hazard ratio of nonfatal stroke within subjects in group V, with a simultaneously increased hazard ratio of CV mortality in group V.

The advantages of this study included being a nationwide prospective cohort from 25 centers across Thailand with a 5-year observation and generalizability representing a Thai population with high CV risk. Several limitations existed.

First, we had a limited number of subjects with albuminuria and LVEF in the baseline characteristics, with 73.65 and 67.21% missing values. Therefore, we could not include both variables in the adjusted models because it would exclude approximately 70% of subjects with missing data. However, we performed sensitivity analyses with about 30% of participants in the adjusted models with LVEF or albuminuria. Still, we did not include LVEF and albuminuria in the same model because it would exclude 96.8% of cases. Second, important cardiovascular and renal variables, such as blood urea nitrogen, quantitative urine albumin and prevalence of left ventricular hypertrophy were not assessed. Patient characteristics requiring 24 h urine collection for adequate assessments of renal function and albuminuria were not measured in this cohort. Among these, aging, obesity and dietary protein intake might have been relevant in our study and could not be controlled for in our analysis. Third, laboratory investigations were made in different centers. A validated central laboratory was not used to assay serum creatinine concentrations. Finally, most reported data sources did not repeat serum creatinine over three months to confirm the chronicity of abnormalities. Use of one measurement of decreased estimated GFR to characterize CKD might have overestimated disease prevalence.

In summary, this analysis from the prospective CORE-Thailand study confirmed the capacity of estimated GFR to independently predict CV events and all-cause mortality in a Thai population with high CV risk. Estimated GFR could be added to the list of criteria, defining subjects at highest risk of future CV events and constitute one of the appropriate methods for the accurate stratification of CV risk.

Acknowledgements We thank the investigators and research assistants associated with the CORE-Thailand study. The study was also supported by the Heart Association of Thailand under the Royal Patronage of HM the King and the National Research Council of Thailand.

Author contributions NA, AK and BS reviewed the literature, provided valuable input in designing the study, drafted the article and revised it critically. OS, RK, and AP provided literature review and critically revised the manuscript. All authors read and approved the manuscript and met the criteria for authorship.

Funding No funding sources supported this study.

Declarations

Conflict of interest The authors declare that no potential conflict of interest exists.

Ethical approval The Joint Research Ethics Committee and Ministry of Public Health, Thailand, approved the study protocol. Informed consent was obtained from all subjects.

References

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–305.
2. Collaboration GBDCKD. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the global burden of disease study 2017. Lancet 2020; 395:709–733
3. Matsushita K, Coresh J, Sang Y, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol. 2015;3:514–25.
4. Nichols GA, Deruaz-Luyet A, Hauske SJ, Brodovicz KG. The association between estimated glomerular filtration rate, albuminuria, and risk of cardiovascular hospitalizations and all-cause mortality among patients with type 2 diabetes. J Diabetes Complicat. 2018;32:291–7.
5. Tonelli M, Muntner P, Lloyd A, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. Lancet. 2012;380:807–14.
6. Culleton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D. Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. Kidney Int. 1999;56:2214–9.
7. Henry RM, Kamp O, Kostense PJ, et al. Mild renal insufficiency is associated with increased left ventricular mass in men, but not in women: an arterial stiffness-related phenomenon–the hoorn study. Kidney Int. 2005;68:673–9.
8. Smith GL, Lichtman JH, Bracken MB, et al. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am Coll Cardiol. 2006;47:1987–96.
9. Garg AX, Clark WF, Haynes RB, House AA. Moderate renal insufficiency and the risk of cardiovascular mortality: results from the NHANES I. Kidney Int. 2002;61:1486–94.
10. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med. 2001;134:629–36.
11. Mann JF, Gerstein HC, Pogue J, Lonn E, Yusuf S. Cardiovascular risk in patients with early renal insufficiency: implications for the use of ACE inhibitors. Am J Cardiovasc Drugs. 2002;2:157–62.
12. Best PJ, Lennon R, Ting HH, et al. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. J Am Coll Cardiol. 2002;39:1113–9.
13. Ruilope LM, Zanchetti A, Julius S, et al. Prediction of cardiovascular outcome by estimated glomerular filtration rate and estimated creatinine clearance in the high-risk hypertension population of the VALUE trial. J Hypertens. 2007;25:1473–9.
14. Clase CM, Gao P, Tobe SW, et al. Estimated glomerular filtration rate and albuminuria as predictors of outcomes in patients with high cardiovascular risk: a cohort study. Ann Intern Med. 2011;154:310–8.
15. van der Velde M, Matsushita K, Coresh J, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality a collaborative meta-analysis of high-risk population cohorts. Kidney Int. 2011;79:1341–52.
16. Yoda S, Nakanishi K, Tano A, et al. Risk stratification of cardiovascular events in patients at all stages of chronic kidney disease using myocardial perfusion SPECT. J Cardiol. 2012;60:377–82.
17. Eastwood SV, Chaturvedi N, Sattar N, Welsh PI, Hughes AD, Tillin T. Impact of kidney function on cardiovascular risk and mortality: a comparison of South Asian and European cohorts. Am J Nephrol. 2019;50:425–33.

18. Major RW, Shepherd D, Medcalf JF, Xu G, Gray LJ, Brunskill NJ. Comorbidities and outcomes in South Asian individuals with chronic kidney disease: an observational primary care cohort. Nephrol Dial Transpl. 2021;37:108–14.
19. Dusing P, Zietzer A, Goody PR, et al. Vascular pathologies in chronic kidney disease: pathophysiological mechanisms and novel therapeutic approaches. J Mol Med (Berl). 2021;99:335–48.
20. Schmidt RJ, Baylis C. Total nitric oxide production is low in patients with chronic renal disease. Kidney Int. 2000;58:1261–6.
21. Amador-Martinez I, Perez-Villalva R, Uribe N, Cortes-Gonzalez C, Bobadilla NA, Barrera-Chimal J. Reduced endothelial nitric oxide synthase activation contributes to cardiovascular injury during chronic kidney disease progression. Am J Physiol Renal Physiol. 2019;317:F275–85.
22. Turkmen F, Emre A, Ozdemir A, Sevinc C, Erisken E, Yesilcimen K. Relationship between aortic valve sclerosis and left ventricular hypertrophy in chronic haemodialysis patients. Int Urol Nephrol. 2008;40:497–502.
23. Sugiyama T, Kimura S, Ohtani H, et al. Impact of chronic kidney disease stages on atherosclerotic plaque components on optical coherence tomography in patients with coronary artery disease. Cardiovasc Interv Ther. 2017;32:216–24.
24. Makin SD, Cook FA, Dennis MS, Wardlaw JM. Cerebral small vessel disease and renal function: systematic review and meta-analysis. Cerebrovasc Dis. 2015;39:39–52.
25. Toyoda G, Bokura H, Mitaki S, et al. Association of mild kidney dysfunction with silent brain lesions in neurologically normal subjects. Cerebrovasc Dis Extra. 2015;5:22–7.
26. Cheung AK, Sarnak MJ, Yan G, et al. Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int. 2000;58:353–62.
27. Iseki K, Fukiyama K. Clinical demographics and long-term prognosis after stroke in patients on chronic haemodialysis the okinawa dialysis study (OKIDS) Group. Nephrol Dial Transpl. 2000;15:1808–13.
28. Toyoda K, Fujii K, Fujimi S, et al. Stroke in patients on maintenance hemodialysis: a 22-year single-center study. Am J Kidney Dis. 2005;45:1058–66.
29. Winkelmayer WC, Liu J, Setoguchi S, Choudhry NK. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. Clin J Am Soc Nephrol. 2011;6:2662–8.
30. Nobakht N, Hanna RM, Al-Baghdadi M, et al. Advances in autosomal dominant polycystic kidney disease: a clinical review. Kidney Med. 2020;2:196–208.
31. Cherng YG, Lin CS, Shih CC, et al. Stroke risk and outcomes in patients with chronic kidney disease or end-stage renal disease: two nationwide studies. PLoS ONE. 2018;13: e0191155.
32. De La Mata NL, Alfaro-Ramirez M, Kelly PJ, Masson P, Al-Shahi Salman R, Webster AC. Absolute risk and risk factors for stroke mortality in patients with end-stage kidney disease (ESKD): population-based cohort study using data linkage. BMJ Open. 2019;9: e026263.