Estimated renal function and cardiovascular or non-cardiovascular mortality in community population: results from the national health and nutrition examination surveys

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Research article

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Abstract

Background

Renal insufficiency is an important risk factor for mortality in various populations. The present study was conducted to determine the optimal equation for the estimation of renal function in predicting adverse events in community population in US.

Methods

We examined the Cockcroft–Gault, modification of diet in renal disease (MDRD), Mayo Healthy-Chronic Kidney Disease (Mayo), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) derived estimated glomerular filtration rates (eGFR) and the association with cardiovascular or non-cardiovascular mortality among 25,677 participants of US National Health and Nutrition Examination Survey from 2005 to 2014.

Results

The cardiovascular mortality and non-cardiovascular mortality increased with decrease in renal function. The MDRD derived eGFR exhibited the lowest predictive ability for all-cause mortality in all participants. For cardiovascular mortality, the Cockcroft–Gault derived eGFR exhibited the highest predictive power compared with the MDRD (area under the curve [AUC]: 0.842 vs. 0.764, $p < 0.001$), Mayo (AUC: 0.842 vs. 0.812, $p < 0.001$) and CKD-EPI (AUC: 0.842 vs. 0.813, $p < 0.001$) derived eGFR. For non-cardiovascular mortality, the Cockcroft–Gault derived eGFR exhibited similar superiority in non-cardiovascular mortality.

Conclusions

The value of the Cockcroft–Gault equation was superior to the other three equations for the prediction of cardiovascular or non-cardiovascular mortality in community population. This equation can serve as a risk-stratification tool for long-term events in community population.

Background

Renal insufficiency is an important risk factor for mortality in various populations. The worse the renal function, the worse the long-term prognosis (1). Numerous studies have suggested the importance of renal function in risk stratification in order to establish personalized follow-up plans and prognostic improvement interventions (2).

To assess renal function, the well accepted gold standard is the measurement of glomerular filtration rate (GFR). However, it is not routinely used in clinical practice due to its invasiveness and high cost (3). In

contrast, the calculation of the estimated glomerular filtration rate (eGFR) and creatinine clearance rate is an effective and simple method which has been widely applied in clinical practice. This is achieved using prediction equations including the Cockcroft–Gault eGFR Eq. (4), modification of diet in renal disease (MDRD) Eq. (5), Mayo Healthy-Chronic Kidney Disease (Mayo) Eq. (6), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Eq. (7).

Previous studies have compared the predicted values of different equations, but the results are inconsistent, probably because of the different populations included. In addition, most of these studies were conducted on people at high risk for some underlying disease. Large sample studies of the general community population to determine the most effective and simple eGFR prediction equation are still lacking. Therefore, the present study was conducted to compare the predictive values of these four eGFR equations on estimated risk of cardiovascular or non-cardiovascular mortality in community population in the community population using data from the Third National Health and Nutrition Examination Survey.

Methods

Study design and population

All the participants were the 2005–2014 National Health and Nutrition Examination Surveys (NHANES) (8, 9). The NHANES was a multistage, stratified, clustered probability sample of the non-institutionalized United States civilian population, nationally representative survey of the conducted by the National Center for Health Statistics of the Center for Disease Control and Prevention. In this study, total of 50,965 subjects was screamed, and participants who were aged < 18 years old, missing data on questionnaire, missing serum creatinine (Scr) were excluded. After applying the exclusion criteria, a total of 25,677 participants were included for analysis (Fig. 1). The survey protocol was approved by the Institutional Review Board of the Centers for Disease Control and Prevention. Informed consent was signed by all participants before enrolled.

Collection of clinical data

A briefly, standard procedure and protocol include questionnaires and examinations, which is available on its official website(10), was performed by NHANES. Baseline data mainly included socio-demographic information (such as age, gender, ethnicity), lifestyle and behaviors (such as smoking status), previous medical history (such as hypertension, diabetes, stroke, and coronary heart disease), and physical examination (such as height, weight).

Body mass index (BMI) was defined as mass (kilograms) divided by the square of height (meters squared). Hypertension was defined as having a history of hypertension, or SBP/DPB ≥ 140/90 mmHg, or using antihypertensive medications. Diabetes was defined as a fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL), hemoglobin A1c (HbA1C) level ≥ 6.5%, 2-hour glucose of Oral Glucose Tolerance Test ≥

200 mg/dL, a self-reported physician diagnosis of DM, a use of glucose-lowering medications, or a use of insulin injections (11).

Stroke, emphysema, cancer, any liver condition, congestive heart failure and coronary heart disease were diagnosis according to self-reported physician diagnosis.

Scr was measured using a kinetic rate Jaffe method. The Cockcroft–Gault, MDRD, Mayo, and CKD-EPI equations for estimating renal function are shown in **Table S1**.

Clinical outcomes

Long-term cardiovascular, and non-cardiovascular mortality were the outcomes of the present study. Mortality status was obtained from a publicly available dataset of the NHANES, which captured the vital status and cause of death of survey participants from baseline to December 31, 2015. For all-cause mortality, we included mortality from all causes. Cardiovascular mortality was defined by International Classification of Diseases, 10th Edition, Clinical Modification System codes (ICD-10) (I00-I09, I11, I13, and I20-I51) derived from death-certificate data (12). All-cause mortality except cardiac relate deaths were defined as non-cardiovascular mortality.

Statistical Analyses

Baseline continuous variables were expressed as mean ± standard deviation (normal distribution) or median and quartile range (non-normal distribution) and categorical variables as a percentage where appropriate. Receiver operating characteristic (ROC) curve analyses were performed to calculate the area under the curve (AUC) and 95% confidence interval (CI) of the eGFR in relation to predicting the occurrence of adverse events. The predictive ability of the Cockcroft–Gault, C-MDRD, Mayo, and CKD-EPI derived eGFR was compared using the non-parametric approach described by DeLong et al. (13) survival analysis was performed using standardized Kaplan–Meier curves and Log rank test. All data were analyzed using the SPSS software version 24.0 (SPSS Inc.; Chicago, IL, USA). For all analyses, a two-tailed $p < 0.05$ was denoted as statistically significant.

Results

Baseline Characteristics

After exclude 25,288 participants, a total of 25,677 cases were enrolled in this study and the baseline characteristics are shown in Table 1. The mean age was 49.3 ± 17.9 years and 51.7% of the cases were female. 8997(35.0%) participants have a history of hypertension, 3045(11.9%) experienced diabetes, 818(3.2%) suffered from congestive heart failure, and 1020(4.0%) with coronary heart disease. In terms of renal function, the Mayo equation estimated the highest mean eGFR value (103.9 ± 23.1) and CKD-EPI (90.7 ± 23.7) the lowest.

Table 1
Baseline characteristics

Characteristics	Value (n = 25677)
Age, years	49.3 ± 17.9
Sex, n (%)	12486(48.6)
Male	13191(51.4)
Female	
Ethnicity, n (%)	13947(54.3)
Non-white	11730(45.7)
White	
BMI	29.0 ± 6.8
Current smoke, n (%)	5450(21.2)
Previous medical history, n (%)	8997(35.0)
Hypertension	3045(11.9)
Diabetes	961(3.7)
Stroke	523(2.0)
Emphysema	930(3.6)
Liver condition	2326(9.1)
Cancer	818(3.2)
Congestive heart failure	1020(4.0)
Coronary heart disease	
Serum creatinine, mg/dl	0.9 ± 0.5
Renal function	101.1 ± 34.9
Cockcroft-Gault	91.2 ± 27.0
MDRD	103.9 ± 23.1
Mayo	90.7 ± 23.7
CKD-EPI	
Follow-up time, years	5.7(3.3,8.1)

Abbreviations: BMI, Body mass index; MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; Mayo, Mayo Healthy-Chronic Kidney Disease

Characteristics	Value (n = 25677)
Long-term death*, n (%)	2012(7.8)
All-cause	353(1.4)
Cardiovascular	1659(6.5)
Non-cardiovascular	

Abbreviations: BMI, Body mass index; MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; Mayo, Mayo Healthy-Chronic Kidney Disease

Long-term outcomes

During a median follow-up of 5.7 years, 31 individuals lost follow up and there were 2012(7.8%) individuals died of all causes. Cardiovascular mortality accounted for 17.5 percent of the total, while 1,659 patients died from non-cardiovascular deaths. The incidents of long-term mortality according to eGFR categories are shown in Fig. 2. Those who with eGFR < 30 mL/min per 1.73 m^2 had the highest all-cause mortality and cardiovascular or non-cardiovascular mortality.

Prediction performance and eGFR equation

ROC curves for all-cause and cause-specific mortality with different equation are presented in Fig. 3. The AUC was larger in Cockcroft–Gault derived eGFR than in the other three equation and all the comparisons amongst them showed significant differences between the four formulas with best performance by Cockcroft–Gault derived eGFR. For cardiovascular mortality, the Cockcroft–Gault derived eGFR exhibited the highest predictive power compared with the MDRD (AUC: 0.842 vs. 0.764, $p < 0.001$), Mayo (AUC: 0.842 vs. 0.812, $p < 0.001$) and CKD-EPI (AUC: 0.842 vs. 0.813, $p < 0.001$) derived eGFR. The AUC for all-cause death was 0.802, 0.726, 0.777, and 0.775, for non-cardiovascular death, the AUC was 0.794, 0.718, 0.770, and 0.766 for the Cockcroft–Gault-, MDRD-, Mayo-, and CKD-EPI derived eGFR, respectively (Fig. 3A-C). The Cockcroft–Gault derived eGFR exhibited similar superiority in non-cardiovascular mortality. Furthermore, there was no significant difference found in the predictive ability of Mayo-, and CKD-EPI derived eGFR equations both for all-cause mortality and cardiovascular or non-cardiovascular mortality.

ROC curves for cardiovascular and non-cardiovascular mortality with Cockcroft–Gault derived eGFR, Scr and blood urea nitrogen are presented in Fig. 4. Similarly, the Cockcroft–Gault derived eGFR exhibited the statistically significant high predictive ability compared with the others ($P < 0.001$). For all-cause mortality, the Cockcroft–Gault derived eGFR exhibited the highest predictive power compared with the Scr (AUC: 0.802 vs. 0.682, $p < 0.001$), blood urea nitrogen (AUC: 0.802 vs. 0.689, $p < 0.001$). The AUC for cardiovascular death was 0.842, 0.730, and 0.724, for non-cardiovascular death was 0.794, 0.672, and 0.681 of the Cockcroft–Gault derived eGFR, Scr and blood urea nitrogen, respectively (Fig. 4A-C).

In the ROC analysis, Cockcroft–Gault derived eGFR < 80 mL/min per 1.73 m^2 had a sensitivity of 75.6% and specificity of 72.7% in predicting all-cause mortality (AUC = 0.802, 95% CI, 0.792–0.813, P < 0.001). Kaplan–Meier survival analysis demonstrated significantly worse outcomes in patients with Cockcroft–Gault derived eGFR < 80 mL/min per 1.73 m^2 compared to those with eGFR ≥ 80 mL/min per 1.73 m^2 (Log-rank = 2225.594, p < 0.001; Fig. 5A-C).

Discussion

This study compared the prognostic value of equations used for the estimation of renal function in community population. We found that the Cockcroft–Gault equation was superior to the other three equations for predicting both all-cause mortality and cardiovascular or non-cardiovascular mortality. In addition, informants with Cockcroft–Gault derived eGFR < 80 mL/min per 1.73 m^2 had a worse prognosis. Thus, the Cockcroft–Gault equation can serve as a risk-stratification tool for mortality in community population.

Scr is a waste product and continually generated via muscle metabolism. Normal-functioning kidneys filter out most of the Scr to maintain its levels within the normal range. Therefore, Scr is an important marker in the assessment of renal function (14). However, Scr is a late indicator and increases only following marked damage to the function of the nephrons. Therefore, this measure is not suitable for the identification of patients with early-stage kidney disease. A more favorable method for the assessment of function is the calculation of the eGFR, which is a non-invasive and inexpensive approach. Our results also confirm that eGFR is a stronger predictor of all-cause mortality and cardiovascular or non-cardiovascular mortality than Scr. CKD-EPI is currently used as the preferred method for GFR estimation in routine clinical practice due to its validity and accuracy (7, 15).

What is even more remarkable, however, is that many studies have confirmed that different equations have different values for predicting long-term adverse events in various populations. Rivera-Caravaca JM (16) analyzed 1,699 acute acute coronary syndrome patients and demonstrated that calculation of the eGFR using the Cockcroft–Gault equation presented higher predictive ability than the MDRD and CKD-EPI equations. Nevertheless, in patients with type 2 diabetes, the MDRD equation is superior in detecting impaired renal function compared with CKD-EPI and Cockcroft–Gault equations (17). Moreover, few studies have included individuals from the communities. Tariq Shafi and colleges (18) examined the association between eGFR and mortality among 16,010 participants and found that CKD-EPI categories improve mortality risk stratification compare with MDRD categories also use data from NHANES. However, it was difficult to reach a consensus based on the different sample size, and the Cockcroft–Gault equation was not examined in their study. Therefore, in this study, we expanded the sample size and also found that the predictive value of CKD-EPI formula was better than that of MDRD, but both significantly lower than that of Cockcroft–Gault equation, whether in all-cause mortality, cardiovascular or non-cardiovascular mortality.

The Cockcroft–Gault equation was proposed by Cockcroft and Gault in 1976 was developed in a Caucasian male population of 236 patients aged 18–92 years in order to predict creatinine clearance (and not GFR) in situations in which renal function was only slightly impaired (19). This original Cockcroft-Gault formula was found to be inaccurate for GFR prediction. Sheila M. Wilhelm and colleges (20) conducted a meta-analysis of 13 English-language trials comparing 24-hour measured creatinine clearance with Cockcroft-Gault estimated creatinine clearance by using various body weights or rounded Scr values and found that using the Cockcroft-Gault equation with no body weight and actual Scr value most closely estimated measured creatinine clearance. Our study also found that Cockcroft-Gault equation with no body weight is simpler and easier to obtain, and has higher predictive value for the long-term prognosis assessment of the general population in the United States, and thus more suitable for community promotion.

In conclusion, the present study, using a national large registry data, was conducted to further determine the optimal prediction equation for individuals in the community population. We found that the Cockcroft–Gault equation to estimate eGFR performed well in predicting all-cause mortality and cardiovascular or non-cardiovascular mortality. We speculated that this equation could accurately estimate GFR, and be simpler and identify more individuals with renal insufficiency, and thus, have higher predictive ability for the occurrence of adverse events.

Limitations

The present study was characterized by several limitations. Firstly, the enrolled population was obtained from a representative survey, and some baseline variables such as previous disease history and history of taking medication were self-reported, which may be some recall errors. Secondly, the GFR measurement was not performed. For this reason, the predictive value of the true renal function was unknown. Therefore, all examined equations of the eGFR in our study were based on Scr. However, the measurement of the Scr-based eGFR is widely used in clinical practice. Finally, Scr was only measured once at baseline, which may not truly reflect the participant's renal function status.

Conclusion

In conclusion, this study compared the predictive value of different eGFR equations in community population and found that the Cockcroft–Gault equation was superior to the Mayo, MDRD, and CKD-EPI equations in predicting all-cause mortality and cardiovascular or non-cardiovascular mortality in community population. In addition, patients with Cockcroft–Gault derived eGFR < 80 mL/min per 1.73 m^2 had a worse prognosis.

Abbreviations

NHANES, National Health and Nutrition Examination Surveys

eGFR, estimated glomerular filtration rates

Scr, serum creatintine

MDRD, modification of diet in renal disease;

CKD-EPI, chronic kidney disease epidemiology collaboration;

Mayo, Mayo Healthy-Chronic Kidney Disease

BMI, Body mass index;

ROC, Receiver operating characteristic

AUC, area under the curve

CIs, Confidence Intervals

Declarations

Ethics approval and consent to participate

The survey protocol was approved by the NCHS Research Ethics Review Board of the Centers for Disease Control (Protocol #98-12; http://www.cdc.gov/ nchs/nhanes/ irba98.htm) and Prevention. Informed consent was signed by all participants before enrolled.

Consent to publish

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the NHANES repository, https://wwwn.cdc.gov/Nchs/Nhanes.

Competing interests

The authors of this paper reported no financial conflicts of interest.

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Authors' Contributions

D.Y. and J.C. contributed to the conception and design. J.H., X.W., M.J., Z.S., Z.Y. and Y.L. contributed to the analysis and interpretation of data. J.H. and X.W. contributed to the drafting of the article. J.H., M.J, D.Y. and J.C. contributed to revising the article. Z.S., Z.Y. and Y.L. provided intellectual content of critical importance to the work described. This manuscript was confirmed to be accurate and approved by all authors.

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Figures

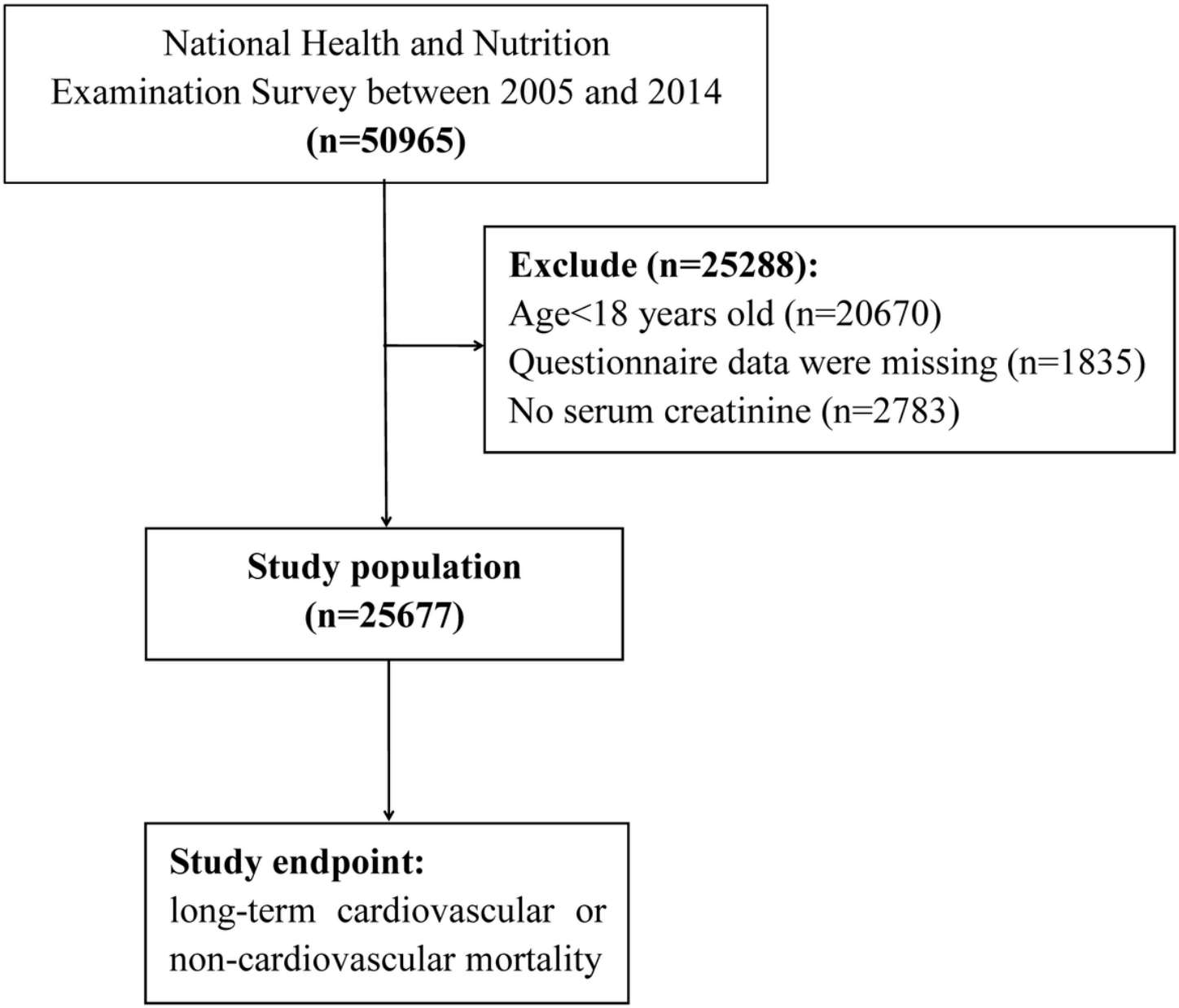

Figure 1

Flow diagram for the selection of the study population

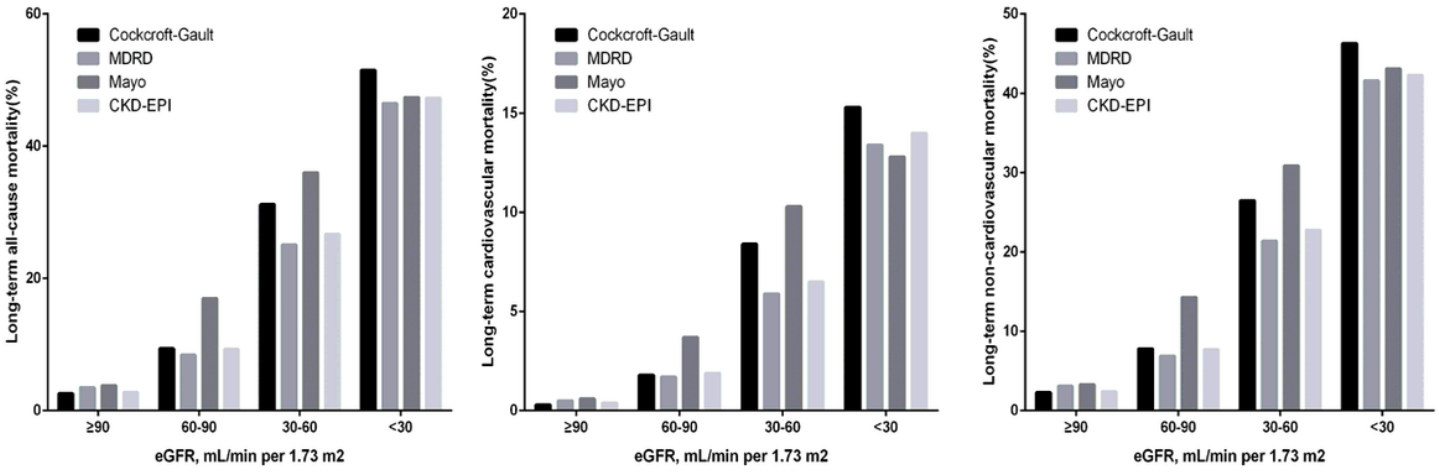

Figure 2

The incidents of long-term mortality according to eGFR categories (A: all-cause mortality; B: cardiovascular mortality; C: non-cardiovascular mortality)

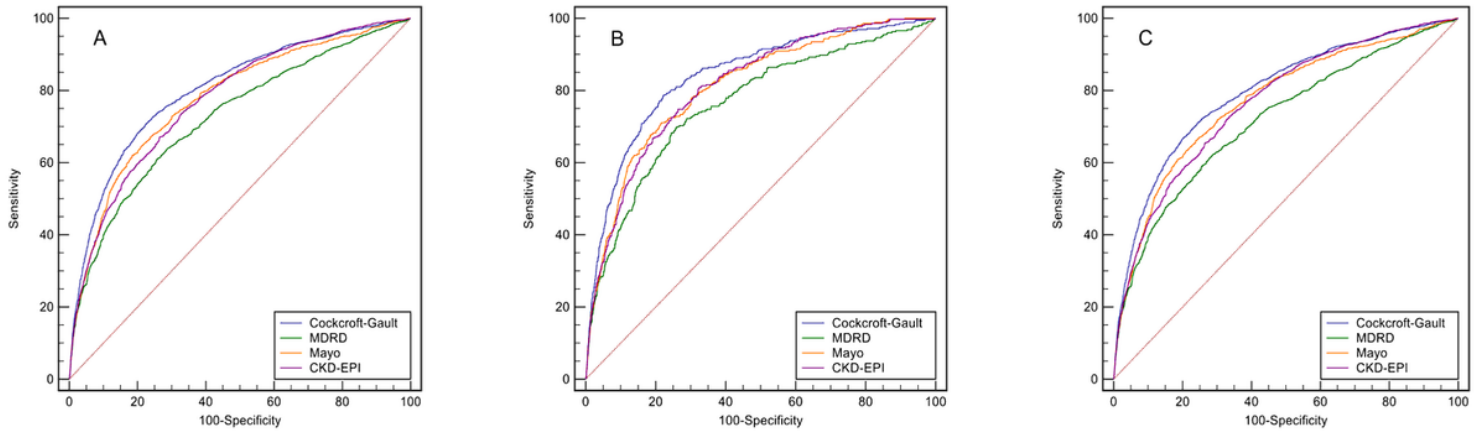

Figure 3

Received operating characteristic curves for mortality according to the different renal function equations (A: all-cause mortality; B: cardiovascular mortality; C: non-cardiovascular mortality)

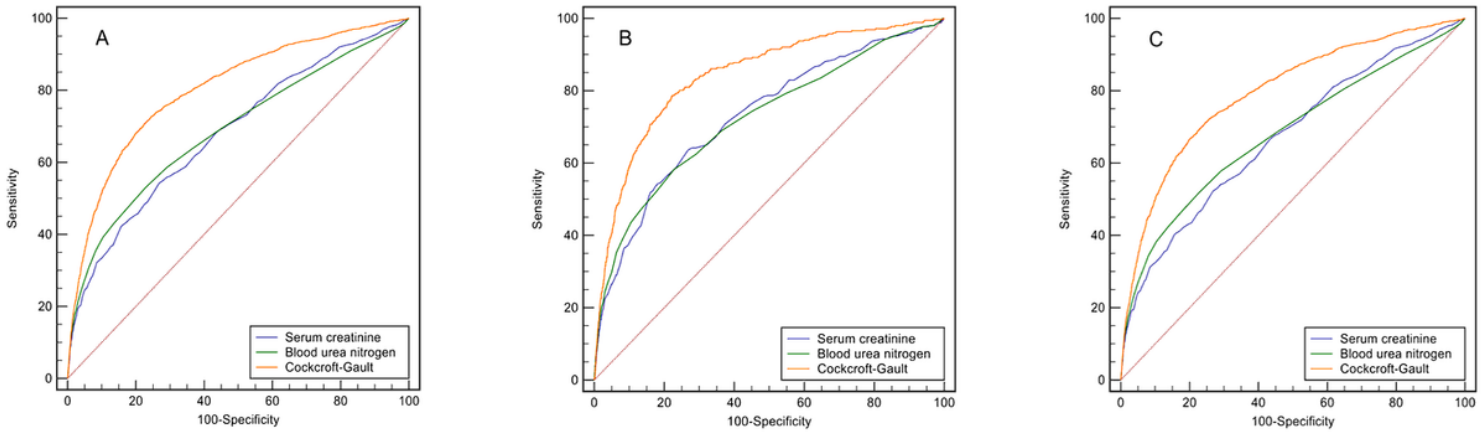

Figure 4

ROC curves for long term mortality according to Cockcroft–Gault derived eGFR, serum creatinine and blood urea nitrogen (A: all-cause mortality; B: cardiovascular mortality; C: non-cardiovascular mortality)

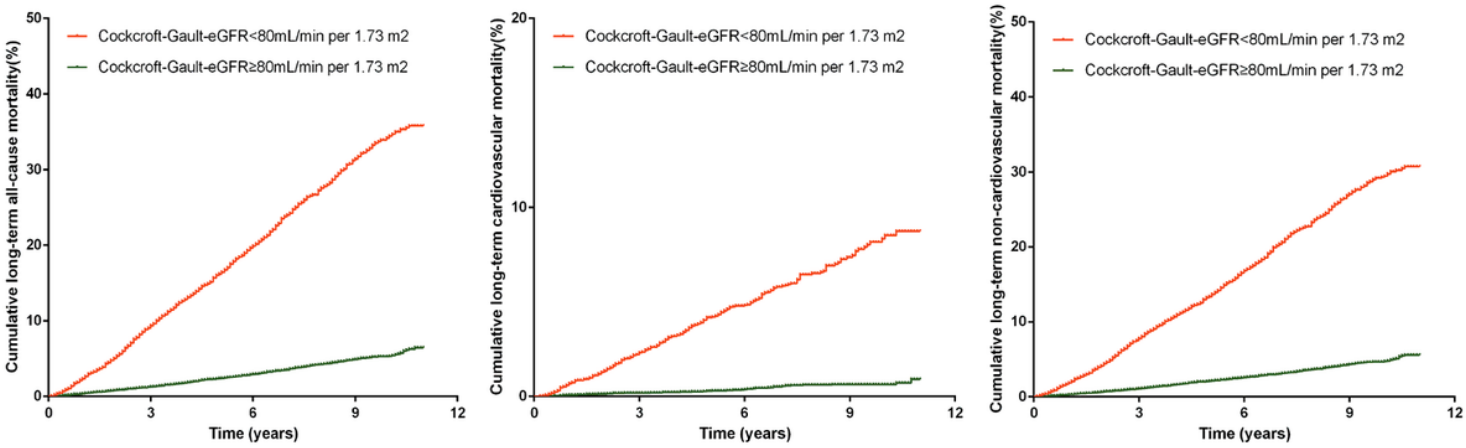

Figure 5

Kaplan–Meier survival curve for long term mortality (A: all-cause mortality; B: cardiovascular mortality; C: non-cardiovascular mortality)