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A Risk Score to Guide Cystatin C Testing to Detect Occult Reduced Estimated Glomerular Filtration Rate

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Abstract

Background/Aims—Persons with occult reduced eGFR (eGFR <60 ml/min/1.73m^2 detected by serum cystatin C but missed by creatinine) have high risk for complications. Among persons with preserved kidney function by creatinine-based estimated glomerular filtration rate ((eGFRcreat) >60 ml/min/1.73m^2), tools to guide cystatin C testing are needed.

Methods—We developed a risk score to estimate an individual's probability of reduced eGFR by cystatin C (eGFRcys<60 ml/min/1.73m^2) in The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study and externally validated in the Third National Health and Nutrition Examination Survey (NHANES III). We used logistic regression with Bayesian model averaging and variables available in practice. We assessed performance characteristics using calibration and discrimination measures.

Results—Among 24,877 adults with preserved kidney function by creatinine, 13.5% had reduced eGFRcys. Older and Black participants, current smokers, and those with higher BMI, lower eGFRcreat, diabetes, hypertension, and history of cardiovascular disease were more likely to have occult reduced eGFR (p <0.001). The final risk function had a c-statistic of 0.87 in REGARDS, and 0.84 in NHANES. By risk score, 72% of occult reduced eGFR cases were detected by screening only 22% of participants.

Conclusions—A risk score using characteristics readily accessible in clinical practice can identify the majority of persons with reduced eGFRcys that is missed by creatinine.

Keywords

kidney disease; Serum Cystatin C; Creatinine; Creatinine-based estimated glomerular filtration rate (eGFRcreat); Cystatin C-based estimated glomerular filtration rate (eGFRcys)

Introduction

Reduced estimated glomerular filtration rate (eGFR), defined as <60 ml/min/1.73m^2, is associated with increased risks of cardiovascular events, death and progression to end stage renal disease (ESRD).[1] Accurate detection and classification of persons at highest risk for

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complications from reduced eGFR is required in order to implement targeted prevention strategies. In fact, international guidelines now recommend that diagnosis and staging of chronic kidney disease (CKD) should be based on categories of both creatinine-based eGFR (eGFRcreat) and urinary albumin levels to reflect disease prognosis.[2] However, reliance on eGFRcreat alone to detect reduced eGFR can misclassify risk associated with CKD. In a meta-analysis of 11 general population cohorts with over 90,000 participants, more than 14% of persons with eGFRcreat >60 ml/min/1.73m^2 were reclassified to an eGFR < 60 ml/min/1.73m^2 by cystatin C. These persons were at significantly higher risks for death, cardiovascular death and ESRD, compared to those not reclassified.[3]

The most recent Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease included a new suggestion to confirm CKD by serum cystatin C (eGFRcys) among persons with eGFRcreat 45-59 ml/min/1.73m^2 and no albuminuria, particularly if the clinician suspects the eGFRcreat may be inaccurate. However, the Guideline provided little guidance on the use of cystatin C in persons with higher eGFRcreat levels. In addition to improved classification of persons with eGFRcreat 45-59 ml/min/1.73m^2, we have previously shown that measurement of cystatin C can capture “occult reduced eGFR”, defined as eGFRcys <60 among persons with eGFRcreat > 60 ml/min/1.73m^2.[4,5] Despite advances in the field, no systematic approaches have been published to identify persons who are most likely to have reduced eGFR that is missed by creatinine. As cystatin C remains relatively more expensive to measure compared with creatinine, guidance is needed to identify persons at high risk for occult reduced eGFR using easily ascertainable clinical and demographic characteristics.

We designed this study to develop and validate a risk score for occult reduced eGFR in large, general population of U.S. adults participating in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study and the National Health and Nutrition Examination Survey (NHANES).

Methods

Participants

To develop a risk score for occult reduced eGFR, we used data from the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. REGARDS is a large, population-based cohort study designed to study factors that contribute to the excess stroke burden among American Blacks and among persons in the “stroke belt” of the United States. Briefly, between 2003 and 2007, REGARDS recruited 30,239 Black and White participants who were 45 years or older. Participants were randomly sampled and recruited by mail and then telephone, followed by an in-home study visit. By design, approximately 50% of REGARDS participants were recruited in North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana and Arkansas. The other 50% was recruited from the remaining forty continental states and Washington D.C. Participant information was first collected via a telephone interview. A trained technician then conducted an in-home examination for the anthropometric and clinical exam, specimen collection and inventory of medications.[6]

For these analyses, we included REGARDS participants who had creatinine-based estimated glomerular filtration rate (eGFRcreat) > 60 ml/min/1.73m^2 and who had a measurement of cystatin C, for a total sample size of 24,877. All appropriate institutional review boards approved this study and participants provided written informed consent.

Outcome

The primary study outcome of interest was occult reduced eGFR. This was defined as having an eGFRcys < 60 and eGFRcreat > 60 ml/min/1.73m^2. Cystatin C was measured by particle-enhanced immunonephelometry (N Latex Cystatin C on the BNII, Dade Behring) after a 12-hour fast and calibrated to the international standard.[7] Serum creatinine was measured and calibrated to isotope dilution mass spectrometry-traceable methods. The eGFRcreat was estimated using the CKD-Epi equation for creatinine (eGFRcreat), and the eGFRcys using the 2012 CKD-Epi cystatin C equation.[8]

Candidate Variables

For these analyses, we considered candidate variables defined *a priori* as being associated with CKD and likely to be readily available in clinical practice. Age, race, sex, and smoking history were determined by self-report during the telephone interview. Height and weight were obtained by a trained technician. Prevalent cardiovascular disease (CVD) was defined by any one of the following: electrocardiographic evidence of a myocardial infarction, self-report of a cardiac procedure (CABG or angioplasty), self-reported myocardial infarction, or self-reported stroke. Hypertension was defined by self-reported use of antihypertensive medications or an average of two seated blood pressure (BP) measurements with systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg. Diabetes was defined as self-reported use of insulin or oral hypoglycemic agents, fasting blood glucose ≥126mg/dL, or a non-fasting blood glucose ≥200mg/dL. A urine albumin to creatinine ratio (ACR) was entered into the model only in a sensitivity analysis described below. For these, the urine albumin was measured by nephelometry using the BNII ProSpec nephelometer (Dade-Behring) and urine creatinine by the Jaffe method using the Modular-P chemistry analyzer (Roche/Hitachi). We defined albuminuria as a spot ACR ≥30mg/g.

Risk Score Development and Evaluation

We first compared demographic and clinical characteristics of REGARDS participants stratified by eGFRcreat category using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. To develop the occult reduced eGFR risk score, we considered the following clinical characteristics as candidate variables: age (continuous), gender, race, body mass index (continuous), diabetes, systolic and diastolic blood pressure (continuous), hypertension, use of antihypertensive medication, history of cardiovascular disease, smoking, and eGFRcreat (continuous). We considered ACR (continuous) only in a sensitivity analysis, as this may not be readily available in practice, particularly among persons without diabetes. We assessed linearity for continuous predictors adding quadratic terms to the models. We evaluated unadjusted generalized additive models to construct smoothing splines in order to examine the relationships of continuous parameters with the outcome.[9] We used linear splines to model age, eGFRcreat, and BMI

due to the curvilinear associations of these variables with occult reduced eGFR. Specifically, the effect of eGFRcreat was modeled linearly but with different slopes in the ranges of 60 to 75 and > 75 ml/min/1.73m^2, based on observed associations, and the effect of BMI had different slopes > or < 40 kg/m^2.

We employed multivariable logistic regression models to evaluate characteristics associated with reduced eGFRcys. We first used stepwise backward selection with a significance level of α=0.05 to remove candidate covariates. We utilized Bayesian model averaging as an alternative model building approach; predictors with posterior probabilities >35% were retained in the model.[10] Models constructed using the two approaches were very similar. We used 10-fold cross-validation to compare candidate models and identify the best fitting model.

Using the final model, we developed a point-based risk score for the presence of occult reduced eGFR, using methods established by the Framingham Heart Study.[11] The total number of points was calculated for each participant using this risk score and associated with the probability of having occult reduced eGFR. We used c-statistics to assess model discrimination, and goodness-of-fit testing to assess calibration. Bootstrap simulation was used to assess over optimism. We assessed model performance by comparing the observed event rates within each decile of probability to expected rates, which represent the predicted rate based on the proportion at risk within each subgroup. These are plotted across the distribution of the risk score for ease of interpretation. We also evaluated the diagnostic performance of discrete risk score thresholds to detect occult reduced eGFR in the population. We plotted the cumulative probability and the cumulative proportion of eGFRcys < 60 across the distribution of the risk score, separately. We also present the proportion of occult reduced eGFR cases detected (# of cases detected/total # cases) and proportion of the population tested at several values of the risk score.

We conducted two sensitivity analyses. In the first, we considered the outcome eGFRcys <60 or ACR ≥ 30 mg/g ml/min/1.73m^2 as this is the definition of CKD. In the second, we included an additional 2053 REGARDS participants with eGFRcreat 45-59, and we considered the outcome eGFRcys <45 ml/min/1.73m^2 due to the known improvement in reclassification by cystatin C across that eGFRcreat range.

External Validation

We validated the risk score from REGARDS using data from the National Health and Nutrition Examination Survey 1988-94 (NHANES III). In this analysis, we included 3,908 persons age>45 years who had measured cystatin C and who had eGFRcreat > 60 ml/min/1.73m^2. Less than 1% of study participants were excluded due to missing covariates. We used SAS procedure SURVEYLOGISTIC to produce point estimates and standard errors incorporating sampling weights to account for the complex survey sampling design.

All analyses were conducted using Stata version 11 and SAS version 9.3. Bayesian model averaging was performed using the BMA package for the R statistical computing language.

Results

Participant Characteristics

Among 24,877 REGARDS participants with an eGFRcreat > 60 ml/min/1.73m^2, approximately 19% had eGFRcreat 60-75, 30% had eGFRcreat 75-90, and 51% had eGFRcreat >90 ml/min/1.73m^2. The median age in the overall sample was 63 (IQR: 57, 70), of whom 54% were female and 41% were Black. There was a high prevalence of obesity in this cohort, with 32% of persons having BMI 30-39.9, and 5.9% with BMI ≥40. Persons in the lower eGFRcreat categories were older and hypertension and cardiovascular disease were most prevalent among persons with the lowest eGFRcreat. (**Table 1**)

Characteristics Associated with Occult Reduced eGFR

Overall, 3,354 (13.5%) persons had occult reduced eGFR. We found that older age, diabetes, hypertension, history of CVD and current smoking were associated with a higher prevalence of eGFRcys <60 ml/min/1.73m^2. A higher BMI was associated with higher prevalence for occult reduced eGFR, but the slope appeared to be steeper at levels of BMI > 40 kg/m^2 (test for non-linearity: p=0.0007). For example, among persons with BMI<40 kg/m^2, each unit increase of BMI was associated with a 9% increased odds of occult reduced eGFR. Among persons with BMI>40, each unit increase in BMI was associated with a 16% increased odds of occult reduced eGFR. Age and eGFRcreat showed stronger associations with eGFRcys <60 at higher and lower levels, respectively (test for nonlinearity: p=0.006 and p<.0001), with inflection points around age 70 and eGFRcreat 75 ml/min/1.73m^2. We detected a statistically significant interaction with race and smoking, where associations appeared stronger in Whites. We therefore allowed estimates to vary by race. While we also detected statistically significant (p <0.05) interactions with race for age, BMI at < 40 kg/m^2, and eGFRcreat at > 75 ml/min/1.73m^2, the estimates were only minimally different between Blacks and Whites. Including linear splines with race-specific slopes to model the associations of age, BMI >40 and eGFRcreat >75 did not significantly change model performance. Therefore, we removed these interactions from the model for ease of interpretation. (**Appendix Table 1)**

Risk Score

In **Table 2**, we present the variables included in the risk score and the points calculated for each characteristic. The range of possible risk scores was 0 (lowest probability) to 32 (highest probability). The observed percentage of participants with occult reduced eGFR ranged from <1% in the lowest decile to 55% in the highest decile, while the expected probability ranged from <1% to 54.8%. Our risk prediction model had good discrimination (overall c statistic 0.87) and calibration, and bootstrap simulation indicated a very low degree of over optimism (bias = 0.0003). In a sensitivity analyses we considered albuminuria in two ways. First, we added ACR to the model, and this did not change model performance. Each doubling of ACR was associated with a 20% increased odds of occult reduced eGFR (OR=1.20 (1.17, 1.23), p<.0001). Model discrimination was similar (c = 0.87, 95%CI: 0.866 to 0.879). We also modeled the alternative outcome eGFRcys <60 ml/min/1.73m^2 or ACR ≥ 30 mg/g. This model also performed well and had a C statistic = 0.78 (95% bias-corrected CI: 0.77 to 0.78).

We were then interested in understanding the value of using the risk score to guide cystatin C testing for an individual and for a population. At the individual level, **figure 1** shows that, for a given value of risk score, the probability that eGFRcys is <60 increases. **Figure 2A-C** can be used to evaluate the performance of a discrete threshold of the risk score in a population. For example, if we assume that, based on clinical judgment, a clinician would want to test persons who have a probability of occult reduced eGFR ≥20%, this threshold corresponds to the 78th percentile of risk (panel A). Among those above the 78th percentile of risk, we would expect 42% to have eGFRcys<60 (panel B). Such a strategy of testing 22% of the population would detect 72% of cases of eGFRcys<60 (panel C).

In a sensitivity analysis including additional participants with eGFRcreat 45-59, we found that the overall probability of eGFRcys <45 was 5.3%. The model was well calibrated, and the probability of eGFRcys <45 rose with increasing risk score (C-statistic was 0.9339, 95% bias-corrected CI: (0.9272, 0.9394)). Among persons with a risk score ≥80th percentile, the probability of eGFRcys <45 was 4%, and it was 14% among persons ≥ 90th percentile. Approximately 36% of persons ≥ 90th percentile would have eGFRcys <45. Only 12% of the population would be expected to have ≥10% probability of eGFRcys <45.

External Validation

Among participants in NHANES, the survey-adjusted prevalence of occult reduced eGFR was 12.5%. The model developed in REGARDS had excellent discrimination, with a c-statistic of 0.84. Associations of each characteristic with occult reduced eGFR in NHANES are presented in **Appendix Table 2**. **Appendix Figure 1** shows a progressive increase in both observed and expected probabilities with increasing decile, which were of similar magnitude, showing good calibration.

Discussion

In this large cohort of Black and White adults in the United States, we found that characteristics easily ascertained in clinical practice are strongly associated with occult reduced eGFR. We developed a risk score for occult reduced eGFR using age, race, eGFRcreat, diabetes, BMI, history of cardiovascular disease, hypertension and current smoking. This risk score had excellent discrimination and calibration, and it performed very well in an external, nationally representative sample. Moreover, using the risk score to guide cystatin C testing to detect occult reduced eGFR results in a more efficient use of cystatin C screening to detect >70% of cases, compared to testing strategies using eGFRcreat cut points alone.

Our report expands on the recent KDIGO guideline suggestion to measure cystatin C for CKD confirmation among persons with eGFRcreat 45-59 ml/min/1.73m^2 and no albuminuria. The guideline panel cited evidence showing that reliance on eGFRcreat alone can misclassify CKD associated risks in large segments of the population.[4,5,12] Our analyses expand on this suggestion, and add information necessary to evaluate the use of cystatin C among persons with eGFRcreat >60 ml/min/1.73m^2. Our previous work has shown that occult reduced eGFR is highly prevalent, and that persons identified as having CKD by eGFRcys but missed by creatinine are at high risk for cardiovascular events, death and

progression to ESRD.[3,4] To our knowledge, this is the first rigorously derived algorithm developed to quantify an individual's probability of having occult reduced eGFR among persons with preserved eGFR by creatinine.

The risk score presented here has several potential implications. As momentum grows for the use of personalized medicine, a clinician may use the risk score to guide the decision on whether or not to order a cystatin C measurement. The value of detecting occult reduced eGFR could be for advising patients on their risk for contrast nephropathy, use of NSAIDs or dosing of chemotherapy. Moreover, the recent guidelines from the Joint National Commission on Hypertension (JNC-8) recommend a different blood pressure threshold in the presence of CKD among persons age >60, and first choice agents may differ for persons with CKD.[13] The risk score may also have important potential uses in research. For example, investigators may use the risk score to screen high risk subjects for potential inclusion in studies of persons with CKD, who may otherwise been excluded. The risk score may also be used in future studies of CKD screening strategies.

A major strength of our study is the large number of participants, the inclusion of Black and White adults across the U.S, and the parsimonious model which makes it easy to use. We are limited by the lack of evaluation in other ethnic groups, such as Hispanics and Asians, who are also at increased risk for CKD complications. We are limited by our inability to validate the risk score among persons with little muscle mass, such as liver disease or severe cachexia. We are unable to determine the specific contributions of non-GFR determinants of creatinine and cystatin C levels because we do not have a direct GFR measure in this study. This is particularly noteworthy among persons with a high BMI because cystatin C levels may be influenced by fat and inflammation,[14] while creatinine is associated with muscle mass.[15] However, direct GFR measurement is not readily available in practice, and clinicians are primarily interested in identifying persons at high risk for CKD complications. Therefore, one should use caution when applying the risk score among persons with very low or very high BMI, and confirmatory tests are likely needed to diagnose CKD. While the model performed very well in NHANES, testing in these and other groups may still be required. Our risk score does not include estimates of albuminuria. These may not be readily available in practice among persons without diabetes, and different models would be required to guide clinicians on ACR testing. Finally, the cost-effectiveness of the strategies presented here need to be evaluated in future studies.

In summary, we developed a user friendly algorithm that estimates an individual's probability of having reduced eGFR that is missed by creatinine but detected by cystatin C. Accurate classification of CKD is important in targeting prevention and treatment strategies to persons at highest risk for complications. Future studies to evaluate the cost-effectiveness of measuring cystatin C guided by this risk score are needed.

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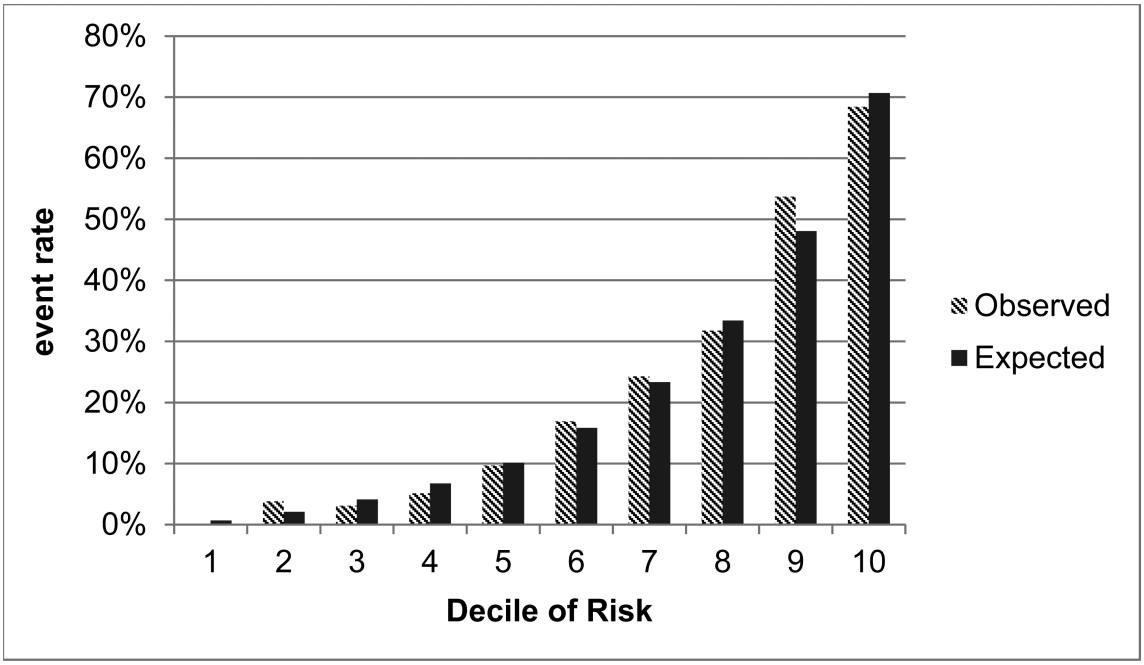
Appendix



Appendix Figure 1.
Observed vs. Expected for NHANES

Appendix Table 1

Beta coefficients and odds ratios for occult reduced eGFR in the risk score model among REGARDS participants

Risk factor	Level	Raw beta coefficient	Odds Ratio (95%CI)
Intercept		−1.5374	
Age (per year)	45-69	0.0735	1.08 (1.07, 1.09)
	70-98	0.1015	1.11 (1.09, 1.12)
eGFRcreat (per 1ml/min/1.73m^2)	60-75	−0.1034	0.90 (0.89, 0.91)
	75-90	−0.0937	0.91 (0.90, 0.92)
	>90	−0.0653	0.94 (0.92, 0.95)
Black	No	0	reference
	Yes	−0.1948	0.82 (0.74, 0.91)
Diabetes	No	0	reference
	Yes	0.3849	1.47 (1.32, 1.63)
Hypertension	No	0	reference
	Yes	0.4509	1.57 (1.42, 1.73)
Hypertension	No	0	reference
	Yes	0.2461	1.28 (1.15, 1.42)
BMI (per kg/m^2)	Up to 40	0.0857	1.09 (1.08, 1.10)
	40+	0.1457	1.16 (1.13, 1.19)

Risk factor	Level	Raw beta coefficient	Odds Ratio (95%CI)
Current Smoking	No	0	reference
	Yes: Black	0.9741	2.65 (2.19, 3.21)
	Yes: White	1.2435	3.47 (2.97, 4.06)

All p values <0.001

C statistic = 0.8692, 95% bias-corrected CI: (0.8630, 0.8749); bias = 0.000344; Pseudo R^2 = 0.30

Goodness-of-fit test passes: p = 0.08

CVD: cardiovascular disease; BMI: body mass index

Appendix Table 2

Results for the REGARDS multivariable logistic regression model of occult reduced eGFR in NHANES

Risk Factor	Level	Raw regression coefficient	Odds Ratio (95% CI)
Age (per year)	45-69	0.1219	1.13 (1.09, 1.17)
	70-98	0.1173	1.12 (1.09, 1.16)
eGFRcreat (per 1ml/min/1.73m^2)	60-75	−0.0876	0.92 (0.88, 0.96)
	75-90	−0.0693	0.93 (0.90, 0.96)
	>90	−0.0141	0.99 (0.94, 1.04)
Black	Yes	−0.3473	0.71 (0.49, 1.02)
Diabetes	Yes	0.2651	1.30 (0.87, 1.96)
Hypertension	Yes	0.6217	1.86 (1.45, 2.39)
CVD	Yes	0.4553	1.58 (0.99, 2.50)
BMI (per kg/m^2)	Up to 40	0.0774	1.08 (1.05, 1.11)
	40+	0.1083	1.11 (0.89, 1.39)
Current Smoking	Black	0.9339	2.54 (1.19, 5.45)
	White	1.1622	3.20 (2.32, 4.40)

CVD: cardiovascular disease; BMI: body mass index

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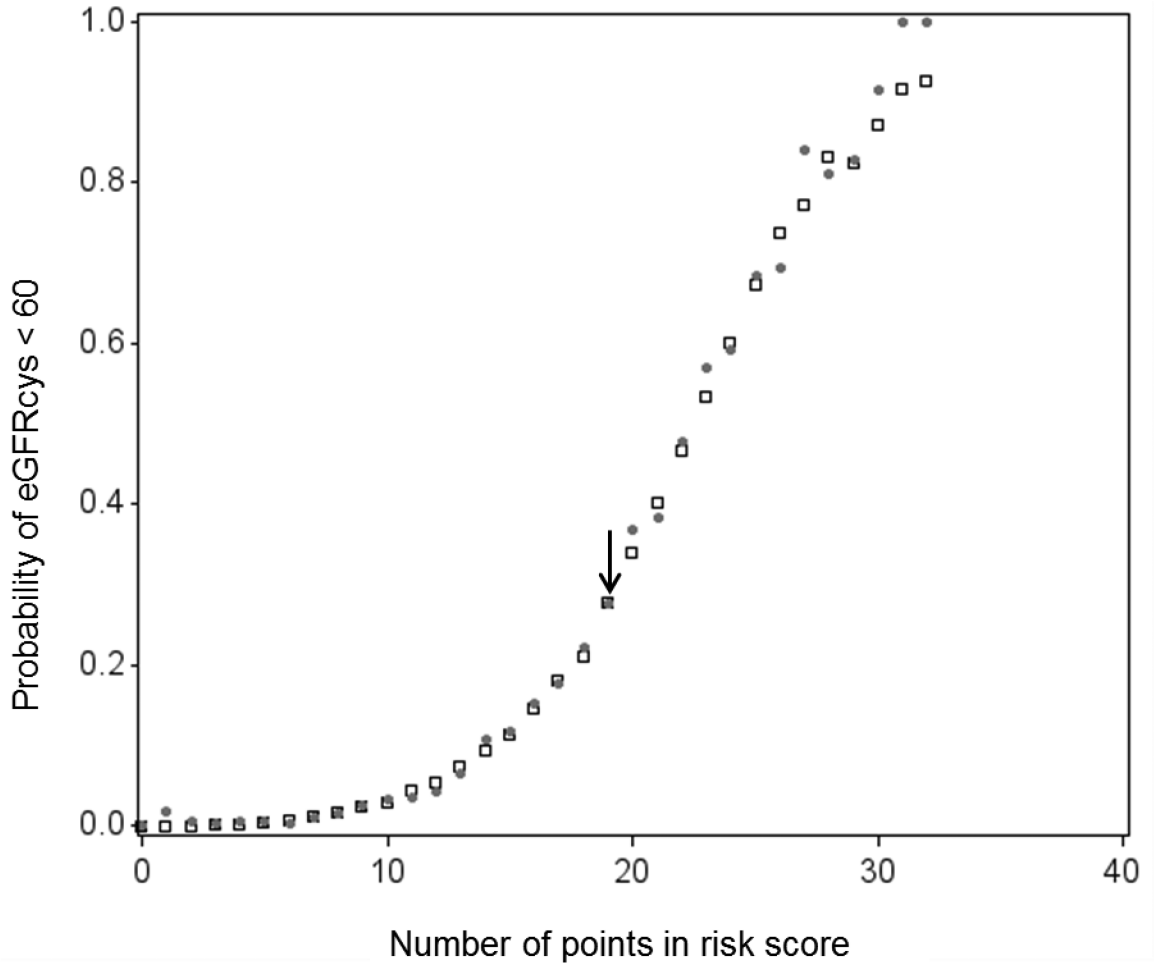

↓ = The risk score calculation for a hypothetical 55 year old Black man with a eGFRcreat 74 ml/min/1.73m², a BMI of 35 kg/m², history of hypertension and current smoking would result in a total score of 19, corresponding to a 31% probability of having reduced eGFRcys.

☐ Open symbol = predicted; ● Closed symbol = observed rate of eGFRcys<60

Figure 1.
Relationship between number of points in risk score and probability of eGFRcys<60

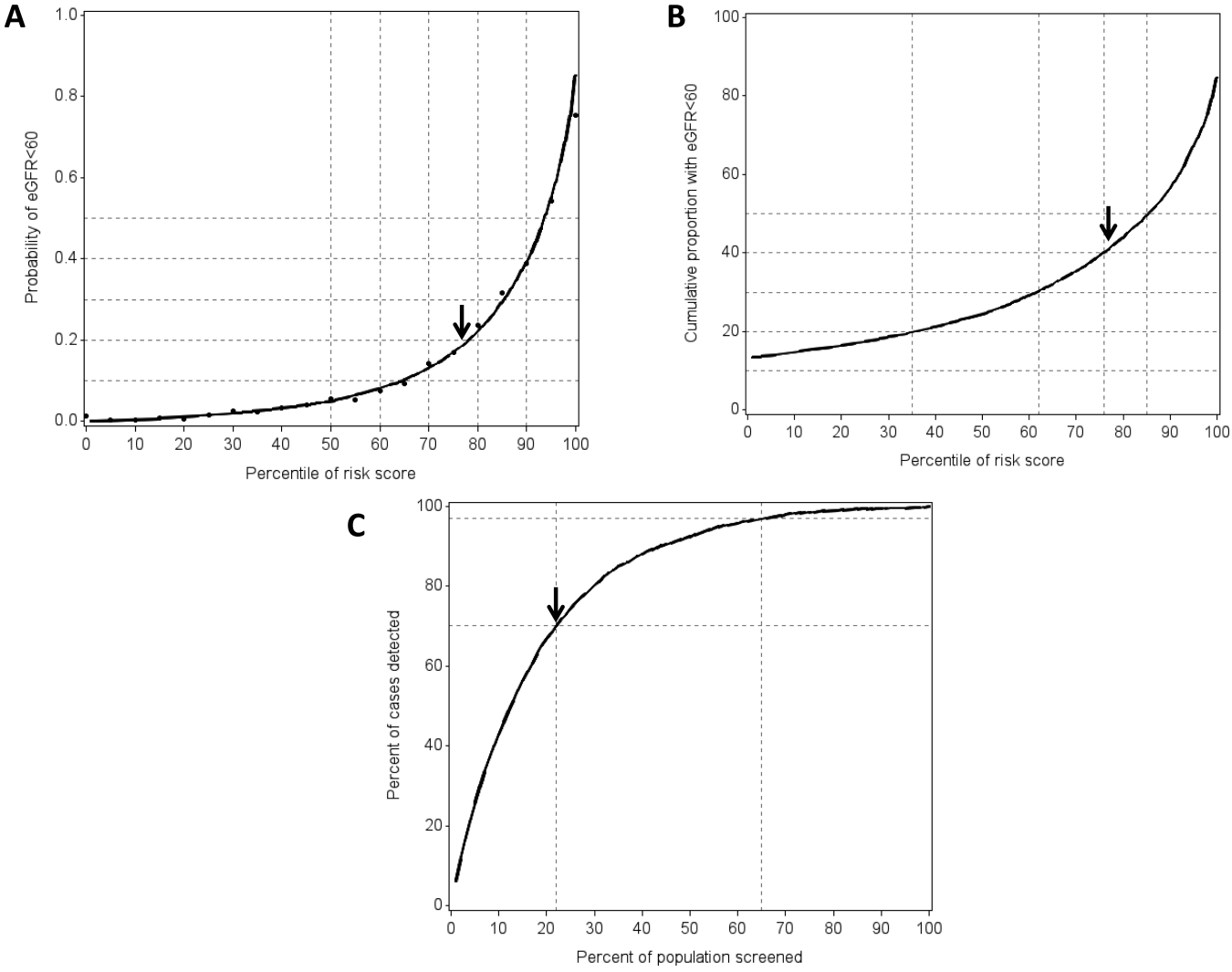

Figure 2A-C. Value of Discrete Thresholds of the Occult Reduced eGFR Risk Score

We present an example of how to evaluate the performance of a discrete threshold of the risk score in a population. If we assume that, based on clinical judgment, a clinician would want to test persons who have a probability of occult reduced eGFR ≥20%, this threshold corresponds to the 78th percentile of risk (panel A). Among those above the 78th percentile of risk, we would expect 42% to have eGFRcys<60 (panel B). Such a strategy of testing 22% of the population would detect 72% of cases of eGFRcys<60 (panel C).

Table 1

Characteristics of REGARDS participants by eGFRcreat category

Parameter	eGFRcreat 60-75 ml/min/1.73m^2 N=4,637	eGFRcreat 75-90 ml/min/1.73m^2 N=7,599	eGFRcreat >90 ml/min/1.73m^2 N=12,641	P-value
Age (y)*	69 (62-76)	67 (60-73)	60 (55-65)	<.0001
<60	703 (15%)	1836 (24%)	6001 (47%)	
60-70	1813 (39%)	3195 (42%)	5404 (43%)	
70-80	1641 (35%)	2169 (29%)	1111 (9%)	
>80	480 (10%)	399 (5%)	125 (1%)	
Female	2372 (51%)	3775 (50%)	7404 (59%)	<.0001
Black	1579 (34%)	2464 (32%)	6039 (48%)	<.0001
Cigarette smoking				<.0001
Current	505 (11%)	871 (11%)	2360 (19%)	
Past	1974 (43%)	3212 (42%)	4704 (37%)	
Never	2135 (46%)	3496 (46%)	5524 (44%)	
Diabetes mellitus	943 (20%)	1245 (16%)	2593 (21%)	<.0001
CVD	1073 (24%)	1313 (18%)	1526 (12%)	<.0001
Hypertension	3012 (65%)	4212 (56%)	6732 (53%)	<.0001
Systolic BP (mmHg)	127 (118-138)	125 (118-137)	125 (117-137)	<.0001
Diastolic BP (mmHg)	77 (70-81)	77 (70-81)	78 (71-82)	<.0001
BMI (kg/m^2)	28 (25-32)	28 (25-32)	29 (25-33)	<.0001
ACR (mg/g)	7.5 (4.5-17.3)	6.8 (4.4-13.6)	7.1 (4.7-13.2)	<.0001
ACR ≥ 30 mg/g	724 (16%)	861 (12%)	1386 (11%)	<.0001

CVD:cardiovascular disease; BP: blood pressure; BMI: body mass index; ACR: albumin/creatinine ratio

Table 2

Point based calculation of occult reduced eGFR risk score

Risk factor	Level	Points
Age	45-49	0
	50-59	1
	60-69	3
	70-79	6
	80-89	9
	90-98	11
eGFRcreat (per 1ml/min/1.73m^2)	60-69	14
	70-74	12
	75-89	8
	90-99	4
	100-110	2
	>110	0
Diabetes	Yes	1
Hypertension	Yes	1
CVD	Yes	1
BMI	<22	0
	22-29	1
	30-39	3
	40+	8
Current Smoking	Black	2
	White	3

* Calculated by adding points for each characteristic on the left. Possible range of scores 0-39, observed range of scores 0-32

CVD: cardiovascular disease; BMI: body mass index