

Incorporation of Cystatin C Testing in Clinical Practice: Real World Experience in Sweden



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Cystatin C is a kidney filtration marker that, when used in combination with serum creatinine, provides a more precise estimate of glomerular filtration rate (eGFR) than using serum creatinine alone.¹ Major kidney organizations, including the National Kidney Foundation, the American Society of Nephrology, and the Kidney Disease: Improving Global Outcomes have urged incorporation of cystatin C testing in routine clinical care.^{2,3} Despite these recommendations, prevalence of cystatin C testing is low and many clinicians are unfamiliar with the assay.⁴ In contrast, cystatin C testing has been widely performed in Sweden for over a decade.⁵ Using the health system in Stockholm, Sweden as a model, we report rates of cystatin C testing and clinical characteristics associated with cystatin C testing.

METHODS

Study Sample

We used data from the Stockholm Creatinine Measurements project, a healthcare utilization cohort from the region of Stockholm, Sweden with data collected between 2006 to 2019, the details of which have been described previously.⁶ In brief, 20% to 25% of the population of Sweden resides in the Stockholm region and are covered by universal health care. Data from these individuals on demographics, laboratory testing, vital measurements, medications, and diagnoses was extracted as part of the Stockholm Creatinine

Measurements project. The Regional Ethical Review Board in Stockholm approved the study (reference 2017/793–31); informed consent was not deemed necessary since all data were de-identified at the Swedish Board of Health and Welfare.

We included all adult patients (age ≥ 18 years) with a plasma creatinine tested between January 1, 2010, and December 31, 2018 ($N = 1,369,183$).

Supplemental methods detail the measurements for eGFR_{cr} and eGFR_{cys} as well as the covariates and outcomes.

Analyses

Detailed analyses description may be found in the **Supplement**. In brief, we described the number of participants with cystatin C testing by year and then, using 2014 as a cross-sectional sample, compared people who received additional cystatin C testing with those who received creatinine testing alone. We used logistic regression to examine associations of all covariates with cystatin C testing status in a multivariate model.

We evaluated the frequency of re-testing of cystatin C within 5 years and evaluated characteristics associated with retesting using multivariate logistic regression. Within those individuals who had cystatin C testing prior to 2014 and re-testing 1 to 5 years later, we compared the percent change in eGFR_{cr} with the

percent change in eGFR_{cys}, estimating the sensitivity and specificity of 30% decline in eGFR_{cr} for detecting a 30% decline in eGFR_{cys}.

RESULTS

From 2010 through 2018 in the Stockholm region, 1,369,183 adults received creatinine tests, and of those, 11.2% ($N = 152,669$) ever had cystatin C tested. On an annual basis, between 4% to 7% of individuals with creatinine testing had cystatin C testing each year (Supplementary Figure S1). The highest proportion of cystatin C testing was among individuals with lower eGFR_{cr} and higher albuminuria (Supplementary Table S1, Supplementary Figure S2).

Those who had both creatinine and cystatin C tested were more likely to be male, have a lower eGFR_{cr}, and have more comorbidities, compared to those with only creatinine tested (Table 1). Those with albuminuria testing were much more likely to receive cystatin C testing than those without (12% vs. 4.8%; adjusted odds ratio [95% CI]: 2.27 [2.22, 2.33]; Supplementary Figure S3, Supplementary Table S2–S3). Among people without albuminuria testing, older age was a strong predictor for receiving cystatin C testing. The odds of cystatin C testing per 10 years older was 0.80 (0.79, 0.81) in those with albuminuria testing and 1.13 (1.12, 1.15) in those without albuminuria testing. Women were much less likely to receive cystatin C testing than men in both groups. This was consistent in all years of data from 2010–2018 (Supplementary Table S4A–S4I).

Of the 80,560 individuals with an initial cystatin C test before 2014, 41,109 (51%) were retested within the subsequent 1 to 5 years. The clinical characteristics related to retesting cystatin C in the subsequent 5 years were like those related to initial testing: patients with retesting were more likely to have a lower eGFR and higher albuminuria, and more likely to have had albuminuria measured (Supplementary Table S5). Patients who underwent retesting were no longer likely to have large discrepancies (>30%) between eGFR_{cys} and eGFR_{cr} than people who were not retested.

To assess whether increased cystatin C testing could identify people with unrecognized, meaningful kidney function decline, we assessed the incidence of >30% decline in eGFR_{cr} and eGFR_{cys} as well as the sensitivity and specificity of the former to detect the latter. Among people with cystatin C retesting, more individuals had a decline of more than 30% in eGFR_{cys} than in eGFR_{cr} (18.4% with decline of more than 30% in eGFR_{cys} and 11.4% with decline of more than 30% in eGFR_{cr}; Figure 1). For a decline of more than 30% in eGFR_{cys}, a more than 30% decline in eGFR_{cr} had a sensitivity of 47% and a specificity of 97%.

Table 1. Characteristics of individuals tested for creatinine and/or cystatin C in 2014

Characteristics	Overall	Cystatin C and creatinine tested	Only creatinine tested
<i>N</i>	552909	37100	515809
eGFR _{cr} (SD), ml/min per 1.73m ²	90 (22)	75 (27)	91 (21)
eGFR _{cys} (SD), ml/min per 1.73m ²	69 (32)	69 (32)	
KDIGO G-stage by eGFR _{cr} , %			
eGFR 90 + ml/min per 1.73m ²	55	33	57
eGFR 60–89 ml/min per 1.73m ²	36	38	36
eGFR 45–59 ml/min per 1.73m ²	5.6	14	5.1
eGFR 30–44 ml/min per 1.73m ²	2.3	9.5	1.8
eGFR <30 ml/min per 1.73m ²	1.0	6.3	0.64
Any urine protein measured, %	26	47	24
ACR/PCR measured, %	13	34	11
Dipstick measured, %	13	13	13
ACR/PCR ^a (IQR), mg/g	14 (4–69)	16.8 (4.4–110.6)	8.0 (2.7–23.9)
Dipstick + and above, %	6.1	8.2	5.9
Age (SD), yr (OR per 10 yr)	58 (19)	63 (18)	57 (19)
Female, %	55	46	55
Hypertension, %	47	68	45
Hypertension medication use, %	44	64	42
RAAS inhibitor use, %	30	45	28
Diuretics, %	19	34	18
Diabetes, %	13	23	13
Statin, %	19	29	18
History of coronary heart disease, %	6.7	12	6.3
History of cerebrovascular disease, %	5.7	9.8	5.4
History of heart failure, %	5.5	13	5.0
History of peripheral artery disease, %	1.2	2.7	1.04
History of atrial fibrillation, %	8.0	15.8	7.4
Liver disease, %	2.4	3.7	2.3
Recent cancer, %	12	17	11
Chronic obstructive pulmonary disease, %	4.1	6.8	3.9
Potassium >5 mmol/l, %	0.28	1.1	0.22
Anemia by hemoglobin, ^b %	4.3	9.1	4.0

ACR/PCR, albumin-to-creatinine ratio or protein-to-creatinine ratio; eGFR_{cr}, estimated glomerular filtration rate based on creatinine; eGFR_{cys}, estimated glomerular filtration rate based on cystatin C; RAAS, renin-angiotensin-aldosterone system.

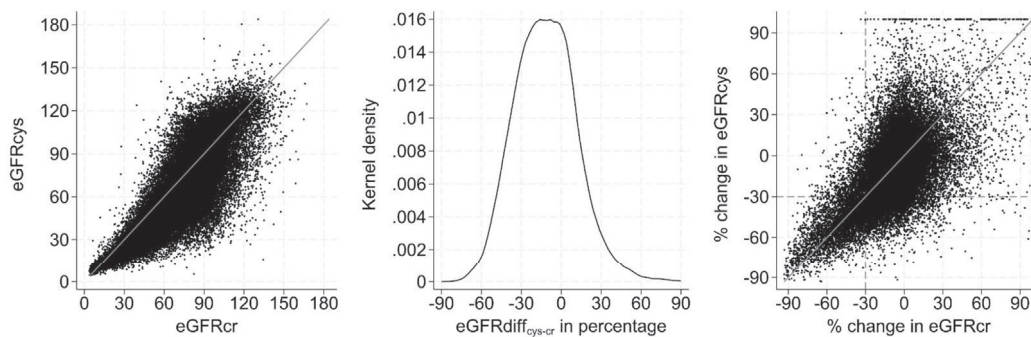
^aACR measured in 2014, imputed by PCR if ACR was not available.

^bAnemia is defined as hemoglobin <12 g/dL for female and <13 g/dL for male.

Measurement from 2014 used as a representative cross-sectional sample. Percents are of the column sample.

DISCUSSION

Using practice patterns in Stockholm, Sweden, as an example of how cystatin C is used in real-world clinical care, we highlighted which patients were tested, how often they were tested, and what extra insight cystatin C might bring to clinical care. Among 1,369,183 adult individuals who received creatinine testing, 11% were also tested for cystatin C, at a rate of approximately 5% annually. While much higher than estimates of current use in the US, this is still a modest amount of testing given the long-standing availability and low cost of cystatin C in Sweden. Cystatin C measurement is recommended in Kidney Disease: Improving Global Outcomes guidelines for CKD staging, as a confirmatory test in circumstances in which serum creatinine may be less



% change in eGFR		More than 30% decline	
eGFRcr		11.35% (4644 / 41109)	
eGFRcys		18.38% (7555 / 41109)	

% change in eGFRcr	% change in eGFRcys		Total
	More than 30% decline	30% decline or less	
More than 30% decline	3531	1133	4664
30% decline or less	4024	32421	36445
Total	7555	33554	
Sensitivity of eGFRcr		46.7%	
Specificity of eGFRcr		96.6%	

Figure 1. Plot of eGFRcys vs. eGFRcr values at first measurement, kernel density of difference of eGFRcys-eGFRcr at first measurement, percent change in eGFRcys vs. eGFRcr over up to 5 calendar years, and the sensitivity and specificity of a decline of 30% or more in eGFRcr. Included the population with any cystatin C measurement by 2014 to allow for up to 5 years of follow-up for retesting. eGFRcr, estimated glomerular filtration rate based on creatinine; eGFRcys, estimated glomerular filtration rate based on cystatin C.

accurate, and where precision is required for medication dosing.³ Specific patient characteristics were highly correlated with cystatin C testing. Individuals with testing for albuminuria, a vastly underutilized biomarker,⁷ were more likely to have testing for cystatin C. For example, almost half of individuals with cystatin C testing in 2014 also had albuminuria testing. Cystatin C testing was also more likely among an older population. We can speculate that clinicians treating this older patient group were concerned about the non-GFR determinants of creatinine in the setting of frailty and muscle loss. These practice patterns are consistent with the detailed scenarios described by Chen *et al.*⁴ in which non-GFR determinants may affect creatinine and inform clinical management.⁴

Our observation that declines in eGFRcr and declines in eGFRcys are not fully consistent builds upon previous evidence that there are frequently cross-sectional differences in the 2 measures and that the proportion of individuals with a large difference may increase over time.⁸ It has been shown that eGFRcr-cys is the best measure with respect to measured GFR in most settings,^{1,9} including when there are large discrepancies^{S3} Discrepant eGFRcr and eGFRcys is a strong risk factor for mortality and other clinical outcomes,^{8,S4-S6} and our results show a 30% decline in eGFRcr had only moderate sensitivity for a decline of 30% in eGFRcys, underscoring the utility of testing both creatinine and

cystatin C over time in order to best assess the kidney function of patients.^{S4}

Strengths of this study include the large sample size in a unique setting in which there is a longstanding history of cystatin C testing in routine care. However, we are limited in that we can only provide provider reasons for testing and any subsequent actions, as we do not have access to medical notes. Given the unique nature of the setting for this analysis, these results may not translate to other settings in which costs of testing, including the costs for reagents, laboratory time, and reimbursement logistics, lack of health care insurance coverage, and provider awareness and comfort of using cystatin C in routine care are large factors.

This study provides a real-world account of cystatin C testing, finding testing rates reach 4% to 7% of patients with serum creatinine tests. Decline in eGFRcr and eGFRcys were only moderately concordant, underlying the potential utility in testing both markers.

DISCLOSURES

Dr. Nitsch reports other support from UK Kidney Association outside the submitted work. Dr. Fu reports grants from Dutch Kidney Foundation, grants from Netherlands Organization of Scientific Research, and grants from Karolinska Institute during the conduct of the study. All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

Supplementary Methods.

Supplementary References.

Figure S1. Proportion with cystatin C testing by calendar year among individuals with measured serum creatinine

Figure S2. Trends in proportion of the population with cystatin C testing by year, stratified by G- and A-stage.

Figure S3. Percent with cystatin C testing in 2014, stratified by eGFRcr stages and albuminuria testing status.

[Supplementary File \(xlsx\)](#)

Table S1. Population with serum creatinine tested and proportion with testing cystatin C by year, stratified by G- and A-stage.

Table S2. Characteristics of individuals tested for creatinine and/or cystatin C in 2014, stratified by ACR testing status.

Table S3. Odd ratios and 95% CIs for cystatin C testing, overall and by ACR testing status.

Table S4A–I. Characteristics of individuals tested for creatinine and/or cystatin C in 2010–2018.

Table S5. Characteristics at first cystatin C measurement and odd ratios and 95% CIs for cystatin C re-testing.

Table S6. Definition of study covariates.

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