Cystatin C Predicts Renal Recovery Earlier Than Creatinine Among Patients With Acute Kidney Injury

Kamel A. Gharaibeh¹, Abdurrahman M. Hamadah¹, Ziad M. El-Zoghby¹, John C. Lieske¹,²,³, Timothy S. Larson¹,² and Nelson Leung¹,⁴

¹Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA; ²Division of Clinical Core Laboratory Services, Mayo Clinic, Rochester, Minnesota, USA; ³Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, Minnesota, USA; and ⁴Division of Hematology, Mayo Clinic, Rochester, Minnesota, USA

Introduction: Serum cystatin C increases earlier than creatinine during acute kidney injury. However, whether cystatin C decreases earlier during recovery is unknown. This retrospective study aimed to determine the temporal trend between creatinine and cystatin C in acute kidney injury.

Methods: We identified hospitalized patients with nonoliguric acute kidney injury who had serial creatinine and cystatin C values measured between May 2015 and May 2016. Demographic and laboratory data, causes of acute kidney injury, and relevant comorbidity data were collected through chart review.

Results: For the 63 identified patients, mean (SD) age was 58.7 (13.9) years; male sex, 62%; white race/ethnicity, 95%. Baseline median (range) creatinine was 1.1 (0.5–3.0) mg/dl; 13% were kidney transplant recipients and 37% received corticosteroids. Comorbidities included malignancy (38%), diabetes mellitus (33%), heart failure (19%), and thyroid disorder (16%). The cause of kidney injury was acute tubular necrosis in 71%, 61% had acute kidney injury stage III, and 33% required dialysis. Cystatin C began to decrease before creatinine in 68% of patients: 1 day earlier, 46%; 2 days earlier, 16%; and 3 days earlier, 6%. In 24% of cases, both began decreasing on the same day; in only 8%, cystatin C decreased after creatinine. Overall, cystatin C mean (95% confidence interval) decrease was 0.92 (0.65–1.18) days before creatinine ($P < 0.001$).

Conclusion: In summary, cystatin C decreases before creatinine in most hospitalized patients with acute kidney injury. If confirmed in large prospective studies, these findings may have important management implications, possibly shortening hospital stay and reducing costs.

Key words: acute kidney injury; cystatin c; creatinine

© 2017 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Cystatin C (CysC) is an endogenous biomarker of renal function produced by all nucleated cells at a near-constant rate, independent of muscle mass, and is cleared from circulation through glomerular filtration without reabsorption or secretion. CysC performs equally as Scr as a marker of renal function in most AKI cases and outperforms Scr in some cases. Limited evidence suggests that the concentration of CysC peaks earlier than Scr during AKI, and it may detect kidney dysfunction earlier than creatinine. Less is known about CysC level during the renal recovery phase. Predicting recovery of renal function following AKI is a highly sought-after issue in the AKI research field. Earlier identification of AKI recovery could result in less intensive resource utilization and earlier hospital discharge.

We conducted an observational retrospective study to determine the relative time course of Scr and CysC levels of hospitalized patients with AKI. We hypothesized that serial measurement of CysC detects kidney function recovery before Scr by at least 24 hours in 30% of patients with AKI.

**METHODS**

**Study Population**

The study was approved by the Mayo Clinic Institutional Review Board. Using an institution-wide clinical database, we identified all adult patients with AKI at the Mayo Clinic in Rochester, Minnesota, between May 1, 2015, and May 31, 2016, who had serial Scr and CysC values (at least 3 consecutives) measured during their hospitalizations. In this interval, CysC was measured with the routine laboratory tests as part of their hospitalizations. In this interval, CysC was measured with the routine laboratory tests as part of clinical care in nonoliguric patients (defined as urine output >400 ml/d) who had AKI and regardless of the AKI stage or the patient location (medical and surgical intensive care unit and non-intensive care unit). We excluded patients who were oliguric because the kidney function is not expected to recover during the time they were still oliguric. AKI was defined on the basis of Acute Kidney Injury Network criteria. Baseline demographic data (age, race, and sex), body mass index, smoking status, other significant comorbidities (i.e., heart failure, chronic kidney disease, hypertension, diabetes mellitus, thyroid disorder, history of kidney transplant, active malignancy, and active infection), corticosteroid use, and diuretic use were collected by review of health records. We also collected the cause of AKI, need for RRT, baseline Scr, estimated GFR (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation, serial Scr and CysC, daily urine output, and the cause and duration of hospitalization.

**Statistical Analysis**

Continuous variables were summarized by mean and SD when normally distributed and as median (interquartile range) when skewed. Group comparisons for continuous variables were done with t test or Wilcoxon rank sum test for normally and nonnormally distributed data, respectively. Categorical variables were summarized by count and percentage, and groups were compared using the $\chi^2$ test. We then performed an exploratory univariate logistic regression analysis to determine variables associated with a decrease in serum CysC that preceded a decrease in serum creatinine. The dependent outcome was defined as a decline in the serum level of CysC that was at least 1 day earlier than a decrease in serum level of creatinine. The independent variables included were based on their associations with CysC based on prior studies and included age, sex, cause of AKI (acute tubular necrosis vs. non–acute tubular necrosis), AKI stage, body mass index, diabetes mellitus, heart failure, infection, hypothyroidism, malignancy, and corticosteroid use. All analyses were performed using JMP Pro software version 10.0 (SAS Institute Inc., Cary, NC). A $P < 0.05$ was considered statistically significant.

**RESULTS**

The study included 63 patients. Their clinical characteristics are summarized in Table 1. Mean (SD) age was 58.7 (13.9) years, 62% of the patients were men, and 95% were white. Baseline median (range) Scr before AKI was 1.1 (0.5–3.0) mg/dl; peak median

| Variable | Value $^a$ |
|----------|------------|
| Age, mean (SD), yr | 58.7 (13.9) |
| Male sex | 39 (61.9) |
| White race/ethnicity | 60 (95) |
| Smoker or ex-smoker | 29 (48) |
| BMI, median (IQR), kg/m² | 27.8 (25–35.6) |
| Baseline eGFR, mean (SD) (range), ml/min per 1.73 m² | 70 (27.4) (19–138) |
| Diabetes mellitus | 21 (33) |
| Heart failure | 12 (19) |
| Hypertension | 33 (52) |
| Corticosteroid use | 23 (37) |
| Infection | 34 (54) |
| Hypothyroidism | 10 (16) |
| Malignancy | 24 (38) |
| Kidney transplant | 8 (13) |
| Serum creatinine, median (IQR), mg/dl | 1.1 (0.9–1.3) |
| Baseline | 3.6 (2.8–5.2) |
| At discharge | 1.9 (1.4–2.9) |

BMI, body mass index; eGFR, estimated glomerular filtration rate based on the Chronic Kidney Disease Epidemiology Collaboration equation; IQR, interquartile range.

$^a$Values are presented as number and percentage of patients unless specified otherwise.
(interquartile range) Scr before recovery was 3.6 (2.8–5.2) mg/dl (range, 1.4–9.1 mg/dl). At discharge, Scr was 1.9 (1.4–2.9) mg/dl (range, 0.8–9.0 mg/dl). None of these patients were receiving dialysis at hospital discharge. Median (range) urine output was 1590 (525–5000) ml/d.

Severity and Causes of AKI
Most patients had severe AKI; 38 (61.3%) had stage III AKI based on the Acute Kidney Injury Network classification⁸ and 21 (33.3%) required RRT (3 underwent only continuous RRT, 10 underwent intermittent hemodialysis only, and 8 underwent continuous RRT followed by intermittent hemodialysis). Eighteen patients (29%) had stage II AKI and 6 (10%) had stage I AKI. The most common cause of AKI was acute tubular injury (n = 45, 71%) followed by prerenal AKI (n = 9, 14%) (Table 2).

Renal Recovery Based on Serum CysC and Scr
Serum CysC began to decrease before Scr for 43 patients (68%), on the same day for 15 (24%), and after Scr for 5 (8%) (Figure 1). Specifically, serum CysC declined 1 day earlier than Scr for 29 patients (46%), 2 days earlier for 10 (16%), and 3 days earlier for 4 (6%). Serum CysC declined 1 and 2 days after Scr in 4 and 1 patient, respectively. Overall, the mean (95% confidence interval) decrease in CysC was 0.92 (0.65–1.18) days before Scr (P < 0.001) and indicated recovery from AKI before or at the same time as Scr in 92% of patients. Figure 2 illustrates 3 examples of serial CysC and Scr in which serum CysC declined before, on the same day as, and after Scr. Of note, among the 21 patients who underwent RRT, CysC began to decrease before Scr in all but 3 who received intermittent hemodialysis alone.

Exploratory Analysis
The logistic univariate analyses did not suggest an association between patient characteristics (i.e., age, sex, acute tubular necrosis vs. non–acute tubular necrosis, AKI stage, body mass index, diabetes mellitus, heart failure, infection, hypothyroidism, malignancy, and corticosteroid use) and the timing of CysC decrease compared with Scr decrease, except for a lower baseline eGFR. Indeed, CysC was more likely to decrease before Scr for patients with a lower baseline eGFR (beta estimate, −0.35 per 15 ml/min increment in eGFR; 95% confidence interval, −0.71 to −0.04; P = 0.04).

DISCUSSION
Creatinine is derived from the metabolism of creatine in skeletal muscle and from dietary meat intake, which explains the variations in Scr level observed among different age groups and geographic, ethnic, and racial groups. Creatinine is freely filtered across the glomerulus and is neither reabsorbed nor metabolized by the kidney. Creatinine level rises and it accumulates when the GFR suddenly decreases.¹¹ The published GFR formulas can be used to calculate eGFR only when kidney function is stable.¹² These formulas do not accurately calculate eGFR when Scr is increasing or decreasing. For example, early in the course of AKI, GFR is significantly reduced, but there has not been enough time for creatinine to accumulate. Therefore, Scr does not reflect the degree of renal dysfunction, and eGFR formulas overestimate the real GFR. This effect is also true in the early phase of AKI recovery, when Scr level stays high initially and does not reflect GFR accurately. Hence, eGFR formulas underestimate the real GFR. Use of Scr to estimate GFR has multiple limiting factors. These include variations in creatinine production, tubular secretion, and extrarenal creatinine excretion and the issues associated with creatinine measurement.¹¹

Given these limitations with Scr, serum CysC has been analyzed to more precisely calculate GFR. Serum CysC level may correlate better with GFR than Scr

Table 2. Causes of acute kidney injury among the 63 patients

| Cause                               | Patients, n (%) |
|-------------------------------------|-----------------|
| Acute tubular necrosis              | 45 (71.4)       |
| Prerenal disease (including CRS and HRS) | 9 (14.3)       |
| Contrast medium nephropathy         | 3 (4.8)         |
| Obstruction                         | 1 (1.6)         |
| Delayed transplant graft function   | 1 (1.6)         |
| Pigment nephropathy                 | 1 (1.6)         |
| Cast nephropathy                    | 1 (1.6)         |
| Acute interstitial nephritis        | 1 (1.6)         |
| Unknown                             | 1 (1.6)         |

CRS, cardiorenal syndrome; HRS, hepatorenal syndrome.
level. Multiple studies identified serum CysC as a more accurate marker for mild reductions in kidney function than Scr alone. Combining Scr and CysC into a single equation provides a better estimate of GFR than equations that use either creatinine or CysC alone.

Chen proposed a simple formula to estimate GFR in the clinical setting of nonsteady renal function called kinetic eGFR (KeGFR). The KeGFR formula requires the initial creatinine, creatinine production rate, the difference between consecutive plasma creatinine over a specified time, and volume of distribution. Although KeGFR calculations were developed early (since 1972), they are not widely used or taught. The KeGFR has been simplified recently for use at the bedside in the assessment of AKI recovery. This approach to characterize clearance is adaptable to alternative circulating filtration biomarkers, including serum CysC. Serum CysC is distributed only in extracellular fluid, not in total body water. It has a smaller distribution volume than Scr (almost one-third), and therefore it approaches steady state 3 times faster than Scr after GFR is altered, which reflects a more cohesive relationship between real GFR (kinetic) and eGFR.

The present study compared the temporal trend of serum CysC and Scr in nonoliguric patients with AKI. It found that serum CysC indicated renal recovery by at least 1 day earlier than Scr in 68% of patients and performed similarly to or better than Scr in 92% of the study population.

CysC is a useful discovery marker of AKI and may detect AKI 1 or 2 days earlier than Scr. The literature that evaluates CysC in renal recovery is sparse. Hall et al. concluded from their research that CysC performed better than Scr in predicting early graft function after deceased-donor kidney transplantation. Our study is one of the first to investigate CysC as a potential biomarker for renal recovery in humans. In our study, CysC failed to indicate renal recovery before Scr for only 5 patients (8%). On review of these 5 patients, we hypothesized that for 3 patients, several reasons may explain this CysC failure. One patient was receiving chemotherapy and may have internally released CysC from the destroyed nucleated cells. Another patient had evidence of bone marrow engraftment, resulting in rapid increase in the nucleated cells, with possible release of CysC in the serum. The third patient had bilateral ureteral obstruction, and severe pyelonephritis eventually developed, which could have resulted in slower CysC metabolism and clearance by the damaged renal tubular cells.

We believe that the use of CysC holds considerable promise in the monitoring and management of AKI in the hospital, compared with the current standard of care using Scr. The use of CysC affected the care of several patients in this study, which led to a shorter hospital stay, fewer dialysis sessions, and avoidance of unnecessary kidney biopsies for some patients (Table 3). Figure 3 illustrates the case of a patient who could have been discharged from the hospital earlier on the basis of a serum CysC trend that indicated kidney function recovery 2 days before Scr. However, this patient had other medical issues that required further inpatient care.

Although not routinely used in clinical practice even among nephrologists, we computed serial kinetic eGFR
and compared it with CysC. Renal function recovery was predicted earlier, at the same time, and later with KeGFR in 24%, 52%, and 24% of the patients, respectively (data not shown). Of note, 4 of the 63 patients were excluded from the calculation because baseline creatinine was not available. Based on these data, KeGFR appears to provide additional information to CysC; however, it is cumbersome to use by busy clinicians and requires calculation and data input by the clinician on a day-to-day basis to assess the eGFR trajectory. Of interest, compared with serum creatinine, KeGFR predicted kidney function recovery earlier, the same day, and later in 58%, 37%, and 5%, respectively.

The present study reports a single-center experience and has several limitations. Most of our patients were white, which makes the results difficult to generalize to different populations. Its small sample size did not allow us to perform multivariate analyses to evaluate factors that may be associated with a better or worse performance of CysC, such as various patient characteristics (e.g., native kidneys vs. kidney allografts). In addition, most patients in this study had severe AKI (stage III), and many required RRT. However, this population does not represent most hospitalized patients with AKI. Last, CysC is easily obtainable at our center as part of routine clinical practice, but this option may not be available in most community hospitals to make timely clinical decisions. In addition, CysC is more expensive than Scr, but the cost is less than or equivalent to the cost of other commonly ordered tests, such as C-reactive protein, parathyroid hormone, 25-hydroxyvitamin D, and Troponin T. This extra cost is easily offset by avoiding an extra dialysis treatment or shortening the length of hospitalization.

In conclusion, the findings in this study suggest that CysC decreases earlier than Scr and thus is an earlier biomarker of AKI recovery in hospitalized patients (68%), with only 8% of patients showing delayed improvement of CysC compared with Scr. If confirmed by large prospective studies, these findings may have important clinical implications for managing AKI, with potential for shortened hospital stay and reduced resource utilization and costs.

**DISCLOSURE**

All the authors declared no competing interests.

**Table 3. Clinical implications of use of serum cystatin c instead of serum creatinine to monitor renal recovery after acute kidney injury**

| Clinical decision                        | Patients, n (%) |
|------------------------------------------|-----------------|
| Dialysis avoided                         | 15 (24)         |
| Drug dose more appropriate               | 10 (16)         |
| Kidney biopsy avoided                    | 6 (10)          |
| Earlier nephrology service sign-off      | 4 (6)           |
| Earlier hospital discharge               | 4 (6)           |

**Figure 3.** Temporal evolution of serum CysC and Scr after an acute kidney injury episode of a patient hospitalized for resection of total hip arthroplasty. Serum CysC (mg/l) started to decrease 2 days earlier than Scr (mg/dl) (vertical solid line and dashed line, respectively). Assuming no other reason to keep the patient in the hospital besides awaiting kidney function recovery, the patient could be discharged 2 days earlier on the basis of decrease in serum CysC (vertical blue line) rather than Scr (vertical green line). CysC, cystatin C; Scr, serum creatinine.
This work was presented in part at the Annual Meeting of the American Society of Nephrology, November 17, 2016, Chicago, Illinois, USA.

ACKNOWLEDGMENTS
This publication was supported by grant UL1 TR000135 from the National Center for Advancing Translational Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

We thank the scientific publication staff at Mayo Clinic for editorial assistance.

REFERENCES
1. Waikar SS, Curhan GC, Wald R, et al. Declining mortality in patients with acute renal failure, 1988 to 2002. J Am Soc Nephrol. 2006;17:1143–1150.
2. Susantitaphong P, Cruz DN, Cerda J, et al. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol. 2013;8:1482–1493.
3. Hsu RK, McCulloch CE, Dudley RA, et al. Temporal changes in incidence of dialysis-requiring AKI. J Am Soc Nephrol. 2013;24:37–42.
4. Bellomo R, Ronco C, Kellum JA, et al, Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8:R204–R212.
5. Tenstad O, Roald AB, Grubb A, Aukland K. Renal handling of radiolabelled human cystatin C in the rat. Scand J Clin Lab Invest. 1996;56:409–414.
6. Hall IE, Doshi MD, Poggio ED, Parikh CR. A comparison of alternative serum biomarkers with creatinine for predicting allograft function after kidney transplantation. Transplantation. 2011;91:48–56.
7. Herget-Rosenthal S, Marggraf G, Husing J, et al. Early detection of acute renal failure by serum cystatin C. Kidney Int. 2004;66:1115–1122.
8. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.
9. Liu X, Foster MC, Tighiouart H, et al. Non-GFR determinants of low-molecular-weight serum protein filtration markers in CKD. Am J Kidney Dis. 2016;68:892–900.
10. Knight EL, Verhave JC, Spiegelman D, et al. Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. Kidney Int. 2004;65:1416–1421.
11. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. N Engl J Med. 2006;354:2473–2483.
12. Rule AD, Bergstralh EJ, Slezak JM, et al. Glomerular filtration rate estimated by cystatin C among different clinical presentations. Kidney Int. 2006;69:399–405.
13. Newman DJ, Thakkar H, Edwards RG, et al. Serum cystatin C measured by automated immunoassay: a more sensitive marker of changes in GFR than serum creatinine. Kidney Int. 1995;47:312–318.
14. Dharmidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis. 2002;40:221–226.
15. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367:20–29.
16. Stevens LA, Coresh J, Schmid CH, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. Am J Kidney Dis. 2008;51:395–406.
17. Chen S. Retooling the creatinine clearance equation to estimate kinetic GFR when the plasma creatinine is changing acutely. J Am Soc Nephrol. 2013;24:877–888.
18. Jelliffe R. Estimation of creatinine clearance in patients with unstable renal function, without a urine specimen. Am J Nephrol. 2002;22:320–324.
19. Sjostrom P, Tidman M, Jones I. Determination of the production rate and non-renal clearance of cystatin C and estimation of the glomerular filtration rate from the serum concentration of cystatin C in humans. Scand J Clin Lab Invest. 2005;65:111–124.
20. Endre ZH, Pickering JW, Walker RJ. Clearance and beyond: the complementary roles of GFR measurement and injury biomarkers in acute kidney injury (AKI). Am J Physiol Renal Physiol. 2011;301:F697–F707.
21. Delaney P, Cavalier E, Morel J, et al. Detection of decreased glomerular filtration rate in intensive care units: serum cystatin C versus serum creatinine. BMC Nephrol. 2014;15:9.
22. Zhang Z, Lu B, Sheng X, Jin N. Cystatin C in prediction of acute kidney injury: a systemic review and meta-analysis. Am J Kidney Dis. 2011;58:356–365.
23. Shlipak MG, Mattes MD, Peralta CA. Update on cystatin C: incorporation into clinical practice. Am J Kidney Dis. 2013;62:595–603.