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

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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.

I n acute kidney injury (AKI), sudden decrement in renal function takes place within hours and days, resulting in fluid and electrolyte abnormalities that may require hospitalization and renal replacement therapy (RRT). The annual incidence of AKI is increasing, especially in the United States.[1] AKI is common among hospitalized patients, its incidence between 2004 and 2012 is reported to be as high as 20%, and it is associated with substantially increased morbidity and mortality rates.[2] AKI severity can range from mild renal dysfunction to severe renal failure that requires RRT. A study of the Nationwide Inpatient Sample database reported an increased incidence rate of AKI requiring dialysis.[3] Renal recovery after AKI can occur spontaneously and is defined as improved kidney biomarker levels. The thresholds to start and to discontinue RRT for AKI are highly variable. Although no clear consensus exists to define renal recovery in severe AKI that requires dialysis, the term is generally defined as no further need of RRT.[4] Renal recovery is an important criterion for hospital discharge. A patient is usually discharged when convincing evidence shows declining serum creatinine (Scr) concentration.

Assessment of renal recovery can be difficult, especially for patients receiving RRT. The biomarker Scr is commonly used to daily assess kidney function. However, Scr does not accurately reflect a true glomerular filtration rate (GFR) when renal function is not in a steady state, such as during an AKI episode.

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.[5] CysC performs equally as Scr as a marker of renal function in most AKI cases and outperforms Scr in some cases.[6] Limited evidence suggests that the concentration of CysC peaks earlier than Scr during AKI, and it may detect kidney dysfunction earlier than creatinine.[7] 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 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.[8] 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 χ^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 dependant 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.[9,10] 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

Table 1. Characteristics of the 63 study patients

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 (46)
BMI, median (IQR), kg/m²	27.8 (25–35.5)
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	
Baseline	1.1 (0.9–1.3)
Peak	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 1950 (525–5000) ml/d.
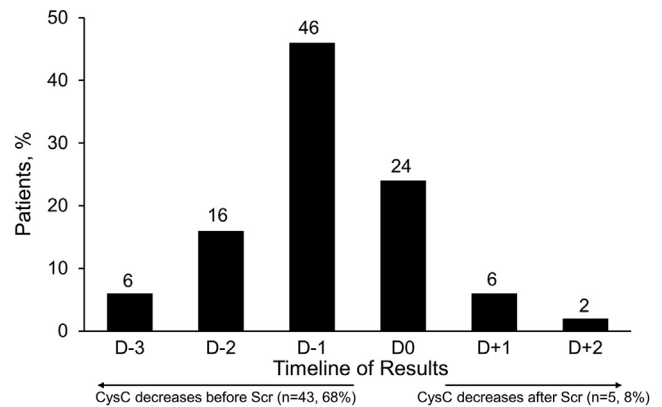
Severity and Causes of AKI

Most patients had severe AKI; 38 (61.3%) had stage III AKI based on the Acute Kidney Injury Network classification[8] 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

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.

Figure 1. Percentage of patients in whom serum CysC started to decrease before, the same day as, or after Scr. CysC, cystatin C; D-3, CysC peaked 3 days before Scr; D-2, CysC peaked 2 days before Scr; D-1, CysC peaked 1 day before Scr; D0, CysC peaked on the same day as Scr; D+1, CysC peaked 1 day after Scr; D+2, CysC peaked 2 days after Scr; Scr, serum creatinine.

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; $P = 0.04$).
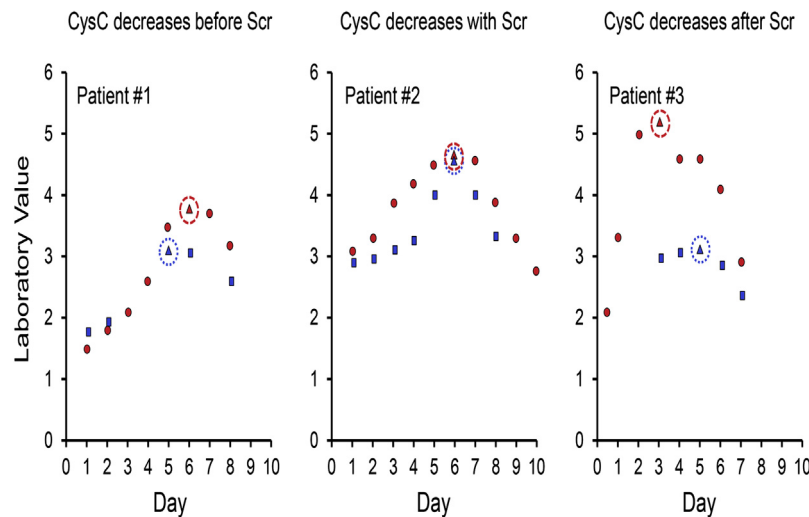
DISCUSSION

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

Figure 2. Examples of patients with various temporal trends between serum CysC and Scr. Each Scr value (mg/dl) is represented as a red dot (as a triangle for Scr peak) and each serum CysC (mg/l) as a blue rectangle (as a triangle for CysC peak). CysC, cystatin C; Scr, serum creatinine.

level.[13] Multiple studies identified serum CysC as a more accurate marker for mild reductions in kidney function than Scr alone.[14] Combining Scr and CysC into a single equation provides a better estimate of GFR than equations that use either creatinine or CysC alone.[15,16]

Chen[17] 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.[18] 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.[17] Serum CysC is distributed only in extracellular fluid, not in total body water.[19] 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.[20] However, like creatinine-based equation, eGFR based on the CysC is difficult to interpret in unstable conditions in which there is an acute change in GFR.[21]

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.[7,22] The

literature that evaluates CysC in renal recovery is sparse. Hall *et al.*[6] 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

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)

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.[23] 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 that 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.
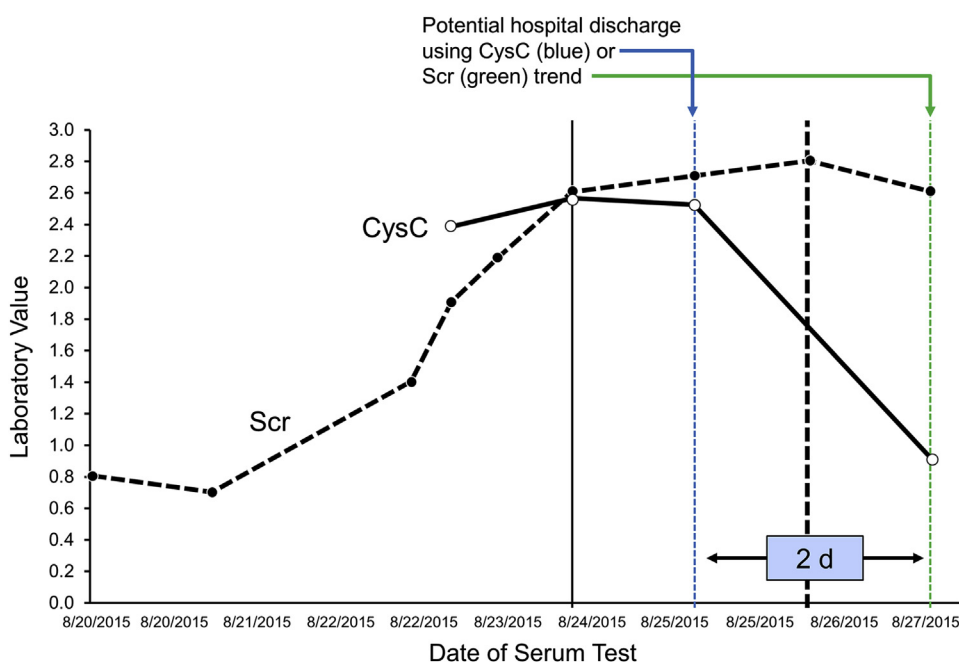
Figure 3. Temporal evolution of serum CysC and Scr after an acute kidney injury episode of a patient hospitalized for resection of total hip arthroplasty. Serum CysC (mg/l) started to decrease 2 days earlier than Scr (mg/dl) (vertical solid line and dashed line, respectively). Assuming no other reason 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.

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