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Comparison of Serum Creatinine and Cystatin C for Early Diagnosis of Contrast-Induced Nephropathy after Coronary Angiography and Interventions

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BACKGROUND: The diagnostic accuracy of serum creatinine and cystatin C (Cys) as early predictors of contrast-induced nephropathy (CIN) has been debated. We investigated the diagnostic sensitivities, diagnostic specificities, and variations from baseline for serum creatinine and Cys in CIN.

METHODS: We prospectively evaluated 166 patients at risk for CIN at baseline, and at 12, 24, and 48 h after exposure to contrast media. CIN occurred in 30 patients (18%). Changes (Δ) compared to baseline in serum creatinine and Cys were evaluated at the predefined time points. ROC curve analysis was performed for the Δ 12-h basal serum creatinine and Cys.

RESULTS: The Δ serum creatinine at 12 h from baseline was the earliest predictor of CIN [area under the ROC curve (AUC) = 0.80; $P < 0.001$]. The Δ serum creatinine 15% variation [0.15 mg/dL (13.2 μmol/L)] yielded 43% diagnostic sensitivity and 93% diagnostic specificity. The ΔCys at 12 h from baseline performed significantly worse than serum creatinine (AUC = 0.48; $P = 0.74$).

CONCLUSIONS: Variations from the serum creatinine baseline offer better diagnostic accuracy for predicting CIN at an earlier stage than similar variations in Cys. An additional diagnostic value of Cys over the determination of serum creatinine in the setting of CIN was not observed.

Acute kidney injury (AKI)[5] is a well-recognized complication following angiographic examinations. AKI prolongs hospitalization, may cause renal failure, and substantially increases morbidity and mortality *(1–3)*. The most common form of AKI after cardiovascular invasive procedures with administration of iodine contrast media is contrast-induced nephropathy (CIN), conventionally defined as an acute impairment of the renal function, expressed as a relative increase in serum creatinine concentration of at least 25% or an absolute increase in serum creatinine from 0.3 mg/dL or up to 0.5 mg/dL within 48 h in the absence of other related causes *(4–6)*. CIN is generally considered to cause transient damage, with return to basal renal function occurring within approximately 1 week of the exposure to the iodine contrast medium, although irreversible renal damage and even end-stage renal disease may occur *(7)*. The reported incidence ranges from <5% in low-risk patients to 50% in high-risk populations *(2–8)*; in particular, a preexisting chronic kidney disease (CKD) and the volume of contrast are the most important predictors of CIN. Among patient-related factors, age, sex, diabetes, anemia, and heart failure with hypovolemia or low cardiac output are associated with CIN *(3, 9, 10)*.

CIN is diagnosed on the basis of the dynamic changes in serum creatinine after exposure to iodine contrast media. However, because serum creatinine is not a perfect glomerular filtration rate (GFR) biomarker owing to its tubular secretion and variable production rate, the perception is that serum creatinine is insensitive to early changes in GFR *(11)*.

Cystatin C (Cys) is a cationic low molecular weight cysteine protease that is produced at a constant rate by

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[5] Nonstandard abbreviations: AKI, acute kidney injury; CIN, contrast-induced nephropathy; CKD, chronic kidney disease; GFR, glomerular filtration rate; Cys, cystatin C; AUC, area under the ROC curve.

all nucleated cells, is not metabolized in the serum, and is freely filtered by the glomeruli *(12)*. Cys has been proposed as an alternative to serum creatinine to evaluate GFR, owing to the absence of variations related to age, sex, and muscle mass *(12, 13)*. Furthermore, in some studies changes of Cys have enabled investigators to detect earlier changes of GFR than creatinine after administration of contrast media *(14, 15)*. A few studies have investigated the kinetics of Cys and serum creatinine variations in patients undergoing coronary angiography. However, the case populations were small, diagnostic performance in detecting CIN was not analyzed, and the first assessment time point was relatively late (24 h) *(16)*. The diagnostic performance of Cys vs serum creatinine was analyzed in this clinical setting by Kato et al. *(17)*, but only in terms of CIN detection by use of different biomarker thresholds. The investigators did not address the issue of performance in the early diagnosis of CIN.

Thus, true "head-to-head" comparisons of serum creatinine and Cys are lacking, and the assumption of a better diagnostic performance of Cys needs more extensive evaluation. In the study reported here, we compared the diagnostic sensitivity and diagnostic specificity of serum creatinine and Cys for early CIN prediction in a population of patients undergoing coronary angiography and interventions who were at risk for AKI.

Methods

STUDY POPULATION

The study was approved by the ethics committee of our institution, and all participating patients provided written informed consent. Between June 2007 and May 2008, patients who were older than 18 years, presented risk characteristics for developing CIN, and underwent coronary angiography and/or angioplasty were enrolled in a prospective study on the basis of availability of a basal assessment of renal function before the procedure. These patients were followed thereafter for a minimum of 48 h.

For inclusion in the study, patients had to have at least one of the following clinical criteria of risk for CIN: age ≥75 years, diabetes, or known mild or moderate CKD [stages 2 or 3 *(18)*, i.e., GFR = 60–89 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ and evidence of renal damage (mostly proteinuria at the standard urine examination), or GFR = 30–59 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$, respectively]. These patients belonged to a larger series recently described in a report that provides further details on the protocol *(19)*.

Patients were excluded from the study if they had stage 4 CKD [GFR <30 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$].

Renal function was assessed by simultaneous determination of serum creatinine and Cys. Baseline GFR was also calculated by use of the Modification of Diet in Renal Disease formula *(20)*. According to the conventional definition, patients with a relative increase in serum creatinine concentration of at least 25% compared to baseline within 48 h after the procedure were identified as having developed CIN *(7)*.

Because serum creatinine concentrations may be biased by extrarenal variables, we did not use any threshold value of serum creatinine but instead used the changes (Δ) compared to baseline (i.e., the difference between the observed values of serum creatinine and Cys at a prespecified time point and the baseline). The resulting positive (+) or negative (–) differences indicated either an impairment or an improvement of the renal function, respectively.

BLOOD SAMPLE MEASUREMENTS AND TIMING

The study was designed so that serum creatinine measurements were performed as the samples were received from the cardiology ward, whereas Cys was measured in a single batch at the end of the study on samples stored at −80 °C. Serum creatinine was quantified with the kinetic Jaffè method (Dimension®, Dade Behring; reference intervals: male, 0.8–1.3 mg/dL; female, 0.6–1.0 mg/dL).

Cys was measured by an immunonephelometric method that used monospecific antisera on an Immage 800 (Beckman Coulter) [reference intervals: 0.55–1.15 mg/L (age 1–50 years), 0.63–1.44 mg/L (age >50 years)]. The interassay CVs for serum creatinine and Cys were 4.5% at 1.1 mg/dL and 4.6% at 1.2 mg/dL, respectively. Renal function was assessed at baseline before angiography under preventive hydration and at 12, 24, and 48 h thereafter.

STATISTICAL METHODS

The Kolmogorov–Smirnov test was performed to evaluate the normality of data distribution. Continuous data are expressed as the mean or as the median and interquartile range, as appropriate. Categorical variables are reported as absolute numbers and percentages.

Univariate analysis was performed by use of a *t*-test or a Fisher exact test, except for skewed data, which were evaluated with a nonparametric Kruskal–Wallis test. Multivariate analysis among predictors of CIN was made by using a logistic regression model.

The diagnostic accuracy of the change (Δ) at 12 h from the baseline of serum creatinine was evaluated by calculating the ROC curve and assessing the area under the curve (AUC). The cutoff value of the test was chosen by the analysis of tabular ROC curve data to obtain the best possible sensitivity and specificity. A probability (*P*) <5% was considered statistically significant.

Table 1. Baseline characteristics of the groups of patients.

Characteristic	CIN+ (n = 30)	CIN− (n = 136)	*P*
Age, median (interquartile range), years	75.0 (64.3–79.8)	72.5 (63.0–81.3)	0.75
Males, n (%)	20 (66.7%)	100 (73.5%)	0.50
Diabetes mellitus, n (%)	15 (49.6%)	66 (50%)	0.99
Body mass index, mean (SD), kg/m^2	27.5 (5.0)	26.9 (4.3)	0.26
Basal GFR, mean (SD), $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$	71.6 (25.5)	68.6 (22.8)	0.39
CKD mild–moderate [GFR $>30\ mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$], n (%)	23 (76.7%)	110 (80.9%)	0.60
Hypertension, n (%)	24 (80.0%)	118 (86.8%)	0.34
Smoking habit, n (%)	12 (40%)	65 (47.8%)	0.44
Hyperlipidemia, n (%)	15 (50%)	90 (66.2%)	0.10
Metabolic syndrome, n (%)	13 (43.3%)	70 (51.9%)	0.40

Computer-aided analysis was made with SPSS version 11 for Windows (SPSS) and Excel version 2003 for Windows (Microsoft).

Results

The study population comprised 166 patients who completed all in-hospital observations mandated by the protocol, including concurrent determinations of serum creatinine and Cys at every prespecified time point.

According to the conventional definition, CIN occurred in 30 patients (18%). Table 1 shows demographic and clinical data of patients who developed CIN, compared with those without CIN: none of these characteristics were significantly different between the 2 groups of patients. Table 2 and Supplemental Table 1 (see the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol58/issue2) show serum concentrations and changes (Δ) in serum creatinine and Cys in the 2 groups at the different time points.

Serum creatinine in CIN+ patients was significantly higher than in the CIN– group only after 48 h (Table 2), whereas serum creatinine Δ values at the prespecified time points yielded highly significant differences as early as 12 h after exposure to contrast media ($P < 0.001$).

The measurement of Cys was not more informative for detecting patients with CIN. Cys concentrations in serum in the CIN+ vs CIN– groups did not reach statistically significant differences, including at 48 h. Cys Δ values were statistically different in the 2 groups only starting from the 24-h time point.

PREDICTIVE VALUES, DIAGNOSTIC SPECIFICITY, AND DIAGNOSTIC SENSITIVITY

The different diagnostic sensitivities and specificities for the early diagnosis of CIN based on the Δ values

Table 2. Baseline and changes at the predefined time points of serum creatinine and Cys concentrations in the 2 groups of patients.[a]

Biochemical variables	Serum creatinine			Serum Cys		
	CIN+ (n = 30)	CIN− (n = 136)	*P*	CIN+ (n = 30)	CIN− (n = 136)	*P*
Basal, mg/dL	1.00 (0.77–1.50)	1.02 (0.90–1.38)	0.19	1.17 (0.94–1.68)	1.20 (0.99–1.39)	0.81
12-h value, mg/dL	1.13 (0.93–1.62)	1.03 (0.90–1.33)	0.38	1.23 (1.05–1.66)	1.20 (1.03–1.46)	0.90
24-h value, mg/dL	1.21 (0.95–1.59)	1.03 (0.87–1.33)	0.17	1.31 (1.01–1.84)	1.19 (1.02–1.43)	0.32
48-h value, mg/dL	1.19 (0.97–2.00)	1.04 (0.87–1.34)	0.008	1.27 (1.11–2.01)	1.23 (1.02–1.46)	0.18
Δ 12-h basal, mg/dL	0.10 (0.03–0.20)	−0.01 (−0.08 to 0.05)	<0.001	0.00 (−0.07 to 0.09)	0.02 (−0.03 to 0.06)	0.84
Δ 24-h basal, mg/dL	0.17 (0.10–0.27)	−0.01 (−0.07 to 0.06)	<0.001	0.06 (−0.03 to 0.19)	−0.01 (−0.06 to 0.07)	0.01
Δ 48-h basal, mg/dL	0.27 (0.16–0.48)	0.00 (−0.14 to 0.09)	<0.001	0.10 (0.06–0.27)	0.02 (−0.05 to 0.09)	<0.001

[a] Values are expressed as median (interquartile range). Δ 12-h basal indicates the difference in the serum concentration of the corresponding marker at 12 h from baseline; same at 24 h and 48 h.

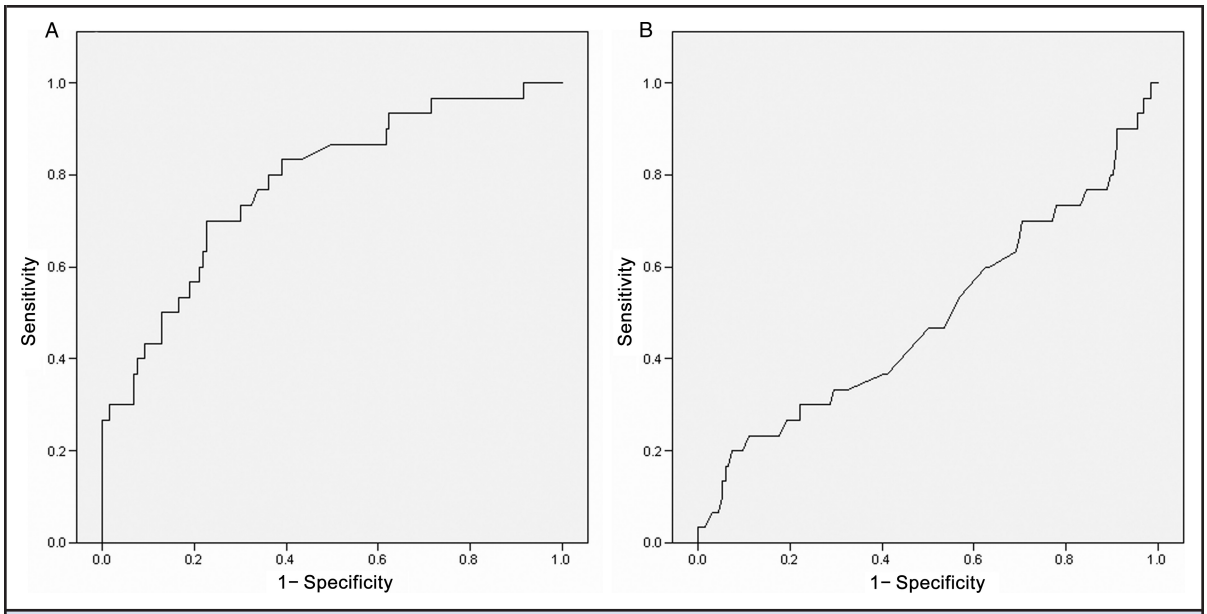

Fig. 1. ROC curves and AUCs showing (A), the different diagnostic sensitivities and specificities for the early diagnosis of CIN of Δ serum creatinine at 12 h from baseline (AUC, 0.80), and (B), ΔCys at 12 h from baseline (AUC, 0.49).

of serum creatinine and Cys at 12 h from baseline were calculated by use of ROC curve analysis and AUC assessment (Fig. 1).

The cutoff value of the test was chosen by the analysis of tabular ROC curve data to obtain the best diagnostic sensitivity and specificity for each index. The Δ serum creatinine at 12 h from baseline was a strong predictor of CIN in our sample (AUC = 0.80; $P < 0.001$). A serum creatinine increment from preprocedure values of 5%, 10%, and 15% of the baseline median value [0.05 mg/dL (4.4 μmol/L), 0.10 mg/dL, and 0.15 mg/dL, respectively] offered 70%, 50%, and 43% diagnostic sensitivity; 76%, 86%, and 93% diagnostic specificity; and negative predictive values of 93%, 89%, and 87%, respectively.

The ΔCys at 12 h from baseline was not predictive of CIN (AUC = 0.49; $P = 0.87$), and increments of 0.06 mg/dL (0.05 mmol/L), 0.12 mg/dL, and 0.18 mg/dL (5%, 10%, and 15% of the baseline median value, correspondingly) yielded lower performance (diagnostic sensitivity: 46.7%, 46.7%, and 46.8%; diagnostic specificity: 47.8%, 48.5%, and 49.3%, respectively).

SUBGROUP ANALYSIS

The ROC curve analysis of the Δ values of serum creatinine and Cys at 12 h from baseline was performed in subgroups of patients according to age >75 years, female sex, body mass index <25 kg/m^2, diabetes, moderate CKD, and mild CKD. In all the prespecified subgroups, Δ serum creatinine yielded better AUCs compared to ΔCys (data not shown).

Discussion

This investigation is the first "head-to-head" comparison of serum Cys and serum creatinine for the early prediction of CIN in patients at risk for AKI and scheduled to undergo coronary angiography and/or interventions.

We found that absolute changes in serum creatinine proved more accurate than Cys for predicting CIN at an early stage (12 h after the renal insult). Theoretically, there are numerous reasons why Cys should be a better biomarker of GFR (e.g., a constant production rate irrespective of muscle mass, a plasma concentration determined by glomerular filtration alone), and several studies have revealed that Cys is more accurate for diagnostic purposes than serum creatinine in various clinical settings *(14–17)*. In the present study, however, serum creatinine proved clearly superior to Cys.

Serum concentrations of the 2 biomarkers were of little help in identification of patients who were developing CIN (Table 2); changes in their concentrations vis-à-vis the baseline proved more useful. In patients developing CIN, significant changes in serum creatinine concentrations occurred 12 h earlier than any changes in Cys (Table 2; also see online Supplemental

Table 1). The stronger diagnostic power of the changes in serum creatinine compared with those in Cys is supported by the ROC curves, in which Δ serum creatinine returned a larger AUC (Fig. 1). The reasons for the discrepancies between our own and other published studies probably lie in the way we used our laboratory data. What is clinically important in this particular clinical setting is to establish whether a given patient's renal function is deteriorating. The clinical application of a test designed to detect significant changes in the serum concentration of a given analyte should also take into account the parameter's biological variability and the likely variations deriving from the method used to measure it. In this respect, there are important differences between serum creatinine and Cys. Studies in which the biological variability of the 2 markers was compared *(21, 22)* consistently revealed much lower intraindividual variability for serum creatinine (approximately 4.5%) than for Cys (approximately 10%) and a correspondingly lower index of individuality for the former (approximately 0.3 and approximately 0.9, respectively). These biological features make serum creatinine a useful parameter for detecting temporal changes in a patient's kidney function, especially in the early stages of renal impairment *(11)*, but at the same time make it less suitable for screening purposes. The opposite can be said of Cys, given its greater intraindividual variability (approximately 10%) and higher index of individuality *(23)*.

With the use of available data on biological variability *(21, 22)* and the analytical CV of the laboratory test, the calculated reference change value *(24)* that we can use to interpret our findings is 14.8 for serum creatinine and 25.6 for Cys. The lower relative change value obtained for serum creatinine further confirms the ability of this biomarker to distinguish small, but nonetheless clinically important, changes and thus guide medical decisions. In a given individual, a 15% increase in serum creatinine between 2 successive measurements can indicate a clinically significant change in their renal function. The ROC curves in Fig. 1 clearly show that serum creatinine changes are more useful for diagnostic purposes than ΔCys; a difference of 0.15 mg/dL (13.2 μmol/L) (around 15%) shows good diagnostic accuracy, but even smaller differences [0.10 mg/dL (8.8 μmol/L) and 0.05 mg/dL] perform better than Cys in detecting CIN—albeit with a decreasing diagnostic specificity [93% for a difference of 0.15 mg/dL (13.2 μmol/L) and 86% and 76%, respectively, for differences of 0.10 and 0.05 mg/dL]. Although Cys has been recommended as a better marker of renal function in particular subsets of patients, this recommendation is not supported by our findings. In fact, serum creatinine performed better than Cys in all of our subgroups of patients characterized by specific clinical phenotypes.

As mentioned previously, the data we obtained appear to contradict the results of several recent studies *(14–17)*. In one recent investigation on patients with CKD, Cys was claimed to perform better than serum creatinine in the early diagnosis and prognosis of CIN *(18)*. The authors found that "changes" in Cys concentrations ≥10% in 24 h compared to the baseline were more useful as a predictor than "absolute" increments in serum creatinine ≥0.3 mg/dL (26.5 μmol/L) after 24 h. But if an absolute, fixed "change" in serum creatinine (0.3 mg/dL) is compared with a "change" in Cys that is really a percentage shift from the baseline, the resulting difference between them is more likely to derive from the 2 different types of measurement involved than from any diversity between the 2 biomarkers, as we have recently pointed out *(25)*. In our study, we directly compared the absolute changes in the 2 biomarkers, and this comparison demonstrated the diagnostic superiority of serum creatinine.

In a different clinical setting, a cohort of patients with CKD and the use of a different experimental design from the present study, Spanaus et al. *(26)* compared the performance of a cross-sectional determination of serum biomarkers of GFR with the rate measured by using iohexol. These investigators found that serum creatinine was at least as good as Cys in terms of establishment of the diagnosis and prediction of the risk of progression. The authors obtained this result because they did not consider the biomarkers' reference intervals; instead, they rightly analyzed the serum concentrations of the biomarkers as continuous variables *(11)*.

Measuring temporal changes in serum creatinine, as we did in the present study, is another way of handling serum creatinine as a continuous variable, because it exploits the parameter's biological characteristics, such as its ability to detect small changes in GFR even within reference intervals owing to its low intraindividual variability *(11)* and because it allows for the fact that individuals all have their own narrow reference intervals that differ substantially from one individual to another *(21)*.

The good performance of serum creatinine vs Cys in this clinical setting may also stem from the particular clinical condition we investigated, because the deranged tubular secretion of creatinine induced by AKI may magnify the changes already occurring in serum creatinine concentrations secondary to GFR reduction, a mechanism that does not affect Cys.

It is worth noting that for diagnosis of renal dysfunction, changes in serum creatinine are as good as, if not better than, the changes identifiable by measuring urinary neutrophil gelatinase–associated lipocalin 18 h

after cardiac surgery (AUC, 0.80) *(27)*, or urinary kidney injury molecule 1 after 12 h (AUC, 0.83) *(28)*. Similar results were also obtained at 24 h in a series of patients undergoing coronary angiography performed by use of urinary neutrophil gelatinase–associated lipocalin to detect CIN (AUC, 0.73) *(29)*. Unfortunately, the biological variability of most of the latest AKI biomarkers, including neutrophil gelatinase–associated lipocalin and kidney injury molecule 1, is not known, so it is impossible to compare them with serum creatinine variability. Moreover, these modern biomarkers can pose major problems in terms of availability and related costs.

Our study has some limitations. On the basis of the theoretical trajectory of serum creatinine in AKI, it has recently been suggested that AKI should be diagnosed on the strength of an absolute increase in serum creatinine of 0.3 mg/dL (26.5 μmol/L) within 48 h, rather than a 25% increase *(30)*. The time required for serum creatinine to peak was shown to depend on baseline renal function, with the time being longer the lower the baseline GFR. Because our study focused on patients with a relatively preserved GFR, the 25% increase in serum creatinine needed for a diagnosis of CIN was probably reached within 48 h, so the use of an absolute Δ for changes in serum creatinine would not have changed the number of CIN patients identified.

Our data may not apply to AKI due to other causes, such as in cases with a less prominent hemodynamic component or when procedures cannot be standardized sufficiently to minimize preanalytical variations in serum creatinine and Cys. As mentioned in the Methods, however, our serum creatinine measurements were obtained during routine laboratory work, performed as the samples arrived from the cardiology ward, whereas the Cys measurements were performed on stored samples in a single batch at the end of the study. Although measured under better analytical conditions, the changes in Cys proved less useful for diagnostic purposes than the changes in serum creatinine because of the former parameter's greater biological variability. This finding reinforces our conclusion that serum creatinine changes can be used reliably to detect CIN in clinical practice. It would not be advisable to use a difference in serum creatinine as low as 5% [0.05 mg/dL (4.4 μmol/L)], however, unless the CV is around 2% at serum creatinine concentrations within reference intervals.

Finally, our findings apply to a population of patients at risk of CIN who are about to undergo cardiac catheterization and who have a relatively well-preserved renal function. The findings do not apply to patients with known, more severe renal insufficiency.

We believe that, in addition to demonstrating the superiority of serum creatinine over Cys in the diagnosis of CIN and AKI, our findings could also contribute to modification of the widespread negative perception of the usefulness of serum creatinine for monitoring renal function in many clinical conditions, as highlighted in the pivotal editorial by R.N. Dalton in this journal *(11)*. Serum creatinine is an inexpensive, standardized parameter that is available around the clock at any clinical chemistry laboratory the world over, whereas many of the new GFR biomarkers lack one or more of these essential features.

The ability to detect diagnostically important changes in serum creatinine concentrations as early as 12 h after administration of a contrast agent has a number of important clinical implications: (*a*) the measurement of the absolute serum creatinine concentration for detecting CIN could be replaced by the detection of changes in serum creatinine concentrations; (*b*) the delay before patients who subsequently develop CIN are treated can be reduced; and (*c*) given the very high negative predictive value of 93% for this diagnostic approach, patients unlikely to develop CIN can be discharged safely as early as possible.

Finally, before Cys or other new biomarkers can be recommended in clinical guidelines as better solutions than serum creatinine for detecting CIN and AKI, their diagnostic superiority must be unequivocally demonstrated.

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