Serum and urine cystatin C are poor biomarkers for acute kidney injury and renal replacement therapy

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Abstract

Purpose: To evaluate whether cystatin C in serum (sCyC) and urine (uCyC) can predict early acute kidney injury (AKI) in a mixed heterogeneous intensive care unit (ICU), and also whether these biomarkers can predict the need for renal replacement therapy (RRT).

Methods: Multicenter prospective observational cohort study in patients ≥18 years old and with expected ICU stay ≥72 h. The RIFLE class for AKI was calculated daily, while sCyC and uCyC were determined on days 0, 1, and alternate days until ICU discharge. Test characteristics were calculated to assess the diagnostic performance of CyC.

Results: One hundred fifty-one patients were studied, and three groups were defined: group 0 (N = 60), non-AKI; group 1 (N = 35), AKI after admission; and group 2 (N = 56), AKI at admission. We compared the two days prior to developing AKI from group 1 with the first two study days from group 0. On Day –2, median sCyC was significantly higher (0.93 versus 0.80 mg/L, \( P = 0.01 \)), but not on Day –1 (0.98 versus 0.86 mg/L, \( P = 0.08 \)). The diagnostic performance for sCyC was fair on Day –2 [area under the curve (AUC) 0.72] and poor on Day –1 (AUC 0.62). Urinary CyC had no diagnostic value on either of the two days prior to AKI (AUC <0.50). RRT was started in 14 patients with AKI; sCyC and uCyC determined on Day 0 were poor predictors for the need for RRT (AUC ≤0.66).

Conclusions: In this study, sCyC and uCyC were poor biomarkers for prediction of AKI and the need for RRT.

Keywords

Urine cystatin C · Serum cystatin C · Acute kidney injury · Renal replacement therapy · Predictive biomarkers · Intensive care unit
Introduction

Acute kidney injury (AKI) is a common complication of critical illness and carries high mortality despite significant advances in medical care [1, 2]. This apparent lack of improvement may result from the use of more aggressive medical and surgical interventions in an ever-ageing population [3]. On the other hand, potentially effective therapeutic interventions for AKI may currently fail because they are applied late in the course of injury after an obvious increase of serum creatinine (sCr) is observed [4]. Due to the delayed rise in sCr following injury, recent efforts have focused on identification of an early and reliable biomarker of kidney injury [5, 6].

Cystatin C (CyC) is a 13-kDa, nonglycosylated basic protein, produced at a constant rate by all nucleated cells. It is freely filtered by glomeruli and catabolized in tubules. In high-risk patients, serum CyC (sCyC) detected AKI 1–2 days earlier than sCr [7]. Moreover, although CyC is normally not detected in urine, it has been found in urine of patients with tubular disease, suggesting that it is a tubular marker [8–13]. One drawback of use of CyC at present is a lack of recognition of its potential value for use in the general critical care setting, in which the population is heterogeneous and AKI etiology and timing are often unclear.

In the present study in a heterogeneous intensive care unit (ICU) population we collected serial samples of sCyC and uCyC, and determined the first day of AKI based on the RIFLE classification system [14]. We hypothesized that these markers predict AKI 1–2 days earlier than the RIFLE criteria in patients developing AKI after entry, and that these biomarkers predict the need for renal replacement therapy (RRT) on the first day of AKI. The preliminary findings of this study were presented in abstract form [15].

Concise methods

Patients

The protocol was approved by the institutional review board of all participating institutions, and written informed consent was obtained from all patients or their authorized representatives. The study was a prospective observational cohort study in adult patients with expected duration of mechanical ventilation of at least 48 h, and/or expected length of ICU stay of at least 72 h. Patients were enrolled within 48 h of ICU admission. Detailed methods (e.g., exclusion criteria) are described in Electronic Supplementary Material (ESM) file 1.

Demographic data, admission diagnosis, Acute Physiology and Chronic Health Evaluation (APACHE) II, and Simplified Acute Physiology Score (SAPS) II scores were documented upon ICU admittance [16, 17]. Routine laboratory data were measured daily.

Definition of acute kidney injury

The patients were scored daily for AKI using the creatinine and urine output criteria of the RIFLE classification system for AKI [14]. To define the baseline renal function we compared the premorbid sCr within 1 year prior to ICU admission with the sCr at ICU admission. The lower of these two values served as baseline renal function. If the premorbid sCr was unavailable, it was estimated by solving the modification of diet in renal disease (MDRD) equation as recommended by the Acute Dialysis Quality Initiative (ADQI) working group [18].

The premorbid sCr was not estimated in patients with history of kidney insufficiency. In these patients, admission sCr served as baseline when the premorbid sCr was unknown.

The first day of AKI was termed Day 0, while the two days prior to this day were termed Day −1 and Day −2, respectively.

Statistical analysis

The primary endpoint was the first RIFLE event (risk, injury or failure). The secondary endpoint was initiation of RRT. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS, Chicago IL, USA) for Windows. Continuous variables are expressed as mean ± standard deviation (SD) or median with interquartile range. Cystatin C levels below the detection limit of 0.05 mg/L were considered to be 0.025 mg/L. Categorical variables are expressed as counts and percentages. Normally distributed variables were compared using one-way analysis of variance with Bonferroni’s correction for multiple comparisons. For significant findings, post hoc t-test was applied. Kruskall–Wallis one-way analysis of variance was used to compare non-normally distributed variables. Chi-square testing was used to test frequencies between groups. Linear
mixed models were used to compare CyC levels among RIFLE stages. All testing was two-tailed, and \( P < 0.05 \) was considered statistically significant. Test characteristics were calculated to assess the diagnostic performance of CyC.

### Results

**Patients**

We enrolled 170 patients from April 2006 to November 2007 and excluded 19 patients during the analysis because of incomplete sampling, leaving 151 patients for analysis. One hundred thirty-three patients (88%) were included on the first day of ICU admission, and 18 patients (12%) were included the next day of admission. We defined three groups: group 0 (\( N = 60 \)), never developed AKI, serving as controls; group 1 (\( N = 35 \)), developed AKI after admission; and group 2 (\( N = 56 \)), presented with AKI at admission. AKI developed after a median of 2 [1–2] days (range 1–7 days) in group 1: 17 patients (49%) were classified for AKI by the creatinine criteria, 14 patients (38%) by the urine criteria, and in 3 patients (9%) the creatinine and urine scores were identical. In group 2, 28 patients (50%) had AKI at admission by the creatinine criteria, 13 patients (23%) by the urine criteria, and in 17 patients the creatinine and urine scores were identical. Table 1 compares the baseline clinical data of the three groups, while renal and outcome data are shown in Table 2. The maximum RIFLE class was higher in group 2 compared with group 1. In group 1 the maximum RIFLE class was achieved by the creatinine criteria in 21 patients (60%), by the urine criteria in 8 patients (23%), and in 6 patients (17%) the creatinine and urine AKI classification were identical. In group 2 the maximum RIFLE class was achieved by the creatinine criteria in 24 patients (43%), by the urine criteria in 13 patients (23%), and in 17 (30%) patients the creatinine and urine AKI classification were identical.

**Serum and urinary cystatin C levels**

Cystatin C was measured in 582 blood samples (3.8 ± 3.2 samples/patient) and 569 urine samples (3.8 ± 3.1 samples/patient). Cystatin C level was below the detection limit in 171 (30%) urine samples. Serum CyC levels increased significantly with increasing RIFLE class (Table 3). Urinary CyC levels also increased with increasing RIFLE class; however, the difference between RIFLE risk and RIFLE injury was not statistically significant.

Figure 1 compares the longitudinal trend of sCr, sCyC, and uCyC starting from 2 days prior to AKI (group 1) with the non-AKI trend (group 0). On Day –2, median sCyC was significantly higher (0.93 versus 0.80 mg/L, \( P = 0.01 \)), but not on Day –1 (0.85 versus 0.86 mg/L, \( P = 0.08 \)). Serum CyC levels, however, did

### Table 1 Baseline characteristics grouped according to AKI status

|                          | Group 0 (\( N = 60 \)) | Group 1 (\( N = 35 \)) | Group 2 (\( N = 56 \)) | \( P \)         |
|--------------------------|------------------------|------------------------|------------------------|----------------|
| Age (years)              | 59.2 ± 16.1            | 68.4 ± 15.4            | 74.6 ± 9.3             | <0.001        |
| Male (%)                 | 39 (65)                | 24 (69)                | 34 (62)                | 0.81          |
| BMI (kg/m\(^2\))         | 24.6 ± 4.3             | 26.5 ± 3.8             | 29.6 ± 12.8            | 0.11          |
| APACHE II                | 18.5 ± 9.9             | 19.6 ± 8.3             | 24.2 ± 12.9            | 0.016         |
| SAPS II                  | 37.2 ± 13.3            | 44.1 ± 14.2            | 47.6 ± 16.4            | 0.01          |
| Comorbidities (%)        |                        |                        |                        |               |
| Hypertension             | 15 (26)                | 14 (40)                | 24 (44)                | 0.12          |
| Diabetes                 | 7 (12)                 | 5 (14)                 | 8 (15)                 | 0.92          |
| CKD                      | 2 (3)                  | 1 (3)                  | 6 (11)                 | 0.17          |
| TSH (mU/L)               | 0.40 (0.18–0.87)       | 0.42 (0.25–1.0)        | 0.41 (0.21–1.20)       | 0.83          |
| FT4 (pmol/L)             | 13.2 ± 3.5             | 12.8 ± 3.3             | 13.6 ± 3.6             | 0.67          |
| Admission category (%)   |                        |                        |                        | 0.68          |
| Medical                  | 29 (48.3)              | 17 (48.6)              | 23 (41.8)              |               |
| Surgical                 | 31 (51.7)              | 18 (51.4)              | 33 (59)                | 0.21          |
| Primary diagnosis (%)    |                        |                        |                        |               |
| Cardiovascular failure   | 2 (3.3)                | 4 (11.4)               | 4 (7.1)                |               |
| Cerebrovascular event    | 2 (3.3)                | 0                      | 0                      |               |
| Hemorrhagic shock        | 7 (11.7)               | 2 (5.7)                | 6 (10.7)               |               |
| Multiple trauma          | 4 (6.7)                | 2 (5.7)                | 1 (1.8)                |               |
| Elective major surgery   | 1 (1.7)                | 1 (2.9)                | 5 (8.9)                |               |
| Respiratory failure      | 23 (38.3)              | 11 (31.4)              | 14 (25)                |               |
| Septic shock             | 20 (33.3)              | 13 (37.1)              | 26 (46.6)              |               |

AKI acute kidney injury, group 0 no AKI, group 1 developed AKI after admission, group 2 AKI at admission. BMI body mass index, APACHE Acute Physiology and Chronic Health Evaluation, SAPS Simplified Acute Physiology Score, CKD chronic kidney disease, TSH thyroid-stimulating hormone
not rise earlier than sCr. On the 2 days prior to AKI, uCyC levels did not differ significantly between group 1 and group 0 (median 0.13 [0.025–0.88] mg/L versus median 0.16 [0.025–1.50] mg/L, \( P = 0.89 \), and median 0.14 [0.025–0.37] mg/L versus median 0.17 [0.025–0.84] mg/L, \( P = 0.57 \), Day –2 and Day –1, respectively).

### Table 2 Renal characteristics and outcome grouped according to AKI status

|                          | Group 0 (\( N = 60 \)) | Group 1 (\( N = 35 \)) | Group 2 (\( N = 56 \)) | \( P \) |
|--------------------------|-------------------------|-------------------------|-------------------------|---|
| **Premorbid sCr (\( \mu \text{mol/L} \))** |                         |                         |                         |   |
| Actual\(^a\)             | 92 ± 30 (\( N = 37 \))  | 91 ± 25 (\( N = 28 \))  | 83 ± 23 (\( N = 37 \))  | 0.31 |
| Estimated\(^b\)          | 88 ± 12                 | 86 ± 12                 | 83 ± 11                 | 0.05 |
| **Study inclusion**       |                         |                         |                         |   |
| sCr (\( \mu \text{mol/L} \)) | 72 (61–94)              | 87 (76–87)              | 139 (97–211)            | <0.001 |
| sCyC (mg/L)              | 0.80 (0.65–1.04)        | 0.91 (0.81–1.17)        | 1.14 (0.88–1.94)        | <0.001 |
| uCyC (mg/L)              | 0.16 (0.025–1.47)       | 0.18 (0.07–0.68)        | 0.59 (0.10–3.47)        | 0.46 |
| uCyC\(_{corr}\) (g/molCr) | 0.03 (0.01–0.30)        | 0.04 (0.01–0.13)        | 0.13 (0.01–0.67)        | 0.47 |
| **Maximum RIFLE class (%)** |                         |                         |                         | <0.001 |
| Risk                     | –                       | 27 (77)                 | 22 (39.3)               |   |
| Injury                   | –                       | 5 (14.3)                | 14 (25)                 |   |
| Failure                  | –                       | 3 (8.6)                 | 20 (35.8)               |   |
| CVVH (%)                 | 1 (1.7)                 | 4 (11.4)                | 10 (17.6)               | 0.01 |
| ICU treatment (days)      | 5 (3–8)                | 8 (5–18)                | 6 (3–9)                 | 0.002 |
| ICU mortality (%)         | 0                      | 4 (11.4)                | 11 (19.6)               | 0.002 |
| Hospital mortality (%)    | 4 (6.7)                | 6 (17.1)               | 18 (32.1)               | 0.002 |

AKI acute kidney injury, group 0 never AKI, group 1 developed AKI after admission, group 2 AKI at admission, sCyC serum cystatin C, uCyC urine cystatin C, uCyC\(_{corr}\) urine cystatin C normalized for urinary creatinine, CVVH continuous venovenous hemofiltration, ICU intensive care unit

\(^a\) Baseline serum creatinine based on premorbid serum creatinine within 1 year prior to ICU admission

\(^b\) Baseline serum creatinine based on solving the modification of diet in renal disease (MDRD) equation [18]

### Table 3 Cystatin C per RIFLE class

|                  | None | Risk | Injury | Failure | \( P \) |
|------------------|------|------|--------|---------|---|
| Serum samples    |      |      |        |         |   |
| Number           | 399  | 109  | 35     | 31      |   |
| CyC (mg/L)       | 1.15 (1.05–1.25) | 1.34 (1.22–1.45) | 1.75 (1.59–1.92) | 2.31 (2.09–2.52) | <0.001 |
| Urine samples    |      |      |        |         |   |
| Number           | 391  | 104  | 40     | 34      |   |
| CyC (mg/L)       | 1.02 (0.54–1.51) | 2.36 (1.52–3.19) | 2.77 (1.43–4.12) | 5.87 (4.24–7.51) | <0.001 |
| CyC\(_{corr}\) (g/mol Cr) | 0.43 (0.28–0.59) | 0.44 (0.21–0.68) | 0.34 (0.04–0.72) | 0.79 (0.32–1.24) | 0.46 |

Values are mean and 95% confidence interval. The \( P \) value represents the difference among groups by linear mixed models

sCyC serum cystatin C, uCyC urine cystatin C, uCyC\(_{corr}\) uCyC normalized for urinary creatinine

### Fig. 1 Time course of serum creatinine, serum cystatin C, and urine cystatin C. Time courses are from 2 days prior to acute kidney injury (AKI) for patients developing AKI after entry (open circles), and from entry for the non-AKI group (closed circles). Values are mean and standard error of the means. The number of patients investigated is shown in italics at each time point. * \( P < 0.05 \) compared with the non-AKI group

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not rise earlier than sCr. On the 2 days prior to AKI, uCyC levels did not differ significantly between group 1 and group 0 (median 0.13 [0.025–0.88] mg/L versus median 0.16 [0.025–1.50] mg/L, \( P = 0.89 \), and median 0.14 [0.025–0.37] mg/L versus median 0.17 [0.025–0.84] mg/L, \( P = 0.57 \), Day –2 and Day –1, respectively). The
diagnostic performance for sCyC was fair on Day –2 (area under the curve (AUC) 0.72) and poor on Day –1 (AUC 0.62), while uCyC had no diagnostic value on Day –2 and Day –1 (Fig. 2). The test characteristics of sCyC at various cutoff levels are shown in ESM Table 1.

Fourteen (15%) out of 91 AKI patients received continuous venovenous hemofiltration (CVVH): 4 patients from group 1, and 10 patients from group 2. Median duration between Day 0 and initiation of CVVH was 1.5 [0–4] days. In comparison with the non-CVVH patients, the AKI patients requiring CVVH had significantly higher APACHE II scores on admission (28 [21–33] versus 19 [14–27], P = 0.01) and produced less urine (740 [400–1,088] mL/day versus 1,660 [1,028–2,918] mL/day, P = 0.001). Systemic and urinary CyC determined on Day 0 were poor predictors for the need for RRT (AUC ≤ 0.66, Fig. 3).

Discussion

In this prospective multicenter cohort study in a heterogeneous ICU population, sCyC and uCyC increased with increasing RIFLE class. However, the predictive ability of these biomarkers for AKI was poor. Approximately one-third of the patients without AKI at ICU admission developed AKI during the ICU treatment, and in these patients sCyC was significantly higher 2 days prior to AKI compared with patients who did not develop AKI. Of note, sCyC levels did not rise earlier than sCr. The diagnostic performance of sCyC was at best fair for Day –2 and poor on Day –1. Levels of uCyC were not different in patients prior to AKI in comparison with patients who did not develop AKI and had no diagnostic accuracy for AKI.

Previous studies investigating whether CyC increases before development of AKI are limited and their results inconsistent; however, comparison among studies is hampered by case mix and heterogeneity in study designs [7, 12, 20–24]. Notably, no two studies used identical definitions for AKI, and this definition is critical in biomarker research. Nejat et al. [20, 25, 26] recently reported on the predictive performance of CyC in two subanalyses of the EARLYARF study. Notably, while 3,966 patients were screened for the EARLYARF study, only 444 patients (11%) were included in the subanalyses, suggesting selection bias [25]. Based on the sCr criteria used...
by the Acute Kidney Injury Network definition [27], 125 (28%) patients had AKI on entry, 73 (16%) patients developed AKI over the subsequent 7 days (AKI 7d), and 246 (55%) patients did not [20, 26]. sCyC rose prior to sCr in 66% of the patients developing AKI after entry [20]. sCyC on entry was predictive for sustained AKI (AUC 0.80), defined as an increase in sCr of at least 50% from baseline for 24 h or longer, but not for AKI 7d (AUC 0.65) [20]. A subanalysis of sepsis patients showed that only uCyC was predictive of AKI within 48 h (AUC 0.71) and not sCyS, while uCyC was not predictive of AKI in patients without sepsis (AUC = 0.45) [26]. Ahslstrom et al. [21] studied 202 patients in a mixed ICU, of whom 49 developed AKI according to the urine output and/or sCr RIFLE failure criteria. In that study sCyC showed excellent predictive value for AKI; however, sCyC did not rise earlier than sCr [21]. Herget-Rosenthal et al. [7] analyzed 85 ICU patients at high risk of developing AKI and used the creatinine risk criteria of the RIFLE classification to define AKI (N = 44). In contrast to our findings, sCyC was shown to detect AKI 1–2 days earlier than sCr (AUC 0.82 and 0.97 on day –2 and day –1, respectively) [7]. In the study by Haase-Fielitz et al. [23] in 100 patients following cardiopulmonary bypass surgery (CPB), 23 patients developed AKI, defined as increase in sCr of ≥50% from baseline within the first five postoperative days. In that study, sCyC on ICU arrival and at 24 h after CPB were good predictors of AKI (AUC ≤ 0.83). Notably, the authors suggested that presence of chronic kidney disease (CKD) could affect the diagnostic performance of CyC, because exclusion of the CKD patients reduced the diagnostic performance of sCyC. This reduction in diagnostic performance, however, may have been caused by the smaller sample size (N = 15), rather than by the exclusion of CKD patients [23]. We did not evaluate the effect of CKD, because only one patient had CKD on day –2 and day –1. In another, small (N = 30) CPB study, 15 patients developed AKI defined as 50% or greater increase in sCr from baseline within 72 h, and the optimal diagnostic performance for sCyC (AUC 0.83) was 10 h post CPB [22]. In the CPB study (N = 72) of Koyner, 34 patients developed AKI defined as sCr rise of ≥25% from baseline within the first 3 days or need of RRT [12]. Serum CyC at ICU arrival and at 6 h were poor predictors for AKI (AUC 0.62 and 0.63, respectively), while urine CyC at ICU arrival and at 6 h were fair predictors (AUC 0.69 and 0.72, respectively) [12]. In the study by Liangos et al. [24] (N = 103), uCyC measured 2 h post CPB did not predict AKI (N = 13), defined as sCr increase of ≥50% from post CPB to peak value within the first 3 days (AUC 0.50). In a very small study in septic patients (N = 29) no correlation was found between sCyC at ICU admission and occurrence of AKI (N = 10) defined as sCr >267 µmol/L or diuresis <30 mL/h [28]. Four small studies in ICU patients reported that sCyC was superior to sCr to identify glomerular filtration rate (GFR) <80 mL/min per 1.73 m² [29–32]. The GFR studies, however, can be criticized because they used derivatives for GFR and not the real “gold standard” based on clearance of exogenous substances [33].

In the present study, 56 (37%) patients had AKI at admission, which is similar to a previous AKI biomarker study in a heterogeneous ICU population [34]. It makes little sense to predict AKI in patients with AKI; however, in these patients, CyC may help to identify those requiring RRT. Unfortunately, in our study both sCyC and uCyC determined on day 0 were poor predictors for the need for RRT, although it must be mentioned that RRT was started in 14 patients only. Our findings agree with the findings of Perianayagam et al. [35], but disagree with three earlier reports suggesting excellent diagnostic performance of sCyC [11, 20, 23]. Several factors may explain the conflicting results, including case mix and the reason for starting RRT. In our study, oligo/anuria often triggered RRT, while low GFR probably triggered RRT in the study by Herget-Rosenthal et al., including exclusively nonoliguric patients [11]. In the study by Haase-Fielitz et al. only five patients fulfilled the composite endpoint (need for RRT and in-hospital mortality) [23]. Nejat et al. do not report many patients received RRT [20].

Fig. 3 Receiver-operating curves demonstrating the performance of cystatin C (CyC) for prediction of the need of renal replacement therapy. (N = 80, disease prevalence 0.16). Area under the curve (AUC) is depicted in each panel.
Another potential role for biomarkers is to allow differentiation between extrinsic and intrinsic causes of AKI; however, our study was not designed to investigate this issue. Nearly 40% of our patients never developed AKI, yet some of these patients had increased levels of CyC according to the reference intervals reported in literature [10]. Several factors may be responsible for this finding. First, the published reference intervals were determined in healthy volunteers with no history of renal disease, and may not apply to our critically ill population. Although sCyC is less influenced by age, sex, and muscle mass compared with serum creatinine level, it still can be affected by these patient variables [36]. Moreover, sCyC levels can be affected by levels of glucocorticosteroids [37], thyroid hormones [38], and insulin [39] as well as markers of inflammation such as white blood cell count and C-reactive protein level [40]. All these factors play an important role in critically ill patients and could affect the reference interval. Second, we did not use any protease inhibitor in the storage of the urine to clear all disturbing elements in the urine. However, Herget-Rosenthal reported good agreement between uCyC measurement with and without stabilization buffer [10]. Finally, the consensus RIFLE definition for AKI is based on sCr and/or urine output. These are functional parameters and may not be appropriate for detection of injury to the kidney. We cannot rule out that increased CyC levels indeed reflect damage to the kidneys which is not recognized by the RIFLE criteria. Notably, in the present study, prevalence of AKI was high, and therefore a low sCyC of <0.80 mg/L resulted in high [negative predictive value (NPV)] 75–95% despite its low specificity. Therefore, in a critically ill population with high prevalence of AKI, sCyC may be helpful to rule out AKI.

Our study is the first multicenter study investigating whether CyC can predict development of AKI in the general critical care setting in which the population is heterogeneous and AKI etiology and timing are often unclear. However, there are some limitations. First, a small percentage of our patients (12%) were enrolled the day following admission, and specimens were collected on alternate days after the first 2 days. As a result, our sample size was relatively small, particularly on Day −2. Second, MDRD-based baseline sCr was used in 18% of our patients. Missing preadmission sCr value is a recognized problem in AKI research, which may lead to misclassification of AKI incidence [41, 42]. On the other hand, use of surrogate measures for baseline renal function avoids selection bias. Third, we did not evaluate whether CyC concentrations were affected by other factors (e.g., inflammatory state, insulin or hydrocortisone therapy). Finally, the definition of AKI is critical in biomarker research, and the RIFLE criteria may not be an adequate gold standard for AKI.

Conclusions

In this relatively small multicenter study in a heterogeneous ICU population and using the RIFLE classification system to define AKI, sCyC and uCyC were poor biomarkers for AKI. Moreover, on the first day of AKI these biomarkers did not predict the need of RRT. However, sCyC <0.80 mg/L had high NPV in our population with high incidence of AKI.

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Conflict of interest The authors declare that they have no competing interests.

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