Cystatin C as a Marker of Acute Kidney Injury in the Emergency Department

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Background and objectives: The diagnosis of acute kidney injury (AKI) is usually based on changes in serum creatinine, which is a poor marker of early renal dysfunction. The discriminative and predictive abilities of serum and urinary cystatin C were examined for the prediction of AKI.

Design, setting, participants, & measurements: In this prospective cohort study, serum and urinary cystatin C were serially measured in a heterogeneous group of patients ($n = 616$) presenting to a tertiary care emergency department. The primary outcome was AKI, classified according to RIFLE and AKIN criteria. The secondary outcome was an adjudication based on clinical criteria to AKI, prerenal azotemia, chronic kidney disease (CKD), and normal kidney function.

Results: Patients were adjudicated to have AKI in 21.1%, prerenal azotemia in 25.8%, CKD in 2.4%, and normal kidney function in 50.7%. For the diagnosis of AKI, the discriminatory ability of urinary creatinine and cystatin C was marginal. Both serum cystatin C and serum creatinine (at presentation and 6 hours later) showed high discriminatory ability for the diagnosis of AKI. However, only serum cystatin C attained a significant early predictive power (Hosmer-Lemeshow P value > 0.05). Serum cystatin C could differentiate between AKI and prerenal azotemia, but not between AKI and CKD.

Conclusions: Serum cystatin C is an early, predictive biomarker of AKI, which outperforms serum creatinine in the heterogeneous emergency department setting. However, neither biomarker discriminated between AKI and CKD. Additional biomarkers continue to be needed for improved specificity in the diagnosis of community-acquired AKI.

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The incidence of acute kidney injury (AKI) is increasing globally, affecting about 6% of all hospitalized patients in whom it is an independent predictor of mortality and morbidity (1). Much is now known about the epidemiology of AKI in the hospital-acquired and critical care settings (2). AKI occurring in a community setting is also common but quite distinct, and published data are scarce. Community-acquired renal dysfunction encountered in the emergency department (ED) is frequently caused by volume depletion, whereas hospital-acquired AKI often accompanies other organ disease processes and complicates their management and outcomes (3). In the ED, the clinician's priorities are (*1*) to detect AKI early so that preventive and therapeutic approaches may be implemented in a timely manner, and (2) to differentiate between prerenal azotemia (preR), chronic kidney disease (CKD), and intrinsic AKI. Unfortunately, neither is possible with serum creatinine (SCr) measurements, since changes in SCr lag behind both renal injury and renal recovery, and are influenced by several nonrenal factors (4,5).

A number of novel plasma and urinary biomarkers have recently been proposed for the early diagnosis of AKI and its clinical outcomes in a variety of clinical settings (6,7). Among these, cystatin C appears to be a useful detection marker for AKI (8). It is a low molecular weight cysteine proteinase that is stably produced by all nucleated cells in a constitutive fashion. It is freely filtered by the renal glomeruli and totally reabsorbed in the proximal tubule, without secretion. Serum concentration of cystatin C is thus determined primarily by GFR. Cystatin C is not normally found in urine in significant amounts (9). Elevated urinary levels of cystatin C may reflect tubular dysfunction independent of GFR (10,11) and may provide an early indication of AKI in the cardiac surgery (12) and critically ill (13) patients. Multiple studies evaluating serum cystatin C (SCysC) as a GFR marker have shown that it performs at least as well as SCr in the population at large, and it is superior to SCr in specific patient populations (14). SCysC has also been proposed as an early biomarker of AKI in the intensive care (15,16), cardiac surgery (17), and radiocontrast administration (18) settings.

The aim of this prospective cohort study was to evaluate the

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accuracy of SCysC and urinary cystatin C (UCysC) as early biomarkers of AKI in an unselected, heterogeneous group of patients admitted to the ED in a large tertiary care hospital. The primary end point was a diagnosis of AKI fulfilling the SCr-based RIFLE (19) and AKIN (20) criteria. The secondary end point was the differentiation between preR, intrinsic AKI, and CKD at the time of presentation to the ED.

Materials and Methods

Patient Population

Patients admitted to the nonsurgical ED of the Fernando Fonseca Hospital from March to November 2008 were enrolled in a consecutive manner after informed consent was obtained. Exclusion criteria were: age under 18 years or over 80 years of age, complete anuria, established CKD stage 4 or greater (21), urinary obstruction, cytotoxic therapy, and patients predicted to be admitted for less than the 48-hour sample collection period.

Biomarker Measurements

The baseline renal function using SCr was obtained from the Fernando Fonseca Hospital electronic records, for 1 to 6 months before admission. A prospective renal function assessment was carried out by measuring SCr, urinary creatinine (UCr), SCysC, and UCysC. Serial blood and urine samples were obtained at 0, 6, 12, 24, and 48 hours from presentation to the ED (Figure 1). After transfer to the medical unit, SCr was followed until hospital discharge. Creatinine was measured in plasma and urine by modified Jaffe kinetic reaction. Cystatin C was measured in plasma and urine by particle-enhanced immunonephelometry (BN Systems, Dade-Behring, Marburg, Germany) with N latex Cystatin C assay (22).

Clinical Adjudication

GFR was estimated by using the Modification of Diet and Renal Disease formula (23). On the basis of baseline and prospective measurements of SCr, all patients were adjudicated to one of four diagnostic categories: Normal kidney function (NF), nonprogressive CKD, preR, or AKI. This renal function classification was performed in consensus by the nephrologists of the study group who were blinded to the biomarker results, as described previously (24). All classifications were subsequently independently verified by three nephrologists who were blind to the study and belonged to the Nephrology staff of three other hospitals in Lisbon. NF was defined as a baseline estimated GFR (eGFR) >60 ml/min per 1.73 m^2 and no increase in SCr during the hospitalization. Nonprogressive CKD was defined as a sustained and unchanging decrease in GFR that met criteria for CKD (eGFR <60 ml/min per 1.73 m^2) and persisted for more than 3 months before admission (21). preR was defined as a new-onset increase in SCr that resolved within 48 hours and returned to the baseline NF level. AKI was defined according to the RIFLE criteria (19) and modified according to AKIN criteria (20) with new-onset of at least 1.5-fold increase or ≥0.3 mg increment of SCr values from baseline, sustained for more than 48 hours.

To analyze factors that predispose to AKI, nature and timing of the inciting event, and the response of the kidney to the insult, variables included in the "Multidimensional Criteria" (25) were recorded, including "susceptibility" (pre-existing kidney disease and risk of developing acute injury), nature and timing of the "insult" on the basis of the specific insult and the time interval from the insult to the point of evaluation (in this case the admission to the ED), "response" corresponding to the RIFLE classification, and nonrenal organ dysfunction.

Statistical Analysis

Categorical data were presented as frequencies and percentages, and continuous variables as mean or median, SD or interquartile range (25th percentile to 75th percentile). Nonparametric (χ^2, Mann-Whitney U, and Kruskall-Wallis) tests were used because of the existence of outliers, high variability, and skewed distributions. The 95% confidence intervals (CI) were also calculated whenever appropriate.

The logistic regression model was fitted to the data not only to determine the influence of each of the studied variables on the risk of AKI but also to study the ability of the models to predict AKI (by the Hosmer-Lemeshow goodness-of-fit test and calibration plots) and to discriminate between those patients who will develop AKI from those who will not (by the area under the receiver operating characteristic or ROC curve). A value of 0.50 is obtained when a model discriminates no better than chance, and a value of 1.0 means perfect accuracy (26). The Hosmer-Lemeshow test compares observed and expected frequencies of AKI patients based on the values of the estimated probabilities obtained by the logistic regression model (27). In this test, a high *P* value indicates that the model is performing well, *i.e.*, there is not a large discrepancy between observed and expected AKI.

Generalized Additive Models (GAMs), for binary response, were used to calculate cut-off points for SCr and cystatin C. To assess the performance of those diagnostic tests, sensitivity, specificity, and positive and negative predictive values (PPV and NPV) were calculated as well as the likelihood ratios, which incorporates both the sensitivity and specificity of the test and provides a direct estimate of how much a test result will change the odds of having AKI.

The significance level $\alpha = 5\%$ was considered. All data were ana-

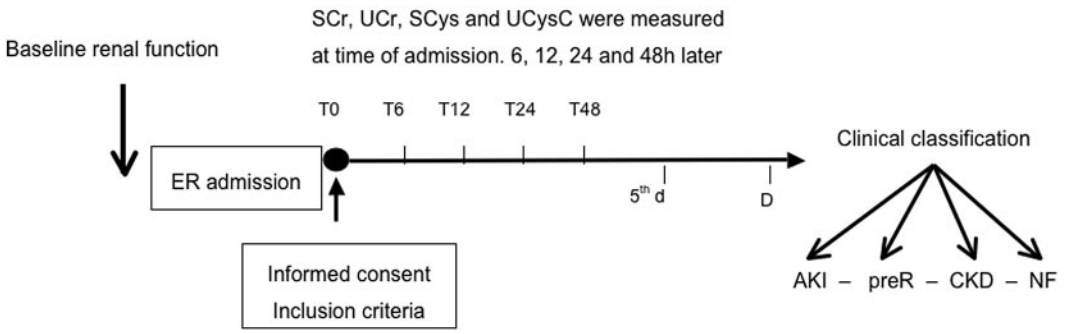

Figure 1. Study flow diagram. Patients hospitalized following presentation to the emergency room (ER) were included if they met the eligibility criteria. SCr, UCr, SCysC, and UCysC were measured during the hospitalization, at the indicated times, until discharge (D). At the end of the study, patients were adjudicated as having AKI, preR, CKD, or NF.

Table 1. Patients characteristics

Characteristic	All Patients (616)	AKI 21.1% (130)	PreR 25.8% (159)	CKD 2.4% (15)	NF 50.7% (312)	*P* Value
Mean age (SD)	59.1 (15.8)	66.3 (12.2)	58.4 (16.1)	68.5 (11.5)	56.0 (15.7)	<0.001[a]
Men (%)	386 (62.70)	84 (64.60)	93 (58.50)	10 (66.70)	199 (63.80)	0.645[b]
Nonblack (%)	536 (87.00)	114 (87.70)	137 (86.20)	15 (100.00)	270 (86.50)	0.559[b]
SCr baseline (P_{25} to P_{75})	0.8 (0.60 to 0.90)	0.95 (0.70 to 1 to 0.20)	0.70 (0.60 to 0.90)	1.20 (1.10 to 1.90)	0.70 (0.60 to 0.80)	<0.001[c]
Serum median (P_{25} to P_{75})						
CysC						
T0	0.84 (0.68 to 1.16)	1.40 (1.09 to 1.95)	0.90 (0.74 to 1.14)	1.26 (1.00 to 1.44)	0.73 (0.62 to 0.85)	<0.001
T6	0.84 (0.68 to 1.14)	1.41 (1.08 to 1.97)	0.89 (0.75 to 1.15)	1.17 (1.07 to 1.54)	0.71 (0.62 to 0.86)	<0.001
T12	0.84 (0.68 to 1.14)	1.43 (1.11 to 1.96)	0.90 (0.73 to 1.11)	1.27 (1.14 to 1.41)	0.71 (0.62 to 0.85)	<0.001
T24	0.84 (0.68 to 1.14)	1.43 (1.06 to 1.92)	0.91 (0.73 to 1.14)	1.33 (1.14 to 1.40)	0.72 (0.63 to 0.86)	<0.001
T48	0.83 (0.68 to 1.13)	1.38 (1.06 to 1.89)	0.88 (0.74 to 1.05)	1.25 (1.10 to 1.41)	0.72 (0.62 to 0.83)	<0.001
SCr						
T0	0.90 (0.70 to 1.20)	1.60 (1.20 to 2.40)	1.00 (0.80 to 1.30)	1.40 (1.20 to 1.70)	0.80 (0.60 to 0.90)	<0.001
T6	0.90 (0.70 to 1.20)	1.50 (1.20 to 2.40)	1.00 (0.80 to 1.20)	1.30 (1.10 to 1.60)	0.70 (0.60 to 0.90)	<0.001
T12	0.90 (0.70 to 1.20)	1.60 (1.20 to 2.30)	1.00 (0.80 to 1.20)	1.40 (1.20 to 1.60)	0.80 (0.60 to 0.90)	<0.001
T24	0.90 (0.70 to 1.20)	1.60 (1.20 to 2.10)	0.90 (0.70 to 1.20)	1.40 (1.20 to 1.60)	0.80 (0.60 to 0.90)	<0.001
T48	0.90 (0.70 to 1.20)	1.50 (1.20 to 2.10)	0.90 (0.80 to 1.02)	1.40 (1.20 to 1.60)	0.80 (0.60 to 0.90)	<0.001
Urinary median (P_{25} to P_{75})						
UCysC/Cr						
T0	0.33 (0.17 to 0.69)	0.49 (0.21 to 1.08)	0.34 (0.17 to 0.71)	0.44 (0.29 to 0.68)	0.29 (0.15 to 0.55)	<0.001
T6	0.32 (0.18 to 0.58)	0.46 (0.26 to 1.04)	0.32 (0.19 to 0.69)	0.42 (0.29 to 0.50)	0.27 (0.16 to 0.46)	<0.001
T12	0.29 (0.17 to 050)	0.39 (0.23 to 0.70)	0.31 (0.19 to 0.64)	0.42 (0.24 to 0.75)	0.26 (0.16 to 0.40)	<0.001
T24	0.29 (0.16 to 0.54)	0.40 (0.22 to 1.0)	0.29 (0.15 to 0.56)	0.37 (0.29 to 0.70)	0.25 (0.15 to 0.44)	<0.001
T48	0.27 (0.16 to 0.49)	0.28 (0.18 to 0.86)	0.31 (0.14 to 0.53)	0.54 (0.24 to 0.75)	0.24 (0.15 to 0.39)	0.001
UCr						
T0	82.00 (43.75 to 150.00)	61.00 (34.00 to 121.50)	93.00 (46.50 to 160.00)	54.00 (39.75 to 77.00)	86.00 (47.50 to 159.50)	0.006
T6	86.00 (50.00 to 146.00)	68.00 (40.00 to 101.00)	97.00 (51.00 to 155.00)	67.00 (48.50 to 88.25)	93.50 (56.75 to 159.50)	0.001
T12	88.50 (55.25 to 149.75)	76.50 (48.25 to 130.50)	92.00 (55.00 to 152.00)	57.00 (51.00 to 105.00)	97.00 (62.00 to 157.00)	0.009
T24	90.00 (56.00 to 154.00)	78.00 (53.00 to 114.00)	103.00 (57.75 to 169.75)	70.50 (48.75 to 91.75)	92.00 (58.00 to 163.00)	0.003
T48	95.00 (58.00 to 153.50)	97.00 (48.50 to 138.50)	89.00 (59.50 to 170.75)	74.00 (32.50 to 122.00)	102.00 (59.00 to 159.00)	0.111
Outcome						
HD	6 (1%)	6	0	0	0	—
Mortality	27 (4.4%)	15 (55.6%)	5 (18.5%)	0	7 (25.9%)	<0.001

Biomarkers units are expressed as mg/L (SCysC), mg/dl (SCr), mg/g (UCystC/Cr), and mg/dl (UCr).

[a]Age *P* value < 0.001 comparing AKI with preR and NF patients; *P* value 0.496 comparing AKI with CKD patients; *P* value 0.007 comparing preR with CKD patients.

[b]*P* value calculated by Chi-squared test; all the other *P* values were calculated by Kruskal-Wallis test.

[c]SCr baseline *P* value < 0.001 except between preR and NF patients (*P* value = 0.797).

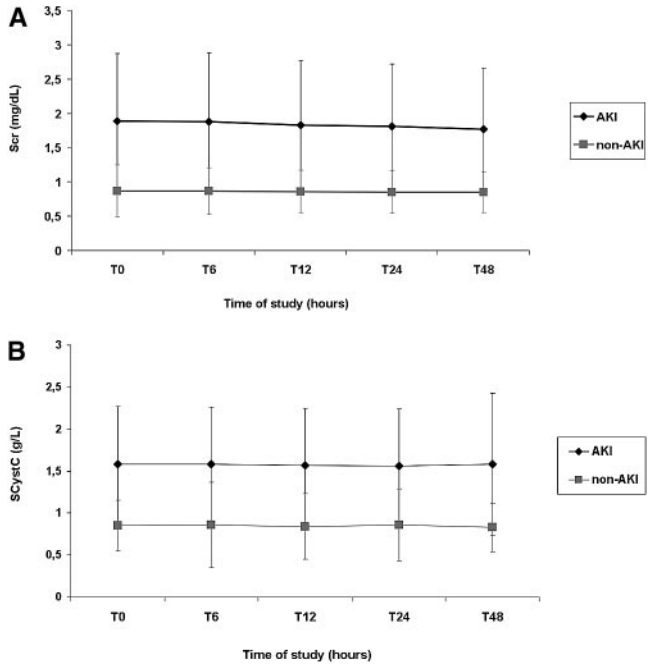

Figure 2. Pattern of biomarkers in AKI and non-AKI patients over time. (A) SCr. (B) SCysC. Mean values are displayed with error bars representing SD.

lyzed using the Statistical Package for the Social Sciences for Windows 15.0 (SPSS, Inc.), the S-PLUS 6.0 (Insightful Corp.) package, and Intercooled Stata 9.2 for Windows (StataCorp LP, USA).

Results

Patient Characteristics

A total of 800 patients were enrolled, but 172 were excluded because they met one or more exclusion criteria, and an additional 12 declined to continue with their participation. In total, 616 subjects consented and completed the protocol with a mean age of 59.1 years (95% CI: 57.9 to 60.3). As listed in Table 1, 130 patients (21.1%) met AKI criteria, 159 (25.8%) had preR, 15 (2.4%) had stable CKD, and 312 (50.7%) had NF. In the AKI group, 44 subjects (34%) had pre-existing CKD. Patient characteristics by diagnostic classification are indicated in Table 1. Patients diagnosed as AKI and CKD were significantly older than those with a diagnosis of preR and patients with NF ($P < 0.001$).

On the basis of retrospective analysis of renal function and associated diseases, all patients were assigned to susceptibility stages I to IV (25). By this analysis, 67.2% of patients were in stage I; 21.4% in stage II; 4.9% in stage III; and 6.5% in stage IV. Majority of subjects assigned to the two last stages corresponded to AKI patients (63.3% for stage III and 62.5% for stage IV). Decreased renal perfusion was the principal clinical condition that caused AKI (66.2%: $n = 86$). Almost 77% (100) of the patients with AKI were classified as stage 1 by AKIN criteria, corresponding to a large proportion of patients classified as "Risk" by RIFLE criteria. Six patients (1%) needed renal replacement therapy, and 27 died (15 in the AKI group).

Previous baseline SCr values were not available for only 2.4% of the patients. In these subjects, baseline renal function was calculated using previously published formulas (19). Furthermore, these values were confirmed after 1 year of follow-up. None of the subjects without previous baseline SCr was classified as having AKI.

Differential Diagnosis

The highest concentrations of SCr and SCysC were noted in patients who developed AKI (median 1.6 mg/dl and 1.4 mg/dl, respectively, at baseline), as shown in Table 1 and Figure 2. On average, patients with preR, stable CKD, or NF had significantly lower concentrations of SCysC and SCr, as shown in Table 1 and Figure 3. In terms of urinary measurements, the median values of the UCysC /Cr ratio were similar in all groups. There was a significant difference only between AKI patients and those with NF ($P < 0.001$).

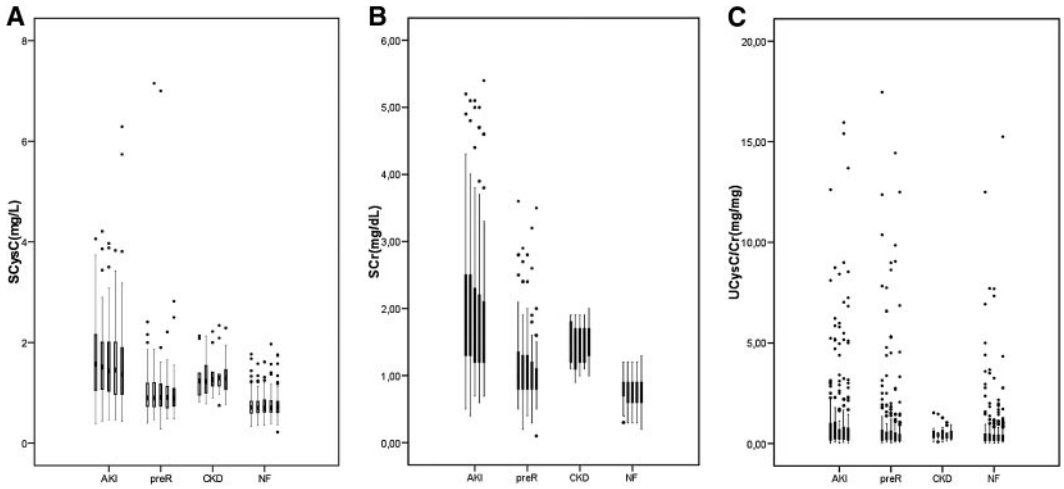

Figure 3. Distribution of biomarker values by diagnostic group. Scatter plots of SCysC, SCr, and UCysC/Cr ratio. Within each group, *i.e.*, AKI, preR, CKD, or NF, values are shown for each of the serially measured time points. Both SCysC and SCr could discriminate AKI from preR and NF ($P < 0.001$). UCystC/Cr could discriminate AKI from NF ($P < 0.001$).

When AKI patients were compared with the other three groups combined (preR, CKD, and NF), all biomarkers (SCr, SCysC, and UCysC/Cr ratio) showed greater levels in patients with AKI than those without ($P < 0.001$), as shown in Figure 3. Both SCr and SCysC concentrations were noted to be increased at baseline in patients who were subsequently adjudicated to have AKI. The pattern of the UCysC/Cr ratio was quite different, with highest levels at baseline (median 0.49 mg/g) and decreasing over 48 hours (0.28 mg/g). Therefore it was not a sustained diagnostic marker of AKI.

Predictive and Discriminative Ability for the Diagnosis of AKI

ROC curves were generated at all time points for all biomarkers, to test the ability to detect AKI. The results are listed in Table 2. UCysC, UCr, and UCysC/Cr ratios were not useful predictors of development of AKI, with low values for the areas under the ROC curve (AUC-ROC). In contrast, the AUC-ROC was greater than 0.86 for SCysC and greater than 0.88 for SCr at all five study points, indicating excellent discriminatory ability for the early diagnosis of AKI (all $P < 0.001$), as shown in Table 2 and represented in Figure 4. There were no differences between the ROC curves for SCysC and SCr at the critical first two time points of the study ($P = 0.288$ and $P = 0.141$ for the initial presentation and 6-hour time points, respectively). However, the model with SCysC was particularly well-calibrated with high Hosmer-Lemeshow P values of 0.667, 0.080, 0.463, 0.502, and 0.504 for each of the five time points examined, indicating no evidence of lack of fit. Furthermore, the observed event rates appeared close to predicted event rates when plotted across possible point probabilities, as shown in Figure 5. On the contrary, a significantly lower value for the Hosmer-Lemeshow P

Table 2. Predictive and discriminative ability of all biomarkers at different time points

Biomarker	AUC	95% CI	*P* Value	Hosmer-Lemeshow *P* Value
Serum				
Cr				
T0	0.88	0.85 to 0.92	<0.001	<0.001
T6	0.9	0.86 to 0.93	<0.001	0.053
T12	0.9	0.87 to 0.94	<0.001	0.095
T24	0.92	0.89 to 0.94	<0.001	0.012
T48	0.92	0.90 to 0.95	<0.001	0.032
CysC				
T0	0.87	0.83 to 0.90	<0.001	0.667
T6	0.87	0.83 to 0.91	<0.001	0.080
T12	0.88	0.84 to 0.91	<0.001	0.463
T24	0.86	0.82 to 0.90	<0.001	0.502
T48	0.87	0.83 to 0.91	<0.001	0.504
Urinary				
Cr				
T0	0.59	0.53 to 0.65	0.003	
T6	0.62	0.56 to 0.67	<0.001	
T12	0.58	0.52 to 0.63	0.01	
T24	0.6	0.54 to 0.65	0.002	
T48	0.54	0.49 to 0.60	0.163	
CysC				
T0	0.57	0.51 to 0.62	0.032	
T6	0.59	0.53 to 0.64	0.005	
T12	0.59	0.53 to 0.65	0.003	
T24	0.59	0.54 to 0.65	0.002	
T48	0.61	0.55 to 0.67	0.001	
CysC/Cr				
T0	0.61	0.55 to 0.67	<0.001	0.026
T6	0.65	0.59 to 0.71	<0.001	0.011
T12	0.61	0.56 to 0.67	<0.001	0.003
T24	0.64	0.58 to 0.70	<0.001	0.023
T48	0.59	0.53 to 0.65	0.005	0.061

Predictive and discriminative ability of SCysC, SCr, UCr, and UCysC/Cr ratio. AUC, area under the ROC curve; CI, confidence intervals. Hosmer-Lemeshow (HLS) P value not calculated for UCr and UCysC due to low AUC values; HLS considered significant when P value < 0.05.

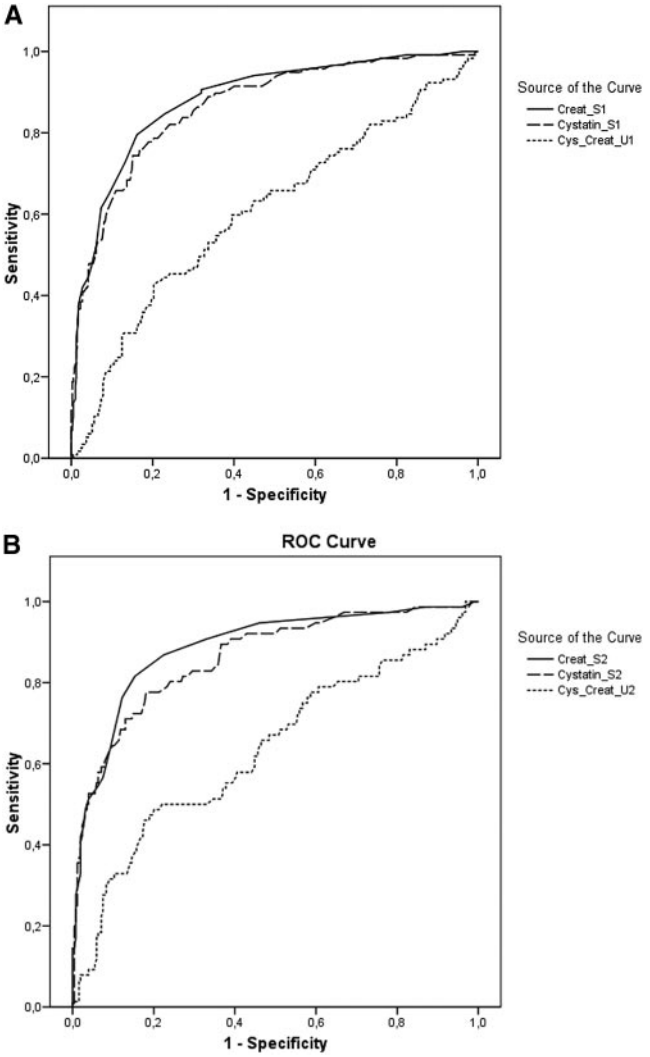

Figure 4. ROC curve of SCysC, SCr, and UCysC/Cr ratio as markers to AKI diagnosis. (A) At T0 and (B) at T6.

value for SCr indicated an inferior performance of this marker with respect to AKI prediction. Thus, SCysC could predict the evolution to AKI more accurately than SCr. In terms of the UCysC/Cr ratio, in addition to the low discriminative power, the *P* values for Hosmer-Lemeshow test were also not acceptable for a good test, as shown in Table 2.

Test Performances

To achieve a more detailed analysis of our data, we applied GAMs. As shown in Figure 6, the shape of the SCr and SCysC curves were similar. Thus, when the SCr or SCysC values were rising, there was a higher risk of developing AKI. The cut-off points were calculated based on the estimated functions obtained through a binary response GAM. The cut-off points at the different study times were 0.98 mg/L for SCysC (Figure 6B), 1.04 mg/100 ml for SCr (Figure 6A), and 0.46 mg/g creatinine for UCysC/Cr ratio.

Performance measures of SCr, SCysC, and UCysC/Cr ratio as AKI biomarkers were validated by calculating sensitivity,

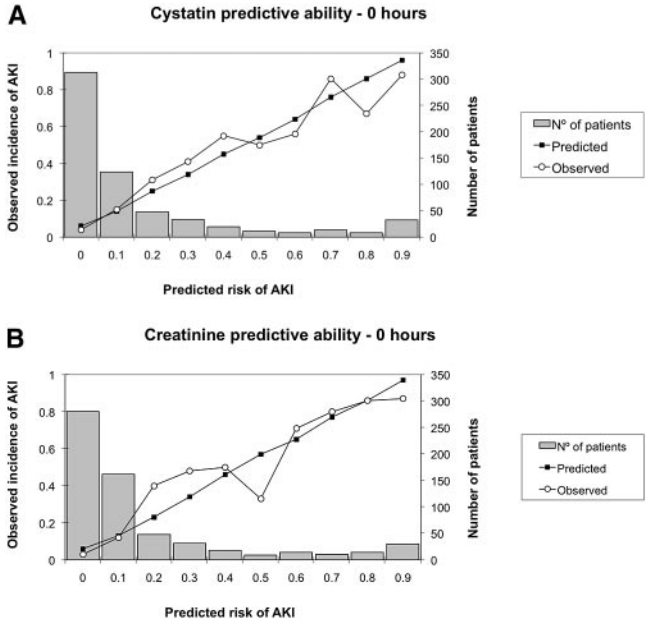

Figure 5. Calibration plots: Predicted risk of AKI *versus* observed AKI rate at T0 for SCysC (A) and SCr (B).

specificity, PPV, and NPV, as well as likelihood ratios (LR+ and LR-). All values are shown in Table 3. SCr and SCysC had a high sensitivity as biomarkers of AKI, but moderate specificity. Both markers had excellent NPV, but borderline PPV. The likelihood ratio values showed that both markers had little effect on the probabilities (odds) of AKI, as none was greater than five or close to zero. Thus, a positive SCysC level did not have strong correlation with AKI, but a negative SCysC level was strongly associated with the absence of AKI at cut-off values calculated by GAMs.

Severity Stratification

Box plots for SCysC, SCr, and UCysC/Cr levels stratified by each AKIN grade are shown in Figure 7. The SCysC concentrations rose significantly according to the severity of AKI (median values 0.78, 1.3, 1.53, and 2.13, corresponding to no AKI, and AKIN stages 1 through 3). UCysC/Cr ratios only rose at stage 3 of AKIN classification. Similarly, when SCysC was stratified according to RIFLE classification, its increasing levels accompanied the increment in severity of AKI (not shown).

Discussion

Hospital acquired AKI is distinct from the community acquired variety, and the incidence and outcomes of the latter still remain unclear. In our study, 21% of the patients enrolled had AKI in evolution at the time of admission, and 25.8% presented with preR. The majority of these patients already had decreased renal function as shown by the median values of SCr and SCysC at admission, indicating that the insult had already occurred. The renal injury had begun 24 to 48 hours before admission in the majority of cases, and more than half of established AKI were due to decreased renal perfusion. These medical conditions would likely be reversible if treated promptly, which would

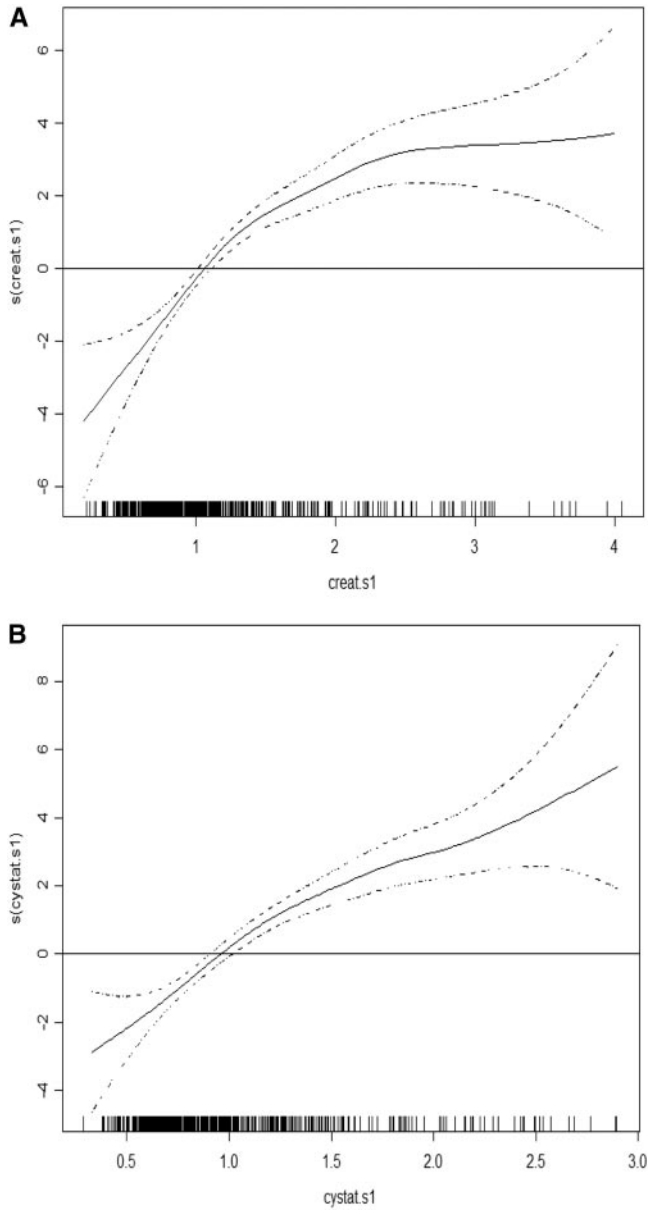

Figure 6. Estimated functions by the fitted GAMs considering SCr (A) and SCysC (B) as the only covariate at T0.

require an accurate diagnosis having been made earlier and discriminating AKI from preR.

The diagnostic approach to AKI in emergency settings still rests on BUN and creatinine, despite being insensitive, nonspecific, and delayed. We hypothesized that SCysC would mark AKI more accurately than SCr in a heterogeneous sample of patients presenting to our nonsurgical ED. Our results indicate that both SCysC and SCr differentiated between patients with AKI and those without AKI ($P < 0.001$). Moreover, we demonstrated that SCysC distinguished AKI from preR, which is a major dilemma for early therapeutic approaches in the emergency settings, since SCr measurements typically cannot make this distinction (24). However, the most significant result was the excellent power of SCysC for predicting AKI even in the early time points (at presentation and at 6 hours), with AUC values greater than 0.87. Surprisingly, these AUC values are comparable to those for SCr, the current standard marker for AKI. However, the calibration of the model of SCysC at all study time points showed no evidence of lack of fit, indicating that all observed events were similar to those predicted. In contrast, the significant lack of fit for SCr indicated a relatively poor performance for this biomarker with regard to prediction of AKI.

Many recent studies have explored improvements in the early diagnosis of AKI (6,7). The majority of those studies have focused on hospital-acquired AKI. We have demonstrated in a prospective manner that community-acquired renal dysfunction at presentation to the ED is strongly associated with increased SCysC but not with UCysC. Our results do not permit us to identify how early in the course of the disease does SCysC detect AKI, because patients with this diagnosis at admission time already had acute renal dysfunction. In a recent study of patients presenting to an ED, the performance of SCr showed high discriminative capacity and performance for AKI (24). However, the event rate was very small, with only 30 patients (4.7%) developing AKI. Furthermore, the mean SCr at admission was much higher (5.6 mg/dl), with greater percentage of patients needing dialysis when compared with the present study. In our study, we have shown in a broad spectrum of patients that SCysC performs better than SCr as an AKI marker. In addition, we demonstrated that SCysC level increased with the severity of AKI. We have not been able to analyze important AKI outcomes such as predicting dialysis requirement or in-hospital death, since these event rates were very small.

This study has important limitations. First, we used SCr as the (flawed) gold standard for the definition of AKI. Second, the degree of renal dysfunction in our cohort of AKI patients was moderate at best, with medium values of SCr of 0.95 mg/dl and only 1% of subjects needing dialysis. Third, it is a single center study, so our results must be validated in larger multicenter studies. Fourth, we excluded patients with CKD stage 4 to 5, which could potentially explain the lower rate of CKD in our cohort. Fifth, SCysC may be influenced by a number of nonrenal factors, including large doses of corticosteroids, thyroid dysfunction, systemic inflammation, neoplasia, age, type of assay used, and even to some extent by muscle mass (28).

In summary, SCysC is an excellent early biomarker for the diagnosis of AKI in the unselected ED setting. Surprisingly, this biomarker also reliably differentiates AKI from preR. The global availability of standardized clinical platforms for the measurement of SCysC (22,29), as well as other promising AKI biomarkers such as neutrophil gelatinase-associated lipocalin (24,30–32) that indicate structural renal injury, potentially bring us closer to a personalized and predictive approach to the diagnosis and management of community-acquired AKI. It is hoped that early identification of intrinsic AKI in the ED setting will allow for risk stratification, disposition planning, and prospective testing of promising interventions that have been effective in preventing and ameliorating AKI in experimental models if instituted early during the course of the injury (33).

Table 3. Performance measure tests

Biomarker	0 Hours	6 Hours	12 Hours	24 Hours	48 Hours
SCr	Cut-off = 1.04[a]	Cut-off = 1.04[a]	Cut-off = 1.04[a]	Cut-off = 1.04[a]	Cut-off = 1.04[a]
Sensitivity	83.80% (76.40 to 89.70)	85.00% (77.60 to 90.70)	87.30% (80.20 to 92.60)	87.90% (80.80 to 93.10)	84.70% (77.10 to 90.50)
Specificity	78.40% (74.50 to 82.00)	80.60% (76.80 to 84.10)	81.10% (77.30 to 84.50)	81.00% (77.20 to 84.50)	84.10% (80.30 to 87.50)
PPV	50.90% (44.00 to 57.80)	54.00% (46.80 to 61.10)	55.00% (47.80 to 62.00)	55.10% (47.80 to 62.10)	61.00% (53.30 to 68.40)
NPV	94.80% (92.10 to 96.70)	95.30% (92.70 to 97.10)	96.00% (93.60 to 97.70)	96.20% (93.80 to 97.90)	94.90% (92.20 to 96.90)
LR (+)	3.88 (3.22 to 4.67)	4.39 (3.60 to 5.35)	4.62 (3.79 to 5.63)	4.63 (3.80 to .65)	5.33 (4.23 to 6.73)
LR (−)	0.21 (0.14 to 0.31)	0.19 (0.12 to 0.28)	0.57 (0.10 to 0.25)	0.50 (0.10 to 0.24)	0.18 (0.12 to 0.28)
SCysC	Cut-off = 0.98[a]	Cut-off = 0.98[a]	Cut-off = 0.98[a]	Cut-off = 0.98[a]	Cut-off = 0.98[a]
Sensitivity	81.40% (73.60 to 87.70)	81.60% (73.70 to 88.00)	81.60% (73.70 to 88.00)	79.50% (71.30 to 86.30)	81.00% (72.90 to 87.60)
Specificity	76.70% (72.70 to 80.40)	77.00% (72.90 to 80.70)	78.50% (74.50 to 82.10)	77.50% (73.40 to 81.20)	80.10% (75.90 to 83.80)
PPV	48.20% (41.40 to 55.00)	48.30% (41.40 to 55.30)	50.00% (42.90 to 57.10)	48.00% (41.00 to 55.10)	54.10% (46.60 to 61.60)
NPV	93.90% (91.10 to 96.10)	94.10% (91.20 to 96.20)	94.20% (91.40 to 96.30)	93.50% (90.60 to 95.80)	93.60% (90.50 to 95.90)
LR (+)	3.49 (2.91 to 4.19)	3.55 (2.95 to 4.27)	3.79 (3.13 to 4.59)	3.53 (2.92 to 4.27)	4.07 (3.30 to 5.02)
LR (−)	0.24 (0.17 to 0.35)	0.24 (0.17 to 0.35)	0.23 (0.16 to 0.34)	0.27 (0.19 to 0.38)	0.24 (0.16 to 0.34)
UCysC/Cr	Cut-off = 0.46	Cut-off = 0.46	Cut-off = 0.46	Cut-off = 0.46	Cut-off = 0.41
Sensitivity	52.50% (43.10 to 61.80)	49.10% (39.70 to 58.60)	41.20% (32.20 to 50.60)	44.70% (35.40 to 54.30)	39.80% (30.50 to 49.70)
Specificity	66.40% (61.60 to 71.00)	70.70% (66.10 to 75.00)	74.50% (70.10 to 78.50)	74.30% (69.90 to 78.40)	72.90% (68.10 to 77.20)
PPV	31.00% (24.70 to 37.90)	31.5% (24.80 to 38.80)	30.80% (23.70 to 38.60)	31.90% (24.70 to 39.70)	29.10% (21.90 to 37.10)
NPV	83.00% (78.50 to 86.90)	83.50% (79.30 to 87.20)	82.10% (77.90 to 85.80)	83.30% (79.20 to 86.90)	81.30% (76.80 to 85.20)
LR (+)	1.56 (1.26 to 1.95)	1.68 (1.32 to 2.12)	1.61 (1.23 to 2.11)	1.74 (1.34 to 2.26)	1.47 (1.11 to 1.95)
LR (−)	0.71 (0.58 to 0.74)	0.72 (0.60 to 0.87)	0.79 (0.67 to 0.93)	0.74 (0.63 to 0.89)	0.83 (0.70 to 0.97)

The cut-off values were calculated by Generalized Additive Models, and with those were calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio (LR). 95% CIs are given in parentheses.

[a]Cut-off points of SCysC and SCr obtained by GAMs shown in Figure 6.

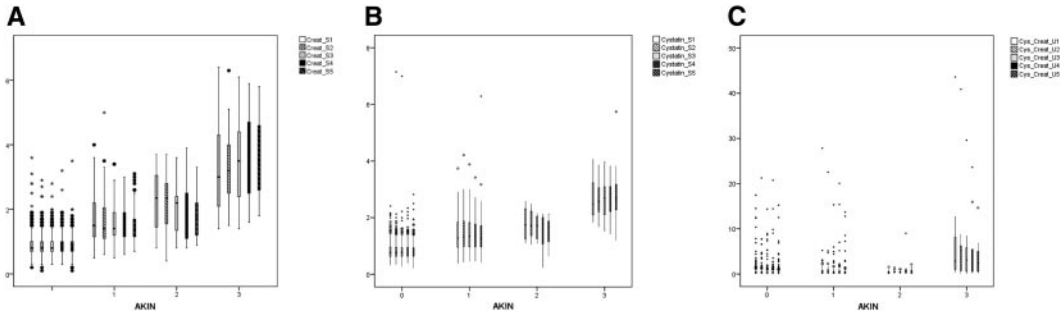

Figure 7. Distribution of biomarker values by AKIN grade. Scatter plots of SCr (mg/dl, A), SCysC (mg/L, B), and UCysC/Cr ratio (mg/g, C). By AKIN classification, 485 patients (78.70%) were without AKI, 100 (16.40%) met AKIN 1, 16 (2.6%) AKIN 2, and 14 (2.3%) AKIN 3 criteria.

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Disclosures

None.

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