Impact of Cystatin C and RIFLE on Renal Function Assessment After Cardiac Surgery

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Impact of Cystatin C and RIFLE on Renal Function Assessment After Cardiac Surgery

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Abstract

The lack of a consensus classification system and of a specific, sensitive, and early-stage biomarker for kidney injury frequently results in late diagnosis of acute kidney injury (AKI). The aim of the present study was to characterize the discriminatory power of cystatin C and the RIFLE and Acute Kidney Injury Network (AKIN) criteria for the assessment of renal dysfunction after cardiac surgery. A longitudinal, quantitative study was conducted in intensive care units of the Heart Institute (São Paulo, Brazil) in which 121 patients were followed for the first 72 hr after cardiac surgery. Most of the patients were male (61.2%), and the mean age was 50 years. The most frequent surgeries were valve replacement (48.8%) and myocardial revascularization (43.8%). AKI was defined as an increase of at least 50%, 0.3 mg/dl or 0.5 mg/dl in baseline serum creatinine. The percentage of participants meeting each of these criteria was 13.2%, 28.1%, and 11.6%, respectively. A progressive increase in cystatin C levels was associated with a worsening of renal function, as classified by RIFLE and AKIN ($p < .05$). Analysis of the receiver operating characteristic (ROC) curves showed the RIFLE and AKIN classification to have good discriminatory power for the assessment of renal function, with the performance of cystatin C being poorer (area under the curve: 0.804 and 0.794 vs. 0.719). However, combining cystatin C and RIFLE resulted in greater discriminatory power for detecting kidney injury in postoperative patients than any marker in isolation.

Keywords

acute renal failure, acute kidney injury, biological biomarker, postoperative period, RIFLE, AKIN, cystatin C

Acute kidney injury (AKI) is a common and serious complication in hospitalized patients, particularly those in the intensive care unit (ICU). The lack of a standardized definition for this syndrome has been a major impediment to the progress of clinical and basic research in this field (Hoste et al., 2006). Because the early stages of AKI are often reversible, clinicians should ideally treat it with different approaches as early as possible after the initiating insult or before serum creatinine begins to rise. Among patients recovering from cardiac surgery, the prevalence of AKI ranges from 5% to 31%, depending on the criteria used for its definition. The risk of mortality among those patients who do develop AKI during the postoperative period, however, increases exponentially, with a mortality rate that can reach 60% (Abel et al., 1976). In the case of postoperative dialysis, AKI is considered to be an independent risk factor for death (Chertow, Levy, Hammermeister, Grover, & Daley, 1998).

Different therapeutic interventions aimed at attenuating renal failure and increasing postoperative survival have failed. Advances in the current understanding of the pathophysiology of AKI are mainly based on experimental models. In this context, the success rate of preventive measures established for the early stages of the disease (i.e., immediately prior to or immediately after injury) is fairly significant.

Among the clinical factors that have limited interventions for the prevention of AKI, two are particularly significant: the lack of a disease classification system that permitted the identification of the degree of dysfunction and the lack of more precise, early-stage biomarkers (Bellomo, Kellum, & Ronco, 2004) that are applicable in clinical practice. In 2002, the Acute Dialysis Quality Initiative (ADQI) developed a classification system for renal dysfunction called RIFLE: R = risk, I = injury, F = failure, L = loss, and E = end-stage (Kuitunen, Vento, Suojaranta-Ylinen, & Pettilä, 2006). The RIFLE system permits the categorization and stratification of renal function based on glomerular filtration rate (GFR) and urinary output criteria. In 2007, the Acute Kidney Injury Network (AKIN) proposed refinements to the RIFLE system designed to increase its sensitivity by setting a 48-hr window on the first

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documentation of criteria and broadening the risk category to include increases in serum creatinine of $\geq$ 0.3mg/dl, even if this increase does not reach the 50% increase over baseline called for in the original RIFLE criteria (Mehta et al., 2007). Both classification systems support the discriminatory power of creatinine and permit the use of urinary output as an independent criterion for renal function assessment. Moreover, the combination of these criteria produces a higher level of diagnostic accuracy and stronger stratification power regarding the degree of renal involvement than either marker (i.e., creatinine and urinary output) alone.

The other limiting factor, as mentioned above, is the lack of an ideal biomarker. Despite the existence of numerous renal function biomarkers, clinicians continue to use serum creatinine concentration for diagnostic purposes. However, this marker is not sensitive enough to detect moderate reductions in renal function since it increases unequivocally only when the GFR is less than 50% of the normal rate (Star, Hostetter, & Hortin, 2002). Cystatin C shows promise as a measure of GFR. It is freely filtered by the renal glomeruli due to its low molecular weight and is then almost completely reabsorbed and metabolized in the proximal tubules, which explains its low concentration in normal urine (Reed, 2000). Cystatin C might, thus, be a much more sensitive endogenous marker for glomerular filtration than creatinine.

The identification of an alternative biomarker that better reflected GFR and offered higher precision in early detection of AKI than serum creatinine would be a significant advancement in the field. The objectives of the present study were to monitor renal function in patients recovering from cardiac surgery using the RIFLE and AKIN classification systems, cystatin C, creatinine, and estimated creatinine clearance and to determine the discriminatory power of cystatin C, RIFLE, AKIN, and combinations of these methods for the assessment of renal dysfunction after cardiac surgery.

Materials and Methods

The Ethics Committees of the Heart Institute of the University of São Paulo, Brazil, approved this prospective longitudinal study, which we conducted in two surgical ICUs.

Participants

We selected consecutive patients during the preoperative period according to their medical records. Participants included 121 patients, aged 19–65, who had been admitted to the ICU and had undergone elective cardiac surgery (myocardial revascularization, valve replacement, and combined surgery). We excluded patients with a history of renal injury, those using corticoids for a prolonged period of time and those with existing malignant diseases or thyroid disease. Study outcomes included hospital discharge or death of the patient.

Measures

We defined AKI as an abrupt decline in kidney function characterized by a peak of at least a relative increase of 50%, an absolute increase of 0.3 mg/dl or an absolute increase of 0.5 mg/dl in the admission or known baseline serum creatinine level. We studied the variables serum creatinine, estimated creatinine clearance, and serum cystatin C. Those who assessed the data were blind to the protocol.

We determined creatinine concentration by a traditional method (Jaffe method). We calculated estimated creatinine clearance using the modification of diet in renal disease simplified equation recommended by the Dialysis Outcomes Quality Initiative (DOQI) of the National Kidney Foundation:

$$GF = 186 \times SCr^{-1.154} \times age^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$$

where GF = glomerular filtration, expressed as ml/min/1.73 m^2, and SCr = serum creatinine, expressed as mg/dl.

We quantified serum cystatin C concentrations via immunonephelometry using a specific kit (Dade Behring, Marburg, Germany) and the Behring nephelometer 100 system analyzer (Behringwerke Diagnostica, Marburg, Germany).

Statistical Analysis

We used the nonparametric Kruskal–Wallis test to compare the mean between different groups. This test evaluated the hypothesis that the means from different groups were the same (null hypothesis) against the hypothesis that at least one of them was different (alternative hypothesis). The null hypothesis was rejected when $p < .05$. We constructed receiver operating characteristic (ROC) curves based on the sensitivity and specificity of the different markers using the AKI definitions for this study as the gold standard.

Results

The study sample predominantly consisted of caucasian (92.0%) males and had a mean body mass index of 25.6 kg/m^2. The majority of the patients were hypertensive, and more than 20% were diabetic. The percentages of patients who underwent myocardial revascularization and valve replacement surgery were similar. In addition, the great majority of the patients received short-term circulatory support and 2.5% died. A high percentage of patients required inotropic drug support (95%); 39 patients (32.2%) had Swan-Ganz catheters inserted with mean cardiac index of 3.66 l/min/m^2 (Table 1).

Figure 1 shows the evolution of postoperative renal function according to the sample mean value of serum creatinine, creatinine clearance, and cystatin C. Only cystatin C levels presented a significant increase ($p < .001$) during the postoperative period.

With respect to the progression of renal function according to the RIFLE and AKIN classifications (Figures 2 and 3), the number of patients classified into the risk (RIFLE) or Stage 1 (AKIN) category increased in the first 24 hr after surgery. After this period, a higher percentage of patients was classified into

Table 1. Demographic and Clinical Characteristics of the Patients Studied ($N = 121$).

Characteristic	*n* (%)/Mean ± SD
Age (years)	50 ± 11
BMI (kg/m^2)	25.6 ± 4.8
Male	74 (61.2%)
Diabetes	27 (22.3%)
Hypertension	113 (93.4%)
Cardiac index[a] (l/min/m^2)	3.66 ± 0.91
Vasopressor/catecholamine use	115 (95.0%)
Surgeries	
Myocardial revascularization surgery	53 (43.8%)
Valve replacement surgery	59 (48.8%)
Combined surgery	9 (7.4%)
Circulatory support time	
≤120 min	95 (78.5%)
>120 min	12 (9.9%)
None	14 (11.6%)
AKI for creatinine increase of 50%	16 (13.2%)
AKI for creatinine increase of 0.3 mg/dl	34 (28.1%)
AKI for creatinine increase of 0.5 mg/dl	14 (11.6%)
Death	3 (2.5%)

Note. AKI = acute kidney injury; BMI = body mass index.
[a] Total patients with Swan-Ganz = 39.

the injury (RIFLE) or Stage 2 (AKIN) category than the risk category. Urinary output was the determinant RIFLE criterion that most indicated AKI; but for AKIN, the serum creatinine criterion was as important as urinary output, at least for the first stage. Analysis of the mean cystatin C levels according to RIFLE and AKIN category also revealed a significant tendency toward an increase in levels with increasing category severity (Figure 4).

Over the 72-hr postsurgery follow-up period, 16 (13.2%), 34 (28.1%), and 14 (11.6%) of the 121 patients developed AKI according to the AKI definitions of creatinine increase of 50%, 0.3mg/dl, and 0.5mg/dl, respectively (Table 1). We also observed that the level of serum cystatin C was significantly higher in the patients with AKI during this period ($p \leq .05$; Table 2).

Figure 5 illustrates the ROC curves of cystatin C, RIFLE, AKIN, and of the combination of both cystatin C and RIFLE for the detection of AKI, according to its three different definitions. The definition of AKI as an increase in the serum creatinine level of 50% presented the highest areas under the curve: 0.719 (0.620–0.817) for cystatin C, 0.804 (0.746–0.861) for RIFLE, 0.794 (0.725–0.862) for AKIN, and 0.835 (0.772–0.898) for the combination of cystatin C and RIFLE.

Discussion

The essential purpose of this prospective, longitudinal study was to find a better strategy for detecting and diagnosing more subtle alterations in kidney function so that patients recovering from cardiac surgery can be treated early and appropriately. GFR has traditionally been used as an indicator of renal function, but the lack of a minimally invasive method for estimating this indicator that is both precise and simple represents a limiting factor in clinical practice. Serum creatinine alone or in combination with creatinine clearance are the most commonly used routine renal function markers despite the fact that their precision is limited by a number of factors. Several low-molecular-weight proteins, including cystatin C, have been suggested as endogenous markers of GFR.

In the present study, mean cystatin C level significantly increased during the postoperative period, which supports an earlier finding by Haase et al. (2009). In view of the specificity of this marker, clinicians should note discrete alterations in its levels since they reflect significant changes in clinical status and exert an influence on disease prognosis (Turney, 1996). We observed no increase in the mean concentration of the other markers (creatinine clearance and serum creatinine) during the same period.

In recent years, the use of RIFLE and AKIN as consensus definitions of AKI has increased substantially (Cruz, Ricci, & Ronco, 2009). Investigators have extensively evaluated both classification systems across a range of clinical settings and have shown them to have predictive ability, robustness, and clinical relevance (Uchino, Bellomo, Goldsmith, Bates, & Ronco, 2006).

The RIFLE and AKIN classification systems use GFR, urinary output, and serum creatinine levels to define grades of severity. There is accumulating evidence that small increments in serum creatinine are associated, in a variety of settings, with adverse outcomes. Urinary output is far less specific because it is dependent on hydration status, use of diuretics, and hemodynamic status and because severe AKI can occur with normal urine output. On the other hand, because changes in urinary output can occur long before biochemical changes are apparent, it offers the potential for earlier diagnosis of AKI (Mehta et al., 2007).

In the present study, urinary output was the determinant criterion that presented the highest impact on the data described here. This result is in agreement with a study of Bellomo et al. (2004) in which the investigators found the sensitivity of urinary output to renal hemodynamic alterations to be higher than that of biochemical markers. The use of urinary output as an indirect parameter of renal function does not represent an innovative or arbitrary routine but rather is a technique used in the surgical environment. These findings reinforce the importance of combining creatinine levels and urinary output as defined by RIFLE and AKIN classifications instead of using creatinine levels alone, as was customary before the publication of these classification systems.

There were increases in the number of patients classified into the risk and injury categories of RIFLE and AKIN during the 48 and 72 hr after surgery in the present study. The first stages of the RIFLE (risk) and AKIN (Stage 1) systems may be the most important ones because renal failure may still be reversible by preventive or therapeutic intervention at this point in the progression (Van Biesen, Vanholder, & Lameire, 2006).

Despite the unfavorable scenario (i.e., patients in the ICU who underwent cardiac surgery), we observed a high rate of

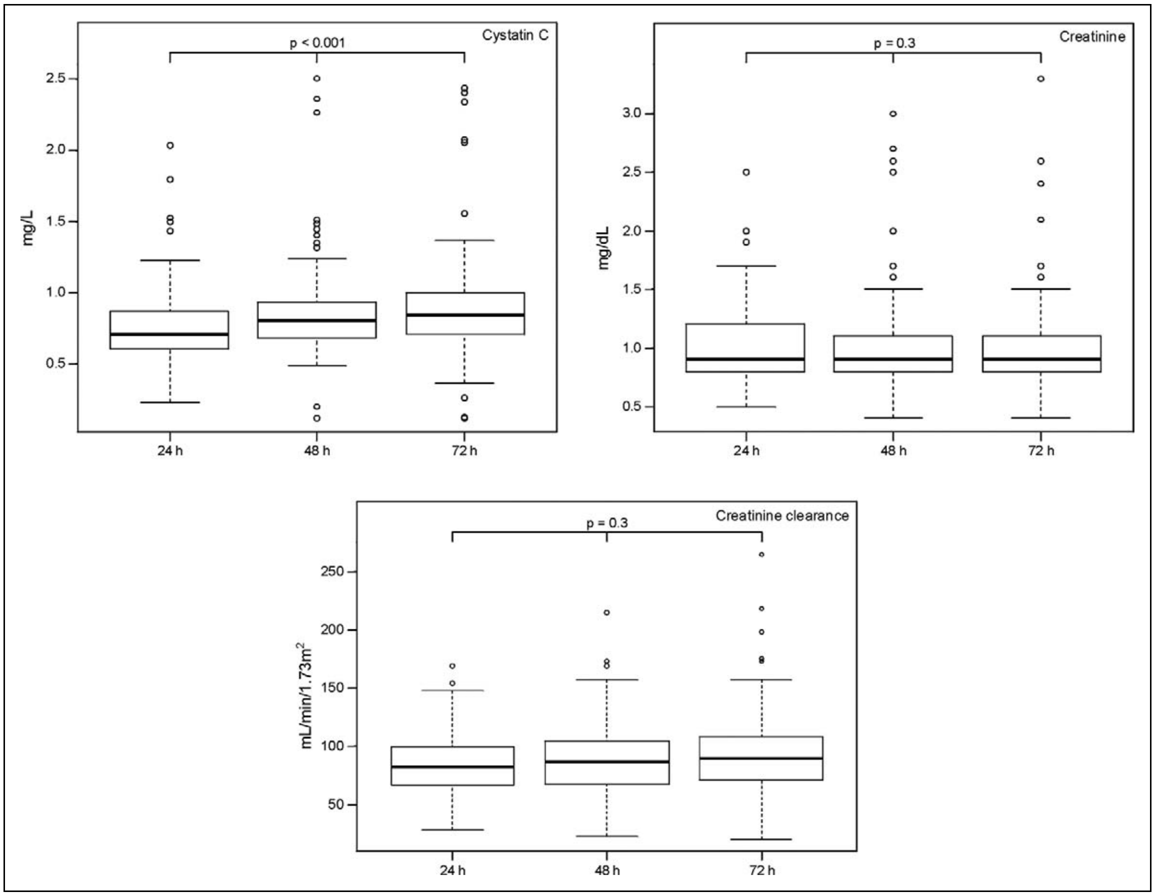

Figure 1. Postsurgical course of the renal function biomarkers cystatin C, creatinine, and creatinine clearance. Kruskal–Wallis test.

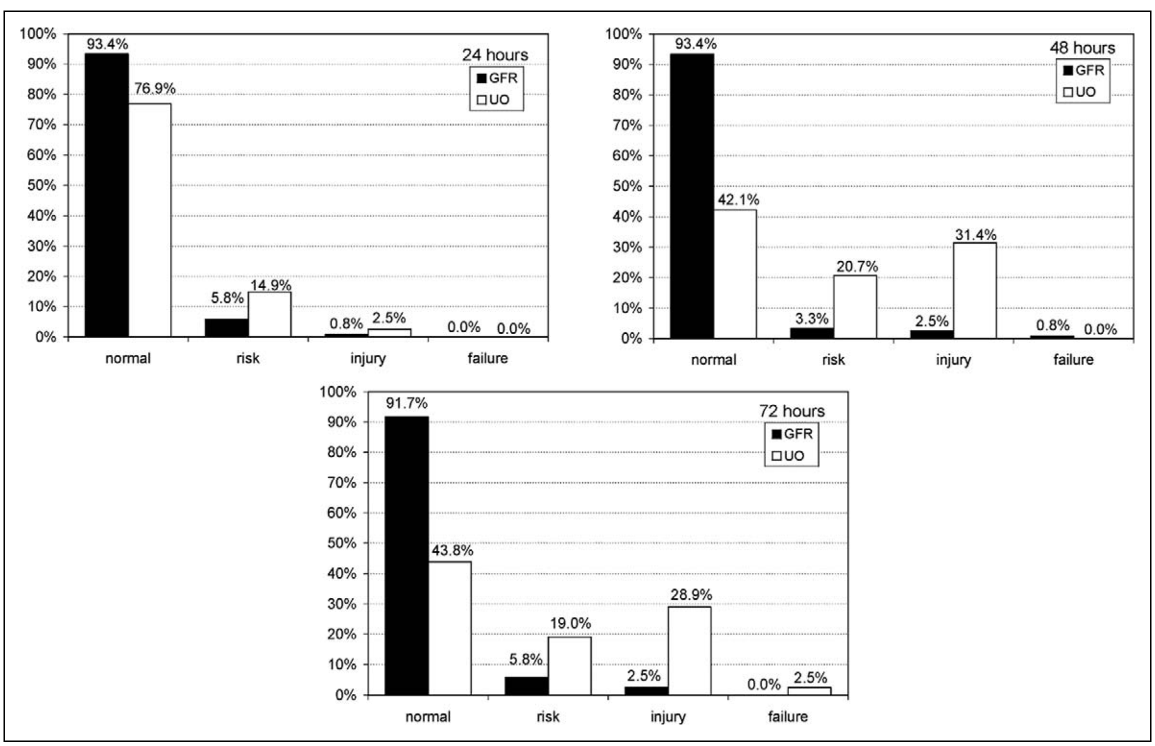

Figure 2. Assessment of renal function according to the RIFLE classification using glomerular filtration rate (GFR) and urinary output (UO) as criteria.

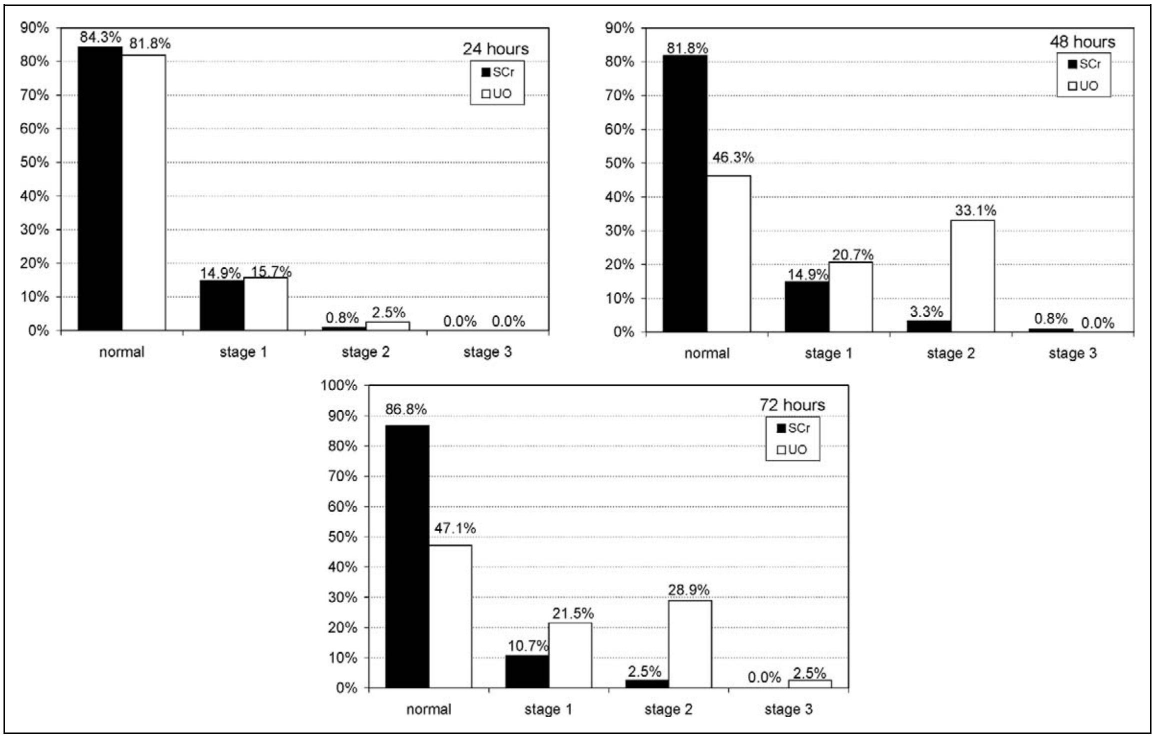

Figure 3. Assessment of renal function according to the Acute Kidney Injury Network (AKIN) classification using serum creatinine (SCr) and urinary output (UO) as criteria.

hospital discharge (97.5%) in the present study, which might have been related to the small number of combined procedures (7.4%) and the relative youth of the patients. Moreover, most patients (90.1%) did not require any or received 120 min or less of circulatory support and presented favorable renal function data on the first postoperative day, which might have contributed to the good clinical response (Biglioli et al., 1994).

The worsening of renal function that we observed on the second and third postoperative days might have been due to the inflammatory reaction that occurs frequently in the first 72 hr of the postoperative period after circulatory pulmonary bypass (CPB). CPB is associated with the generation of free hemoglobin and iron through hemolysis, which typically occurs during the procedure (Wright, 2001) and may contribute to oxidative stress and renal tubular injury (Baliga, Ueda, Walker, & Shah, 1997). Chertow et al. (1998) reported that the type of surgery influences the incidence of AKI, with myocardial revascularization surgery being associated with lower postoperative AKI rates and valve replacement surgery with higher AKI risk.

In clinical practice, cystatin C has proved to be potentially superior to creatinine for the estimation of renal function. Data from prior studies have demonstrated that the production of cystatin C is not affected by age (Finney, Newman, Gruber, Merle, & Price, 1997), gender (Finney et al., 1997), or muscle mass (Vinge, Lindergård, Nilsson-Ehle, & Grubb, 1999). Stevens et al. (2008) recently reported contradictory results indicating that these factors can affect the production of cystatin C. However, the effects were not as significant as those that have been observed for creatinine, at least for the age range studied here.

Investigators have proposed many diagnostic tests in an attempt to optimize the assessment of renal function, looking, in particular, for tests that offer higher specificity and sensitivity and permit earlier detection of problems than current methods (da Silva Magro & de Fatima Fernandes Vattimo, 2004). In the present study, we constructed the ROC curves for cystatin C, RIFLE, and AKIN using the AKI definitions for our study as the gold standard. We observed higher sensitivity and specificity for the RIFLE and AKIN systems (AUC $= 0.804$ and 0.794, respectively) when AKI was defined as a creatinine increase of 50% than when we used the other definitions (i.e., creatinine increases of 0.3mg/dl and 0.5mg/dl), which is in agreement with previous studies (Hoste et al., 2006; Uchino et al., 2006). The discriminatory power of cystatin C was lower but still statistically significant (AUC $= 0.719$; De Mendonça et al., 2000). Surprisingly, the combination of cystatin C and RIFLE showed to be the best strategy for evaluating renal function in this group of patients (AUC $= 0.835$). Reinforcing this finding, many studies (Herget-Rosenthal et al., 2004) have shown cystatin C to increase earlier than serum creatinine in patients developing AKI (by 1.5 ± 0.6 days).

Our findings also revealed that the cystatin C level was significantly higher in patients who developed AKI and that it increased along with the RIFLE and AKIN category (i.e., it increased according to the stage of renal dysfunction), which supports the good sensitivity and specificity of this marker for the detection of renal injury after cardiac surgery. Despite the adequate performance of the RIFLE and AKIN systems, neither is sufficient alone. As cystatin C is a marker of tubular

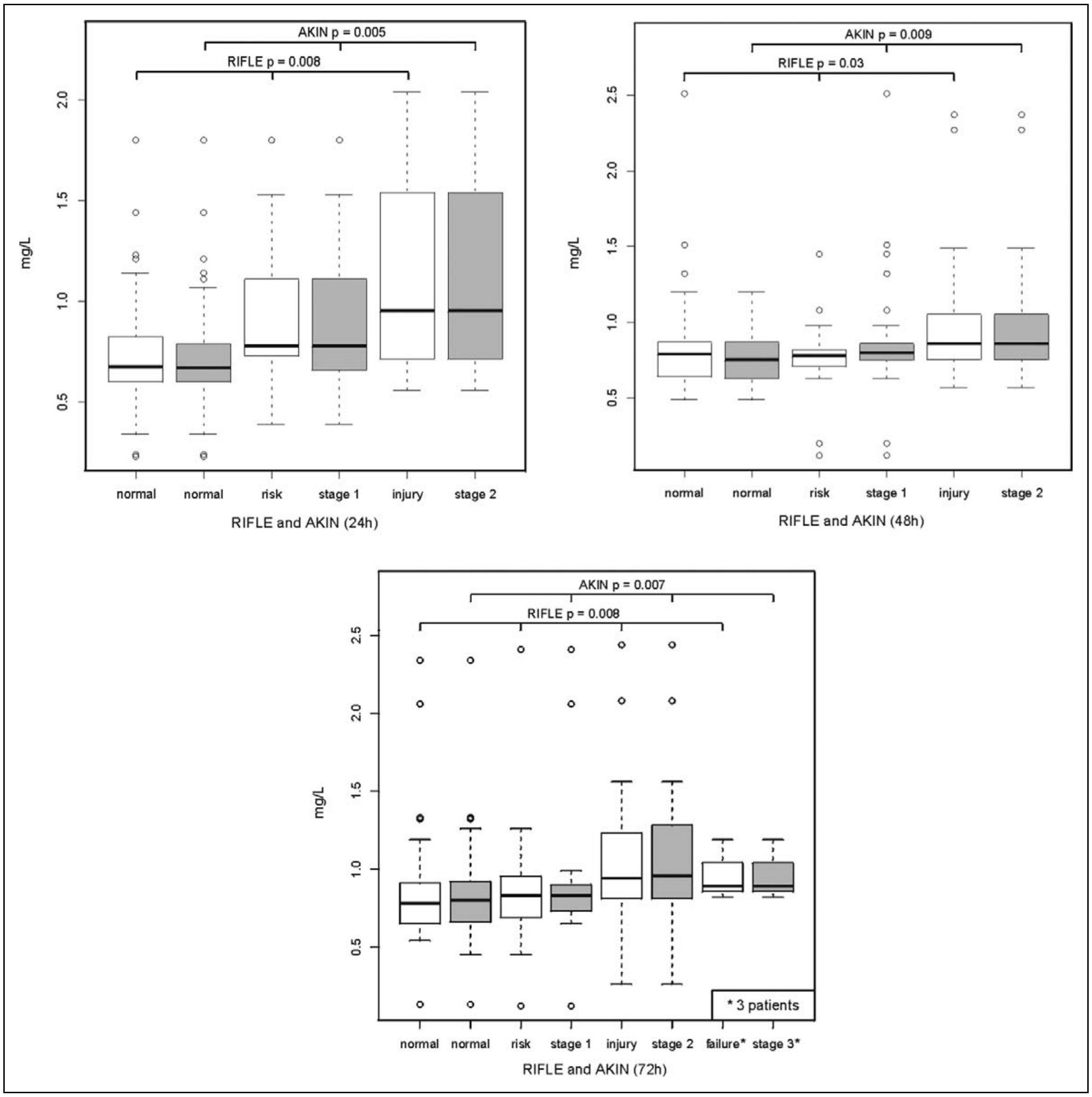

Figure 4. Course of cystatin C level in patients after cardiac surgery according to the RIFLE and Acute Kidney Injury Network (AKIN) classifications. Kruskal–Wallis test.

injury, indicating an insult at the site after 1 or 2 days, and its level is related to the degree of the injury (Westhuyzen, 2006), the combination of cystatin C and RIFLE or AKIN as a clinical standard for diagnosing and classifying AKI would enhance the ability to manage postcardiac surgery patients, not only by identifying the injury stage but also by describing the extent and site of renal impairment.

Conclusion

Our findings suggest that clinicians could determine deterioration of renal function throughout the postoperative period by means of the RIFLE or AKIN classification system combined with cystatin C levels. This combination of classification and diagnostic markers shows the potential for improving the daily assessment of renal function. Moreover, as Herget-Rosenthal et al. (2004) have suggested, replacing the serum creatinine criteria with cystatin C criteria in the RIFLE and AKIN classification systems may improve their performance. The use of cystatin C as a diagnostic biomarker for AKI thus may

Table 2. Median (25th–75th Percentiles) Serum Cystatin C Levels in Patients With or Without Established AKI Defined as a Creatinine Increase of 50%.

Cystatin C	No AKI (n = 105)	AKI (n = 16)
IPO	0.69 (0.60–0.85)	0.82 (0.73–1.06)
1st POD	0.79 (0.66–0.88)	0.95 (0.81–1.20)
2nd POD	0.81 (0.69–0.95)	1.09 (0.91–1.25)

Note. Change in level was significant for all three time periods ($p < .05$). Similar results were achieved for the other two AKI definitions. AKI = acute kidney injury; IPO = immediate postoperative period; POD = postoperative day.

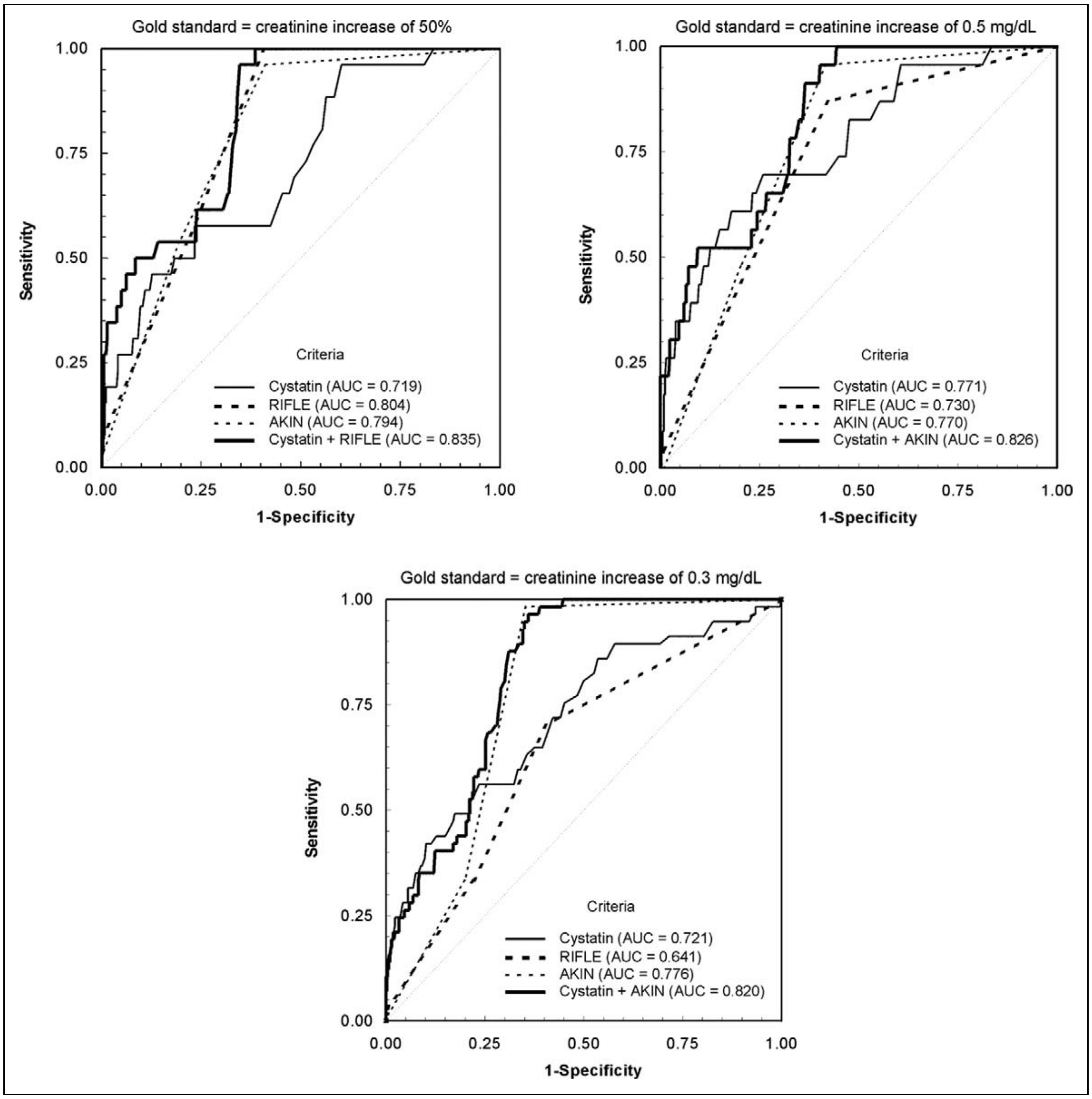

Figure 5. Comparative diagnostic performance of serum cystatin C, RIFLE, Acute Kidney Injury Network (AKIN), and cystatin C combined with RIFLE for the identification of established acute kidney injury (AKI) using the area under the receiver operating characteristic curve (AUC-ROC) and serum creatinine level as the gold standard.

represent a promising step forward for clinical and research activity in critical care nephrology (Bagshaw et al., 2009).

In addition to contributing to future refinements to the RIFLE and AKIN classification systems, the use of novel biomarkers could improve AKI detection and enhance opportunities to prevent or manage kidney injury. Ultimately, a combination of clinical and biomarker data should provide the tools for physicians and nurses to recognize AKI, characterize the course of the disease, define specific points of intervention, and predict outcomes.

Declaration of Conflicting Interests

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