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Original Article

# Early Acute Kidney Injury based on Serum Creatinine or Cystatin C in Intensive Care Unit after Major Trauma

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## Abstract

**Background:** Acute kidney injury (AKI) is a common problem in critically ill patients and is independently associated with increased morbidity and mortality. Recently, serum cystatin C has been shown to be superior to creatinine in early detection of renal function impairment. We compared estimated GFR based on serum cystatin C with estimated GFR based on serum creatinine for early detection of renal dysfunction according to the RIFLE criteria.

**Methods:** During 9 months, three hundred post trauma patients that were referred to the intensive care unit of a referral trauma hospital were recruited. Serum creatinine and serum cystatin C were measured and the estimated GFR within 24 hours of ICU admission was calculated. The primary outcome was the incidence of AKI according to the RIFLE criteria within 2$^{nd}$ to 7$^{th}$ day of admission.

**Results:** During the first week of ICU admission, 21% of patients experienced AKI. After adjusting for major confounders, only the patients with first day's serum cystatin level higher than 0.78 mg/l were at higher risk of first week AKI (OR=6.14, 95% CI: 2.5-14.7, P<0.001). First day's serum cystatin C and injury severity score were the major risk factors for ICU mortality (OR=3.54, 95% CI: 1.7-7.4, P=0.001) and (OR=4.6, 95% CI: 1.5-14, P=0.007), respectively.

**Conclusion:** Within 24 hours after admission in ICU due to multiple trauma, high serum cystatin C level may have prognostic value in predicting early AKI and mortality during ICU admission. However, such correlation was not seen neither with creatinine nor cystatin C based GFR.

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**Keywords** ● Acute kidney injury ● Trauma ● Cystatin C ● Creatinine ● Glomerular filtration rate

## Introduction

Acute kidney injury (AKI) is a common problem in critically ill patients and is independently associated with increased morbidity and mortality.[1-3] Observational data indicates that the incidence of AKI is rising and associated with high mortality despite several advances in its management.[4] In a large heterogeneous cohort study of critically ill patients, the incidence of AKI was about 36% among intensive care unit (ICU)

patients.[5] There is neither an agreement on the best method for evaluating renal function nor universally accepted definitions for acute kidney dysfunction. However, most definitions have common factors, including serum creatinine and urine output. A new classification, RIFLE (risk, injury, failure, loss, end stage) for the definition of AKI was consensually proposed by the ADQI (acute dialysis quality initiative) group.[6] In this classification, the staging is based on changes in serum creatinine and urine output. Numerous clinical studies have been published in accordance with the RIFLE classification in specific patient populations.[5,7-10]

There are a few studies about the epidemiology of AKI in trauma critical care patients, however, 10% of all ICU admissions are due to major trauma.[5,11,12] The early detection of AKI is important because of the identification of high risk population, development of preventive strategies (i.e. removal of stimulus for injury) and potential therapeutic measures (i.e. renal replacement therapy RRT).[13]

Serum or plasma creatinine is the most common marker of glomerular filtration rate (GFR). Despite its common use, creatinine has limitation as a marker for renal function due to the inter-individual variation in muscle mass, delayed rise after renal insult, and tubular secretion of creatinine.[14,15]

Recently, another biomarker for functional injury of the kidney (cystatin C) has been shown to be superior to creatinine in early detection of renal function impairment.[16-18] It has some advantages over the creatinine. It is produced by all nucleated cells and freely filtered by the glomerular membrane, entirely catabolized by proximal tubule, without secretion, and serum concentration of cystatin C is determined by GFR. Cystatin C is less dependent on factors other than renal function (specially gender, muscle mass, age) than creatinine. Multiple studies evaluated the validity of serum cystatin C as a GFR marker in critical care patients, but there are limited data on cystatin C in trauma patients.[15,17]

We prospectively recruited our adult trauma patients to obtain information on the epidemiology of early AKI defined by the RIFLE criteria within 24 hours of ICU admission. Our primary objective was to compare calculated GFR based on serum cystatin C with calculated GFR based on serum creatinine for early detection of renal dysfunction. We used the RIFLE criteria to categorize patients and to compare outcomes of ICU admission such as mortality, duration of ICU admission and the need for renal replacement therapy.

## Materials and Methods

This prospective cohort study was conducted during January 2009-December 2010. During this period, all adult post-trauma patients who were admitted to the ICU of Rajaee Trauma Hospital (Shiraz, Iran) for more than 24 hours were recruited. The institutional review board approved the study and consent was obtained from every patient or his/her next of kin. The exclusion criteria were patients less than 18 years old, pure neurotrauma, burn, known history of renal disease and injury severity score (ISS) less than 15.

Collected data included demographic information, admission diagnosis, operative status, need for mechanical ventilation, primary and secondary ICU diagnosis, previous medical and drug history, co-morbidities (e.g. allergy, hypertension, diabetes, cigarette smoking, and drug abuse), need for renal replacement therapy(RRT), important ICU outcomes (mortality, ICU and hospital length of stay, days under mechanical ventilation), the acute physiology and chronic health evaluation (APACHE) IV score, injury severity score (ISS) and acute physiology score (APS). Urine output was measured and documented every hour.

Plasma concentration of creatinine was measured by the Jaffe colorimetric method on the first day of admission and every day thereafter. Cystatin C concentration was assessed by human cystatin C ELISA kit (BioVendor, England) only on the first day of ICU admission. Serum samples for cystatin C measurement were collected and frozenat -80°C until analyzed. AKI severity was classified according to the RIFLE criteria[6]twice; once based on first day serum creatinine and then based on first day serum cystatin C. All patients with a negative history of kidney disease were assumed to have normal renal function prior to trauma. Since the baseline serum creatinine before the admission was not known, serum creatinine was estimated based on the abbreviated modification of diet in renal disease (MDRD) formula,[19] whereGFR is expressed as ml/min per 1.73 $m^2$ and serum creatinine according to age, gender and ethnicity.[20]

The baseline serum creatinine, assuming normal GFR at the lower end of the normal range (i.e.75cc/min per 1.73 $m^2$)[5-9,10,20] would be:

$$\text{Estimated serum creatinine (Scr)} = \frac{75}{186.3^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ for female})}$$

The last part of the formula, "×(1.21 if black)", was omitted because no black patient was

present in this study. We also calculated GFR expressed in ml/min from plasma cystatin C level in mg/l with Dade-Behring calibration of cystatin C method,[21] $\gamma=77.24\times cyst^{-1.2623}$. We assumed the normal range of cystatin C for Asian population as 0.54-0.78 mg/l.[22]

Urine output was measured in all trauma patients within the first 24hours (at 6, 12, and 24 hours). However, it was difficult for us to measure the exact patient's weight, thus we applied a minor modification to the RIFLE urine output criteria by assuming 70kg as an average patient weight. This modification has been performed previously and was shown to be associated with meaningful clinical outcomes.[5-9] Therefore, the patients were accordingly divided into three groups, urine output <210 cc/6hr (risk), <420cc/12h (injury) and <500 cc/24hr (failure). The primary outcome was a comparison between GFR based on serum creatinine and serum cystatin C of the first day of ICU admission to predict renal dysfunction during the first week of admission according to the RIFLE criteria. Secondary outcomes included all-cause mortality during ICU and hospital admission, duration of mechanical ventilation and the need for RRT.

**Table 1:** Demographic data of trauma patients admitted in intensive care unit (n=300)

| Variable | Mean (SD) [range] |
|---|---|
| Age (years) | 34.8 (15.9) [18-80] |
| Height (cm) | 172.13 (65) [155-185] |
| Male (n,%) | 270/300 (90%) |
| APACHE IV | 59 (21) [19-164] |
| APS | 57.3 (21) [8-164] |
| ISS | 31.5 (9.7) [16-65] |
| Mechanical ventilation (day) | 6.4 (4.6) [1-35] |
| *Duration of admission (day) | 11.5 (7.1) [2-40] |
| ICU mortality (n,%) | 57 (19) |
| APACHE IV≥25 (n,%) | 288 (99.3) |
| APS≥50 (n,%) | 166 (55.3) |
| ISS≥25 (n,%) | 222 (74) |
| Need for mechanical ventilation (n,%) | 247 (82-3) |
| History of comorbid problems | |
| HTN (n,%) | 34 (11.3) |
| Smoking (%) | 137 (45.7) |
| Drug abuse (%) | 55 (18.3) |
| Diabetus (%) | 8 (2.7) |
| Nephrotoxic drug (%) | 26 (8.7) |
| Multiple trauma (%) | 238 (79.3) |
| Renal replace therapy (n,%) | 3 (1) |
| Age≥65 (%) | 19 (6.3) |

*Excluding mortality; APACHE: Acute physiology and chronic health evaluation; APS: Acute physiology score; ISS: Injury severity score; ICU: Intensive care unit; HTN: Hypertension; DM: Diabetes mellitus

*Statistical Analysis*

Demographic data are presented as mean±SD, 95% confidence interval, and range (Table 1). Student t-test and Chi-square test were employed in univariate analyses to evaluate statistical significance (Table 2). Multivariate logistic regression analysis was conducted to identify independent predictors of acute kidney injury in the first week and all-cause hospital mortality to obtain the odds ratios. Variables that were found to be significant risk factors in univariate analysis were entered simultaneously in the multivariable model (enter method), as shown in Table 3. Odds ratios were estimated from the obtained b coefficients with respect to 95% confidence interval. The statistical package SPSS (version 18) was used for all statistical analysis. P values <0.05 were considered statistically significant for all comparisons.

## Results

Three hundred patients above18 years of age with trauma diagnosis were prospectively recruited. Overall, the mean age of patients was 34.8 (18-80 years), mean height was 172.1 (155-185) cm, mean APACHE IV 59 (19-164), mean APS 57.3 (8-164) and mean ISS was 31(16-65). There was a significant dominance for male gender (male 90%,

**Table 2:** Univariate logistic regression analysis of the risk factors for acute kidney injury in the first week of ICU admission

| Variable | P value | Variable | P value |
|---|---|---|---|
| APACHE | 0.03 | Patient's age | <0.001 |
| APS | <0.001 | Mechanical | 0.006 |
| ISS | 0.002 | Hypertension | 0.002 |
| Cystatin | <0.001 | Smoking | 0.007 |
| GFR based on cystatin (first day) | 0.041 | Opium addiction | <0.001 |
| GFR based on creatinine (first day) | <0.001 | | |

APACHE: Acute physiology and chronic health evaluation; APS: Acute physiology score; ISS: Injury severity score; GFR: Glomerular filtration rate

**Table 3:** Univariate logistic regression analysis of the risk factors for intensive care unit mortality

| Variable | P value | Variable | P value |
|---|---|---|---|
| APACHE | <0.001 | Patient's age | 0.014 |
| APS | 0.001 | Opium | 0.005 |
| ISS | <0.001 | GFR based on cystatin C | <0.001 |
| Cystatin C | <0.001 | GFR based on creatinine | <0.001 |

APACHE: Acute physiology and chronic health evaluation; APS: Acute physiology score; ISS: Injury severity score; GFR: Glomerular filtration rate

n=270). Incidence of single trauma was 20.7% and multiple trauma 79.3%, as shown in Table 1.

Comorbid problems were history of hypertension 11.3%, smoking 45.7%, drug abuse 18.3%, diabetes mellitus 2.7%, and history of nephrotoxic drug consumption 8.7%.The percentage of the need for mechanical ventilation was 82.3, mean mechanical ventilation duration was 6.5 days, and the overall mean hospital stay 11days. The incidence of Scr based and serum cystatin C based AKI of the first day of ICU admission was 14.7% and 7%, respectively.

The incidence of high serum cystatin C (more than 0.78 mg/L) was 23%. Of 300 patients, 63 patients (21%) experienced AKI according to the RIFLE criteria (risk 12%, injury 5.6% and failure 3.3%) during the first week of ICU admission(from 2nd to 7th day). 85.7% of patients with AKI had multiple trauma and 14.3% had single trauma.The incidence of AKI during the entire course of ICU admission in all patients was 23.6%. Fifty-seven patients died during ICU admission. AKI, either during the first week or total period of ICU admission, was significantly associated with mortality (P<0.001).

We calculated GFR based on either serum creatinine or serum cystatin C of the first day of ICU admission, to predict renal dysfunction during the first week of admission according to the RIFLE criteria. The logistic regression model was fitted to the data to determine the influence of each studied variables on the risk of AKI and ICU mortality. Age, APACHE IV score, APS, ISS, first day's high absolute cystatin C level, Scr based RIFLE category, cystatin C based RIFLE category, the need for mechanical ventilation and history of hypertension, smoking, and drug abuse were significantly associated with AKI during the first week of ICU admission (Table 2). All of these risk factors were entered into a binary logistic regression model, however; only the first day's high cystatin C level (more than 0.78) was significantly associated with AKI during the first week of ICU admission(OR= 6.14, 95% CI: 2.5-14.7, P<0.001).

Age, APACHE IV score, APS, ISS, first day's high cystatin C level, Scr based RIFLE category, serum cystatin C based RIFLE category and history of drug abuse were significantly associated with mortality during ICU admission (Table 3). The association of these risk factors with mortality during ICU admission was evaluated using binary logistic regression. First day's high cystatin C level and ISS score remained significant. Thus, these two factors were independently associated with mortality. Patients with cystatin levels higher than 0.78 had a higher risk of death (OR=3.54, 95% CI: 1.7-7.4, P=0.001). ISS more than 25 was also associated with a higher risk of mortality (OR=4.6, 95% CI: 1.5-14, P=0.007).

## Discussion

To the best of our knowledge, this is the first prospective study to compare serum cystatin C with serum creatinine for the estimation of renal dysfunction after severe trauma according to the RIFLE criteria in intensive care unit. Our cohort study demonstrates that Scr based AKI defined by the RIFLE criteria occurred in 14.7% of patients during first day, 21% during 2nd to 7th day, and 23.6% during the entire course of their ICU admission. This result was higher than the incidence of AKI in trauma patients (18.1%) and lower than general critically ill patients (36%) as reported in some studies.[5,12] Suchdifferences may be related to different patient population. Our patients were relatively sick; 238 patients (79.3%) had multiple traumas, APACHE IV score higher than 50 was seen in 55.3 %, and ISS more than 25 in 74%.Also, different admission policies or different hydration protocols that are used in emergency ward in major trauma patients may explain these differences.

Since we did not have a baseline serum creatinine before the admission, we estimated serum creatinine according to the MDRD formula. In trials or epidemiologic studies, Pickering et al.[23] concluded that the use of estimated serum creatininefor baseline creatinine is problematic. However, in a comparison of observed versus estimated baseline creatinine for the determination of RIFLF class, Baghaw et al.[24] found that after the exclusion of patients with chronic kidney disease from their analysis, the rate of misclassification in the RIFLE category and correlation between estimated Scr and observed Scr improved markedly.

There are several studies focusing on serum cystatin C as a replacement for serum creatinine in estimating GFR.[25,26] Some studies recommend to combine Scr and serum cystatin C for a better estimation.[27] Nejat et al. showed that plasma cystatin C is a more sensitive marker of renal function in comparison with plasma cr.[28]

In a meta-analysis of 24 studies, Roos et al.[29] recommended a cut-off level of 0.9-1.4 mg/L for abnormal cystatin C to rule in renal impairment. Two studies in Asian population showed that the formula for the estimation of GFR needs some modification because of over- or under-estimation in this population.[30,31] Therefore, we considered a cut-off level of 0.78 mg/l for abnormal serum cystatin C[22] and 23% of our patients had abnormally high level of cystatin C.

Soto et al. demonstrated that although both serum cystatin C and serum creatinine are beneficial for the diagnosis of AKI, serum cystatin C has more predictive power.[32]

These recommendations are challenged with two shortcomings. First, there are some evidences that serum cystatin C is partially influenced by muscle mass and other demographic variables such as ethnicity.[33] Second, there are several cystatin C based equations for the estimation of GFR in different clinical settings, none of which are designed for critically ill patients.[34-36]

We measured serum cystatin C level on the first day of ICU admission and after calculating GFR based on serum cystatin C. According to the RIFLE criteria, we categorized patients into AKI and non-AKI groups. The incidence of AKI in the first day with this method was 7%, which was much lower than serum cr based AKI (14.7%).However, in previous studies, cystatin C has been shown to be more sensitive in early detection of AKI.[16-18]

One may presume that the lower incidence of AKI in our patients, when cystatin C based equation was used for the estimation of GFR, could be due to applying inappropriate formula. This hypothesis is reinforced when we observed that high serum levels of cystatin C of the first day of ICU admission per se was the only robust predictor of AKI during the following week of ICU admission (OR=6.14, 95% CI: 2.5-14.7, P<0.001).

Not surprisingly, serum cr based estimation of GFR and AKI of the first day of ICU admission was not sensitive enough to predict the occurrence of AKI in the first subsequent weeks in our patients. This observation may be explained by the well-known slow rise of serum creatinine after acute renal insults.[37]

Although not our primary objective, post-hoc analysis of data showed a significant relation between abnormally high serum cystatin C level and both early AKI in ICU and all-cause ICU mortality.

Numerous investigators have shown that AKI in ICU is an independent risk factor for mortality.[1-3,7] However, few studies looked at the association of mortality with AKI in trauma patients.[12] The all-cause mortality was 19% in our study. This is comparable with other similar studies. Like many other studies, AKI during entire ICU admission was significantly associated with ICU mortality (P<0.001). However, the only predictors of mortality during ICU admission on the 1st day of admission were high serum cystatin C and ISS.

We noticed a poor correlation between APACHE IV score and ISS to predict mortality of our patients. We are unaware of any other study on the validity of APACHE IV scoring system in critically ill trauma patients. However, in agreement with our results, there are some reports on poor association between APACHE II and common trauma scoring systems such as ISS.[38,39]

As a secondary objective, we could not find any significant relationship between AKI during ICU admission and important clinical outcomes such as ICU length of stay and the need for mechanical ventilation. The difference between our results and other investigators could be due to inadequate implementation of discharge and weaning protocols in our ICU. Another major concern in our study was the unavailability of continuous renal replacement therapy in our ICU, which resulted in a relatively late and uncommon use of RRT in just three patients.

Other limitations in our study were its observational analysis methodology that did not give the opportunity to search for the effect of different interventions (e.g. early dialysis) on the outcome of patients. Furthermore, we only analyzed the collected data from AKI occurrences within the initial 24 hours of ICU admission and did not include the data related to AKI improvement or deterioration over the subsequent days. Pre-trauma baseline serum creatinine level and exact patient's weight were merely an estimate rather than exact values.

Finally, we should declare that the young male adult patients, not typical for AKI in other setting, put the present group into a special category.

## Conclusion

Early serum cystatin C level (within 24 hours after ICU admission) has prognostic value in predicting AKI during the first week of ICU admission and estimation of mortality during ICU admission. However, this correlation was not seen with estimated GFR according to neither serum creatinine nor serum cystatin C.

**Conflict of interest:** None declared.

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