Evaluation of Sepsis/Systemic Inflammatory Response Syndrome, Acute Kidney Injury, and RIFLE Criteria in Two Tertiary Hospital Intensive Care Units in Turkey

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Key Words
Acute renal failure • RIFLE criteria • Sepsis/systemic inflammatory response syndrome

Abstract
Sepsis is a common cause of acute renal failure in intensive care units (ICU) with mortality rates as high as 60%. In this study, the clinical and laboratory predictors of acute kidney injury (AKI) in critically ill Turkish patients with sepsis/systemic inflammatory response syndrome were identified. We studied 139 (67 females/72 males) patients admitted to our ICUs with sepsis/systemic inflammatory response syndrome without renal failure. The clinical and laboratory parameters and treatments were recorded. Patients were classified as those without AKI (n = 60; 43.20%) and those with AKI (n = 79; 56.80%) based on the RIFLE (Risk, Injury, Failure, Loss, End-stage renal disease) criteria. Those with AKI were further classified as: risk in 27 (19%), injury in 25 (17.9%), failure in 25 (17.9%), and loss in 2 (1.4%). We found that the mortality rate increased with the severity of renal involvement: 56% in risk, 68% in injury, 72% in failure, and 100% in loss categories. Patients with AKI had a more positive fluid balance, higher central venous pressure, more vasopressor use, and lower systolic blood pressure. In multivariate analysis, the sequential organ failure assessment score, blood pressure, serum creatinine, and fluid balance were risk factors for the development of AKI. In this population, the incidence of AKI was higher and contrary to previous knowledge. A positive fluid balance also carries a risk for AKI and mortality in septic ICU patients. The RIFLE criteria were found to be applicable to our ICU population.
Acute Dialysis Quality Initiative (ADQI) workgroup to overcome this problem. These criteria were proposed to include the entire spectrum of the syndrome, ranging from minor changes in renal function to end-stage renal failure. Small changes in kidney function in hospitalized patients are important and associated with significant changes in short-term and possibly long-term outcomes [2].

Sepsis is reported to be the most common cause of AKI in the ICU [3]. Despite our increasing ability to support vital organs and resuscitate patients, the incidence and mortality of septic AKI remains high. A possible explanation of this problem might be related to our limited understanding of septic ARF and its pathogenesis [8, 9]. A critical appraisal of the clinical findings and possible predictors of AKI is essential for both the management and prevention of AKI [10].

Clinical and laboratory parameters of sepsis and systemic inflammatory response syndrome (SIRS) were investigated at the University Hospital ICU, Ghent, Belgium, in 2000–2001 to identify patients who were at risk of developing AKI [10]. In that study, bilirubin levels, older age, higher creatinine, and central venous pressure values had an impact on the development of septic AKI. The aim of the current study was to assess the applicability of these findings and the recently developed RIFLE criteria in the Turkish population.

Materials and Methods

This prospective observational dual-center parallel study was undertaken at two University Hospital ICUs from March 2006 to March 2008. All patients with sepsis and/or SIRS as defined by the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM) consensus [11, 12] and who had serum creatinine levels < 2 mg/dl were included in the study. Based on this consensus, SIRS is defined as temperature > 38°C or < 36°C, heart rate > 90/min, respiratory rate > 20/min or PaCO₂ < 32 Torr, and white blood cell count > 12,000/mm³ or < 4,000/mm³ or with > 10% bands. Sepsis was defined as a condition in which the patient met the criteria for SIRS and presented with either a documented or suspected infection.

We excluded from our study those patients with a previous history of kidney disease and/or impairment or creatinine levels > 2 mg/dl on admission, those who survived < 24 h following admission to ICU, and those who were younger than 17 years of age. Patients transferred from other hospitals were included only if they developed criteria 24 h after admission to our ICU.

One hundred and thirty-nine patients who met the inclusion criteria were enrolled into the study. Demographic, physiologic, laboratory, treatment, and hospital outcome information of the patients as well as comorbidities were recorded [10]. All patients included in the study were also evaluated according to the RIFLE criteria as defined by the ADQI group [13]. Only the criteria for serum creatinine were taken into account; urine output was not included for practical reasons. We calculated the baseline creatinine level using the modification of diet in renal disease (MDRD) equation as recommended by the ADQI group [14, 15]. Based on the RIFLE criteria, the patients were then divided into two groups whether they had AKI or not.

Medical history of liver cirrhosis was defined as having primary hepatic failure. Chronic obstructive pulmonary disease was defined as continuous use of bronchodilator drugs. Cardiovascular disease was defined as cardiomyopathy, ischemic heart disease, or peripheral vascular disease, and diabetes mellitus was defined as the need for blood glucose-controlling drugs for at least 1 year prior to admission and/or the presence of diabetic retinopathy. Malnutrition was diagnosed if the serum albumin level was < 3.0 g/dl on admission. Patients with HIV, hematologic malignancies, and those treated with corticosteroids or other immunosuppressive drugs were considered immunosuppressed. Clinical and laboratory parameters of patients were followed for 2 weeks or until discharge and/or death after developing sepsis/SIRS. Severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation system (APACHE II) during the first 24 h after admission [16]. The sequential organ failure assessment (SOFA) score was also calculated based on data from the day of inclusion into the study [17].

The research ethics boards of the two university hospitals reviewed and accepted the study protocol before the study began.

Statistical Analysis

SPSS software, version 13.00, was used for the statistical analysis (SPSSInc., Chicago, Ill., USA). Continuous data are expressed as mean ± SD, median, range and percentage, where appropriate. When data were distributed normally, we compared the means by using Student’s t test for unpaired samples. Otherwise, the Mann-Whitney U test was used. Dichotomous variables were compared using the χ² test. Ordinal variables were examined using the linear × linear test (χ² trend). A logistic regression model for the development of AKI was constructed using parameters showing a significant difference between the AKI and non-AKI groups in univariate analysis. The two-tailed significance level was set at p < 0.05. We analyzed hospital survival across the groups using the χ² and Kaplan-Meier methods, and tested the difference between groups using the log-rank test. Data from patients alive at the time of hospital discharge were censored.

Results

One hundred and thirty-nine patients (109 from Kocaeli University Medical School Hospital, Kocaeli, 9-bed medical/surgical ICU; 30 from Marmara University Medical School Hospital, Istanbul, 7-bed medical ICU) were included in this study. The study was conducted from March 2006 to March 2008. The demographic and clinical findings are shown in table 1.

The study population included 67 females and 72 males; mean age 54.89 ± 17.77 years. Patients with AKI
were significantly older than those without AKI (58.70 ± 15.77 vs. 49.82 ± 19.12 years, respectively, p = 0.003; table 1). Of 139 patients, 110 (77.50%) had evidence of infection and 66 (47.10%) had positive hemocultures: 35 (52.90%) Gram-positive, 19 (13.60%) Gram-negative, and 12 (8.60%) with both Gram-positive and Gram-negative growth.

Of 139 patients, 79 (56.83%) had AKI. According to the RIFLE criteria, 27 (19.0%) were in the risk category, 25 (17.90%) in the injury category, 25 (17.90%) in the failure category, and 2 (1.40%) in the loss category.

The overall mortality rate in these tertiary hospital ICUs was 20% during the study period. The total mortality rate of the septic cases was 51.40%: the mortality of septic cases classified as non-AKI according to the RIFLE criteria was 35%, and in the AKI cases, this ratio was increased up to 65% (OR 3.45, CI 1.71–6.96; p = 0.001). The mortality rates of the different stages of RIFLE were 56, 68, 72 and 100%, respectively (fig. 1). When the $\chi^2$ for trend test was performed on the whole group of patients, trend for increasing mortality between stages was highly significant ($\chi^2 = 15.037$ and $p < 0.001$).

Relevant laboratory findings of the patients are shown in table 2.

### Table 1. Clinical characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 139)</th>
<th>AKI (n = 79)</th>
<th>Non-AKI (n = 60)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>54.89 ± 17.77</td>
<td>58.7 ± 15.77</td>
<td>49.82 ± 19.12</td>
<td>0.003</td>
</tr>
<tr>
<td>Gender, female</td>
<td>67 (47.20)</td>
<td>42 (52.50)</td>
<td>25 (41.70)</td>
<td>0.234</td>
</tr>
<tr>
<td>APACHE II score*</td>
<td>20.98 ± 7.96</td>
<td>21.89 ± 7.04</td>
<td>19.47 ± 9.00</td>
<td>0.090</td>
</tr>
<tr>
<td>SOFA score**</td>
<td>9.68 ± 1.97</td>
<td>10.07 ± 2.07</td>
<td>9.15 ± 1.71</td>
<td>0.006</td>
</tr>
<tr>
<td>Number of hemoculture-positive patients***</td>
<td>81 (57)</td>
<td>44 (55)</td>
<td>37 (61.70)</td>
<td>0.558</td>
</tr>
<tr>
<td>Number of patients that used nephrotoxics</td>
<td>80 (56.30)</td>
<td>48 (60)</td>
<td>32 (53.30)</td>
<td>0.430</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>46 (32.4)</td>
<td>30 (37.5)</td>
<td>16 (26.7)</td>
<td>0.177</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29 (20.40)</td>
<td>22 (27.50)</td>
<td>7 (11.70)</td>
<td>0.034</td>
</tr>
<tr>
<td>Lowest systolic BP, mm Hg**</td>
<td>96.16 ± 22.52</td>
<td>92.61 ± 21.82</td>
<td>100.83 ± 22.76</td>
<td>0.032</td>
</tr>
<tr>
<td>Lowest CVP, cm H2O**</td>
<td>8.18 ± 3.93</td>
<td>9.25 ± 3.83</td>
<td>6.95 ± 3.73</td>
<td>0.007</td>
</tr>
<tr>
<td>Fluid balance (intake-output), ml/24 h**</td>
<td>1,331.12 ± 2,477.12</td>
<td>1,778.31 ± 2,849.96</td>
<td>724.21 ± 1,699.39</td>
<td>0.015</td>
</tr>
<tr>
<td>Number of patients on vasopressors**</td>
<td>69 (48.60)</td>
<td>50 (62.50)</td>
<td>19 (31.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of patients that used diuretics**</td>
<td>91 (66.00)</td>
<td>57 (72.20)</td>
<td>34 (57.60)</td>
<td>0.075</td>
</tr>
<tr>
<td>Dialysis treatment</td>
<td>15 (18.98)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died in hospital</td>
<td>73 (51.40)</td>
<td>52 (65)</td>
<td>21 (35)</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of patients that stayed longer than 20 days in the ICU</td>
<td>47 (33.80)</td>
<td>25 (53.19)</td>
<td>22 (46.80)</td>
<td>0.502</td>
</tr>
</tbody>
</table>

AKI = Acute kidney injury; BP = blood pressure; CVP = central venous pressure. Values are expressed as mean ± SD; statistically significant differences are expressed in italics.

* Calculated when they applied to the ICU. ** Calculated when they were included into the study. *** During follow-up. Numbers in parentheses denote percentages.
Fifteen (18.99%) patients received dialysis treatment: 7 hemodialysis, 3 died, and another 5 patients received hemofiltration but all died. Three patients received combined hemodialysis and hemofiltration treatment, but only 1 survived.

In multivariate analysis, the SOFA score on day 1, creatinine level, and the difference between input and output on day 1 contributed significantly to the development of AKI according to the logistic regression model when APACHE II, SOFA score (bilirubin levels >1.5 mg/dl), lowest pH (<7.20), difference between input and output on day 1, lowest systolic blood pressure on day 1, age >65 years, and gender were entered simultaneously (table 3).

**Discussion**

We evaluated the clinical and laboratory parameters for sepsis and SIRS patients in a Turkish critically ill population with the aim of determining if the features of patients who are more prone to develop AKI are predictable.
and if this features were comparable with the Ghent study population reported previously [10]. Furthermore, in this study the RIFLE criteria were taken for the definition of AKI. In this Turkish study population, the incidence of AKI was much higher (56.83%) than in previously reported studies. The incidence of AKI was reported to be 35.8% by Ostermann and Chang [18], and 10.8 and 18.0% in other similar studies [19, 20].

The clinical and laboratory evaluation of sepsis/SIRS patients has been studied previously in the ICU of a tertiary hospital in Ghent, Belgium [10]. In the latter study, 256 patients were evaluated in a similar manner as used in this study and we noticed some differences. The mean age of the study population was slightly younger in the Turkish population (56.5 ± 17.1 vs. 54.89 ± 17.77 years). Our study population had higher APACHE II scores reflecting that they are more severe than in the study population in Ghent (20.98 ± 7.96 vs. 17.34 ± 6.67). Although the incidence of AKI was reported as 11.30% in the original study when ARF was defined as serum creatinine level >2 mg/dl, the data from the Ghent study were reevaluated retrospectively according to the RIFE criteria and, as expected, the incidence of AKI increased up to 29.30%. The mortality rate was 51.3% in the AKI population and 18.3% in the non-AKI septic cases (OR 4.70, CI 2.610–8.447; p = 0.001). In the present study, the mortality rate was 65% in the septic AKI cases which appears to be higher than in the Ghent study [unpubl. data]. The results of both studies are consistent and suggest that despite more vasopressor use and more fluid resuscitation, kidney damage starts very early in septic ICU cases and that it is difficult to reverse.

Furthermore, the use of a diuretic (furosemide) was similarly frequent in both the AKI and the non-AKI cases in our study population (total 64.1%; 71.3 and 56.7%, respectively; p = 0.075), whereas it was significantly more frequent in patients with ARF in the Ghent study. This finding may indicate a delay in intervention and nephrology consultation in Turkish ICUs. Although it has been suggested that diuretics are responsible for increased mortality [21–23] and may further harm damaged kidneys, diuretics are still used extensively in ICUs.

In the logistic regression model, SOFA score, the lowest blood pressure, creatinine level, and the difference between input and output on day 1 were significant predictors for AKI in our study population (table 3). In the Ghent study, bilirubin levels higher than 1.5 mg/dl (OR 9.7, CI 1.65–60.3), older age (OR 1.1, CI 1.03–1.13), higher creatinine levels (OR 1.02, CI 1.007–1.04) and a higher central venous pressure (OR 1.5, CI 1.26–1.80) were reported as predictive factors for the development of ARF [10]. Higher serum creatinine levels at the beginning of sepsis/SIRS appear to be an important predictive factor for AKI. This study showed that a 0.1-mg/dl increase in the serum creatinine level leads to an 87% risk of developing AKI. These results demonstrate that, with the exception of bilirubin levels, the findings of the two studies are in agreement. The reason for this difference may be the paucity of patients with hepatic failure in our study population (1.3 vs. 27%).

In accordance with previously published studies, our results also revealed that the development of AKI contributes significantly to the mortality rates in septic ICU patients. Our mortality rates for AKI (65%) and non-AKI (35%) were similar to previously published mortality rates in these patients; this translates to a mortality risk in the AKI population of 3.45 times greater than that in the non-AKI population. Furthermore, the mortality rate correlated positively with the severity of AKI when classified according to the RIFE criteria: 56% in the risk, 68% in the injury, and 72% in the failure categories. Although the mortality rate appears to reach 100% in the loss group, this should certainly be looked upon with caution since this group consisted of only 2 patients.

Bagslov et al. [24, 25] evaluated 1,753 patients with AKI and reported that sepsis was the cause of AKI in 47.5%. When they compared the clinical and laboratory parameters of septic AKI to the nonseptic AKI parameters, the septic AKI cases were found to be more severe, associated with greater aberrations in hemodynamics, lower mean arterial pressure and higher central venous pressure, more frequent oliguria, and a higher hospital mortality rate (70.2 vs. 51.8%, p < 0.001). The findings of this latter study as well as those of some previous reports were very similar to what we found in this study [10, 24, 26].

Although there is some controversy about this model, it is the most recognized method till now [27–29], and our study demonstrated that the RIFE criteria can be applied to critically ill Turkish patients with sepsis/SIRS. Even though the number of patients is small, it appears that in the Turkish ICU population there is a high incidence of AKI (56.83%) in septic patients, and that the RIFE criteria are useful in predicting the mortality rate in ICU sepsis/SIRS patients in our population.

The laboratory and clinical features of septic AKI in critically ill patients are distinct, and management strategies should differ. Early intervention is especially important in these patients. Fluid resuscitation needs particular attention as excessive fluid resuscitation may result in in-

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increased intra-abdominal pressure leading to the abdominal compartment syndrome, which has been recently recognized as an important cause of AKI. In our study, the difference between fluid input and output was significantly higher in AKI patients and 1 liter of positive fluid balance increases the risk of developing AKI to 56% (OR 1.56, CI 1.029–2.373; p = 0.036) (table 3). There are some previous reports that support these findings [30, 31]. Similarly, it has been reported that cumulative positive fluid balance is associated with increased mortality in patients with sepsis, with an odds ratio of 1.2 after adjustment for disease severity [32]. Furthermore, in a retrospective pilot study in septic shock patients, it was demonstrated that if negative fluid balance was not achieved in the first 3 days, mortality is increased up to 5 times (OR 5.0, 95% CI 2.3–10.9) [33]. Increased abdominal pressure has been demonstrated to cause multiorgan failure in critically ill patients [34, 35]. In addition to the impairment of cardiac function and lung injury, fluid overload may also contribute to the development of AKI and increase the mortality risk in critically ill patients [36].

Although the results of the present study were inconsistent with those of the previous studies, including more centers in Turkey into the study would increase the validity of the data. Besides, using a better formula for the calculation of the baseline serum creatinine level and including urinary output to determine the stage according to the RIFLE criteria would be more reasonable.

In conclusion, our study confirms the increased mortality rate after the development of AKI in critically ill sepsis patients. The most important risk factor leading to the development of AKI is an increment in the creatinine level. Although early fluid resuscitation is essential in the management of sepsis, overhydration may also have an impact on mortality and the development of AKI. We have also observed that the RIFLE criteria help further stratify the risk in these patients and are also applicable to the Turkish ICU population. Further studies may help achieve earlier recognition of kidney damage with other markers and clarify the earlier steps of pathogenesis.

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