Value of the RIFLE classification for acute kidney injury in diffuse proliferative lupus nephritis

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Abstract

Background. There are many studies on the RIFLE classification to evaluate the occurrence rate and/or outcome of acute kidney injury (AKI) in ICU patients, but there are no studies on the RIFLE classification to evaluate the outcome of AKI in lupus patients.

Methods. This retrospective study analysed the short-term outcomes of 79 diffuse proliferative lupus nephritis patients according to the RIFLE classification.

Results. A total of 46% of patients were No AKI, 23% AKI-R, 16% AKI-I and 15% AKI-F according to the maximum RIFLE class reached on the first day of admission. The percentage of progression of AKI to the more severe RIFLE class was 6% for AKI-R, 23% for AKI-I and 75% for AKI-F (P < 0.0001), and there was an increased odds ratio (OR) of progression rate with more severe RIFLE category (OR 7.7, 95% CI 2.3–25.7, P < 0.001). The recovery rate at the end of a 24-week follow-up was 100% for AKI-R, 92% for AKI-I and 33% for AKI-F (P < 0.0001). The mean time to recovery for the groups AKI-R, AKI-I and AKI-F was 4, 11 and 20 weeks, respectively (P < 0.0001). The area under the ROC curve for progression to chronic kidney disease (CKD) was 0.96 (95% CI 0.91–1.0, P < 0.001).

Conclusion. The RIFLE classification is predictive of progression and short-term prognosis of AKI in diffuse proliferative lupus nephritis.

Keywords: acute kidney injury; acute renal failure; lupus nephritis; RIFLE

Introduction

Acute kidney injury (AKI) is well recognized for its impact on the outcome of patients admitted to the intensive care unit (ICU). To establish a uniform definition for AKI, the acute dialysis quality initiative (ADQI) formulated the Risk, Injury, Failure, Loss and End-stage Kidney (RIFLE) classification [1]. Studies were recently published that used the RIFLE classification to evaluate the occurrence rate and/or outcome of AKI in critically-ill patients [2–16]. The clinical characteristics and predictive ability of this classification have not, however, been clinically validated in AKI caused by glomerular nephritis. The aims of this study were therefore to characterize AKI defined by the RIFLE classification, to examine the progression between stages of the classification and to relate this classification to the short-term prognosis of AKI caused by lupus glomerular nephritis.
dosage of prednisone for patients who improved clinically was gradually tapered over a 24-week period to 10–15 mg/day. Patients whose renal function had worsened at 4 weeks were continued on the initial high-dosage prednisone for an additional 4 weeks or another course of intravenous methylprednisolone pulses. Of the 79 patients, 56 (71%) received intermittent intravenous cyclophosphamide according to a protocol of National Institutes of Health [20] and the others received mycophenolate mofetil therapy.

### Data collection

Standard demographic, clinical, pathologic and laboratory data were retrieved. Demographic information included age, sex and duration of hospital stay. Clinical data included blood pressure (BP), diagnosis and need for renal replacement therapy. Pathologic data included microscopic and immunofluorescent description. Laboratory data included serum creatinine, serum albumin, haemoglobin, 24-h proteinuria and serum C3 complement component. Serum creatinine was used to calculate the GFR assessed by the Modification of Diet in Renal Disease (MDRD) equation.

### Study end point and follow-up

The primary study end point was renal function recovery, defined as the return to normal values of serum creatinine or GFR levels. All patients had follow-up for 24 weeks after admission. Serum creatinine was measured at least once weekly in-hospital. After patients had improved clinically and were discharged from the hospital, follow-up was carried out in an outpatient service and serum creatinine was measured biweekly or monthly.

### Statistical methods

Normally or near normally distributed variables were reported as means with standard deviation (SD) and compared by Student’s t-test or the analysis of variance (ANOVA) test. Categorical data were tested using the chi-square test. Multivariable logistic regression analysis was used to assess the association of the RIFLE classification with progression. Discriminative power was assessed using the area under a receiver operating characteristic (AUROC) curve [21]. Data were presented as odds ratios (OR) with 95% confidence intervals (CI). Recovery curves as a function of time were produced with the Kaplan–Meier approach and compared using the log-rank test. All statistical tests were two tailed; \( P \leq 0.05 \) was considered statistically significant. Data were analysed using the SPSS version 11.5 for Windows 95 (SPSS, Inc., Chicago, IL, USA).

### Results

#### Baseline clinical and serologic characteristics

A total of 46% of patients were No AKI, 23% AKI-R, 16% AKI-I and 15% AKI-F according to the maximum RIFLE class reached on the first day of admission. The baseline clinical and serologic characteristics are shown in Table 1. There were no significant differences in age, gender, systolic BP, anti-dsDNA antibody, serum albumin and C3 among the groups at baseline. Diastolic BP was significantly higher in patients with AKI-F compared with patients without AKI. Haemoglobin was significantly lower in patients with AKI-F compared with both No AKI and AKI-R patients. Twenty-four-hour proteinuria was significantly higher in patients with AKI-F compared with that in No AKI.

### Histological features

The histological features at biopsy are shown in Table 2. The proportion of patients with ISN/RPS IV+V and diffuse global (IV-G) lesions were not significantly different among the groups. A more advanced RIFLE category was associated with higher proportion of patients with \( >30\% \) of the glomeruli containing characteristic crescent (\( P < 0.0001 \)). Only three patients in AKI-F were diagnosed crescentic nephritis (with \( >50\% \) of the glomeruli containing characteristic crescent).

### Progression of AKI

The clinical course of patients during follow-up is shown in Figure 1. The percentage of progression of AKI to the more severe RIFLE class was 6% for AKI-R, 23% for AKI-I and 75% for AKI-F (\( P < 0.0001 \)) (Figure 2). In multivariable

### Table 1. Baseline clinical characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No AKI</th>
<th>AKI-R</th>
<th>AKI-I</th>
<th>AKI-F</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n ) (%)</td>
<td>36(46)</td>
<td>18(23)</td>
<td>13(16)</td>
<td>12(15)</td>
<td></td>
</tr>
<tr>
<td>Age (years, mean ± SD)</td>
<td>29</td>
<td>29</td>
<td>30</td>
<td>26</td>
<td>NS</td>
</tr>
<tr>
<td>Female, ( n ) (%)</td>
<td>34(94)</td>
<td>17(94)</td>
<td>12(92)</td>
<td>10(83)</td>
<td>NS</td>
</tr>
<tr>
<td>BP (mmHg; mean ± SD)</td>
<td>132 ± 27</td>
<td>135 ± 22</td>
<td>141 ± 20</td>
<td>147 ± 20</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic</td>
<td>86 ± 20</td>
<td>90 ± 12</td>
<td>96 ± 15</td>
<td>102 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>Scr (mg/dl; mean ± SD)</td>
<td>0.8 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>2.2 ± 0.3</td>
<td>5.2 ± 2.5</td>
<td>0.0001b</td>
</tr>
<tr>
<td>Alb (g/dl; mean ± SD)</td>
<td>2.7 ± 0.8</td>
<td>2.5 ± 0.6</td>
<td>2.5 ± 0.7</td>
<td>2.1 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Hb (g/dl; mean ± SD)</td>
<td>9.9 ± 2.2</td>
<td>9.1 ± 2.5</td>
<td>8.6 ± 2.5</td>
<td>7.0 ± 1.9</td>
<td>0.009c</td>
</tr>
<tr>
<td>Anti-dsDNA Ab (%; mean ± SD)</td>
<td>49 ± 25</td>
<td>46 ± 19</td>
<td>53 ± 24</td>
<td>45 ± 24</td>
<td>NS</td>
</tr>
<tr>
<td>Positivity, ( n ) (%)</td>
<td>31(86)</td>
<td>15(88)</td>
<td>11(85)</td>
<td>11(92)</td>
<td>NS</td>
</tr>
<tr>
<td>C3 (mg/dl; mean ± SD)</td>
<td>0.4 ± 0.2</td>
<td>0.3 ± 0.2</td>
<td>0.4 ± 0.2</td>
<td>0.4 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Proteinuria (g/day; mean ± SD)</td>
<td>4.0 ± 2.5</td>
<td>5.0 ± 2.9</td>
<td>4.8 ± 3.1</td>
<td>7.7 ± 8.6</td>
<td>NSd</td>
</tr>
<tr>
<td>eGFR (ml/min; mean ± SD)</td>
<td>94 ± 24</td>
<td>49 ± 6</td>
<td>29 ± 5</td>
<td>13 ± 5</td>
<td>&lt;0.0001e</td>
</tr>
</tbody>
</table>

Scr, serum creatinine; Alb, serum albumin; Hb, haemoglobin; Ab, antibody; eGFR, evaluated GFR by the Modification of Diet in Renal Disease (MDRD) equation.

\( a P < 0.05, \) AKI-F versus No AKI.

\( b P = 0.04, \) AKI-R versus No AKI; \( P = 0.02, \) AKI-I versus AKI-R; \( P < 0.0001, \) AKI-F versus AKI-I

\( c P < 0.01, \) AKI-F versus No AKI; \( P = 0.02, \) AKI-F versus AKI-R.

\( d P = 0.03, \) AKI-R versus No AKI.

\( e P < 0.0001, \) AKI-R versus No AKI; \( P < 0.02, \) AKI-I versus AKI-R; \( P < 0.03, \) AKI-F versus AKI-I.
Table 2. Baseline histological features

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No-AKI</th>
<th>AKI-R</th>
<th>AKI-I</th>
<th>AKI-F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>36 (46)</td>
<td>18 (23)</td>
<td>13 (16)</td>
<td>12 (15)</td>
<td></td>
</tr>
<tr>
<td>ISN/RPS IV+V, n (%)</td>
<td>12 (33)</td>
<td>6 (33)</td>
<td>2 (15)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>ISN/RPS IV, n (%)</td>
<td>24 (67)</td>
<td>12 (67)</td>
<td>11 (85)</td>
<td>12 (100)</td>
<td></td>
</tr>
<tr>
<td>ISN/RPS IV-G, n (%)</td>
<td>29 (81)</td>
<td>14 (78)</td>
<td>13 (100)</td>
<td>12 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>Crescent ≥30%, n (%)</td>
<td>1 (2.8)</td>
<td>1 (5.6)</td>
<td>3 (23)</td>
<td>6 (50)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Crescent ≥50%, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (25)</td>
<td></td>
</tr>
<tr>
<td>EnPG, n (%)</td>
<td>29 (80)</td>
<td>17 (94)</td>
<td>11 (84)</td>
<td>11 (92)</td>
<td>NS</td>
</tr>
<tr>
<td>MsPG, n (%)</td>
<td>6 (17)</td>
<td>1 (6)</td>
<td>1 (8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>MPG, n (%)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>1 (8)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

ISN/RPS, international society of nephrology and renal pathology society; IV-G, diffuse global lesions; crescent ≥30%, refers to patients with >30% of the glomeruli containing characteristic crescent; crescent ≥50%, refers to patients with >50% of the glomeruli containing characteristic crescent; EnPG, endocapillary proliferative glomerular nephritis; MsPG, mesangial proliferative glomerular nephritis; MPG, membranoproliferative glomerular nephritis.

Outcomes

The recovery rate was 100% for AKI-R, 92% for AKI-I and 33% for AKI-F (P < 0.0001) (Figure 2). The percentage of chronic kidney disease (CKD) at the end of follow-up was 0% for AKI-R, 8% for AKI-I and 67% for AKI-F (P < 0.0001) (Figure 2). There was an increased OR of the proportion of patients progressed to CKD with the more severe RIFLE category (OR 27, 95% CI 3–249, P = 0.003). The mean time to recovery for the groups AKI-R, AKI-I and AKI-F was 4, 11 and 20 weeks, respectively (P < 0.0001). A more advanced RIFLE category was associated with a longer time to recovery (Figure 3). The ROC curve model represents the true-positive and false-positive rates for progression to CKD, and the area under the ROC curve for progression to CKD was 0.96 (95% CI 0.91–1.0) (P < 0.001) (Figure 4).

Discussion

The ADQI working group developed the evidence-based RIFLE definition/classification system for ARF [1]. There were several studies to evaluate the RIFLE classification for AKI in critically-ill patients [2–16], but we did not find the evidence of the RIFLE classification based on AKI caused by glomerular diseases. Severe lupus nephritis is one of the
A kidney biopsy is essential in establishing diagnosis and prognosis. The prognosis of the lesion is predicted by the class, activity and chronicity of the glomerular pathology. In order to minimize the interference of the prognosis caused by different pathologic classes of lupus nephritis, we selected patients in diffuse proliferative lupus nephritis (ISN/RPS IV) with active changes as our object of study. Melvin M. Schwartz et al. found that WHO-III ≥50% and WHO-IV lupus nephritis are not congruent with ISN/RPS IV-S and IV-G, respectively. The ISN/RPS minimizes pathological and outcome differences between classes IV-S and IV-G that result in the loss of informational content from the renal biopsies [26]. The ISN/RPS does not detect pathogenetic or clinical differences among patients with severe lupus GN [26,27]. We also found that there is no difference in ISN/RPS IV-S and IV-G among the groups. Austin et al. found that the combination of cellular crescents and interstitial fibrosis was particularly ominous [28]. In our study, we found that a higher RIFLE category was associated with a higher proportion of patients with >30% of the glomeruli containing characteristic crescent. In multivariable logistic regression analysis, we did not find that crescents ≥30% could affect the renal recovery. But we found that three patients with crescents ≥50% all entered into CKD at the end of follow-up (one entered into the third stage of CKD, two ESRD).

In our study, we showed that 1 of the 18 patients (6%) with AIK-R, 3 of the 13 (23%) with AKI-I and 9 of the 12 (75%) with AKI-F progressed to more severe RIFLE classes after therapy. The lower progression rate with less severe RIFLE class may be attributed to the active immunosuppressive therapy after diagnosis. Our findings suggest that early diagnosis and treatment are very important for the prognosis of lupus nephritis patients with AIK. Ioannidis et al. found that one of the most significant predictors of a failure to attain a remission is the delay in the time from diagnosis of nephritis to the initiation of therapy. A delay in treatment of >3 months resulted in a 42% reduction in likelihood of attaining a remission in proteinuria [29]. Bertoli et al. found the importance of social support in the course of SLE [30]. In our study, most of the patients with AKI-F came from a rural area of poverty and did not go to hospital as early as possible for a check-up when they had little or no symptoms. This may be the main cause of the delay in diagnosis and treatment.

The baseline serum creatinine has been found to be predictive for the prognosis of lupus patients [31–33]. In this study, we found that the RIFLE classification according to the initial serum creatinine level was a predictor of renal function recovery to lupus nephritis patients with AIK. The more advanced RIFLE class was associated with the lower renal function recovery rate. The recovery rate was 100% for AKI-R, 92% for AKI-I and 33% for AKI-F. Furthermore, the more advanced RIFLE class needs more time to recovery. The mean recovery time was 4 weeks for AKI-R, 11 weeks for AKI-I and 20 weeks for AKI-F. We use the ROC curve model to evaluate the specificity and sensitivity of the RIFLE classification for prognosis. AUROC curve for the RIFLE classification was 0.96. This confirmed the good discriminatory power of the RIFLE classification system in predicting the prognosis of diffuse proliferative lupus
nephritis with AKI. Such analytical results suggest that the RIFLE classification is a good tool for measuring disease severity in lupus patients with AKI.

There are limitations to our study that warrant discussion. First, we were unable to describe the association of an initial RIFLE category with other clinical outcomes such as long-term survival, relapse and complete remission because of short-term follow-up. However, it was enough to evaluate renal function recovery. Second, we were unable to determine baseline creatinine values, and this may contribute to a misclassification. However, this problem is not uncommon. We thus used the lowest creatinine value during the follow-up, the mean creatinine value of patients without AKI or the CrMVRD creatinine recommended by the ADQI [1] as the baseline value. In our study, the mean level of serum creatinine was 0.8 mg/dl in patients without AKI (Table 1) and was in accordance with CrMVRD creatinine recommended by the ADQI [1]. Third, we did not use the activity index (AI) determined by the Pathology Reading Committee for each biopsy. Schwartz MM et al. found that there was no level of either AI or chronicity index (CI) that predicted the outcome of death or renal failure with sufficient sensitivity and specificity to be useful in the individual patient [34]. We believe that it did not affect our conclusion. Finally, this retrospective study was conducted at a single medical centre and the number of patients with AKI was also few; thus, this study’s findings may be limited.

In conclusion, we found that each increase in severity of the RIFLE category was associated with an increase in renal function progression and a decrease in recovery. Analytical data also confirmed the good discriminative power of the RIFLE classification system for predicting the prognosis of lupus nephritis patients with AKI. We recommend that physicians use the RIFLE classification to assess the short-term prognosis of AKI in lupus nephritis patients, and further investigations or clinical trials should focus on the RIFLE classification as a means of identifying AKI in severe lupus nephritis.

Acknowledgements. The study was supported by the Department of Nephrology and Department of Rheumatology, The First Affiliated Hospital of Wenzhou Medical College.

Conflict of interest statement. None declared.

References
The relationship between adipokines, osteocalcin and bone quality in chronic kidney disease

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Abstract

Objectives. Osteocalcin, a small peptide secreted by osteoblasts, has been recently described as a circulating hormone involved in the regulation of energy metabolism. In addition, experimental data suggest a regulation of adipocytes by bone, with a stimulation of adiponectin synthesis by osteocalcin and an inverse relationship between serum adiponectin and bone mineral density (BMD). However, this relationship has not been explored during chronic kidney disease (CKD).

Methods. Osteocalcin, adiponectin and leptin were prospectively measured in a cohort of 61 CKD patients. A new non-invasive 3D bone imaging technique was performed (high-resolution peripheral quantitative computed tomography, HR-pQCT), measuring volumetric BMD (vBMD) and microarchitecture parameters at the distal tibia.

Results. Patients’ mean age was 67.2 ± 13.9 years and mean GFR 33 ± 12 mL/min/1.73 m². We found a positive association between serum osteocalcin and adiponectin (r = 0.29, P = 0.021). Univariate analysis showed inverse correlations between serum adiponectin and total vBMD (r = −0.33, P = 0.01), cortical thickness (r = −0.34, P = 0.008) and trabecular vBMD (r = −0.27, P = 0.04). These associations remained significant in multivariate analysis between serum adiponectin and total vBMD, cortical vBMD and cortical thickness.

Conclusion. We report for the first time an inverse relationship between bone density and adiponectin, as well as a positive association between osteocalcin and adiponectin in CKD II–IV patients.

Keywords: adiponectin; bone imaging; chronic kidney disease; HR-pQCT; osteocalcin

Introduction

Osteocalcin, a small 46- to 50-amino-acid non-collagenic peptide secreted by osteoblasts and also called bone-Gla protein [1] has recently been described as a circulating hormone involved in the regulation of energy metabolism [2]. At the ‘local’ bone level, osteocalcin induces bone resorption, by stimulating adhesion and chemotaxis of osteoclasts [1]. At a ‘systemic’ level, recent experimental data demonstrate that osteocalcin differentially regulates pancreatic β cell proliferation and adipocyte gene expression,