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Original Article

A proposed Oxford classification-based clinicopathological nomogram for predicting short-term renal outcomes in IgA nephropathy after acute kidney injury

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ABSTRACT

Background: This study aimed to investigate the effect of acute kidney injury (AKI) on the progression of renal disease and to develop a clinico-pathological nomogram to predict the renal outcome of IgA nephropathy (IgAN) patients, based on Oxford classification score.

Methods: This is a retrospective observational study. A total of 988 IgAN patients treated at our hospital between 2006 and 2011 were included and divided into AKI (n = 82) and non-AKI group (n = 906). The primary outcome measure was the composite renal endpoint. The secondary outcome measure was all-cause mortality. Clinical and pathologic features were assessed with multivariable Cox regression to predict the outcome in IgAN patients. A nomogram was developed to predict the renal outcome.

Results: The median follow-up time was 48.6 months (range: 34.4 to 62.7). The incidence of AKI was 8.30%. The AKI group had more severe pathological characteristics and a significantly poor survival outcome than the non-AKI group. The multivariate Cox regression analysis showed that the AKI group had a 2.84 times higher risk of the composite renal endpoint as compared with the non-AKI group ($P < 0.001$). A clinico-pathological nomogram was developed using the seven predictors for the primary renal composite endpoint. The AUC for the nomogram model was 0.81 (sensitivity = 0.78, specificity = 0.85), and the C-index was 0.91 (95% CI = 0.85–0.97).

Conclusions: For IgAN patients, AKI is an independent risk factor for the progression of renal disease. Our nomogram model has good prediction power for the renal outcome of IgAN patients.

1. Introduction

Acute kidney injury (AKI) is a common complication in hospitalized patients, characterized by a sudden deterioration of kidney function [1], resulting in a prolonged hospital stay and high mortality. The global incidence of AKI in the hospitalized patients ranges from 7 to 18% [2,3], but can be increased to 70% in the critically ill patients [4]. In China, AKI affects 0.99%–9.1% of hospitalized patients and has become a huge medical burden [5,6].

Several clinical studies have reported that the severity of AKI is associated with the risk of developing the end-stage renal disease (ESRD), chronic kidney disease (CKD) and mortality [7–9]. A meta-analysis including 48 studies and 47,017 participants reports that the annual incidence of CKD after an episode of AKI is 7.8% and the rate of ESRD is 4.9% [10]. Another meta-analysis of 13 cohort studies shows that patients with AKI have a higher risk of CKD, ESRD, and mortality than those without AKI [11]. These studies suggest that AKI has adverse effects on the prognosis of patients.

IgA nephropathy (IgAN) is the most common type of primary glomerular disease worldwide, characterized by predominant Mesangial IgA deposition in the glomeruli [12,13]. In China, IgAN accounts for 37–58% of all primary glomerulonephritis [14–16]. Approximately 20–30% of IgAN patients progress ESRD within 10–20 years after initial diagnosis [17,18]. Currently, the risk factors for progression of renal disease and the prognosis of IgAN patients are still not fully understood. In addition, the studies on AKI in the IgAN population are still limited. The purpose of this study was to investigate the effect of AKI on the progression of renal disease and to develop a clinic-pathological nomogram to predict the renal outcome of IgAN patients.

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2. Methods

2.1. Patients

This was a single center, retrospective observational study. A total of 988 IgAN patients treated in the First Affiliated Hospital of Sun Yat-sen University between 2006 and 2011 were included. The inclusion criteria were: 1) patients aged ≥14 years; 2) pathological examination showed glomeruli (≥10% of biopsy specimens). The exclusion criteria were: 1) patients had secondary IgAN (e.g. hepatitis B-related nephritis, Henoch-Schonlein purpura nephritis, lupus nephritis); 2) patients had transplantation-related IgAN; 3) patients had malignancy; 4) patients had no at least two serum creatinine data within one week after admission; 5) loss of follow-up; 6) eGFR < 15 mL/min/1.73 m^2. The median follow-up time was 48.6 months (range: 34.4 to 62.7). This study was approved by the Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University, and written informed consent was obtained from each patient.

2.2. Data collection

The medical records of the patients were reviewed. The dose and duration of all medications (e.g. angiotensin-Converting Enzyme Inhibitors (ACEI), angiotensin II receptor blockade [ARB], diuretics, corticosteroid and immunosuppressants) were recorded.

The examinations included a complete blood count, routine serum biochemical profile (serum creatinine [Scr], glucose, uric acid, calcium, phosphorus, sodium, potassium, cholesterol, triglycerides, total protein, and serum albumin), 24-hour proteinuria. For the AKI patients, all the data were collected before and after an AKI episode. All patients had at least one hospitalization between 2006 through 2011. The first hospitalization in this period was defined the index admission. The baseline Scr assessment period was extended to the outpatient values before admission, because the AKI may start to develop before the index admission. During hospitalization, Scr was monitored at least once a week. The peak Scr value during AKI was recorded. After patients had improved clinically and discharge from index admission, follow-up was carried out in an outpatient service and serum creatinine was measured monthly.

Each renal biopsy specimen was examined by light, immunofluorescence and electron microscopy and was graded according to the Oxford classification system including mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T) and crescents (C) [19] by two pathologists. Pathological characteristics included tuft necrosis, glomeruli with crescents (cellular crescent, fibrocellular crescent, and fibrous crescent), acute tubular injury or necrosis, interstitial cell infiltration and vascular lesions.

2.3. Definitions of AKI and outcome

AKI was defined according to the guideline by 2012 KDIGO (Kidney Diseases: Improving Global Outcomes) criteria as follows: increase in Scr by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h; or increase in Scr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 mL/kg/h for 6 h. Due to the incomplete data on hourly urine volumes, only the serum creatinine criteria were used to determine the AKI categories in the current study.

The primary outcome measure was a composite renal endpoint comprising a doubling of serum creatinine and ESRD which was defined as eGFR < 15 mL/min/1.73 m^2 or the start of renal replacement therapy (RRT) including hemodialysis, peritoneal dialysis, and kidney transplantation. The secondary outcome measure was all-cause mortality.

2.4. Statistical analyses

Binary variables were presented as counts (n) and percentages (%) and were compared using chi-square or the Fisher exact test (if expected value ≤ 5). Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (Q1 and Q3) and were compared using Student's independent *t*-test or Kruskal-Wallis test, respectively.

The hierarchical linear modeling (HLM) analysis was used to analyze the interactive relationship between the composite endpoint and all risk factors. The continuous variables were transformed into standard scores (z-score) and the interaction terms were calculated by multiplying AKI group (0, 1) and z-scores. Interaction tests were performed by checking P-values of model change and the coefficient of interaction terms. Significance means there is interaction existing between that factor and the relationship.

To develop a predictive nomogram for the renal outcome of the IgAN patients, the predictors of primary renal composite endpoint were generated by Cox proportional hazard model. The predictive power of the nomogram model was evaluated using the Receiver Operating Characteristic (ROC) analysis and concordance index (C-index). The area under the ROC curve (AUC) was corrected for overfitting using bootstrap validation with 200 iterations, and the calibration of the model was carried out using the observed AKI rate and the predicted of AKI risk. The bootstrap distribution of C statistic values was used to obtain 95% confidence interval (CI) around the AUC. The statistical significance level for all the tests was set at a P-value < 0.05. All analyses were performed using R statistics software Version 3.3.3 and IBM SPSS Version 20 (SPSS Statistics V20, IBM Corporation, Somers, New York, USA).

3. Results

3.1. Demographic and clinical characteristics

A total of 988 IgAN patients (mean age = 32.90 ± 10.32 years) were included and divided into AKI group (n = 82, 8.30%) and non-AKI group (n = 906, 91.7%). Among the demographic and clinical characteristics, there were significant differences in the age, gender, pre-existing kidney dysfunction, hypertension, malignant hypertension, macroscopic hematuria, serum creatinine, proteinuria, uric acid, phosphate, cholesterol, triglyceride, hemoglobin, serum total protein, serum albumin, medication of diuretics, oral corticosteroid, methylprednisolone impulse treatment and immunosuppressant (Table 1, all P < 0.05) between groups.

3.2. Pathological characteristics

The histopathological characteristics were compared between groups. Compared to the non-AKI group, the AKI group had higher incidences of global sclerosis, segmental sclerosis, glomeruli with crescents, and higher degrees of the fibro-cellular crescent, tubular atrophy, interstitial cell infiltration and interstitial fibrosis (all P < 0.05, Table 2). No difference was found in the cellular crescents, mesangial proliferation and tuft necrosis (Table 2).

3.3. Outcomes of follow-up

After a median follow-up period of 48.6 months (range: 34.4 to 62.7), 107 (10.8%) patients progressed to a doubling of serum creatinine, 91 (9.2%) patients developed ESRD, and 13 (1.4%) patients died. Kaplan-Meier survival analysis showed that AKI group had a significantly poor survival outcome than the non-AKI group (Log rank = 128.75, P < 0.001, Fig. 1). The estimated cumulative survival rates at 1-year, 3-year, 5-year were 99%, 96%, 91% and 96%, 74.0%, 44% for the non-AKI and AKI group, respectively.

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