Clinicopathological features and risk factors analysis of IgA nephropathy associated with acute kidney injury

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ABSTRACT

Objective: The aim of this work is to investigate the distinctive clinicopathological characteristics of AKI in Chinese IgAN population and possible risk factors for AKI.

Methods: We performed a retrospective analysis of 1512 patients with biopsy-proven primary IgAN in the period 2006 through 2011 in The First Affiliated Hospital of Sun Yat-sen University. AKI was defined as 2012 KDIGO (Kidney Diseases: Improving Global Outcomes) criteria, and the patients were divided into AKI group (n = 145) and non-AKI group (n = 1367).

Results: The prevalence of AKI of the IgAN patients in our center was 9.59% (145/1512). Most AKI patients were older age, male, with higher percentage of smoke, hypertension, hyperlipidemia and preexisting impaired kidney function (Scr > 133 µmol/L), and higher serum creatinine, proteinuria, uric acid, whilst less onset of macroscopic hematuria as well as lower serum albumin and hemoglobin (p < 0.05). The pathological features were much more severe in AKI group as well. Acute tubulointerstitial nephritis was found as the most predominant pathological change of intrinsic AKI in our IgAN population instead of macroscopic hematuria associated acute tubular injury/necrosis. In multivariate logistic regression analysis, we found that older age, male gender, malignant hypertension, proteinuria, cellular crescent, fibrocellular crescent, glomerular sclerosis > 50% were possible risk factors for AKI.

Conclusions: AKI is commonly seen among IgAN population. The clinicopathological features are much more severe in IgAN patients with AKI. Useful clinicopathological predictors are recognized to improve the identification of IgAN patients who are at high risk for AKI.

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Introduction

Acute kidney injury (AKI) is a well-known increasingly common and potentially acute complication in hospitalized patients. AKI increases the patients’ mortality and prolongs the time of hospitalization, eventually resulting in developing chronic kidney disease, end-stage renal disease, and death in some patients. However, the prevalence and outcomes of AKI were widely varied because of underreporting, regional disparities, and differences in definition and case mix. Understanding its complex epidemiological features and defining the associated risk factors would help greatly in identification of AKI.

IgA nephropathy (IgAN) is the most prevalent idiopathic glomerular disease throughout the world, with diverse clinical manifestations and prognosis. Approximately 20–30% of IgAN patients progress to end stage renal disease (ESRD) within 10–20 years of onset. Nevertheless, less AKI data about IgAN population in recent years, studies about the great importance of AKI in IgAN patients focused more on macroscopic hematuria (MH) related AKI rather than the distinctive characteristics in clinical and pathological aspect.

Previous studies have showed that acute renal failure (ARF)/AKI associated with MH is a widely known complication of IgAN. Tubular damage and obstruction by red blood cell casts in pathology of renal biopsy may play a significant role in the pathogenesis of this complication. However, there were few studies related pathological features with IgAN clinical manifestations. Whilst the distinctiveness of clinicopathological features relevant to AKI-IgAN was not truly understood which may be responsible for the potential predictor value of the AKI.

Here we performed a retrospective analysis of 1512 patients who had biopsy-proven primary IgAN in the period 2006 through 2011 in the department of...
Materials and methods

Patients and methods

Biopsy-proven primary IgAN patients older than 14 years, having more than 10 glomeruli in renal specimen in The First Affiliated Hospital of Sun Yat-sen University from January 2006 to December 2011 were enrolled in this study. Patients with secondary IgAN (Henoch-Schölein purpura, systemic lupus erythematosus, and hepatitis B) and post-transplanted IgAN and those complicated with severe malignancy were excluded. Finally, a total of 1512 patients were included into this study.

Demographic data were collected including age, gender, habit of smoke or drink, history of hypertension, blood pressure, episode of MH, medication of Angiotensin-Converting Enzyme Inhibitor (ACEI), Angiotensin II receptor blockage (ARB), diuretics, corticosteroid, and immunosuppressant. Laboratory data involved complete blood count, routine serum biochemistry profile (including serum creatinine (Scr), glucose, uric acid, calcium, phosphorus, sodium, potassium, cholesterol, triglycerides, total protein, and serum albumin), proteinuria, and hematuria. Especially for the AKI patients, all the documented records before or after AKI attack were reviewed again to gain complete information, as well as the peak Scr when AKI attack during hospitalization, medication history in details. During hospitalization, Scr of all patients was monitored at least once every week. The peak Scr value that was registered during AKI was recorded. The definition and categories of AKI referred to the 2012 Kidney Diseases: Improving Global Outcomes (KDIGO) criteria.10

Statistical methods

Results of continuous variables are summarized with mean ± standard deviation (SD) for normal distribution or median with first and third quartiles for skewed distribution. For categorical variables, the results were expressed as frequencies and percentages. Continuous data were compared by means of Student’s t test; proportions were compared with chi-square test or Fisher’s test. Multivariate logistic regression was used to identify correlates of AKI and variables that were clinicopathological relevant base on professional knowledge in univariate analysis. Variables with p < 0.05 in univariate analysis for a relationship with AKI were entered into multivariate analysis as covariates. Results are presented as odds ratios (ORs) with 95% confidence interval (CI). All tests were two-sided and p < 0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS version16.0 statistical software (SPSS Inc., Chicago, IL, USA).
Results
Baseline demographic and clinical characteristics of patients with AKI

From January 2006 to December 2011, 145 fulfilled the AKI criteria out of the 1512 patients diagnosed as primary IgAN in our center. The cumulative prevalence of AKI in this study was 9.59% (145/1512). There were 78 (53.8%), 31 (21.4%), and 36 (24.8%) patients in IgAN-AKI stage I, II, III respectively. Mean baseline versus peak Scr in AKI staging I, II, III was 235.27 ± 196.81 μmol/L versus 390.57 ± 338.01 μmol/L (p < 0.001), 191.38 ± 154.43 μmol/L versus 457.11 ± 354.34 μmol/L (p < 0.001), 140.36 ± 56.16 μmol/L versus 807.23 ± 491.64 μmol/L (p < 0.001) respectively. Of the 145 AKI patients, 27 patients needed several sessions of hemodialysis because of the severity of worsening renal function.

Table 1 describes the demographics and baseline clinical data between those who did and did not have an episode of AKI. Among the 145 AKI patients, there were 92 males and 53 females, with a mean age of 32.94 ± 10.34 years. Patients who experienced AKI were older (34.90 ± 12.36 years versus 32.74 ± 10.09 years, p = 0.017), more often males (63.4% versus 44.4%, p < 0.001) and higher rates of hypertension (71.0% versus 34.0%, p < 0.001) (especially malignant hypertension 4.1% versus 0.3%, p < 0.001), anemia (46.9% versus 19.4%, p < 0.001) as well as smoke (13.2% versus 7.3%, p = 0.021). Meanwhile, AKI group had much lower percentage of MH (11.0% versus 23.3%, p < 0.001). Among the 145 AKI patients, there were 16 cases of MH. AKI patients had higher systolic blood pressure, diastolic blood pressure, Scr, proteinuria, uric acid, cholesterol, and triglyceride (p < 0.001) and had lower total serum protein (p < 0.001), serum albumin (p < 0.001), and immunoglobulin A titer (p = 0.023). There were 16 nephrotic syndrome cases in AKI group. A greater proportion of AKI patients applied diuretics, oral corticosteroid, and methylprednisolone impulse treatment (p < 0.01) while fewer AKI patients applied ACEI/ARB medication.

Histopathological characteristics of patients with AKI

The main histopathological findings were presented in Table 2. Compared with non-AKI group, there was a higher proportion of global sclerosis, segmental sclerosis, tubular atrophy, and interstitial fibrosis in AKI group (p < 0.01). Besides, the percentage of glomeruli with crescent/fibrocellular crescent and interstitial cell infiltration were significantly higher in AKI group (p < 0.01), especially the percentage of cellular crescent ≥ 25% and fibrocellular crescent ≥ 25% was higher in AKI group, while there was more mesangial proliferation (M1, oxford criteria) (p = 0.020) in non-AKI group.

Among the 145 AKI patients, there were 28 intrinsic pathological changes of AKI involved in IgAN can be found in Table 3: (1) crescent glomerulonephritis (2, 1.4%); (2) acute tubular injury or necrosis (6, 4.1%), two of them accompanied with documented MH episode; (3) acute tubulointerstitial nephritis (TIN) (14, 9.7%), while one case of them overlaps with crescent glomerulonephritis; and (4) malignant hypertensive renal lesion (6, 4.1%).

The associated risk factors with AKI

Variables independently associated with AKI in IgAN are shown in Table 4. AKI was most strongly associated with several clinical findings: older age (OR 1.27, 95% CI 1.07–1.51 for per 10 years, p = 0.007), malignant hypertension (OR 8.47, 95% CI 2.02–35.54, p = 0.003) and proteinuria (OR 1.27, 95% CI 1.14–1.41, p < 0.001) as well as several pathological findings: cellular crescent (OR 2.03, 95%CI 1.13–3.64, p = 0.018), fibrocellular crescents (OR 2.09, 95%CI1.34–3.26, p = 0.001), glomerular sclerosis ≥50% (OR 2.02, 95%CI 1.16–3.51, p = 0.013).

Discussion

Until recently, the epidemiology of AKI reported in previously published studies have varied widely among different clinical settings with different definition of AKI. IgAN is the most common primary glomerular disease worldwide. However, AKI-IgAN studies have been almost exclusively studied among MH-related AKI. Quantification of AKI prevalence and its clinicopathological characteristics as well as risk factors in IgAN populations are important for clinicians, so that appropriate identification, prevention, and treatment strategies can be tested. The major finding of this study is that the overall prevalence of AKI in IgA nephrology in our center is high (9.59%). Also, our study provided new clinical and pathological information about the characteristics of AKI in IgAN population.

Our study showed that AKI-IgAN patients had much severe clinical change than non-AKI counterpart. Previous descriptions have reported that preexisting chronic kidney disease, either manifesting as reduced estimated glomerular filtration rate or proteinuria, is one of the most potent risk factors for AKI. For the specific IgAN population, we also found a high percentage of 51.0% who had preexisting impaired kidney function (elevated baseline Scr more than 133 μmol/L) in AKI group. Though multivariate logistic regression analysis has not identified as an independent risk factor of AKI,
### Table 1. Demographic and clinical features at baseline between AKI and non-AKI group.

| Characteristics                     | All (1512) | Non-AKI group (1367) | AKI group (145) | p Values |
|--------------------------------------|------------|----------------------|-----------------|----------|
| Age (year)                           | 32.94 ± 10.34 | 32.74 ± 10.09 | 34.90 ± 12.36 | 0.017    |
| Male (n, %)                          | 699 (46.2) | 607 (44.4) | 92 (63.4) | <0.001  |
| Preexisting impaired kidney function (Scr > 133 μmol/L) (n, %) | 296 (19.6) | 222 (16.2) | 74 (51.0) | <0.001  |
| Smoke (n, %)                         | 118 (7.9) | 99 (7.3) | 19 (13.2) | 0.021    |
| Drinks (n, %)                        | 44 (2.9) | 38 (2.8) | 6 (4.2) | 0.305    |
| Hypertension (n, %)                  | 568 (37.6) | 465 (34.0) | 103 (71.0) | <0.001  |
| Malignant hypertension (n, %)        | 10 (0.7) | 4 (0.3) | 6 (4.1) | <0.001  |
| Macroscopic hematuria (n, %)         | 334 (22.1) | 318 (23.3) | 16 (11.0) | <0.001  |
| SBP (mmHg)                           | 127.60 ± 19.71 | 125.92 ± 18.34 | 143.39 ± 24.68 | <0.001  |
| DBP (mmHg)                           | 80.62 ± 13.65 | 79.65 ± 13.03 | 89.76 ± 15.80 | <0.001  |
| Baseline Scr (μmol/L)                | 83 (63,115) | 79 (61,106.75) | 135 (89,622,15) | <0.001  |

### Table 2. Comparison of pathological features between AKI and non-AKI group.

| Variables                              | All (1512) | Non-AKI group (1367) | AKI group (145) | p Values |
|----------------------------------------|------------|----------------------|-----------------|----------|
| Glomeruli with GS (%)                  | 12.00 (2.52, 33.33) | 10.70 (0.29,4)  | 41.40 (14.37, 70.12) | <0.001  |
| Glomeruli with crescents (n, %)*       | 0.00 (0.7,1) | 0.00 (0.6,70) | 4.0 (0.10,90) | <0.001  |
| Cellular crescent (n, %)               |             | 0.04                |                 | 0.007    |
| <25%                                   | 552 (84.5) | 495 (86.1) | 57 (73.1) | 0.004    |
| 25–50%                                 | 32 (4.9) | 23 (4.0) | 9 (11.5) | 0.001    |
| 50–100%                                | 69 (10.6) | 57 (9.9) | 12 (15.4) | 0.023    |
| Fibrocellular crescent (n, %)          |             | 0.001               |                 | 0.006    |
| <25%                                   | 461 (70.6) | 420 (73.0) | 41 (52.6) | 0.001    |
| 25–50%                                 | 53 (8.1) | 43 (7.5) | 10 (12.8) | 0.002    |
| 50–100%                                | 139 (21.3) | 112 (19.5) | 27 (34.6) | 0.001    |
| Fibrous crescent (n, %)                |             | 0.915               |                 | 0.001    |
| <25%                                   | 547 (83.8) | 481 (83.7) | 66 (84.6) | 0.001    |
| 25–50%                                 | 22 (3.4) | 20 (3.5) | 2 (2.6) | 0.003    |
| 50–100%                                | 84 (12.9) | 74 (12.9) | 10 (12.8) | 0.001    |
| Mesangial proliferation, M1 (n, %)     | 1360 (89.9) | 1238 (89.6) | 122 (84.1) | 0.020    |
| Endothelial cell proliferation, E1 (n, %) | 277 (18.3) | 253 (18.5) | 24 (16.0) | 0.062    |
| Glomeruli with SS, S1 (n, %)           | 691 (45.7) | 606 (44.3) | 85 (58.6) | 0.001    |
| Tubular atrophy/interstitial fibrosis, T (n, %) | 1158 (76.6) | 1092 (79.9) | 66 (45.5) | 0.001    |
| T0                                    | 275 (18.2) | 226 (16.5) | 49 (33.8) | 0.001    |
| T2                                    | 79 (5.2) | 49 (3.6) | 30 (20.7) | 0.001    |
| Intestinal cell infiltration (n, %)    |             | 0.001               |                 | 0.001    |
| <25%                                   | 1210 (80.0) | 1140 (83.4) | 70 (48.3) | 0.001    |
| 25–50%                                 | 241 (15.9) | 193 (14.1) | 48 (33.1) | 0.001    |
| 50–100%                                | 61 (4.0) | 34 (2.5) | 27 (18.6) | 0.025    |

Notes: SBP: systolic blood pressure; DBP: diastolic blood pressure; Scr: serum creatinine; Hb: hemoglobin; UA: uric acid; TP: total serum protein; ALB: albumin; Chol: cholesterol; TG: triglycerol; IgA: immunoglobulin A; MP: methylprednisolone; ACEI: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin II receptor blocker; immunosuppressant: including cyclosporine A; tacrolimus, mycophenolate mofetil, and cyclophosphamide; NA: lack of data. Values are expressed as mean ± SD; categorical variables are expressed in percentage.

Notes: GS: global sclerosis; SS: segmental sclerosis.

*All kinds of crescents (cellular, fibrocellular, and fibrous crescent) were calculated; Variables (Glomeruli with GS, crescents) are expressed as median; other variables are expressed in percentages.
this can be explained by the small sample size, mixed confounder, and also we did not use SCR > 115 μmol/L as the definition of preexisting impaired kidney function. 13–16 We found a higher risk of AKI with older age, malignant hypertension as well as proteinuria, which was in accordance with other studies. 1,17–19

Previous studies performed have shown a relationship between macroscopic glomerular hematuria and AKI. 7–9 Several pathophysiological mechanisms may account for the tubular injury found on renal biopsy specimens. 20 However, in our series, MH was only seen in 16 patients in AKI group, and we did not differentiate recurrent MH and isolated MH in this retrospective study. We found that MH was a protective factor for AKI in univariate analysis in our study. The mechanism remains unanswered in this study, 21 one explanation has been hypothesized that patients with MH were much earlier to be detected and received treatments in time during clinic work. Only a prospective study with large numbers of patients can answer that question clearly.

For the pathological features aspect, AKI group showed significantly higher proportion of glomeruli with cellular crescent, fibrocellular crescent, interstitial cell infiltration, global sclerosis, segmental sclerosis, tubular atrophy, and interstitial fibrosis. Meanwhile, we found cellular crescent (OR 2.03, 95% CI 1.13–3.64, p = 0.018), fibrocellular crescents (OR 2.09, 95% CI 1.34–3.26, p = 0.001), and glomerular sclerosis ≥ 50%

### Table 3. Possible special pathological changes involved in IgAN associated with AKI.

| Possible pathological spectrum                          | Percentage |
|-------------------------------------------------------|------------|
| Crescentic glomerulonephritis                          | 2 (1.4%)   |
| Acute tubular injury/necrosis                          | 6 (4.1%)   |
| Acute tubulointerstitial nephritis                     | 14 (9.7%)  |
| Malignant hypertensive renal lesion                    | 6 (4.1%)   |
| Unclassified*                                          | 117 (80.7%)|

*Including different degree of chronic sclerosing glomerulonephritis, or mild mesangioliprotective type with/without segmental sclerosis/global sclerosis/fibrous crescents/hypertensive renal lesion, or minimal change type as well as focal segmental sclerosing type.

(OR 2.02, 95% CI 1.16–3.51, p = 0.013) were possible risk factors for AKI in IgAN population in adjusted multivariable models which was similar with the study of Walsh et al. 22 Still, the features of AKI-IgAN on light microscopy varied greatly among patients and within the individual biopsy samples. There were 28 cases presenting special intrinsic kidney injuries in renal biopsy samples as follows to be discussed.

The most frequent histological findings in MH-associated AKI are acute tubular injury/necrosis and intraluminal obstruction by RBC or hemoglobin casts. 21 However, in our series, the percentage of acute tubular injury/necrosis was only 4.1% (six cases), meanwhile, MH related acute tubular injury/necrosis was only seen in two cases which were different from previous studies and inadequate to explain the severe deterioration in renal function, this difference may be attributed to the genetic varieties in different regions. 15,16 Moreover, our retrospective studies did not record the relationship between severity and duration of the glomerular MH with the tubular damage. These findings are important because different pathophysiological mechanisms of AKI require different therapeutic intervention.

Our histopathological findings suggested that a positive correlation between crescent formation and AKI which is similar to other studies. 9,23–25 And we also found that only cellular or fibrocellular crescents were responsible for AKI rather than the fibrous one. However, the percentage of crescentic glomerulonephritis was not so severe (two cases, 1.4%), which was also in accordance with other studies. Moreover, there were six patients (4.1%) of malignant hypertensive renal lesion were found. The explanation might attribute to excessive arterial pressure leads to endothelial damage of arterioles and capillaries. The ischemic collapse of glomeruli promotes further irreversible renal injury, and eventually leads to renal failure. 26

Another striking pathological finding of AKI-IgAN in our study was significantly noticed acute TIN in AKI
group, which was the most predominant change of intrinsic AKI in IgAN population in our study. Acute TIN is a common cause of ARF, characterized by inflammatory cell infiltration in the interstitium of the renal biopsy specimen. The percentage of acute TIN was 9.7% in IgAN population. The tubulointerstitial injuries were due to immune-allergic reaction to certain medications or infections. According to previous studies, non-steroidal anti-inflammatory drugs (NSAID) and antibiotics are the most important etiology for TIN.\textsuperscript{23} Besides, we also found that Traditional Chinese Medicine (TCM) as well as certain nephrotoxic drugs (Rifampin, PTU, and Contrast) might induce the tubulointerstitial injuries in our experience, probably due to prescription habits and drug overuse in developing countries. For the study was retrospective without complete etiologies of AKI about patient. Further evidences are needed to identify such changes.

Except for the 28 direct intrinsic kidney injury cases have been mentioned above, there are still 117 patients were clinically diagnosed as AKI without direct intrinsic renal injuries in histopathology, we have presumed to be pre-renal or post-renal reasons such as over intake of protein, volume depletion, systemic hypotension, renal vascular stenosis, diastolic cardiac failure, and obstruction of the urinary tract. However, in our retrospective study, the information in documented medical record is not complete which shows severe limitation.

For the treatment of AKI, identification and correction of potentially reversible causes of kidney damage (such as various pre-renal, renal, or post-renal risk factors) are of paramount importance.\textsuperscript{1} Supportive and symptomatic treatment is recommended. Corticosteroid treatment is based mainly on clinical judgment and the extensiveness of histopathologic abnormalities (such as the percentage of crescents) as well as on the intensity of acute tubulointerstitial nephritis, with a short course of methylprednisolone is introduced (Case by case, generally 500 mg intravenous pulse for 3 days, followed by oral prednisolone for 8–16 weeks). Renal replacement treatment (RRT) will also be applied in AKI patients, however, accurate timing and mode of initiation of RRT is still a matter of debate.\textsuperscript{27} Standard guidelines for RRT (when to start, which type of RRT to use in what dose and when to stop) are lacked. There were 27 AKI patients received hemodialysis in this study.

However, several limitations of this study should be mentioned. First, our retrospective study is single-center, cross-sectional, and the data is incomplete without urine data and accurate etiologies of AKI about patient. Second, given that some patients had received treatment in local hospitals after the AKI attack and then transferred to our hospital, some mild AKI without severe clinical manifestations and a short course might not have been diagnosed or documented in our record. Also, we might miss those patients who had already got Scr increased to peak levels before admission. Thus, we may have underestimated the exact prevalence of AKI. Third, we only used Scr criteria of AKI in our study.

**Conclusion**

The prevalence of AKI among IgAN population in our center is 9.59% (145/1512). Simple clinicopathological predictors are recognized to improve the identification of IgAN patients who are at high risk for AKI. Acute TIN is the most predominant intrinsic pathological change of AKI. The pathological type of AKI cannot be determined precisely if renal biopsy is not performed, selection of accurate treatment should be based on both the clinical and histopathologic features.

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**Disclosure statement**

The authors declare that they have no relevant financial interests.

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