主論文の要約

The Japanese Histologic Classification and T-score in the Oxford Classification system could predict renal outcome in Japanese IgA nephropathy patients

（日本人 IgA 腎症患者の腎病理組織における Japanese Histologic Classification と Oxford 分類の T スコアは腎予後を予測しうる）

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【Introduction】

IgA nephropathy (IgAN) is one of the most common glomerulonephritis in the world, with a higher incidence in the Pacific Rim and Mediterranean countries. Renal biopsy confirms the diagnosis of IgAN, assesses disease severity, and guides therapeutic strategies in clinical practice. Although several pathological classifications have been developed from expert opinion, each has its limitations and none has achieved widespread agreement. Therefore, the International IgA Network and Pathology Society developed the Oxford Classification of IgAN in a cohort of 265 patients included with IgAN comprising mainly Caucasians, which included 20 (9.7%) and 28 (13.6%) adult-patients with IgAN from Japan and China, respectively. Meanwhile the Japanese Society of Nephrology developed the Japanese Histologica Classification (JHC) of IgAN in Japan. Since these two histopathological classification of IgAN have been used widely in Japan to predict renal outcome based on histopathological features, thus we aimed to analyze clinical usefulness of these two classification in association to renal outcomes in the same cohort.

【Methods】

This retrospective cohort study was conducted at the Nagoya University Hospital. All patients with IgAN were enrolled between 2001 and 2009. Patients with the following criteria (age ≥18 years, primary IgAN, follow-up period >1 year) and specimens with ≥8 glomeruli were included. Clinical and laboratory data at the time of biopsy were available for all patients. One patient with IgA vasculitis, 5 patients with less than 8 glomeruli in renal biopsy specimens, and 30 patients with a follow-up period of less than 12 months were excluded from the study, leaving a final study sample of 86 patients with IgAN.

All the histopathological specimens were assessed according to the Oxford and JHC grading criteria by seven independent nephrologists. The JHC grades (G1, G2, G3+4) and the Oxford classification's histopathological independent features─Mesangial hypercellularity (M), Endocappilary prolifirations (E), Segmental glomeruloscelerosis (S), tubular atrophy (T), and crescents were analyzed in association with renal outcome in the same cohort, defined as a 50% increase in serum creatinine.

【Results】

Clinical and histologic characteristic

During a median 6.8 years of follow-up, 13 (15%) patients reached a renal outcome. A total of 72 patients (84%) were treated with renin angiotensin aldosterone system blockers and nearly 57 patients (66%) were treated with intensive pulse methyl prednisolone regimen. At the end of follow-up, the median eGFR was 62 [IQR: 45-86] ml/min/1.73m^2, and proteinuria was decreased to 0.8 [IQR: 0.6-1.4] g/24h.

According to MEST scoring system, the proportion of M_1,E_1,S_1,T_1/$_2$, and positive

crescents (C_1) were 21%, 41%, 67%, T (6/8%), and (45%), respectively in the Oxford classification. Whereas, 49%, 36%, 15% of patients stratified into HG1, HG2, and HG3+4 according to JHC. In the correlation study, a significant but mild correlation was demonstrated only between the T score and JHC ($r = 0.28$, $p= 0.03$).

Renal outcome studies

Kaplan-Meier survival curves are shown in Fig. 1. The Log-rank test revealed significant differences between T0 and T1+2 ($p < 0.001$), and among HG1, HG2, and HG3+4 ($p < 0.001$). Cox regression analyses revealed that the amount of proteinuria, serum creatinine (SCr), estimated glomerular filtration rate (eGFR), and serum uric acid (UA) among clinical variables, and the T score (T0/1+2), JHC (HG1/2/3+4) in histologic variables were significantly associated with renal outcome in univariate analyses. Multivariate analyses were performed for sex, amount of proteinuria, eGFR, UA and T score (T0/1+2), with the addition of the JHC in model 2. Although SCr and eGFR were significant variables in univariate analyses, only eGFR was included in multivariate analyses because of theoretical confounding. In model 1, only the T score was a significant variable for renal outcome (HR: 4.28, 95% CI: 1.15-16.00, $p = 0.03$). In model 2, only the JHC was demonstrated as a significant variable (HR: 42.85, 95% CI: 1.04-7.84, $p = 0.04$).

【Discussion】

In this study, significant associations were demonstrated in the JHC and T score with the renal outcome. This was the first known study to analyze both the JHC and Oxford classifications in regards to renal outcomes in the same cohort. In a good agreement the predictive value of the JHC study in 2013 and the JHC validation study in 2015 [25] were reproduced in current study. Hazard ratios of HG3/4 and HG2 were 8.29 and 2.89, respectively, compared to HG1 (HR: 1) in current study.

patients in present study exhibited a lower proportion of M1 (21% vs. 78/%) and T1/2 (14% vs. 24/21%), but higher proportions of E1 (41% vs. 37/11%) and crescents (45% vs. 41/9%) compared to the original Oxford and VALIGA studies, which would suggest that Japanese patients were diagnosed in earlier and more active phases, because of annual urinalysis screening programs. Due to different inclusion criteria, 11 patients with eGFR less than 30 ml/min/1.73 m^2, and 13 patients with proteinuria less than 0.5 g/day were included in this study. In addition, we excluded pediatric patients (<18 years) from our cohort study, while the pediatric population accounted for 9.1% of patients in the 2013 JHC study and 22% of patients in the Oxford classification. Furthermore, we studied the end point with a 50% increase in SCr but not a 50% decrease in eGFR, end-stage renal disease and the rate of renal function decline. Although the proportion of renal outcome was 15% in this study, the median observation period was longer than the original Oxford

and VALIGA studies. This is most likely because Japanese IgAN patients were diagnosed and treated with immunosuppressive therapies at earlier phases.

In summary, the JHC and tubular atrophy in the Oxford classification were associated with renal outcome among Japanese patients with IgAN. Clinical values of the JHC as prognostic prediction indexes should be validated with large study population and cohort studies in different ethnicities.