Clinical and Histological Predictors of Renal Survival in Patients with Biopsy-Proven Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is one of the most important complications of diabetes and has become the leading cause of end stage renal disease (ESRD). However, clinical and pathological factors alone can’t reliably predict renal survival in patients with biopsy-proven DN, potentially resulting in the delayed treatment of patients at a high risk of renal failure. Therefore, this study sought to develop and validate a predictive model incorporating both clinical and pathological markers to predict renal outcomes in patients with biopsy-proven DN.

Methods: A predictive nomogram was developed based upon data pertaining to 194 patients with biopsy-proven DN. The prognostic relevance of individual clinicopathological variables was assessed through univariate and multivariate Cox regression analyses. A prognostic nomogram was then developed and validated based upon concordance (C)-index values, area under curve (AUC) and calibration curves. Internal validation was conducted through bootstrap resampling, while the clinical utility of this model was assessed via a decision curve analysis (DCA) approach.

Results: Nephrotic-range 24-hour proteinuria, late-stage chronic kidney disease (CKD stage 3-4), glomerulatert III-IV, and an IFN-γ score of 2-3 were all identified as independent predictors of poor renal outcomes in DN patients and were incorporated into our final nomogram. Calibration curves revealed good agreement between predicted and actual 3- and 5-year renal survival in DN patients, while the C-index value for this nomogram was 0.845 (95% CI 0.826-0.864) and the 3- and 5-Year AUC were 0.933 (95% CI 0.898-0.968), 0.923 (95% CI 0.886-0.960). DCA analysis revealed that our nomogram was superior to models based solely upon clinical indicators.

Conclusions: A predictive nomogram incorporating clinical and pathological indicators was developed and validated for the prediction of renal survival outcomes in patients with biopsy-proven DN. This tool will be of value to clinicians, as it can serve as an easy-to-use and reliable tool for physicians to guide patient management based on individualized risk in order to improve patient outcomes.

Histological Diabetic Nephropathy in Autopsied Diabetic Cases with Normoalbuminuria from a Japanese Community-Based Study: The Hisayama Study

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Background: Albuminuria is a clinical indicator of diabetic nephropathy (DN). However, it is controversial whether pathological DN lesions are present in diabetic individuals without normal albuminuria. We investigated the association between albuminuria levels and the frequency of DN lesions in autopsied diabetic cases from a Japanese community.

Methods: Autopsied specimens obtained from deceased people in the town of Hisayama from 2002 to 2017 were used in the present study. During this period, 131 deceased individuals with diabetes underwent autopsy examinations. A total of 106 autopsied cases with diabetes mellitus (mean age 76 years, 43.4% male) who died within 6 years since the last health examination were included in the study. Urinary albumin-creatinine ratio (UACR) levels were divided into three groups: <30.0, 30.0-299.9, and ≥300.0 mg/g. The kidney specimens were evaluated with light microscopy, and were categorized into class 0-1, IIa, IIb, and III glomerular DN lesions according to the Renal Pathology Society’s criteria. A Cochrane-Armitage test was used to examine the association between the UACR levels and the presence of class IIa or higher glomerular DN lesions.

Results: In the overall cases, the frequency of class IIa or higher glomerular DN lesions was 63.2% (IIa, 36.8%; IIb, 3.8%; and III, 22.6%). Its frequencies increased significantly in the higher UACR levels (P for trend = 0.02, Figure). Even in individuals with UACR of <30 mg/g, the frequency of class IIa or higher glomerular DN lesions was 51.2%.

Conclusions: The present study showed a positive association of the UACR levels with the presence of class IIa or higher glomerular DN lesions, which were also frequently found even in the normoalbuminuric range, among autopsied diabetic cases from a Japanese community.

Figure.

Clinical Pathological Significance of Orai1 Expression in Human Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) causes about half of ESRD. The attempts for targeted therapy for DN have been lacking to date. Store-operated Ca entry (SOCE) is a primary Ca influx mechanism in non-excitatory cells that is mediated by pore-forming subunit Orai1. Currently, it has been argued whether Orai1 overexpression protects against renal pathologies. Here, we investigate the significance of Orai1 expression in human DN.

Methods: Ninety-three DN patients from 2009 to 2019 were enrolled. The paraffin blocks were used to perform immunohistochemical staining for Orai1 (figure). Renal Pathology Society DN classification (RPS) and clinical parameters were compared with Orai1 expression. The results were compared by dividing them into a glomerulus (G) and tubulo-interstitium (T-I).

Results: In T-I, Orai1 was overexpressed in DN, and Orai1 expression was significantly correlated with the higher RPS and interstitial fibrosis & tubular atrophy score (p < 0.001). While Orai1 expression was correlated with serum Cr and CKD stages, eGFR and HbA1c were inversely associated with Orai1 expression (p < 0.001). By logistic regression, Orai1 expression was significantly correlated with the higher RPS and the advanced CKD stage. Moreover, Orai1 expression was strongly associated with the advanced CKD stage by the multivariate logistic regression (p = 0.002) (table). The result of G was similar to that of T-I.

Conclusions: It is suggested that Orai1 is a valuable biomarker for predicting the progression and prognosis of DN, that provides new perspectives on therapeutic targets for DN.

Funding: Government Support - Non-U.S.

The correlation between Orai-1 expression and CKD stage in DN (Multivariate logistic regression)

BMI, body mass index; HTN, hypertension; G, glomerulus; T-I, tubulo-interstitium