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Clinical predictors differentiating non-diabetic renal diseases from diabetic nephropathy in a large population of type 2 diabetes patients

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ABSTRACT

Aims: Non-diabetic renal diseases (NDRDs) are associated with better renal outcomes than diabetic nephropathy (DN). This study was conducted to determine the common clinical markers predicting NDRDs in type 2 diabetes patients.

Methods: Patients with type 2 diabetes mellitus who underwent a renal biopsy were screened. Eligible patients were categorized into two groups: DN group and NDRD group. Patient's clinical characteristics and laboratory data were collected. Logistic regression analysis was performed to identify risk factors for NDRD development, and the diagnostic performance of these variables was evaluated.

Results: The study included 248 patients, 96 (38.71%) in the DN group and 152 (61.29%) in the NDRD group. Patients in the NDRD group had a shorter duration of DM and higher hemoglobin, estimated glomerular filtration rate, and urine osmotic pressure values as well as a higher incidence of glomerular hematuria than patients in the DN group. In the NDRD patients, the most common pathological type was membranous nephropathy (55, 36.18%). Absence of retinopathy (OR, 44.696, 95% CI, 15.91–125.566), glomerular hematuria (OR, 9.587, 95% CI, 2.027–45.333), and DM history ⩽5 years (OR, 4.636, 95% CI, 1.721–12.486) were significant and independent risk factors for the development of NDRD ($P < 0.01$). Absence of retinopathy achieved the overall highest diagnostic efficiency with a sensitivity of 92.11% and specificity of 82.29%. Glomerular hematuria had the highest specificity (93.75%).

Conclusion: Shorter duration of diabetes (⩽5 years), absence of retinopathy, and presence of glomerular hematuria were independent indicators associated with NDRDs, indicating the need for renal biopsy.

1. Introduction

Non-diabetic renal diseases (NDRDs) are currently recognized as a common complicating condition in type 2 diabetes patients and require accurate differential diagnosis and treatment from diabetic nephropathy (DN). It is generally accepted that NDRDs have a relatively better prognosis, because renal lesions in DN are deemed difficult to reverse. In contrast,

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NDRDs are often treatable and even remittable [1]. In practice, a large proportion of patients with type 2 diabetes mellitus (DM) are not formally evaluated with a renal biopsy [2,3]. Instead of pathological diagnosis, DN is usually diagnosed based on clinical symptoms, and NDRD patients are potentially misdiagnosed with DN [4] and thus do not receive proper treatment.

Because NDRDs are associated with significantly better renal outcomes compared with biopsy-proven DN, it is important to identify diabetes patients who are likely to develop NDRDs. Different predicting factors have been identified for NDRDs, such as short duration of DM [5], absence of diabetic neuropathy or retinopathy, and microscopic hematuria [6], but these markers were found to have variable predictive values in different studies. In fact, most knowledge regarding the nature of kidney diseases in type 2 DM patients is derived from studies of patients with type 1 DM. However, patients with type 1 DM show less heterogeneity than their counterparts with type 2 DM, and only 5% of type 1 DM patients have NDRDs [4,7]. Thus, patients are easily diagnosed with type 1 DM if the patient has a relatively longer history of DM or presents with diabetic retinopathy, which corresponds to a rate of pathological diagnosis of 95% [8,9]. On the contrary, NDRDs represent a rare clinical condition in type 1 DM, particularly in patients with a DM history of 10 years, with a rate of 2–3% [10]. In comparison to those in type 1 DM patients, the renal diseases in type 2 DM patients are more complex and heterogeneous, creating difficulties in the differential diagnosis of NDRDs from DN. Also, the occurrence of NDRDs is more common in type 2 DM patients, although different incidences have been reported in different regions [4,7]. Some prospective studies have suggested that biopsy criteria for type 1 DM are not useful for identifying type 2 DM patients with other potentially treatable renal diseases like NDRDs [11]. The present study was conducted to determine the frequency of NDRDs in type 2 DM patients in China and also to identify common clinical markers associated with NDRDs in the type 2 diabetic population. Previous studies usually included patients with coexisting DN and NDRDs [12,13], probably due to limited sample sizes, but this increases systematic errors due to confounding factors. In the present study, we included only patients with either DN or a NDRD in order to evaluate the diagnostic performance of clinical markers for predicting NDRD development in type 2 DM patients.

2. Materials and methods

2.1. Study population

A total of 384 patients with type 2 DM who underwent a renal biopsy between April 2012 and December 2014 in our hospital were screened. The inclusion criteria were: (1) male or female, age $\geqslant$ 18 years; (2) biopsy-proven renal lesion; and (3) proteinuria (>0.15 g/24 h). The exclusion criteria were: (1) incomplete data or unclear medical history; (2) lack of a fundus examination; (3) complications, such as severe infection (urinary tract, respiratory tract, digestive tract, etc.) and/or malignancy; (4) complication with systemic disease (such as allergic purpura, systemic vasculitis, and Goodpasture's syndrome); and (5) pathological diagnosis of DN combined with NDRD. The study was approved by the Ethics Committee of the Chinese People's Liberation Army General Hospital (No. S2014-012-01). All patients provided written informed consent. The eligible patients were categorized into two groups: the DN group, defined as patients with DN only, and the NDRD group, defined as patients with NDRD only.

2.2. Data collection

The following clinical characteristics of patients were collected: gender, age, medical history of DM, family history, body mass index (BMI), presence of hypertension, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure, and presence of retinopathy. Laboratory parameters, including hemoglobin, serum creatinine, estimated glomerular filtration rate (eGFR, calculated by the CKD-EPI formula), serum albumin, glycated hemoglobin, 24-h urine protein, presence of glomerular hematuria, and urine osmotic pressure, were collected at the time of renal biopsy. Diabetic retinopathy lesions were examined by experienced ophthalmologists with an ophthalmoscope after mydriasis. In several patients, difficult diagnoses were confirmed with eye-ground photography or fundus fluorescence angiography. Glomerular hematuria was defined as the presence of 3 or more red blood cells per high power field (hpf), with more than 80% dysmorphic erythrocytes [14,15].

2.3. Renal biopsy and pathological examination

All patients underwent a renal biopsy after they signed the informed consent form. The renal biopsies were performed by an experienced physician, and all renal biopsy specimens were reviewed independently by two pathologists, who solved all discordant cases by discussion. The criteria for DN diagnosis were: mesangial proliferation, diffuse capillary glomerulosclerosis, presence or absence of K-W nodules, diffuse thickening of the glomerular basement membrane (GBM), and exudative injury such as fibrous cap or/and hyaline thrombi [16]. Pathological diagnosis of NDRDs was based on guidelines previously described [17].

2.4. Statistical analysis

All statistical analyses were performed using SPSS software (version 20.0; SPSS Inc., Chicago, IL, USA). Continuous data are expressed as mean ± standard deviation (SD) or median (interquartile range). Categorical data are presented in terms of absolute values and percentages. Comparisons of continuous variables between the groups were performed using independent *t*-test for normally distributed data and the Mann-Whitney *U* test for data not normally distributed. The proportions were compared using the chi-squared test. Univariate and multivariate logistic regression analyses were performed to identify risk factors for development of NDRDs in diabetes patients, with results reported as the odds ratio (OR) and 95% confidence interval (CI). The diagnostic performance of variables was evaluated in terms of sensitivity, specificity, Youden index, positive predictive value (PPV), and negative predictive value (NPV) based on a receiver