Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Clinical outcomes in patients with biopsy-proved diabetic nephropathy compared to isolated lupus or crescentic glomerulonephritis

Yu-Hsiang Chou [a,b], Wei-Chou Lin [c], Yung-Ming Chen [b,*]

[a] Department of Internal Medicine, National Taiwan University Hospital Jin-Shan Branch, No. 7, Yulu Rd., Wuhu Village, Jinshan Dist., New Taipei City 20844, Taiwan

[b] Renal Division, Department of Internal Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, No. 7, Chung Shan S. Rd., Zhongzheng Dist., Taipei City 10002, Taiwan

[c] Department of Pathology, National Taiwan University College of Medicine and Hospital, No. 7, Chung Shan S. Rd., Zhongzheng Dist., Taipei City 10002, Taiwan

ARTICLE INFO

Article history:
Received 25 December 2018
Accepted 9 January 2019
Available online 11 January 2019

Keywords:
Diabetic nephropathy
Crescentic glomerulonephritis
Lupus nephritis
Renal biopsy
End-stage renal disease
Mortality

ABSTRACT

Aims: Diabetic nephropathy (DMN) is usually diagnosed clinically without pathology, and the prognosis of which compared to non-diabetic renal diseases has rarely been investigated especially in ethnic Chinese population. Here we reported the outcome of patients with biopsy-proved DMN compared to those with isolated crescentic glomerulonephritis (GN) or lupus nephritis (LN).

Methods: This retrospective observational study included patients with DMN (n = 55), crescentic GN (n = 48) and LN (n = 82) from an original cohort of 987 adult patients who underwent kidney biopsy. The median follow-up period was 8.3 years. The Cox regression model was used to identify factors associated with the outcome measures of end-stage renal disease (ESRD) and all-cause mortality.

Results: Patients with DMN and crescentic GN exhibited higher rates of ESRD than LN group (65.5%, 66.7% versus 32.9%, $p < 0.001$). After accounting for the competing risk of death, DMN versus LN, along with lower hemoglobin values, lower estimated glomerular filtration rates and severe proteinuria were independent predictors for ESRD. Patients with DMN and crescentic GN displayed higher mortality rates than LN patients following the development of ESRD (38.2% and 29.2% versus 9.8%, $p < 0.001$). Multivariate analysis showed old age (≧65 years) and lower serum albumin levels were independently associated with overall death.

Conclusions: Patients with biopsy-proved DMN, but not crescentic GN, showed a greater risk of ESRD than LN counterparts. Given the grave renal prognosis of DMN, more meticulous follow-up is critical to ensure that best therapeutic strategies are used to avert progression to ESRD.

* Corresponding author at: Department of Internal Medicine, National Taiwan University, College of Medicine, No. 1, Jen-Ai Road, Section 1, Taipei 100, Taiwan.
E-mail addresses: weichou8@ms52.hinet.net (W.-C. Lin), yungmingchen@ntu.edu.tw (Y.-M. Chen).

https://doi.org/10.1016/j.diabres.2019.01.014
0168-8227/

1. Introduction

Chronic kidney disease (CKD) and the resultant kidney failure have emerged as a major public health problem around the world. Among the various etiologies of end-stage renal disease (ESRD), diabetes and its associated kidney disease, i.e., diabetic nephropathy (DMN), accounts for nearly one half of new-onset kidney failure from western countries [1–3]. Moreover, patients with concomitant diabetes and CKD pose the highest risks of morbidity and mortality from cardiovascular disease than either disease alone [4]. Apart from DMN, non-diabetic renal diseases (NDRD) also contribute to the increasing burden of ESRD in many parts of the world. Crescentic glomerulonephritis (GN) and lupus nephritis (LN) represent the most severe forms of NDRD as causes of ESRD. Patients with these two NDRD have also been linked with reduced overall survival in observational studies [5,6].

The prognosis of DMN compared to NDRD has rarely been investigated during the same time frame in Asian population. The paucity of such analysis could be due to the fact that DMN is usually made without the aid of pathology, and most clinicians rely on a meaningful background of diabetes plus typical manifestations of albuminuria, renal dysfunction and retinopathy [7]. That being said, a sizable number of diabetic patients have NDRD or DMN plus NDRD, and renal biopsy is often needed for patients presenting with atypical DMN features such as rapid decline of estimated glomerular filtration rate (eGFR), unexpected onset of severe proteinuria, or prominent hematuria without retinopathy [8]. Nevertheless, only a few researches had been published on renal outcomes of NDRD in patients with type 2 diabetes [9,10]. More recently, Iwai et al reported patients with DMN displayed a higher risk of ESRD and death than groups of NDRD or underlying DM with superimposed non-diabetic CKD [11]. Jiang et al also found increased risk of ESRD in patients with lupus who developed subsequent DM [12]. Such comparisons, however, can be illusive and non-specific because NDRD is constituted of heterogeneous etiologies with distinct pathophysiology which may variably affect the risks of ESRD and mortality.

Given the scarcity of information regarding the prognosis of patients with DMN in comparison with NDRD, we conducted a retrospective observational study based on a prior cohort of patients with renal-biopsy kidney diseases. Our goals were to explore differential risks and predictors of ESRD and all-cause mortality between patients with biopsy-proved DMN and those with isolated NDRD, specifically crescentic GN and LN.

2. Materials and methods

2.1. Study populations and data collection

This retrospective observational study was approved by the Research Ethics Committee of National Taiwan University Hospital (No. 200810046R). This study was performed in compliance with the declaration of Helsinki. From 1993 to 2006, a total of 987 patients older than 18 years underwent renal biopsy for two main indications. The first was diabetics with rapid deterioration of renal function, hematuria and severe proteinuria without evidence of retinopathy or neuropathy. The second was non-diabetics with nephrotic syndrome, unexplained renal failure, or less commonly, persistent urinary abnormalities such as subnephrotic proteinuria or hematuria. From this cohort, we had previously reported the clinical outcome in 580 patients with primary minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, and IgA nephropathy [13]. In this study, we further analyzed patients with more severe renal pathologies, focusing on DMN in comparison with contemporary crescentic GN and LN. Briefly, DMN was confirmed by pathological findings of thickening of glomerular basement membrane and diffuse or nodular (Kimmelstiel-Wilson nodules) mesangial expansion [14]. Crescentic GN was defined by a rapid decline in the eGFR of at least 50% within 3 months plus glomerular crescent formation > 50% of glomeruli [15]. LN was diagnosed and classified according to 1995 WHO classification of lupus nephritis [16]. After screening, total 185 eligible patients were included for final analysis (Fig. 1). The baseline characteristics and biochemistry data of these patients were obtained before biopsy. These variables included age, gender, diabetes, hypertension, serum blood urea nitrogen, serum creatinine, serum albumin and hemoglobin. The magnitude of proteinuria was recorded according to the result of urine dipstick test. Mild and severe proteinuria were defined by the result of $\leq 2+$ and $\geq 3+$, respectively. GFR was estimated using the simplified Modification of Diet in Renal Disease (MDRD) formula [17]. Decline of eGFR was presented by calculating the differences of eGFR normalized by intervals between the time at biopsy and the time at the last clinic visit before occurrence of primary endpoints or end of 2015. Users of renin-angiotensin system (RAS) inhibitors and steroids were defined as starting medications before biopsy or during follow-up. The follow-up was continued until 2015 for occurrence of primary endpoints including death and end-stage renal disease requiring long-term dialysis. Patient and renal survivals were determined either through review of medical record or telephone interview. For the renal outcome of some patients, we additionally crosslinked the registry dataset of Taiwan Society of nephrology, which updates data reports of all dialysis patients every 3 months. Patients free of either endpoint at end of 2015 were administratively censored.

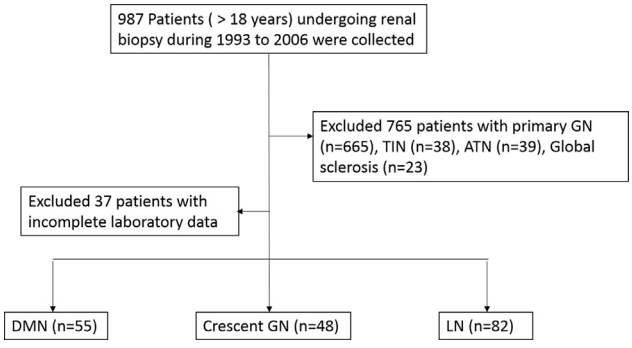

Fig. 1 – Flowchart of the three groups of participants in the cohort. DMN, diabetic nephropathy; LN, lupus nephritis; crescent glomerulonephritis (GN).

2.2. Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics for Windows, version 22.0.0 (IBM Corp., Armonk, NY, USA) and Stata/SE for Windows, version 14 (StataCorp, LP, College Station, TX, USA). Continuous variables were expressed as mean ± SD or median (interquartile range). These variables were analyzed with the one-way analysis of variance (ANOVA) or the Kruskal–Wallis test (non-parametric equivalent of one-way ANOVA) followed by pairwise *post-hoc* comparisons between groups. Categorical variables were presented as percentages and calculated with the chi-square test. Statistically significant was defined as two-sided P value < 0.05. Multivariate Cox proportional hazards models were used to identify independent predictors for time to all-cause mortality. Variables with a P value < 0.05 in univariate analysis were selected for final Cox's multivariate analyses. Because the risk of ESRD could be confounded by the competing risk of death, we constructed a competing risk regression model that treated death as the competing risk for ESRD [18]. The corresponding results were presented by sub-hazards ratio (SubHR). Survival analyses of time to death and ESRD were performed using Kaplan–Meier estimates of survival curves with log-rank testing.

3. Results

3.1. Demographic characteristics and laboratory data

A total of 185 patients entered into the final analysis. The pathological distributions were: DMN (n = 55), class I (0%), class IIa (3.3%), class IIb (3.3%), class III (29.5%), class IV (63.9%); Crescentic GN (n = 48), immune-complex type 45.8% (excluding LN), pauci-immune type 54.2%; LN (n = 82), class I (1.2%), class II (3.7%), class III (14.6%), class IV (67.1%), class V (12.2%), and class VI (1.2%). The median follow-up period was 8.3 (interquartile range = 11.5) years. As shown in Table 1, all baseline demographic characteristics and laboratory data were significantly different among the 3 groups. Patients with LN were mostly female (74.4%) and much younger than patients in the other two groups. Patients with crescentic GN had the highest mean blood urea nitrogen and serum creatinine levels as well as the lowest mean hemoglobin level. Patients with LN showed the highest percentage of severe proteinuria (76.8%) and the lowest mean serum albumin level. More patients in the DMN group received RAS inhibitors therapy (54.5%) while more LN patients received steroid treatment (81.7%).

Crude rate of all-cause mortality before ESRD was not different between the 3 groups, but after ESRD, the DMN and

Table 1 – Baseline demographic characteristics and laboratory data in patients with different types of renal pathology.

	DMN (n = 55)	Crescentic GN (n = 48)	LN (n = 82)	p value
Demographic characteristics				
Age, years	52.4 ± 11.7*	53.2 ± 17.7$^{\#}$	36.5 ± 14.5$^{*,\#}$	<0.001[a]
≧65 years, n (%)	11 (20.0)*	15 (31.3)$^{\#}$	2 (2.4)$^{*,\#}$	<0.001[b]
Male, n (%)	33 (60.0)*	25 (52.1)$^{\#}$	21 (25.6)$^{*,\#}$	<0.001[b]
Diabetes, n (%)	55 (100)$^{*\$}$	1 (2.1)$^{\$}$	1 (1.2)*	<0.001[b]
Hypertension, n (%)	49 (89.1)$^{*\$}$	27 (56.3)$^{\$}$	39 (47.6)*	<0.001[b]
Laboratory data				
BUN, mg/dl	48.5 ± 29.0$^{\$}$	68.4 ± 32.7$^{\#,\$}$	42.7 ± 28.6$^{\#}$	<0.001[a]
Hemoglobin, g/dl	9.8 ± 2.2$^{\$}$	8.6 ± 1.5$^{\#,\$}$	10.2 ± 2.0$^{\#}$	<0.001[c]
Albumin, g/dl	3.1 ± 0.6*	3.1 ± 0.6$^{\#}$	2.6 ± 0.7$^{*,\#}$	<0.001[c]
Creatinine, mg/dl	3.5 ± 2.7$^{*\$}$	6.0 ± 3.6$^{\#,\$}$	2.4 ± 2.2$^{*,\#}$	<0.001[a]
eGFR, ml/min/1.73 m^2	32.4 ± 26.6$^{*\$}$	16.9 ± 17.5$^{\#,\$}$	52.5 ± 36.7$^{*,\#}$	<0.001[a]
≧90, n (%)	1 (1.8)*	1 (2.1)$^{\#}$	14 (17.1)$^{*,\#}$	<0.001[b]
60–89, n (%)	3 (5.5)*	1 (2.1)$^{\#}$	17 (20.7)$^{*,\#}$	<0.001[b]
45–59, n (%)	11 (20.0)$^{*\$}$	2 (4.2)$^{\#,\$}$	9 (11.0)$^{*,\#}$	<0.001[b]
30–44, n (%)	11 (20.0)$^{\$}$	2 (4.2)$^{\#,\$}$	16 (19.5)$^{\#}$	<0.001[b]
15–29, n (%)	12 (21.8)*	9 (18.8)	12 (14.6)*	<0.001[b]
<15, n (%)	17 (30.9)$^{*,\$}$	33 (68.8)$^{\#,\$}$	14 (17.1)$^{*,\#}$	<0.001[b]
Proteinuria				
mild (≦2 +), n (%)	19 (34.5)	21 (43.8)$^{\#}$	19 (23.2)$^{\#}$	0.046[b]
severe (≧3 +), n (%)	36 (65.5)	27 (56.3)$^{\#}$	63 (76.8)$^{\#}$	0.046[b]
Medications				
RAS inhibitors, n (%)	30 (54.5)$^{*,\$}$	3 (6.3)$^{\#,\$}$	16 (19.5)$^{*,\#}$	<0.001[b]
Steroid, n (%)	2 (3.6)$^{*,\$}$	27 (14.6)$^{\#,\$}$	67 (81.7)$^{*,\#}$	<0.001[b]

Abbreviation: LN, lupus nephritis; DMN, diabetic nephropathy; GN, glomerulonephritis; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; RAS, renin-angiotensin system

[a] Kruskal-Wallis H Test.

[b] χ^2.

[c] ANOVA.

$^{*, \#, \$}$ $p < 0.05$.

Table 2 – Crude rates of all-cause mortality and ESRD.

	DMN (n = 55)	Crescentic GN (n = 48)	LN (n = 82)	p value
Mortality before ESRD, n (%)	8 (14.5)	9 (18.8)	15 (18.3)	0.811[a]
Cause of death, n (%)				
Cardiovascular-related	2 (25.0)	0 (0)	2 (13.3)	0.296[a]
Infection-related	0 (0)[*]	1 (11.1)	7 (46.7)[*]	0.025[a]
Other etiology or unclear	6 (75.0)	8 (88.9)[#]	6 (40.0)[#]	0.040[a]
Mortality after ESRD, n (%)	21 (38.2)[*]	14 (29.2)[#]	8 (9.8)[*,#]	<0.001[a]
Cause of death, n (%)				
Cardiovascular-related	4 (19.0)	0 (0)	0 (0)	0.099[a]
Infection-related	2 (9.5)[*]	3 (21.4)	5 (62.5)[*]	0.010[a]
Other etiology	10 (47.6)	8 (57.1)	3 (37.5)	0.667[a]
Unclear	5 (23.8)	3 (21.4)	0 (0)	0.320[a]
ESRD, n (%)	36 (65.5)[*]	32 (66.7)[#]	27 (32.9)[*,#]	<0.001[a]

Abbreviation: LN, lupus nephritis; DMN, diabetic nephropathy; GN, glomerulonephritis; ESRD, end-stage renal disease
[a] χ^2.
[*,#] $p < 0.05$.

crescentic GN groups exhibited higher risks of mortality, compared with the LN counterparts (Table 2). Most mortality of the LN patients was infection-related which was in sharp contrast to the other groups. Crude rates of ESRD were higher in the DMN and crescentic GN groups than in the LN patients (65.5%, 66.7% vs. 32.9%, $p < 0.001$). There was no difference in the rate of eGFR decline between the 3 groups. Interestingly, the eGFR decline rate of the deceased patients were significantly higher than that of the non-ESRD cases in both the DMN (10.1 vs. 0.2 ml/min, $p < 0.001$) and the LN (2.5 vs. 0.1 ml/min, $p = 0.01$) groups. (Supplementary Table S1).

In the original cohort of 987 patients, our Kaplan–Meier analysis for time to ESRD as of 2008 showed that patients with DMN and crescentic GN fared the worst among various renal pathologies which included LN (Supplementary Fig. S1). In this study, we extended the survival analysis till 2015, focusing on the three groups, and found that patients with DMN and crescentic GN developed ESRD more rapidly than the LN counterpart over a median time frame of 8.3 years (Fig. 2). Consistent with this notion, univariate analyses with Cox proportional hazards models found that both DMN and crescentic GN groups compared to the LN group displayed an increased likelihood of progression to ESRD (Table 3). Nevertheless, when the covariates of baseline eGFR and age were included in the final model, only DMN but not crescentic GN compared to LN was associated with an increased risk of ESRD. Additional risk factors of ESRD included lower basal eGFR and hemoglobin levels, as well as severe baseline proteinuria.

To assess the impact of distinct renal pathologies on the hard endpoint of all-cause mortality, a Kaplan–Meier survival plot was generated to unveil any differential risk of death among the 3 groups. We observed that the LN group fared the best, whereas the DMN group performed the worse especially during the later phase of follow-up (Fig. 3). Nonetheless, when multiple risk factors were taken into account in the Cox proportional hazards models, only old age (≧ 65 years) and a lower basal serum albumin level remained independent risk factors of all-cause mortality (Table 4).

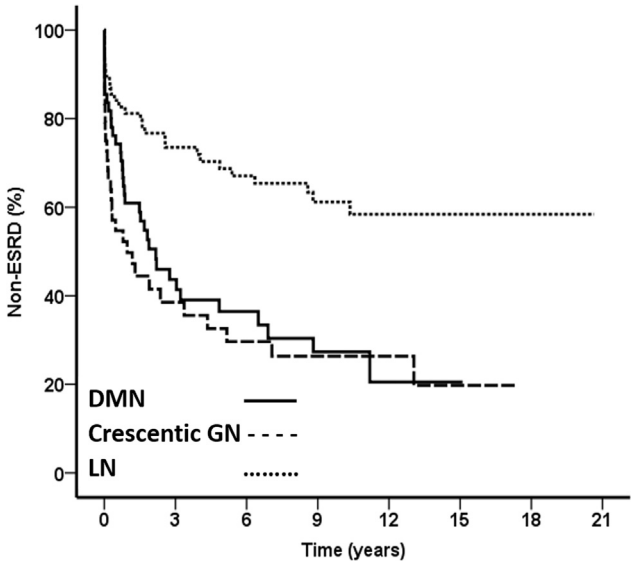

Fig. 2 – Kaplan–Meier survival curve: time to ESRD in patients with DMN, crescentic GN, and LN (Log Rank test $p < 0.001$).

Fig. 4 illustrates the overall distribution of clinical outcomes in the 3 groups. Nearly 60% (58.6%) of patients with LN were alive, and more than one-third (35.4%) remained alive and dialysis-free.

More than half of the patients (52.7%) in the DMN group had died, either before or after ESRD, and 14.5% remained alive and dialysis-free. Nearly half of the patients (48%) in the crescentic GN group had died, and 12.5% remained alive and dialysis-free.

4. Discussion

In this study, we demonstrate that patients with biopsy-proved DMN but not crescentic GN exhibit a higher risk of

Table 3 – Risk of ESRD after adjusting for competing mortality.

	Univariate analysis		Multivariate analysis	
	Sub-HR (95% CI)	p value	Sub-HR (95% CI)	p value
Base model				
DMN vs. LN	2.564 (1.569–4.190)	<0.001	2.421 (1.426–4.110)	0.001
Crescentic GN vs. LN	2.896 (1.715–4.890)	<0.001	2.550 (1.445–4.501)	0.001
Hypertension (yes vs. no)	2.888 (1.773–4.705)	<0.001	2.185 (1.268–3.765)	0.005
Hemoglobin, g/dl	0.775 (0.698–0.861)	<0.001	0.775 (0.699–0.860)	<0.001
Proteinuria (severe vs. mild)	1.817 (1.119–2.950)	0.016	2.310 (1.356–3.935)	0.002
Final model				
DMN vs. LN	2.564 (1.569–4.190)	<0.001	1.918 (1.129–3.260)	0.016
Crescentic GN vs. LN	2.896 (1.715–4.890)	<0.001	1.258 (0.637–2.483)	0.509
Age (≧65 vs. < 65)	1.217 (0.671–2.206)	0.518	0.895 (0.473–1.693)	0.733
Hypertension (yes vs. no)	2.888 (1.773–4.705)	<0.001	1.594 (0.896–2.835)	0.113
Hemoglobin, g/dl	0.775 (0.698–0.861)	<0.001	0.850 (0.756–0.956)	0.007
eGFR, ml/min/1.73 m^2	0.959 (0.942–0.976)	<0.001	0.965 (0.942–0.989)	0.004
Proteinuria (severe vs. mild)	1.817 (1.119–2.950)	0.016	1.967 (1.155–3.352)	0.013

Note: Final model, including age and eGFR.
Abbreviation: LN, lupus nephritis; DMN, diabetic nephropathy; GN, glomerulonephritis; eGFR, estimated glomerular filtration rate.

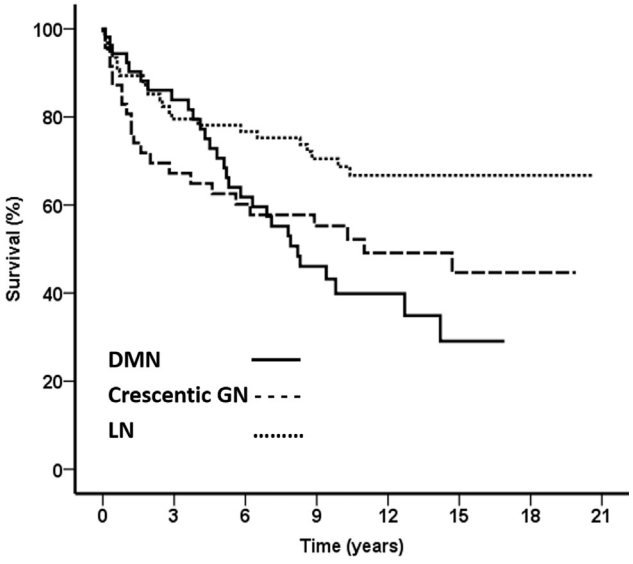

Fig. 3 – Kaplan–Meier survival curve: time to mortality in patients with DMN, crescentic GN, and LN (Log Rank test, p = 0.012).

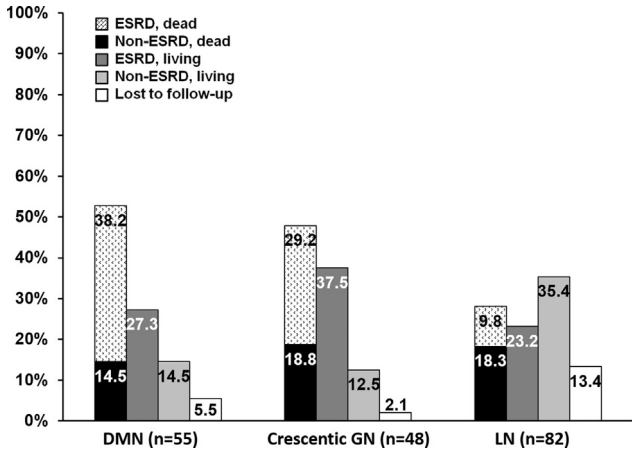

Fig. 4 – Distribution of outcomes in patients with DMN, crescentic GN and LN.

ESRD than their concurrent LN counterpart after long-term follow-up (Table 3). It could be argued that the worse renal outcome of DMN as opposed to LN was due to differences in baseline demographic characteristics and laboratory data between these 2 diseases (Table 1). In an international cohort of systemic lupus, 10-year incidence of ESRD was 4.3% for overall patients and 10.1% for those who developed nephritis [19]. In contrast, Ritz et al observed that nearly 60% type 2 DM patients with proteinuria developed ESRD in 5-year follow-up [20]. Other study showed that up to 30% of type 2 diabetic

Table 4 – Cox proportional hazards models showing predictors for time to all-cause mortality.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
DMN vs. LN	2.184 (1.260–3.788)	0.005	1.862 (0.962–3.603)	0.065
Crescentic GN vs. LN	1.888 (1.059–3.367)	0.031	1.276 (0.619–2.628)	0.509
Age (≧65 vs. < 65)	3.509 (2.126–5.790)	<0.001	2.957 (1.720–5.083)	<0.001
Albumin, g/dl	0.884 (0.650–1.204)	0.435	0.696 (0.487–0.994)	0.046
eGFR, ml/min/1.73 m^2	0.989 (0.980–0.998)	0.014	0.990 (0.980–1.001)	0.068

Abbreviation: LN, lupus nephritis; DMN, diabetic nephropathy; GN, glomerulonephritis; eGFR, estimated glomerular filtration rate.

patients progressed to ESRD within 6-year follow-up even under the coverage of RAS inhibitors [21]. Although the diagnosis of DMN was not biopsy-proved and the duration of follow-up was short, these data support our observation that DMN patients displayed a higher risk of ESRD than LN counterparts. Importantly, DMN vs. LN remains an independent predictor of ESRD even after adjusting for other risk factors and taking into account the competing risk of death (Table 3).

The differential renal outcomes between DMN and LN patients could be related in part to the availability of effective immune therapy for LN but not DMN [22]. Indeed, current strategies to treat DMN rely mostly on strict glycemic control and blood pressure reduction with RAS inhibitors [23,24]. None of these methods, however, can specifically target underlying molecular processes responsible for DMN. The preclinical agents, advanced glycation end products (AGE) inhibitors and protein kinase C (PKC) inhibitors are only effective in attenuateing experimental but not human DMN [25,26]. Some newer therapeutic agents such as glucagon-like peptide 1 analogues and dipeptidyl peptidase-4 inhibitors have been shown to slow the progression of human DMN independently of their hypoglycemic effects [27,28]. While these novel agents show promising results for patients with DMN, there remains room for improvement in renal prognosis.

Pauci-immune GN was more common than immune-complex GN in our crescentic GN group (54.2% vs. 45.8%). Most pauci-immune GN is ANCA-associated and the outcomes of which have improved significantly over the past decades. Robson et al. reported that 14% of ANCA-associated GN progressed to ESRD after an average 7.1-years follow-up [29]. In this study, the initial Kaplan–Meier analysis showed a higher cumulative incidence of ESRD in crescentic GN compared to LN. Nevertheless, the difference in ESRD risks between the 2 groups disappeared after adjusting for demographics, comorbidities, initial eGFR, and competing mortality. These indicate that the strikingly high rate of ESRD in crescentic GN patients was due to more severe renal failure at entry, an average eGFR of 16.9 ml/min/1.73 m^2, which has been considered by far the most powerful predictor of ESRD in ANCA-associated vasculitis [30].

Patients with LN exhibited the lowest risk of overall death among the 3 groups despite the fact that they were more likely to die of infection-related complications, compared with the DMN group (Table 2). The lower all-cause mortality seen in our LN patients could be partially related to their lower likelihood of ESRD onset. This assumption was consistent with a previous study which showed LN patients with ESRD displayed a 4-fold excess in the risk of death compared with LN patients without ESRD [5]. Comparisons between renal pathologies, e.g., DMN vs. LN; crescentic GN vs. LN, was not an independent predictor in the final multivariate model of all-cause mortality (Table 4). Patients with hypertension had a higher risk of mortality which was consistent with previous reports in CKD [31,32]. Another risk factor in association with mortality, particularly that from cardiac events, was hypoalbuminemia, and the validity of which has been demonstrated in numerous studies in dialysis patients and some studies in patients with non-dialysis-dependent CKD [33,34].

Interestingly, the eGFR decline rate of the deceased patients was significantly higher than that of the non-ESRD cases in both the DMN and the LN groups. These findings were more significant in the DMN group which had more risk factors of CKD progression such as old age and hypertension. In addition, the leading cause of mortality in our DMN group was cardiovascular event. CKD has been proved as an equivalent risk factor of cardiovascular disease and the risk increases exponentially with declining kidney function [35]. Patients with rapid decline of eGFR are prone to ESRD development and a large cohort study reported a higher risk of cardiovascular mortality in patients with sustained decrease in eGFR below 60 ml/min/1.73 m^2 [36]. Another cohort study, in which around 30% of patients were diabetic, had directly shown that a higher rate of eGFR decline was closely associated with mortality in patients with CKD [37]. As a whole, the association between high eGFR decline rate and mortality is justifiable because they share multiple common risk factor such as male patients, old age, hypertension, cardiovascular disease and low baseline eGFR [38].

The strength of this study is that all 3 disease entities, i.e., DMN, crescentic GN, and LN, were confirmed by pathologies and the potential bias arising from inaccurate diagnoses can be excluded. There are some limitations to this study. First, due to retrospective nature, a sizable number of LN patients were lost to follow-up, and a portion of DMN patients did not have accessible cause of death. These might lead to misestimation of actual risks of ESRD or death. Second, the criteria for renal biopsy was not protocol-based, it is possible that patients with more severe renal manifestations were selected and those with milder disease were under-represented. As a result, extrapolation of our results to clinical applications should be made cautiously.

In conclusion, this study demonstrated that during a median follow-up period of 8.3 years patients with biopsy-proved DMN, but not crescentic GN, exhibited a greater risk of ESRD than contemporary LN counterparts. These results reiterate the status quo of grave renal prognosis in patients with overt DMN above CKD stage 3b, and underscore the importance of more meticulous follow-up so that best possible therapeutic strategies can be implemented in a timelier manner.

Acknowledgements

The authors thank the physicians and patients who participated in the study.

Funding

This study was supported in part by grants from the National Taiwan University Hospital (105-003126), the Ta-Tung Kidney Foundation, and the Mrs Hsiu-Chin Lee Kidney Research Fund, Taipei, Taiwan.

Contributions

Research idea and study design: YMC, YHC; data acquisition and analysis: YMC; pathology review: WCL; YHC wrote the first draft of the manuscript. YMC, WCL reviewed and edited

the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors have declared that no conflict of interest exists.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.01.014.

REFERENCES

[1] de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA 2011;305:2532–9.
[2] Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA 2009;301:2129–40.
[3] Rathmann W, Giani G. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:2568–9. author reply 9.
[4] Foley RN, Murray AM, Li S, Herzog CA, McBean AM, Eggers PW, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. J Am Soc Nephrol: JASN 2005;16:489–95.
[5] Yap DY, Tang CS, Ma MK, Lam MF, Chan TM. Survival analysis and causes of mortality in patients with lupus nephritis. Nephrol Dial, Transplan: Off Publ Eur Dial Transp Assoc - Eur Renal Assoc 2012;27:3248–54.
[6] Koyama A, Yamagata K, Makino H, Arimura Y, Wada T, Nitta K, et al. A nationwide survey of rapidly progressive glomerulonephritis in Japan: etiology, prognosis and treatment diversity. Clin Exp Nephrol 2009;13:633–50.
[7] Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes Care 2005;28:164–76.
[8] Gonzalez Suarez ML, Thomas DB, Barisoni L, Fornoni A. Diabetic nephropathy: is it time yet for routine kidney biopsy? World J Diabetes 2013;4:245–55.
[9] Byun JM, Lee CH, Lee SR, Moon JY, Lee SH, Lee TW, et al. Renal outcomes and clinical course of nondiabetic renal diseases in patients with type 2 diabetes. Kor J Internal Med 2013;28:565–72.
[10] Wong TY, Choi PC, Szeto CC, To KF, Tang NL, Chan AW, et al. Renal outcome in type 2 diabetic patients with or without coexisting nondiabetic nephropathies. Diabetes Care 2002;25:900–5.
[11] Iwai T, Miyazaki M, Yamada G, Nakayama M, Yamamoto T, Satoh M, et al. Diabetes mellitus as a cause or comorbidity of chronic kidney disease and its outcomes: the Gonryo study. Clin Exp Nephrol 2017.
[12] Jiang MY, Hwang JC, Feng IJ. Impact of diabetes mellitus on the risk of end-stage renal disease in patients with systemic lupus erythematosus. Sci Rep 2018;8:6008.
[13] Chou YH, Lien YC, Hu FC, Lin WC, Kao CC, Lai CF, et al. Clinical outcomes and predictors for ESRD and mortality in primary GN. Clin J Am Soc Nephrol: CJASN 2012;7:1401–8.
[14] Tervaert TW, Mooyaart AL, Amann K, Cohen AH, Cook HT, Drachenberg CB, et al. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol: JASN 2010;21:556–63.
[15] Couser WG. Rapidly progressive glomerulonephritis: classification, pathogenetic mechanisms, and therapy. Am J Kidney Dis: Off J Natl Kidney Found 1988;11:449–64.
[16] Wilhelmus S, Alpers CE, Cook HT, Ferrario F, Fogo AB, Haas M, et al. The revisited classification of GN in SLE at 10 Years: time to re-evaluate histopathologic lesions. J Am Soc Nephrol: JASN 2015;26:2938–46.
[17] Levey AS, Greene T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from serum creatinine. J Am Soc Nephrol 2000;11:155A.
[18] Grams ME, Coresh J, Segev DL, Kucirka LM, Tighiouart H, Sarnak MJ. Vascular disease, ESRD, and death: interpreting competing risk analyses. Clin J Am Soc Nephrol: CJASN 2012;7:1606–14.
[19] Hanly JG, O'Keeffe AG, Su L, Urowitz MB, Romero-Diaz J, Gordon C, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. Rheumatology (Oxford, England) 2016;55:252–62.
[20] Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. New Engl J Med 1999;341:1127–33.
[21] Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. New Engl J Med 2001;345:851–60.
[22] Ghaderian SB, Hayati F, Shayanpour S, Beladi Mousavi SS. Diabetes and end-stage renal disease; a review article on new concepts. J Renal Injury Prevent 2015;4:28–33.
[23] Zoungas S, de Galan BE, Ninomiya T, Grobbee D, Hamet P, Heller S, et al. Combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes: new results from the ADVANCE trial. Diabetes Care 2009;32:2068–74.
[24] Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. New Engl J Med 2008;358:580–91.
[25] Fineberg D, Jandeleit-Dahm KA, Cooper ME. Diabetic nephropathy: diagnosis and treatment. Nat Rev Endocrinol 2013;9:713–23.
[26] Kelly DJ, Zhang Y, Hepper C, Gow RM, Jaworski K, Kemp BE, et al. Protein kinase C beta inhibition attenuates the progression of experimental diabetic nephropathy in the presence of continued hypertension. Diabetes 2003;52:512–8.
[27] Panchapakesan U, Pollock CA. DPP-4 inhibitors-renoprotection in diabetic nephropathy? Diabetes 2014;63:1829–30.
[28] Fioretto P, Zambon A, Rossato M, Busetto L, Vettor R. SGLT2 inhibitors and the diabetic kidney. Diabetes Care 2016;39 (Suppl 2):S165–71.
[29] Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Hoglund P, et al. Damage in the anca-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials. Ann Rheum Dis 2015;74:177–84.
[30] Moiseev S, Novikov P, Jayne D, Mukhin N. End-stage renal disease in ANCA-associated vasculitis. Nephrol Dial, Transplant: Off Publ Eur Dial Transpl Assoc - Eur Renal Assoc 2017;32:248–53.
[31] Singh S, Zhou XJ, Ahn C, Saxena R. A retrospective analysis of clinical presentation of lupus nephritis. Am J Med Sci 2011;342:467–73.
[32] Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol: JASN 2006;17:2034–47.
[33] Menon V, Greene T, Wang X, Pereira AA, Marcovina SM, Beck GJ, et al. C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. Kidney Int 2005;68:766–72.

[34] Friedman AN, Fadem SZ. Reassessment of albumin as a nutritional marker in kidney disease. J Am Soc Nephrol: JASN 2010;21:223–30.
[35] Briasoulis A, Bakris GL. Chronic kidney disease as a coronary artery disease risk equivalent. Curr Cardiol Rep 2013;15:340.
[36] Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. New Engl J Med 2004;351:1296–305.
[37] Perkins RM, Bucaloiu ID, Kirchner HL, Ashouian N, Hartle JE, Yahya T. GFR decline and mortality risk among patients with chronic kidney disease. Clin J Am Soc Nephrol: CJASN 2011;6:1879–86.
[38] Zoppini G, Targher G, Chonchol M, Ortalda V, Negri C, Stoico V, et al. Predictors of estimated GFR decline in patients with type 2 diabetes and preserved kidney function. Clin J Am Soc Nephrol: CJASN 2012;7:401–8.