Clinicopathological features and prognosis in patients with idiopathic membranous nephropathy with hypertension

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Abstract. The present study analyzed the clinicopathological features and prognosis in patients with idiopathic membranous nephropathy (IMN) with hypertension. In the hypertension group, significant differences were found in the age, hypertension history, systolic blood pressure, diastolic blood pressure (DBP), mean arterial pressure, albumin, serum creatinine, low-density lipoprotein, 24 h urine protein levels, calculated estimated glomerular filtration rate (e-GFR), glomerular sclerosis, segmental sclerosis, ischemic sclerosis, interstitial fibrosis, tubular atrophy and vascular lesion compared with the non-hypertension group (P<0.05). The average follow-up time was 35.70 months (5.10-103.77 months). In total, 54 patients reported a 50% decline in e-GFR, eight patients reported progression of disease to end-stage renal disease (ESRD) and nine cases of mortality were reported. Survival analysis results suggested that patients with hypertension had a lower cumulative renal survival rate than those without hypertension (P=0.034). Multivariate Cox hazards regression analysis results suggested that DBP [hazard ratio (H), 5.160; CI, 0.865-0.989; P=0.023], age (H, 5.483; CI, 1.008-1.142; P=0.028), sex (H, 5.680; CI, 0.031-0.714; P=0.017), serum creatinine (H, 20.920; CI, 1.035-1.089; P<0.001), uric acid (H, 4.783; CI, 0.982-0.999; P=0.029), 24 h urine protein (H, 6.318; CI, 1.079-1.850; P=0.012), e-GFR (H, 4.008; CI, 1.001-1.062; P=0.045) and glomerular sclerosis (H, 8.722; CI, 1.860-21.559; P=0.003), segmental sclerosis (H, 7.737; CI, 7.770-13.219; P=0.005), percentage of ischemic sclerosis (H, 4.729; CI, 1.444-11.945; P=0.030), crescents (H, 5.938; CI, 0.003-0.526; P=0.015), interstitial fibrosis and tubular atrophy (H, 8.128; CI, 0.005-1.052; P=0.043), and vascular lesion (H, 4.049; CI, 1.030-9.766; P=0.044) were risk factors for the development of IMN into ESRD. The results suggested that DBP may be an independent risk factor for the development of IMN with hypertension.

Introduction

Idiopathic membranous nephropathy (IMN) is an organ-specific autoimmune inflammatory disease of the kidneys (1). IMN is the primary glomerular disease affecting adults >60 years of age and is a common cause of adult-onset nephropathy syndrome (NS)(1-3). IMN is characterized by thickening of the basement membrane (4) with subepithelial deposits of immune complexes mostly composed of immunoglobulin (Ig)G and the complement protein C3 (5,6), which are detectable using immunofluorescence or electron microscopy. Clinical presentations of IMN vary from subnephropathy range proteinuria to NS with heavy proteinuria, as well as hypertension, renal insufficiency and microscopic hematuria (7). Previous studies of the natural history of IMN have reported that 5-30 and 40% of patients with IMN have spontaneous complete or partial remission after 5 years, respectively, whereas IMN in 30-40% of patients progresses to end-stage renal disease (ESRD) within 5-15 years (8,9). Among hospitalized patients with primary glomerular nephropathy, a decreasing trend in IgA nephropathy and an increasing trend of IMN were reported by some researchers (10). Globally, hypertension acts as one of the leading etiologies for chronic kidney disease (CKD) (11). Moreover, as some patients have CKD due to high blood pressure, hypertension is considered secondary to renal diseases (12). A previous study reported that high blood pressure during renal biopsy is a poor prognostic factor of patients with IMN (13). The association between IMN and hypertension is still not fully understood up to now. The present study hypothesized that hypertension worsens IMN prognosis and serves a central role in IMN disease progression. The present study investigated whether hypertension was associated with clinical parameters in IMN and examined IMN prognosis. Therefore, these clinicians can monitor and treat patients with PMN who may be inclined to hypertension, as to reduce occurrence of patients with PMN with hypertension and delay disease progression.

Materials and methods

Study population. The present retrospective study recruited patients with IMN from The First Affiliated Hospital of Nanchang University (Nanchang, China) between January 2010 and June 2018. NS was defined according to the standard criteria used in Japan (14): i) Urine protein excretion (3.5 g/day); ii) serum
Hypertension was defined as physician using a
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ysician using a
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IgG fixed using acetone at 4˚C for 10 min and washed three times
frozen as 5 µm sections, dried at room temperature for 30 min,
Histopathologic parameters.
In addition, 24 h urine protein was measured.
and was expressed as ml
CKD-EPI creatinine equation recommended by the KDIGO
220 patients with IMN. The e-GFR was calculated using the
glomerular filtration rate (e-GFR) were collected from
low-density lipoprotein (LDL) and calculated estimated
protein (TP), albumin, serum creatinine (Scr), uric acid (UA),
sex, course of the disease, edema, hypertension history, SBP ,
Clinical parameters.
Nanchang University
who underwent renal biopsy at
IMN and hypertension (hypertension group) and 120 patients
seated position. The present study examined 100 patients with
applied to the right arm at heart level after ≥5 min of rest in a
mercury sphygmomanometer and an appropriately sized cuff
was 35.70 months.

Study design. The enrolled patients were divided into two
groups based on the criteria for hypertension: Hypertension
and non-hypertension groups. Hypertension was defined as
average systolic blood pressure (SBP) ≥140 mmHg or average
diastolic blood pressure (DBP) ≥90 mmHg (21). Patients
with a history of hypertension whose BP was not above the
mentioned level following hospitalization with antihyper-
tensive drugs were also classified under the hypertension
group. BP was measured by an experienced physician using a
marchy sphygmomanometer and an appropriately sized cuff
applied to the right arm at heart level after ≥5 min of rest in a
seated position. The present study examined 100 patients with
IMN and hypertension (hypertension group) and 120 patients
with IMN without hypertension (non-hypertension group)
who underwent renal biopsy at The First Affiliated Hospital of
Nanchang University.

Clinical parameters. Basic demographic data included age,
sex, course of the disease, edema, hypertension history, SBP,
DBP and mean arterial pressure (MAP). The present study
measured red blood cell count (RBC), hemoglobin (Hb), total
protein (TP), albumin, serum creatinine (Ser), uric acid (UA),
potassium (K), calcium (Ca), phosphorus (P), triglycerides
(TG), total cholesterol (TC), high-density lipoprotein (HDL),
low-density lipoprotein (LDL) and calculated estimated
glomerular filtration rate (e-GFR) were collected from
220 patients with IMN. The e-GFR was calculated using the
CKD-EPI creatinine equation recommended by the KDIGO
and was expressed as ml/min/1.73 m² of body surface area (22).
In addition, 24 h urine protein was measured.

Histopathologic parameters. The kidney biopsy specimens
frozen as 5 µm sections, dried at room temperature for 30 min,
fixed using acetone at 4˚C for 10 min and washed three times
using PBS. Fluorescein labeled antibody [Rabbit Anti Human
IgG/FITC; cat. no. GF020229; 1:80; Rabbit Anti Human
IgA/FITC; cat. no. GF020429; 1:40; Rabbit Anti Human
IgM/FITC cat. no. GF020329; 1:40; Rabbit Anti Human
Fibrinogen/FITC; cat. no. GF01129; 1:40; Rabbit Anti Human
Clq Complement/FITC; cat. no. GF025429; 1:40; Rabbit Anti
Human C3c Complement/FITC; cat. no. GF020129; 1:20;
all, Gene Tech (Shanghai) Co., Ltd.] was used and incubate
with 37˚C for 30 min. Tissues were watched with PBS three
times and sealed using glycerin. Tissues were then observed
using fluorescence microscope (magnification, x100; eyepiece,
magnification, x10; objective magnification, x10). Renal
biopsy specimens including ≥10 glomeruli were analyzed.
All renal biopsies were processed according to the stan-
dard techniques of light microscopy (magnification, x400),
immunofluorescence microscopy (magnification, x400) and
electron microscopy (magnification, x2,000) (7). To confirm
the pathology, all samples were reviewed by two pathologists
in The First Affiliated Hospital of Nanchang University.
The following parameters were assessed by histopathology:
Glomerular sclerosis, segmental sclerosis, ischemic sclerosis,
crescents, mesangial cells and matrix hyperplasia. In addition,
mesangial hypercellularity, interstitial fibrosis, tubular atrophy
and vascular lesions were measured. These parameters was
analyzed using SPSS software (version 22.0; IBM Corp.).

End-point of the study. Disease progression was defined as
a ≥50% decline in the baseline e-GFR, doubling of Scr levels,
diagnosis of ESRD and requiring renal replacement therapy
after follow-up (23), including hemodialysis, peritoneal dialysis
and kidney transplant, and death. The present study reviewed
the medical record of each patient retrospectively from the
date of renal biopsy to death, the development of ESRD or the
last clinical visit (November 15, 2018). The average follow-up
was 35.70 months.

Statistical analysis. Statistical analysis was performed using
SPSS software (version 22.0; IBM Corp.). Continuous
data are presented as the mean ± SD, whereas categorical data
are presented as frequencies and percentages. Differences in
continuous variables between the two groups were assessed
using independent t-tests. A comparison of univariate
predictors of clinical outcomes between the groups was
performed using χ² test for categorical variables. The renal
progression-free rates were calculated using the Kaplan-Meier
analysis and comparisons between the groups were performed
using the log-rank test. Multivariate Cox proportional hazard
regression analysis was performed to determine independent
variables associated with the renal outcomes. The results are
presented as hazard ratio (H) with a 95% CI. P<0.05 was
considered to indicate a statistically significant difference.

Results

Comparison of demographic and laboratory parameters
between the two groups. IMN is known to be a common cause
of primary glomerulopathy (10). The present study examined
100 patients with IMN associated with hypertension (hyperten-
sion group) and 120 patients with IMN without hypertension
(non-hypertension group) that underwent renal biopsy at The
First Affiliated Hospital of Nanchang University. In the present
study, the prevalence of hypertension was 45.45% among the
patients. Baseline characteristics of patients with and without hypertension are summarized in Table I. Among the patients, 137 (62.2%) were male and 83 (37.7%) were female, with a male to female ratio of 1.65:1. The mean age of patients with IMN was 51.21±12.78 years. A significant difference was found in the age (P=0.001), hypertension history (P<0.0001), SBP (P<0.0001), DBP (P<0.0001), MAP (P<0.0001), albumin (P=0.046), Scr (P=0.001), LDL (P=0.018), 24 h urine protein (P=0.028) and e-GFR (P=0.013) between the groups with and without hypertension. There were no significant differences in the following parameters between the two groups: Sex, course of the disease, edema, RBC, Hb, TP, UA, K, Ca, P, TG, TC and HDL.

**Comparison of pathological parameters between the two groups.** Analysis of pathological parameters between the hypertension and non-hypertension groups is shown in Table II. Ischemic sclerosis and vascular lesions were associated with hypertension in IMN. The present univariate analysis results suggested that glomerular sclerosis, segmental sclerosis, ischemic sclerosis, interstitial fibrosis, tubular atrophy and vascular lesions were associated with the primary outcome in patients with IMN and hypertension.

**Survival analysis of cumulative renal survival rate of hypertension and non-hypertension groups, and risk factors associated with patients with IMN and hypertension developing into ESRD.** Follow-up data were available for 220 patients with IMN with and without hypertension. Average observation time was 35.70 months (range, 5.10-103.77 months). In total, 54 patients reported a 50% decline in e-GFR or doubling of Scr levels. During follow-up, in eight patients IMN had progressed...
to ESRD. There were nine cases of mortality and the cause of death was unknown. The renal survival rates in patients with hypertension were significantly reduced compared with patients without hypertension (log-rank test, P=0.034; Fig. 1). The present Cox proportional hazard regression results suggested that DBP may be an independent risk factor for IMN progression (H, 5.160; CI, 0.865-0.989; P=0.023). The present results suggested that age (H, 4.839; CI, 1.008-1.142; P=0.028), sex (H, 5.680; CI, 0.031-0.714; P=0.017), Scr (H, 20.920; CI, 1.035-1.089; P<0.001), UA (H, 4.783; CI, 0.982-0.999; P=0.029), 24 h urine protein (H, 6.318; CI, 1.079-0.1.850; P=0.012) and e-GFR (H, 4.008; CI, 1.001-1.062; P=0.045) were significant and independent risk factors in patients with IMN with hypertension. Glomerular sclerosis (H, 8.722; CI, 1.860-21.559; P=0.003), segmental sclerosis (H, 7.737; CI, 7.770-13.219; P=0.005), percentage of ischemic sclerosis (H, 4.729; CI, 1.444-11.945; P=0.030), crescents (H, 5.938; CI, 0.003-0.526; P=0.015), interstitial fibrosis (H, 8.128; CI, 0.005-1.052; P=0.043), and vascular lesions (H, 4.049; CI, 1.030-9.766; P=0.044) were also identified as significant and independent risk factors in patients with IMN with hypertension (Table III).

**Discussion**

IMN is the most common primary glomerular disease in individuals >60 years old (24). In patients with IMN, one-third of patients with spontaneous remission report progressive

| Parameter                  | HG       | NHG      | T or χ² | P-value |
|----------------------------|----------|----------|---------|---------|
| GS, case (%)               | 31 (14.09) | 33 (15.00) | 0.778   | 0.036   |
| PGS (%)                    | 0.06±0.11 | 0.04±0.09 | -1.32   | 0.188   |
| SS, case (%)               | 3 (1.36)  | 4 (1.82)  | -0.15   | 0.048   |
| PSS (%)                    | 0.004±0.02| 0.004±0.02| -0.08   | 0.939   |
| IS, case (%)               | 27 (12.27)| 28 (12.73)| -0.822  | 0.011   |
| PIS (%)                    | 0.04±0.10 | 0.05±0.13 | 0.14    | 0.886   |
| Crescent, case (%)         | 8 (3.64)  | 7 (3.18)  | -0.65   | 0.515   |
| Percentage of crescents (%)| 0.02±0.08 | 0.004±0.02| -1.56   | 0.122   |
| MC/MAH                     |          |          |         |         |
| 0                          | 15 (6.82) | 19 (8.64) |         |         |
| <25%                       | 60 (27.27)| 81 (36.82)|         |         |
| 25-49%                     | 25 (11.36)| 20 (9.09) |         |         |
| 50-74%                     | 0 (0.00)  | 0 (0.00)  |         |         |
| >75%                       | 0 (0.00)  | 0 (0.00)  |         |         |
| MEH                        |          |          | 5.915   | 0.2     |
| 0                          | 15 (6.82) | 23 (10.45)|         |         |
| <25%                       | 23 (10.45)| 24 (10.91)|         |         |
| 25-49%                     | 52 (23.64)| 69 (31.36)|         |         |
| 50-74%                     | 8 (3.64)  | 2 (0.91)  |         |         |
| >75%                       | 2 (0.91)  | 2 (0.91)  |         |         |
| IF                         |          |          | 5.399   | 0.038   |
| 0                          | 61 (27.73)| 76 (34.55)|         |         |
| <25%                       | 7 (3.18)  | 6 (2.73)  |         |         |
| 25-49%                     | 26 (11.82)| 36 (16.36)|         |         |
| 50-74%                     | 4 (1.82)  | 0 (0.00)  |         |         |
| >75%                       | 2 (0.91)  | 2 (0.91)  |         |         |
| TA                         |          |          | 9.449   | 0.041   |
| 0                          | 18 (8.18) | 25 (11.36)|         |         |
| <25%                       | 20 (9.09) | 29 (13.18)|         |         |
| 25-49%                     | 53 (24.09)| 64 (29.09)|         |         |
| 50-74%                     | 7 (3.18)  | 0 (0.00)  |         |         |
| >75%                       | 2 (0.91)  | 2 (0.91)  |         |         |
| VL                         |          |          | 1.107   | 0.023   |
| Yes                        | 74 (33.64)| 81 (36.82)|         |         |
| No                         | 26 (11.82)| 39 (17.73)|         |         |

* n=220. Data are presented as mean ± SD or percentages (in brackets). HG, hypertension group; NHG, non-hypertension group; GS, glomerular sclerosis; PGS, percentage of GS; SS, segmental sclerosis; PSS, percentage of SS; IS, ischemic sclerosis; PIS, percentage of IS; MC/MAH, mesangial cell and matrix hyperplasia; MEH, mesangial hypercellularity; IF, interstitial fibrosis; TA, tubular atrophy; VL, vascular lesion.
renal failure, whereas the remaining patients report stable renal function (25). Nephritic syndrome, massive proteinuria, hematuria, impaired renal function and hypertension are common in IMN (26). The results from previous studies on IMN prognostic factors are highly variable (12). In addition, whether demographic parameters, laboratory parameters and histological lesions contribute to the improvement of renal function in patients with hypertension is not fully understood.

The present retrospective study investigated the prognosis and risk factors for renal survival in patients with IMN with hypertension. In the present study, the majority of patients with IMN were >40 years. A higher incidence of hypertension among elderly patients compared with adult patients has previously been reported (27). The present results are consistent with the results of the previous studies (28,29). Moreover, the present study identified that Scr, LDL and 24 h urine protein were increased, and serum albumin and e-GFR were decreased in patients with IMN with hypertension. Huh et al (18) reported that low serum albumin levels at the onset of the disease were associated with poor renal prognosis of patients with IMN. Another previous study reported that high levels of Scr at diagnosis are major predictors of the progression of IMN to ESRD (30). Proteinuria has also been used as a major predictor for renal prognosis of IMN in a conventional predictive model (31). Patients with limited proteinuria are deemed to have a better prognosis (31). Previous studies identified lower e‑GFR to be significantly associated with the risk of progression of IMN to ESRD (32,33). The present results suggested that hypertension may be associated with the severity of IMN, which is consistent with results from previous studies. In the majority of studies, hypertension was not indicated to be an independent predictor of MN (34,35). To the best of our knowledge, the present study was the first to identify primary factors for hypertension development in patients with IMN using a retrospective study design, measuring parameters such as uric acid, age and sex (36).

The mechanism of hypertension and disease severity, and whether hypertension can exacerbate kidney disease is not fully understood. The present results suggested that age and sex were statistically significant between the hypertension and non-hypertension groups, which were in line with findings from a previous study (37). Uric acid was previously reported to be independently associated with prevalent CKD and hypertension (36,38). Hypertension can cause nephroangiosclerosis (39). The severity of renal histological lesions, particularly of interstitial fibrosis, glomerular sclerosis and vasculopathy, are considered negative prognostic indicators for IMN (40). The present results suggested that interstitial fibrosis, glomerular sclerosis, vasculopathy and crescents were significantly different between the hypertension and non-hypertension groups.

Table III. Multivariate Cox hazard regression analysis of the disease risk factors and patients with idiopathic membranous nephropathy with hypertension developing into end-stage renal disease.

| Parameter          | B    | SE   | HR   | P-value | Exp (B) | 95.0% CI       |
|--------------------|------|------|------|---------|---------|----------------|
| Age, years         | 0.070| 0.032| 4.839| 0.028   | 1.073   | 1.008 - 1.142  |
| Sex                | -1.899| 0.797| 5.680| 0.017   | 0.150   | 0.031 - 0.714  |
| DBP, mmHg          | -0.078| 0.034| 5.160| 0.023   | 0.925   | 0.865 - 0.989  |
| Scr, µmol/l        | -0.010| 0.004| 4.783| 0.029   | 0.990   | 0.982 - 0.999  |
| UA, µmol/l         | 0.346| 0.138| 20.920| <0.001 | 1.062   | 1.035 - 1.089  |
| 24 h urine protein, g | 0.030| 0.015| 4.008| 0.045   | 1.031   | 1.001 - 1.062  |
| e-GFR              | 1.846| 0.625| 8.722| 0.003   | 6.333   | 1.860 - 21.559 |
| Segmental sclerosis| 6.942| 2.496| 7.737| 0.005   | 1034.718| 7.770 - 13.219 |
| Percentage of IS   | 3.722| 1.711| 4.729| 0.030   | 41.328  | 14.44 - 119.45 |
| Crescents          | -3.286| 1.348| 5.938| 0.015   | 0.037   | 0.003 - 0.526  |
| Interstitial fibrosis| -0.010| 0.013| 8.128| 0.043   | 1.023   | 0.005 - 1.052  |
| Vascular lesion    | 0.010| 0.057| 4.049| 0.044   | 3.172   | 1.030 - 9.766  |

DBP, diastolic blood pressure; Scr, serum creatinine; UA, uric acid; e-GFR, calculated estimated glomerular filtration rate; IS ischemic sclerosis; B, regression coefficient; SE, standard error.

Figure 1. Survival analysis of the cumulative renal survival rate of the hypertension group and the non-hypertension group.
groups. However, other parameters were not statistically significant in the present study, which may be attributed to the small sample size. The present results suggested that the accumulated survival rate was significantly higher in patients with IMN without hypertension compared with patients with hypertension. In the present study, a multivariate Cox proportional hazards regression analysis was performed to investigate the association of DBP with renal outcomes. A previous study showed that patients with IMN suffered from CKD as a result of hypertension, and that hypertension was secondary to renal disease (18). Therefore, monitoring BP during diagnosis in patients with IMN may facilitate prognosis.

The present study had several limitations, such as a small number of patients with IMN, which limited the statistical power of the study. Therefore, future studies with larger sample sizes and longer periods of follow-up are required to investigate the influence of BP in patients with IMN. In addition, the present study did not analyze antibodies against phospholipase A2 receptors and thrombospondin type I domain-containing 7A, which have been suggested to be correlated with IMN disease severity (41). Finally, the primary outcome of MN can be complete and partial remission, including remission of proteinuria (42); however, in the present study, quantitative proteinuria was not followed up at the end-point of the study.

In conclusion, the present results suggested that patients with IMN with hypertension reported worse clinicopathological features and lower cumulative renal survival rate compared with patients without hypertension. The present results suggested that DBP may be an independent risk factor for the development of IMN with hypertension. Early detection and correction of hypertension could help delay the deterioration of renal function and improve prognosis of patients with IMN.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

WL wrote the manuscript. WL, SG and JL collected and analyzed the study data. SG performed the histological examination of the kidney. YW conceived and designed the study, proofread the manuscript and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by The Ethics Committee of The First Affiliated Hospital of Nanchang University. Patients who participated in this research had complete clinical data. Signed informed consents were obtained from the patients or guardians (when the patient was incapacitated).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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