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Biopsy-proven kidney diseases in the elderly: clinical characteristics, renal histopathological spectrum and prognostic factors

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Abstract

Objective: To explore the clinical characteristics, renal histopathological spectrum and prognostic factors of biopsy-proven kidney diseases in the elderly.

Methods: A retrospective observational study was conducted in elderly patients who had received renal biopsies. Demographic, clinical and pathological data at the time of the biopsy were collected from the medical records. Follow-up records and prognostic factors were studied.

Results: The elderly (≥60 years) accounted for 74 of 434 (17.1%) native renal biopsies that were performed in a 9-year period. In the cohort of included elderly patients ($n = 72$), the prevalence of nephrotic syndrome and acute kidney injury was 62.5% (45 of 72) and 40.3% (29 of 72), respectively. For elderly patients with primary glomerular diseases ($n = 44$), membranous nephropathy was the most frequent pathological type (24 of 44; 54.5%). For elderly patients with secondary glomerular diseases ($n = 25$), anti-neutrophil cytoplasmic antibody-associated vasculitis was the most frequent aetiology (nine of 25; 36.0%). Requirement for renal replacement therapy (RRT) was an independent risk factor for poor prognosis.

Conclusions: Kidney diseases in the elderly have distinctive characteristics. Requirement for RRT was associated with poor prognosis in the elderly with biopsy-proven kidney diseases.

Keywords

Elderly, kidney diseases, renal biopsy, spectrum, prognosis, risk factor

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Introduction

According to data from the Sixth National Census in 2010, China has developed into an aging society.[1] Meanwhile, aging has been highlighted as a global public health problem.[2] As the morbidity of many acute and chronic diseases increases in older people, the number of patients with kidney diseases in this population increases as well.[3] Therefore, kidney diseases in the elderly are worth further investigation. Moreover, there are some key differences between older and younger patients in terms of the epidemiological and clinicopathological characteristics of kidney disease, which impacts on the treatment decision-making process, especially with regard to the use of immunosuppressive medications.

Several studies have analysed the epidemiological and clinicopathological characteristics of renal biopsy-proven kidney disease in elderly patients from the US, Europe and Asia.[4–9] It has been demonstrated that the characteristics vary between countries and regions because of different indications for renal biopsy, social problems, and ethnic predisposition.[10] In China, there have only been a few studies describing the spectrum of kidney diseases in elderly patients in recent years.[4,9] Since China covers a vast geographical area and has an imbalance in the social and economic development of different regions, relatively little is known about kidney diseases in Chinese elderly patients. Furthermore, to the best of our knowledge, there is a lack of studies about the clinical outcomes and risk factors for end stage renal disease (ESRD) and death in elderly patients with biopsy-proven kidney diseases.

This retrospective observational study was conducted in elderly patients with biopsy-proven kidney diseases. In this study, clinical characteristics and the pathological spectrum of biopsy-proven kidney disease in elderly patients were investigated and the factors influencing prognosis were determined.

Patients and methods

Patient selection

This retrospective observational study collected data from all patients who underwent native renal biopsies between 1 January 2006 and 31 December 2014 at the Department of Nephrology, Tongji Hospital, Tongji University, Shanghai, China. The indications for the renal biopsies included proteinuria and/or glomerular haematuria and/or unknown renal dysfunction without small-sized kidneys. A previous publication had two age cut-off criteria ($\geq$60 years versus $\geq$65 years) for being elderly.[9] In this present study, elderly patients were those who were $\geq$60 years. Exclusion criteria included the following: (i) specimens with $<$10 glomeruli for light microscopy where a definite diagnosis could not be made by immunofluorescence or electron microscopy; (ii) patients with two coexistent glomerular diseases. Data collected from the eligible patients included demographic and clinical data before renal biopsy as described below and renal histopathological records.

This study complied with the Declaration of Helsinki and received approval of the Ethics Committee of Tongji Hospital (Approval no. KYSB-2016-87). Verbal informed consent was obtained from the patient or their parents or carers.

Clinical manifestations

The demographic and clinical data were collected, including sex, age, proteinuria, haematuria, serum creatinine (SCr), uric acid (UA), serum albumin (SAlb), estimated glomerular filtration rate (eGFR), acute kidney injury (AKI), nephrotic syndrome (NS), hypertension and requirement for renal replacement therapy (RRT) at the time of biopsy. The eGFR was evaluated

by the Modification of Diet in Renal Disease (MDRD) formula.[11]

The definitions of clinical manifestations were as follows. Proteinuria was defined as urinary protein >0.3 g/day. Glomerular haematuria was defined as red cell count >100 000/ml in urine sediment with dysmorphic red cells accounting for >80%. NS was defined as urinary protein >3.5 g/day and SAlb <30 g/l, with or without oedema and hyperlipidaemia. AKI was defined as: (i) SCr increased by ≥26.5 μmol/l in 48 h; or (ii) SCr increased by ≥0.5 times the baseline, which happened within 7 days; or (iii) urine volume <0.5 ml/kg per h for 6 h.[12] AKI was evaluated by analysing the clinical records of patients. The definition of hypertension was an abnormally elevated blood pressure with a systolic blood pressure of ≥140 mmHg and/or a diastolic pressure of ≥90 mmHg twice or more on different days. The main clinical kidney diseases included NS, nephritic syndrome, asymptomatic urinary abnormalities (AUA) and tubulointerstitial diseases. Nephritic syndrome was defined as urinary protein <3.5 g/day, glomerular haematuria and oedema, with or without an acute decline of renal function. AUA manifested as proteinuria and/or haematuria without oedema, hypertension and renal dysfunction.[13]

Renal histopathology

Kidney biopsy specimens were collected using a spring-loaded biopsy gun. They were examined by the same renal pathologists under light microscopy, immunofluorescence and electron microscopy. For light microscopy, sections (2–3 μm) were stained routinely with haematoxylin and eosin, Masson's trichrome, periodic acid-Schiff and periodic acid-silver methenamine. For immunofluorescence, immunoglobulin (Ig) G, IgA, IgM, complement (C)3, C4, C1q and fibrinogen were detected. When patients were suspected of having renal amyloidosis, the sections were stained with Congo red. Electron microscopy was performed on all biopsy specimens to confirm the light microscopic findings. Histopathological data included glomeruli with crescents, proportion of sclerosed glomeruli and degree of chronic tubulointerstitial lesions.

According to previously published research,[14] the kidney diseases were divided into five categories: (i) primary glomerular disease (PGD); (ii) secondary glomerular disease (SGD); (iii) tubulointerstitial nephropathy; (iv) coexistence of two glomerular diseases; and (v) unclassified. The first three categories were investigated in this present study. If the kidney biopsy specimens demonstrated severe tubulointerstitial lesions that were not consistent with glomerular lesions, the pathological diagnosis of such cases was categorized as tubulointerstitial nephropathy. The degree of chronic tubulointerstitial lesions was evaluated according to the Katafuchi criteria.[15] The score for each lesion (tubular atrophy, interstitial chronic inflammation, and interstitial fibrosis) was 0 – 3 points, giving a total score of 0 – 9 points. According to the total score, chronic tubulointerstitial lesions could be divided into four levels: normal (0 points), mild (1–3 points), moderate (4–6 points), and severe (7–9 points).

Treatment schemes

The treatment schemes used for biopsy-proven kidney diseases were determined according to pathological changes, urinary protein and renal function. The principles of treatment included removal of predisposing factors, immunosuppressive therapy, symptomatic therapy, prevention of complications, slowing the progression of renal disease and RRT.[16] Based on K/DOQI guidelines in 2002 and KDIGO guidelines in 2012,[17,18] the treatment scheme for each pathological type was determined and individualized. With regard to

immunosuppressive therapy, glucocorticoid was the basic drug. Cyclophosphamide, mycophemolate mofeil and immunophillin modulators were also used in some glomerulonephritis cases. The common adverse effects of glucocorticoid were peptic ulceration, osteoporosis, pathoglycaemia and infections. For patients receiving immunosuppressive therapy, a proton pump inhibitor, vitamin D and calcium were used routinely to prevent peptic ulceration and osteoporosis. For patients with pathoglycaemia, dietary restriction and antidiabetic drugs were given. According to the severity of infections, appropriate treatments were administered. The dosage of immunosuppressive agents was reduced if the infections were uncontrolled.

Clinical outcomes

The endpoints were defined as ESRD or death from any cause. Follow-up records included proteinuria, SAlb and SCr. Adverse effects were also recorded during treatment with immunosuppressive agents, which mainly included infections that resulted in hospitalization and steroid-induced diabetes.

The clinical outcomes of kidney diseases were divided into complete remission (CR), partial remission (PR), no remission (NR) and occurrence of endpoints. The remission criteria for glomerular diseases are not uniform and vary widely. However, the outcome measures used in previous studies mainly included changes in proteinuria and changes in kidney function.[18] According to KDIGO guidelines on glomerulonephritis,[18] the CR and PR criteria in this present study were defined as follows. For NS, the CR criteria were proteinuria <0.3 g/day, SAlb ≥ 35 g/l and normal SCr; the PR criteria were reduction of proteinuria to 0.3–3.5 g/day and a $>50\%$ decrease from baseline, plus stable SCr (an increase $<25\%$). For nephritic syndrome, the CR criteria was proteinuria <0.3 g/day and normal SCr; the PR criteria was a $>50\%$ decrease in proteinuria, plus stable SCr (an increase $<25\%$) or improved SCr. In addition, the activity of systemic diseases was also taken into account. No remission (NR) was defined as changes in proteinuria and SCr without reaching the criteria of CR and PR.

Statistical analyses

All statistical analyses were performed using the SPSS® statistical package, version 13.0 (SPSS Inc., Chicago, IL, USA) for Windows®. The mean ± SD was used to express continuous variables. The n of patients (%) was used to express categorical variables. Logistic regression analysis was performed to investigate the connection between different variables and the endpoints of ESRD and death. First, univariate analyses were performed to select variables that would be used in the logistic regression model ($P < 0.1$). Secondly, in the logistic regression model, the odds ratio (OR) was adjusted for sex and age. Then the selected variables were put into the model to calculate the ORs and 95% confidence intervals (CI) for the endpoints. A P-value < 0.05 was considered statistically significant.

Results

Between 1 January 2006 and 31 December 2014, 434 native renal biopsies were performed; and of these 74 (17.1%) were from elderly patients ($\geq$60 years). Two biopsy specimens were excluded from the analyses: one specimen with <10 glomeruli for light microscopy where a definite diagnosis could not be given by immunofluorescence or electron microscopy and one specimen from a patient who had two coexistent glomerular diseases. The remaining 72 elderly patients (51 males and 21 females; sex ratio 2.43:1) were included in the present study. The mean ± SD age was 67.6 ± 6.3

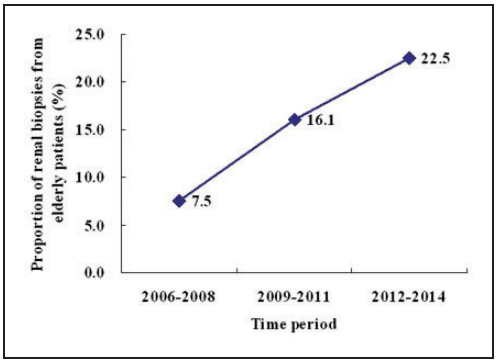

Figure 1. The proportion of renal biopsies that were undertaken in elderly patients (≥60 years) in three different time periods during the course of this retrospective observational study. Using 3-year intervals, the 9 years (2006–2014) were divided into three periods (2006–2008, 2009–2011 and 2012–2014). Raw data: 2006–2008, 7.5% (8 of 107); 2009–2011, 16.1% (19 of 118); 2012–2014, 22.5% (47 of 209).

years (range 60–81 years) at the time of their renal biopsy. As shown in Figure 1, the proportion of renal biopsies that were undertaken in elderly patients (≥60 years) increased dramatically from 7.5% (8 of 107) to 22.5% (47 of 209) in 2006–2008 compared with 2012–2014.

Table 1 presents the clinical manifestations experienced by elderly patients with biopsy-proven kidney diseases. Proteinuria occurred in most elderly patients. The incidences of NS and AKI in the elderly patients were 62.5% ($n=45$) and 40.3% ($n=29$), respectively; and 15.3% ($n=11$) of elderly patients presented with both NS and AKI.

Glomerular diseases were the most common type of kidney disease in the elderly patients included in this study, being diagnosed in 69 out of 72 (95.8%) patients. The ratio of PGD ($n=44$) to SGD ($n=25$) in elderly patients was 1.76. The most frequent pathological type of PGD were membranous nephropathy (MN) ($n=24$; 54.5%) (Table 2). As shown in Table 3, for the

Table 1. The clinical manifestations of elderly patients with biopsy-proven kidney disease ($n=72$).

Clinical manifestations	Elderly patients $n=72$
Proteinuria	69 (95.8)
Haematuria	44 (61.1)
NS	45 (62.5)
AKI	29 (40.3)
NS+AKI	11 (15.3)
Hypertension	37 (51.4)
Requirement of RRT at the time of biopsy	9 (12.5)

Data presented as *n* of patients (%).
NS, nephrotic syndrome; AKI, acute kidney injury; NS + AKI, NS coexisting with AKI; RRT, renal replacement therapy.

Table 2. Distribution of the pathological types of primary glomerular diseases in elderly patients ($n=44$).

Primary glomerular diseases	
Pathological types	Elderly patients $n=44$
MN	24 (54.5)
MCD	8 (18.2)
IgAN	4 (9.1)
FSGS	4 (9.1)
Minor lesion	2 (4.5)
Crescentic nephritis	1 (2.3)
MPGN	1 (2.3)

Data presented as *n* of patients (%).
MN, membranous nephropathy; MCD, minimal change disease; IgAN, IgA nephropathy; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis.

elderly patients with SGD, the most frequent aetiology was anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis ($n=9$; 36.0%). The aetiologies of SGD included autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, and autoimmune thyroid diseases), ANCA-associated vasculitis, infections

Table 3. Distribution of the aetiology of secondary glomerular diseases in elderly patients ($n = 25$).

Secondary glomerular diseases	
Aetiology	Elderly patients $n = 25$
ANCA-associated vasculitis	9 (36.0)
Infections	5 (20.0)
Autoimmune diseases	3 (12.0)
Diabetes	3 (12.0)
Hypertension	2 (8.0)
Amyloidosis	1 (4.0)
Tumours	1 (4.0)
Allergic purpura	1 (4.0)

Data presented as *n* of patients (%).
ANCA, anti-neutrophil cytoplasmic antibody; Infections, including syphilis and hepatitis B virus; Autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, and autoimmune thyroid diseases; Tumours, including gastric cancer.

Table 4. Distribution of the pathological types of nephrotic syndrome in elderly patients ($n = 45$).

Nephrotic syndrome	
Pathological types	Elderly patients $n = 45$
MN	24 (53.3)
MCD	7 (15.6)
FSGS	5 (11.1)
IgAN	2 (4.4)
MPGN	2 (4.4)
DN	2 (4.4)
Amyloidosis	1 (2.2)
Hypertensive nephrosclerosis	1 (2.2)
Cast nephropathy	1 (2.2)

Data presented as *n* of patients (%).
MN, membranous nephropathy; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; MPGN, membranoproliferative glomerulonephritis; DN, diabetic nephropathy.

(syphilis and hepatitis B virus), diabetes, hypertension, amyloidosis, tumours (gastric cancer) and allergic purpura.

As shown in Table 4, for the elderly patients with NS ($n = 45$), the frequent pathological types were MN ($n = 24$; 53.3%), minimal change disease (MCD) ($n = 7$; 15.6%) and focal segmental glomerulosclerosis (FSGS) ($n = 5$; 11.1%). The total proportion of MN, MCD and FSGS in elderly patients with NS was 80.0% ($n = 36$).

A total of 61 out of 72 patients were followed until 31 March 2015 or until the occurrence of one of the endpoints of ESRD or death. The mean follow-up time for these 61 patients was 16 months. Eleven patients dropped out due to loss of contact or failure to attend clinic visits. Among the 61 patients, 38 patients were treated with immunosuppressive agents; and 11 (28.9%) out of these 38 patients exhibited more than one infectious disease for which they required hospitalization. The infectious diseases included pulmonary infectious diseases, herpes zoster, and relapses of tuberculosis. However, no infectious diseases occurred in elderly patients who were not treated with immunosuppressive therapies. Six out of 38 (15.8%) patients exhibited steroid-induced diabetes.

As shown in Figure 2, 26 out of 61 patients (42.6%) developed CR and eight patients (13.1%) developed PR. The total remission rate was 55.7% ($n = 34$). Eleven patients (18.0%) died of acute cerebrovascular disorders (five patients), pulmonary infectious diseases (four patients), gastric carcinoma (one patient) and suicide (one patient). The other 16 patients (26.2%) developed NR.

Among the nine patients who were receiving dialysis at the time of their kidney biopsy, only one patient was able to stop dialysis and the other eight patients died within 3 months. None of the remaining patients ($n = 52$) developed ESRD during the follow-up period.

Of the 38 patients treated with immunosuppressive therapy, six (15.8%) developed ESRD and death compared with five (21.7%) of the 23 patients not treated with

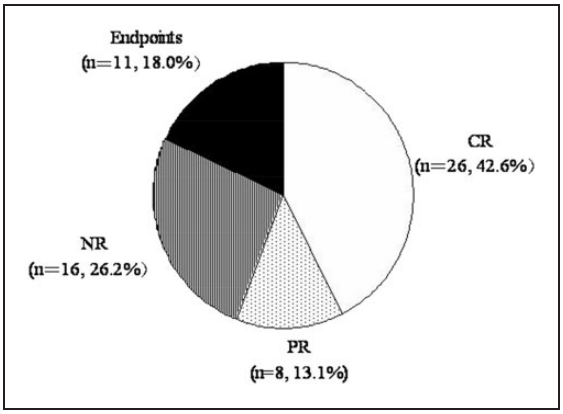

Figure 2. The clinical outcomes of the elderly patients ($n = 61$) with biopsy-proven kidney disease who were followed-up until 31 March 2015 or until the occurrence of one of the endpoints of end stage renal disease or mortality. Data presented as *n* of patients (%). CR, complete remission; PR, partial remission; NR, non-remission.

Table 5. Logistic regression analysis for independent risk factors for end stage renal disease and mortality in elderly patients with biopsy-proven kidney diseases ($n = 61$).

Variables	B	Standard error	Exp(B)	Statistical significance	95.0% CI for Exp(B)
RRT at the time of biopsy	4.546	1.966	94.240	$P = 0.021$[a]	1.997, 4447.041
AKI	−0.610	2.469	0.544	NS	0.004, 68.649
eGFR	−0.018	0.049	0.982	NS	0.893, 1.081
Glomeruli with crescents	0.578	1.387	1.782	NS	0.118, 27.023
Tubulointerstitial lesions	1.159	1.321	3.188	NS	0.239, 42.444
Constant	−6.640	9.119	0.001	NS	

[a]RTT versus no RRT at the time of renal biopsy; logistic regression analysis.
Exp(B), equal to the odds ratio value; CI, confidence interval; RRT, renal replacement therapy; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; NS, not statistically significant ($P \geq 0.05$).

immunosuppressive therapy. However, there was no significant difference between the two groups.

The variables in the univariate analyses included sex, age, proteinuria, eGFR, UA, SAlb, AKI, hypertension, requirement of RRT at the time of biopsy, immunosuppressive therapy, glomeruli with crescents, proportion of sclerosed glomeruli and degree of chronic tubulointerstitial lesions (normal and mild levels as one group, moderate and severe levels as the other group). In the univariate analyses, AKI ($P = 0.001$), lower eGFR ($P < 0.001$), requirement of RRT at the time of biopsy ($P < 0.001$), more severe tubulointerstitial lesions ($P = 0.031$) and crescents in the glomeruli ($P < 0.001$) were associated with reaching the endpoints of ESRD or death. Subjecting all these variables to logistic regression analysis, the requirement of RRT was identified as an independent risk factor for ESRD and death (Table 5). In addition, for all elderly patients, the

requirement of RRT at the time of biopsy correctly predicted reaching the endpoints of ESRD or death in 88.9%.

Discussion

The current study presented comprehensive information regarding biopsy-proven kidney diseases in elderly patients from a 9-year period in one centre in Eastern China. Furthermore, the present study also analysed the clinical outcomes and prognostic factors among all kidney diseases in this cohort of elderly patients, which was a unique aspect of the study. This present study demonstrated that although immunosuppressive therapy increased the risk of infections and other relevant adverse effects, it was not a risk factor for poor prognosis in the elderly patients with biopsy-proven kidney diseases. In contrast, the requirement for RRT at the time of the biopsy was identified as an independent risk factor for ESRD and death.

The present study demonstrated that 17.1% of all patients undergoing a native renal biopsy were elderly (≥60 years). This percentage was far higher than the rate of 2.89% that was reported previously by a large Chinese centre.[4] The likely reason for this disparity between the two studies is that Tongji Hospital is located in an area where the proportion of the general population who are elderly is >20%. Furthermore, this current finding was similar to the rate of 17% that was reported by a study from a developed country.[5] This present study also found that the proportion of the population having renal biopsies who were elderly patients (≥60 years) increased over the 9-year time period. The possible reasons for this observation were the increasing elderly population, and improvements in the economic conditions and health awareness. In this present study, males outnumbered females in the cohort of elderly patients. Male predominance was similar to that observed in other studies.[5,8,19] This finding suggests that males are more susceptible to kidney diseases. In addition, social and economic issues might be associated with the male predominance of kidney diseases.

The present study demonstrated that the major clinical manifestations of biopsy-proven kidney diseases in the elderly were proteinuria and haematuria. NS was a common clinical manifestation (62.5%) in the elderly patients that were investigated in this present study, which was consistent with another report,[13] although the rate was a little higher in the present cohort. This difference in the rate of NS might be related to the reluctance of clinicians to undertake renal biopsies, patient's preference, and life expectancy. Elderly patients are predisposed to AKI because of specific changes that take place in ageing kidneys.[20] The present study demonstrated that 40.3% of elderly patients had AKI and 15.3% patients had both AKI and NS. Thus, NS and/or AKI were the main clinical presentations that resulted in a renal biopsy in the elderly, which was consistent with previous studies.[10,21]

There are some discrepancies in the frequencies and spectrums of glomerular diseases in the elderly in different countries and regions.[10] This present study demonstrated that elderly patients had a high proportion of glomerular disease. Although the elderly patients in the present study had coexistent systemic diseases, there were fewer patients with SGD ($n = 25$) than patients with PGD ($n = 44$). In the global adult population, the most frequent PGD is IgAN.[22] In contrast, MN was the most frequent PGD in the elderly patients in the present study, which was consistent with several studies undertaken in Europe,[23–25] China[4] and Japan.[8] Moreover, MN was the leading pathological type in elderly patients with NS in the present study, which was similar to the findings of a previous Chinese study.[9] The present study found that ANCA-associated vasculitis was the most

frequent aetiology in elderly patients with SGD. This was in accord with the findings of a previous Chinese study.[9] However, another Chinese study reported that diabetic nephropathy (DN) was the most frequent aetiology in SGD, followed by vasculitis and amyloidosis.[4] This discrepancy may be due to different indications for renal biopsy in patients with diabetes. In Tongji Hospital, renal biopsies are not usually performed for patients with DN. However, when patients with diabetes are suspected of suffering from other glomerular diseases other than DN, then renal biopsies would be undertaken.

To the best of our knowledge, there is a paucity of studies reporting on the clinical outcomes and prognostic factors for biopsy-proven kidney diseases in the elderly. A retrospective study found that most elderly patients with primary NS had a good response to immunosuppressive therapy and a favourable prognosis.[26] In the current study, all infectious diseases requiring hospitalization occurred in patients receiving immunosuppressive therapy and the incidence of infectious diseases was higher than that reported previously.[26] Nevertheless, in elderly patients treated with immunosuppressive therapy, the rate of ESRD and death was comparable with that in patients not treated with immunosuppressive therapy. Patients treated with immunosuppressive therapy usually had more proteinuria or more severe acute lesions, so they might have been expected to have a higher rate of the endpoints of ESRD and death. As this was not the case, we speculate that immunosuppressive therapy in the elderly might be effective for preventing ESRD and reducing mortality. Older age did not appear to be a contraindication for immunosuppressive therapy in this present study. However, it is important to note that before making the decision about immunosuppressive therapy, many factors should be considered carefully, such as general health status, comorbidities, risk of infections and life expectancy.

The renal pathological type is an important factor for the prognosis of kidney diseases.[27] In addition to this, higher proteinuria, hypertension and renal insufficiency are well-known risk factors for the development of ESRD in patients with PGN.[27] Older age is a significant risk factor for mortality.[27] Nevertheless, the present study demonstrated that the requirement for RRT at the time of biopsy was an independent risk factor for ESRD and death in the elderly patients with biopsy-proven kidney diseases. This indicated that more attention should be paid to treatment schemes in elderly patients requiring RRT at the time of biopsy.

This study had several limitations. First, as a retrospective study, selection bias would have existed because some older patients were not willing to have biopsies for various reasons, especially those with mild clinical manifestations. Secondly, the number of patients was relatively low. Elderly patients suffering from kidney diseases might be reluctant to undergo renal biopsy. This limited the size of the population of elderly patients who had undergone a renal biopsy.

In conclusion, kidney diseases in the elderly population have distinctive characteristics. Older age is not a contraindication for immunosuppressive therapy, which may be effective for preventing ESRD and reducing mortality in the elderly. The requirement for RRT at the time of the biopsy was a risk factor for ESRD and mortality. Further research in a larger patient population is required to verify these findings.

Declaration of Conflicting of interests

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