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ORIGINAL ARTICLE

Predicting long-term renal and patient survival by clinicopathological features in elderly patients undergoing a renal biopsy in a UK cohort

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ABSTRACT

Background. Several publications have demonstrated the use of renal biopsy in elderly patients in establishing a diagnosis and enabling directed therapy. However, evidence on the long-term outcomes following biopsies is lacking. The aim of this study is to describe the renal and patient outcomes in elderly patients according to indication for biopsy, clinical parameters and the histological diagnosis.

Methods. We performed a retrospective cohort study of 463 patients >70 years old who underwent a renal biopsy at our centre between 2006 and 2015.

Results. The median age of the patients was 74.8 (range 70.0–89.6) years. The most frequent primary diagnoses were pauci-immune crescentic glomerulonephritis (GN; 12%), acute interstitial nephritis (10.8%) and membranous GN (7.1%). Death-censored renal survival at 1 and 5 years following the index biopsy was 85.2 and 75.9%, respectively, and patient survival at 1 and 5 years was 92.2 and 71.6%, respectively. Patients who progressed to end-stage renal disease (ESRD) were at higher risk of dying compared with patients who did not require dialysis [hazard ratio 2.41 (95% confidence interval 1.58–3.68; $P < 0.001$]. On multivariate analysis, factors associated with the risk of progression to ESRD were creatinine ($P < 0.001$), heavy proteinuria ($P = 0.002$) and a non-chronic kidney disease (CKD) biopsy indication ($P = 0.006$). A histological diagnosis of primary GN ($P = 0.001$) or tubulointerstitial nephritis ($P = 0.008$) was associated with a favourable renal outcome, while patients with vasculitis and paraprotein-related renal disease (PPRD) had the highest risk of requiring dialysis ($P = 0.0002$ and $P = 0.003$, respectively). PPRD was also an independent risk factor for death.

Conclusions. This study demonstrates that renal biopsies in the elderly not only enable directed therapy, but also provide prognostic information on renal and patient survival.

Keywords: AKI, chronic renal failure, dialysis, elderly, renal biopsy, survival analysis

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INTRODUCTION

The UK population is ageing and by 2040 it is estimated that one in four people will be >65 years of age [1]. This has major implications for general health care provision and nephrologists alike, with data from one longitudinal study suggesting that one-third of people >70 years of age have moderate chronic kidney disease (CKD) [2]. Data from the UK Renal Registry authenticate the growing number of elderly patients receiving renal replacement therapy (RRT), showing that the median age for starting RRT in the UK is now 64.6 years, with a peak incidence rate in patients >75 years [3]. Unfortunately, data also show that survival rates following initiation of RRT decline significantly with increasing age, with 50% of 70-year-olds surviving <3.5 years [3–6].

Despite the preponderance of elderly patients initiating RRT, there remains a recognized age discrepancy in establishing the cause of end-stage renal disease (ESRD) in young compared with older patients. From registry data, 19.1% of patients >65 years of age compared with only 13.9% of patients <65 years of age had no confirmed aetiology for their ESRD [3]. Pragmatic management decisions may be one explanation for this and another may be the belief that a biopsy is unlikely to result in a therapeutic intervention [6]. However, there are now numerous publications that have demonstrated the use of renal biopsy in elderly patients in terms of establishing a diagnosis and enabling directed therapy, which may in turn stop or reverse renal injury [7–13]. However, evidence on long-term outcomes following renal biopsies in the elderly is lacking, which may impede potential risk–benefit decisions by physicians and patients.

In this study we describe the histological features of a cohort of elderly patients who underwent a renal biopsy and determine the long-term outcomes of these patients. We aim to provide data that will help define the risk of patients progressing to ESRD in their lifetime according to the histological features found.

MATERIALS AND METHODS

We retrospectively analysed all patients ≥70 years of age who underwent a primary native renal biopsy at Imperial College Renal and Transplant Centre between 2006 and 2015. Clinical data were collected from medical records and pathology results.

Biopsy indication definitions

The clinical indications were at the discretion of the referring clinician and are summarized as follows:

- Acute kidney injury (AKI): a rapid decline in renal function, with a ≥50% reduction in the glomerular filtration rate (GFR) over a period of days to weeks.
- CKD: a progressive decline in renal function over a period of months, or non-nephrotic range proteinuria and/or haematuria in the setting of stable function.
- Nephrotic syndrome (NS) with preserved function: a urinary protein:creatinine ratio (UPCR) >300 mg/mmol, serum albumin <30 g/dL and stable function.
- NS with renal dysfunction (NSRD): the same as NS but with a decline in function as defined in AKI or CKD.

Histological methods and classification

All specimens were examined by light microscopy (LM) plus direct immunofluorescence [for immunoglobulin G (IgG), IgA, IgM, C3 and C1q ± kappa and lambda light chains when indicated]. Electron microscopy was performed if indicated by LM findings or clinical indication.

The histological categories are as follows:

- Glomerulonephritis (GN): primary GN (PGN) or secondary GN, excluding pauci-immune and anti-GBM disease
- Tubulointerstitial: including tubulointerstitial nephritis (TIN), acute tubular injury and pyelonephritis
- Vasculitis: pauci-immune GN and anti-glomerular basement membrane (GBM) disease
- Paraprotein-related renal disease (PPRD): injury involving a monoclonal Ig, including those associated with myeloma and lymphoma
- Vascular lesions: including thrombotic microangiopathies and cholesterol emboli
- Scarring, which was subdivided further into two categories:
  - Diabetic-related scarring/sclerosis in the context of diabetic nephropathy
  - Non-diabetic-related scarring/sclerosis secondary to non-diabetic causes (NDMSc), including hypertensive ischaemic damage.

Interstitial fibrosis and tubular atrophy (IFTA) was defined as mild, moderate or severe depending on whether <25, 25–50 or >50%, respectively, of the cortex was involved. Glomerulosclerosis was defined as mild, moderate or severe depending on whether <25, 25–50 or >50%, respectively, of the glomeruli sampled were either obsolete or had segmental scarring.

Serological methods

The 'renal screen' refers to the serological or urinary analysis performed before the biopsy. A positive anti-neutrophil cytoplasmic antibody (ANCA) was defined either by indirect immunofluorescence and/or antigen-specific enzyme-linked immunosorbent assay. A paraprotein screen was considered positive when a paraprotein and/or free serum or urinary light chains were detected. Other serological tests included complement levels, anti-nuclear antibodies, double-stranded DNA and cryoglobulins.

Treatment

Patients with scarring received no additional biopsy-directed treatment outside of cardiovascular and/or glycaemic control optimization. Treatments for the remaining diagnoses were patient centred but incorporated local immunotherapy protocols for each specific diagnosis.

Statistical methods

All statistical analysis was performed using MedCalc version 18.5 (MedCalc Software, Ostend, Belgium). Comparisons of means and frequencies of normally distributed variables were calculated using *t*-tests and the chi-squared test; non-parametric variables were analysed by the Mann–Whitney test. Kaplan–Meier survival analysis was used to calculate renal and patient survival and was determined by log-rank testing. Patient survival was defined by time to death. Renal survival was defined by time to onset of ESRD and censored for death. Multivariate analyses were performed using Cox proportional hazards regression methods unless otherwise stated.

Table 1. Histological classification of biopsies

Category	Subclassification	*n* (%)
GN	PGN	
	Membranous GN	33 (7.1)
	Minimal change disease	22 (4.7)
	Primary focal segmental glomerulosclerosis	14 (3.0)
	IgA/Henoch–Schönlein purpura nephropathy	9 (1.9)
	SGN	
	Lupus nephritis	8 (1.7)
	Post-infectious	2 (0.4)
	C3 GN	0 (0)
	Other (including membranoproliferative GN, e.g. hepatitis C, fibrillary, cryo, etc.)	22 (4.8)
	Total	110 (23.8)
Tubulointerstitial	Acute interstitial nephritis	50 (10.8)
	Acute tubular injury	15 (3.3)
	Acute pyelonephritis/reflux/obstruction	2 (0.4)
	Other (including warfarin-induced obstructive tubulopathy, transitional cell carcinoma, oxalate nephropathy)	3 (0.6)
	Total	70 (15.1)
Vasculitis	Pauci-immune GN	55 (11.9)
	Anti-GBM nephritis	3 (0.6)
	Total	58 (12.5)
PPRD	Cast nephropathy	13 (2.8)
	Light-chain amyloidosis	15 (3.3)
	Monoclonal Ig deposition disease	3 (0.6)
	Others (e.g. cryo type 1, proliferative glomerulonephritis with monoclonal Ig deposits, etc.)	4 (0.9)
	Total	35 (7.6)
Vascular lesions	Thrombotic microangiopathy/scleroderma renal crisis	11 (2.3)
	Cholesterol emboli	1 (0.2)
	Other	0 (0)
	Total	12 (2.6)
Scarring	Diabetic nephropathy	76 (16.4)
	Calcineurin inhibitor toxicity	1 (0.2)
	Cause not specified (including hypertensive nephrosclerosis, secondary focal segmental glomerulosclerosis, ischaemic nephropathy)	98 (21.2)
	Total	175 (37.8)
Inadequate sample		3 (0.85)

RESULTS

A total of 463 of 4170 (11.1%) native biopsies performed during the study period were in patients ≥70 years of age. Three were excluded from the analysis due to inadequate sampling. The median age of the patients was 74.8 (range 70.0–89.6) years with a median follow-up of 5.62 (range 5.02–6.17) years.

Causes of renal insufficiency in the elderly

A summary of the histological features of the biopsies is shown in Table 1. The most common finding on renal biopsy was scarring, with diabetic nephropathy and NDMSc accounting for 16.4 and 21.2% of all biopsies, respectively. The most frequent primary diagnoses were pauci-immune crescentic GN (12%), TIN (10.8%) and membranous GN (7.1%), followed by minimal change disease (4.7%). PPRD comprised 7.6% of cases, with cast nephropathy in 2.8% and light-chain amyloidosis in 3.3%.

Clinical variables associated with histological diagnoses

We compared the clinical variables associated with five main histological subgroups: NDMSc, PGN, TIN, PPRD and vasculitis. A summary of the demographics and clinical variables can be found in Table 2. Details on the demographics and outcomes of the remaining subgroups can be found in the supplementary data.

Compared with patients with NDMSc, patients with vasculitis were older, with a median age of 74.5 (range 73.8–75.1) and 76.2 (range 74.9–78.0) years, respectively ($P = 0.005$). The proportion of females in the NDMSc group, 29/99 (29.3%), was less than in the vasculitis and PPRD groups, with 27/58 (46.6%; $P = 0.038$) and 18/35 (51.4%; $P = 0.02$) females, respectively. There was no statistically significant ethnic distribution between the groups.

Patients with NDMSc were more likely to have undergone a biopsy for CKD: 92/99 (92.9%) patients with NDMSc compared with 63/261 (27.6%) patients with an alternative histological diagnosis had a biopsy for CKD ($P < 0.001$). Patients with PGN and PPRD were more likely to present with NS, with 33/78 (42.3%) and 9/35 (25.7%) patients, respectively, presenting with NS compared with no patients with NDMSc ($P < 0.001$). Patients with PPRD, TIN and vasculitis were all more likely to present with AKI. Compared with 6/99 (6.1%) patients with NDMSc presenting with AKI, 8/35 (22.9%) PPRD patients ($P = 0.005$), 32/58 (55.2%) TIN patients ($P < 0.001$) and 35/58 (60.3%) vasculitis patients ($P < 0.001$) presented with AKI. Patients with PPRD, GN and vasculitis were more likely to have undergone a biopsy for NSRD

Table 2. Summary of patient demographics and clinical variables

Variable	Non-diabetic scarring ($n = 99$)	PGN ($n = 78$)	TIN ($n = 50$)	Vasculitis ($n = 58$)	PPRD ($n = 35$)
Age (years)					
Median (range)	74.13 (73.46–75.13)	75.32 (73.82–76.87)	74.66 (73.42–76.97)	76.23 (74.9–77.99)	74.85 (73.3–76.76)
P-value	*Comparator	0.48	0.48	0.005*	0.26
Ethnicity, *n* (%)					
Caucasian	58 (58.6)	48 (61.5)	40 (69.0)	39 (67.2)	23 (65.7)
Asian	22 (22.2)	19 (24.4)	6 (10.3)	9 (15.5)	4 (11.4)
Afro-Caribbean	12 (12.1)	6 (7.7)	3 (5.2)	7 (12.1)	3 (8.6)
Other	7 (7.1)	5 (6.4)	1 (1.7)	3 (5.2)	5 (14.3)
P-value		0.92	0.19	0.34	0.76
Gender, *n* (%)					
Male	70 (70.7)	54 (69.2)	24 (48.0)	31 (53.4)	17 (48.6)
Female	29 (29.3)	24 (30.8)	26 (52.0)	27 (46.6)	18 (51.4)
P-value		0.52	0.05	0.038*	0.024*
Indication, *n* (%)					
AKI	6 (6.1)	2 (2.6)	32 (84.2)	35 (60.3)	8 (22.9)
CKD	92 (92.9)	21 (26.9)	17 (34.0)	13 (22.4)	12 (34.3)
NS	0 (0)	33 (42.3)	1 (2.0)	3 (5.2)	9 (25.7)
NSRD	1 (1.0)	22 (28.2)	0 (0)	7 (12.1)	6 (17.1)
P-value		<0.0001*	<0.0001*	<0.0001*	0.007*
Renal screen, *n* (%)					
Negative	74 (74.7)	66 (84.2)	36 (72.0)	5 (8.6)	10 (28.6)
Positive	25 (25.3)	12 (15.4)	14 (28.0)	53 (91.4)	25 (71.4)
P-value		0.11	0.72	<0.0001*	<0.0001*
eGFR at biopsy (mL/min/1.72 m^2)					
Median (range)	31 (30–35)	38.5 (32.3–57.7)	19.50 (14.0–30.8)	15 (11–19)	25.5 (14–36)
P-value		0.003*	0.0002	<0.0001*	0.16
Creatinine at biopsy (μmol/L)					
Median (range)	167.5 (156–189)	143.0 (112.4–157.7)	246.5 (220.2–311.4)	330.5 (253–387)	197 (162–294)
P-value		0.001*	<0.0001*	<0.0001*	0.12
UPCR at biopsy (mg/mmol)					
Median (range)	13 (0–49)	603 (415–766)	43.0 (27.6–93.2)	319 (148–296)	578.4 (200–800)
P-value		<0.0001*	0.03*	<0.0001*	<0.0001*
Dialysis at biopsy, *n* (%)					
Yes	1 (1.0)	6 (7.7)	1 (2.0)	15 (25.9)	8 (22.9)
No	98 (99.0)	72 (92.3)	49 (98.0)	43 (74.1)	27 (77.1)
Recovered, *n* (%)	0 (0.0)	5 (83.3)	0 (0)	5 (33.3)	0 (0.0)

compared with the NDMSc group, with 6/35 (17.1%) PPRD patients ($P < 0.001$), 22/78 (28.2%) GN patients ($P < 0.001$) and 7/58 (12.1%) vasculitis patients ($P < 0.001$) having a biopsy for NSRD compared with 1/99 (1.0%) of the NDMSc patients.

Patients with TIN and vasculitis had a higher serum creatinine at the time of biopsy, with a median serum creatinine of 246.5 (range 220.2–311.4) and 330.5 (range 253–387) μmol/L, respectively, compared with 167.5 (range 156–189) μmol/L in the NDMSc group ($P < 0.001$). Patients with PGN had a lower serum creatinine at 143.0 (range 112.4–157.7) μmol/L ($P < 0.001$). Patients with PPRD or vasculitis were more likely to have a positive serological renal screen, with 25/35 (71.4%; $P < 0.001$) and 53/58 (91.4%; $P < 0.001$) patients, respectively, compared with 25/99 (25.3%) of the NDMSc group.

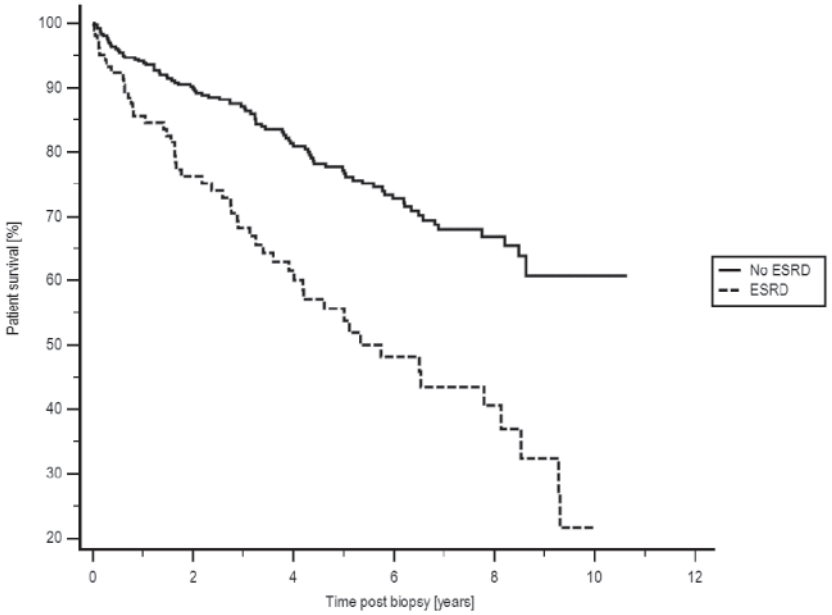
Renal and patient outcomes

During follow-up, 189/460 (41.1%) patients either progressed to ESRD or died. In all, 85/460 (18.5%) patients died without the need for dialysis, while 53/460 (11.5%) patients survived on RRT and 51/460 (11.1%) patients died after requiring RRT. Death-censored renal survival at 1, 3 and 5 years was 85.2, 79.1 and 75.9%, respectively, and patient survival at 1, 3 and 5 years was 92.2, 82.1 and 71.6%, respectively. Patients who progressed to ESRD were at higher risk of dying compared with patients who did not require RRT {hazard ratio [HR] 2.41 [95% confidence interval (CI) 1.58–3.68]; $P < 0.001$}, as shown in Figure 1.

Outcome by indication

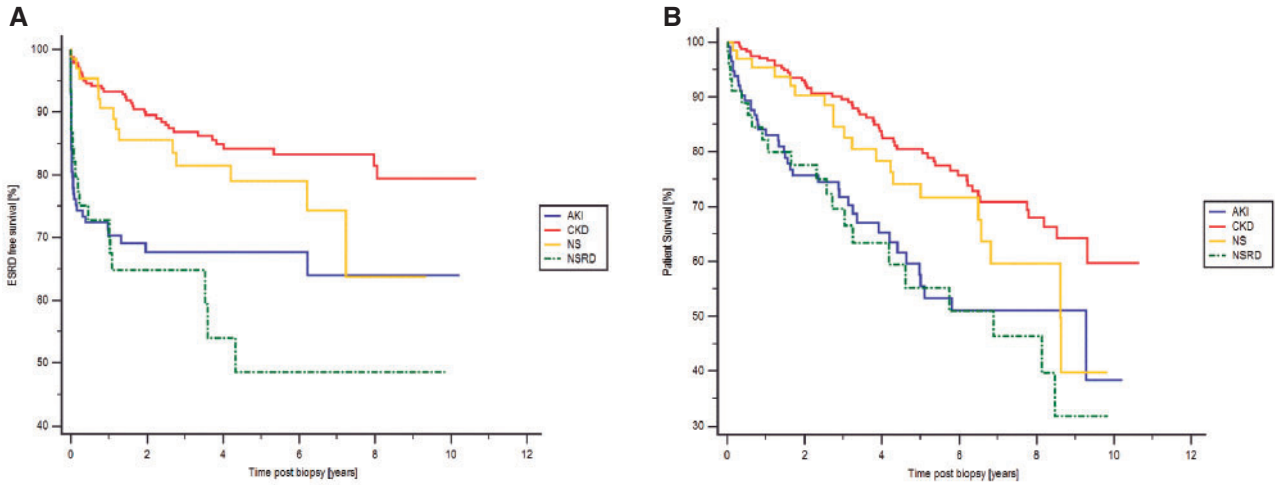
There was no difference in the incidence of ESRD in patients undergoing a biopsy for the indication of CKD compared with NS [HR 0.66 (95% CI 0.38–1.16); $P = 0.16$], as shown in Figure 2A. However, patients undergoing a biopsy for AKI had significantly worse renal survival compared with patients with either CKD [HR 2.95 (95% CI 1.78–4.88); $P < 0.001$] or NS [HR 1.96 (95% CI 1.01–3.80); $P = 0.04$]. Patients with NSRD also had inferior renal survival compared with CKD [HR 3.58 (1.74–7.39); $P < 0.001$] or NS [HR 2.38 (95% CI 1.03–5.52); $P = 0.007$].

There was no difference in patient survival comparing the groups undergoing a biopsy for the indication of CKD compared with NS [HR = 0.69 (95% CI 0.42–1.12); $P = 0.16$], as shown in Figure 2B. However, patients undergoing a biopsy for AKI had a higher risk of death compared with the CKD group [HR 2.34 (95%



356	**275**	**179**	**119**	**53**	**5**	**No ESRD**
104	70	44	23	12	1	ESRD
Number at risk						

FIGURE 1: Patient survival by ESRD post-biopsy. Patients who progressed to ESRD were at higher risk of dying compared with those that maintained renal function [HR 11.40 (95% CI 7.86–15.55) $P < 0.001$].



113	49	29	19	6	1	AKI
237	177	116	80	40	4	CKD
65	46	33	17	4	0	NS
45	23	10	8	4	0	NSRD
Number at risk						

113	67	38	22	8	1	AKI
237	196	132	86	44	5	CKD
65	50	37	22	6	0	NS
45	32	16	12	7	0	NSRD
Number at risk						

FIGURE 2: ESRD and patient survival by indication. (**A**) Death-censored, ESRD-free survival by biopsy indication. Compared with patients undergoing a biopsy for CKD, patients with AKI and NSRD were at higher risk of ESRD [HR 2.95 (95% CI 1.78–4.88); $P < 0.001$ and HR 3.58 (95% CI 1.74–7.39); $P < 0.001$, respectively)]. (**B**) Patient survival by indication. Compared with patients undergoing a biopsy for CKD, patients with AKI and NSRD were at higher risk of death [HR 2.34 (95% CI 1.50–3.66); $P < 0.001$ and HR 2.61 (95% CI 1.41–4.82); $P<0.001$, respectively]. There was no difference in patient survival for patients with NS and CKD [HR 0.69 (95% CI 0.42–1.12); $P = 0.16$].

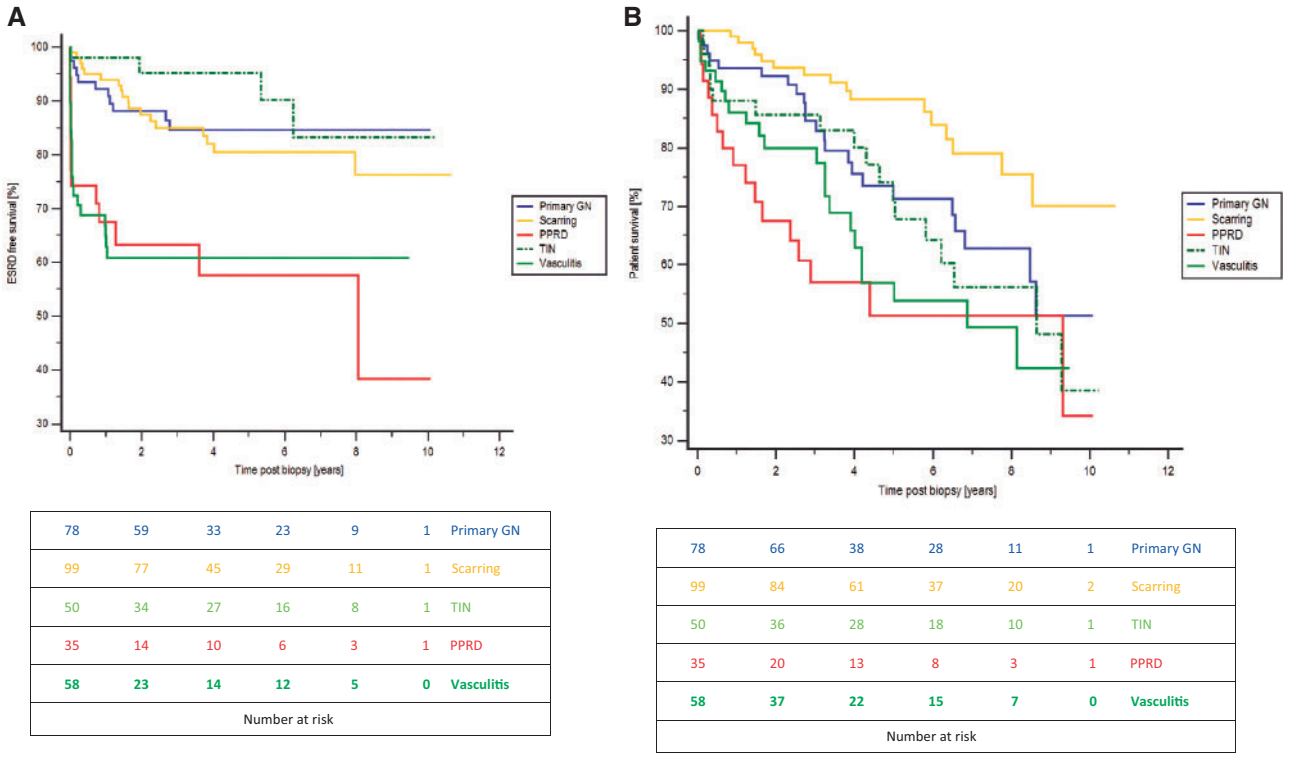


FIGURE 3: Death-censored ESRD and patient survival by histological features. (**A**) Compared with patients with histological features of NDMSc scarring, patients with vasculitis and PPRD were at higher risk of ESRD [HR 3.00 (95% CI 1.52–5.94); P = 0.002 and HR 3.35 (95% CI 1.38–8.13); P = 0.003, respectively]. (**B**) Compared with patients with histological features of NDMSc scarring, patients with vasculitis [HR 0.31 (95% CI 0.17–0.57); P < 0.001], PPRD [HR 0.24 (95% CI 0.11–0.52); P < 0.001], PGN [HR 0.50 (95% CI 0.30–0.85); P = 0.03] and TIN [HR 0.41 (95% CI 0.23–0.75); P = 0.008] had inferior survival.

CI 1.50–3.66); P < 0.001], but no difference in survival compared with either the NS [HR 1.61 (95% CI 0.90–2.89); P = 0.09] or NSRD [HR 0.90 (95% CI 0.45–1.79); P = 0.59] groups. Patients with NSRD had inferior survival compared with patients with CKD [HR 2.61 (95% CI 1.41–4.82); P < 0.001] or NS [HR 1.97 (95% CI 1.09–3.55); P = 0.019].

Outcome by histological diagnosis

Patients with vasculitis and PPRD were at highest risk of requiring dialysis, as shown in Figure 3A. There was no difference in renal survival between patients with vasculitis and those with PPRD [HR 0.93 (95% CI 0.47–1.83); P = 0.84]; however, patients with vasculitis and PPRD were more likely to progress to ESRD than patients with NDMSc [HR 3.00 (95% CI 1.52–5.94); P < 0.001 and HR 3.35 (95% CI 1.38–8.13); P = 0.003, respectively), PGN [HR 3.42 (95% CI 1.68–6.93); P < 0.001 and HR 3.73 (95% CI 1.52–9.16); P < 0.001, respectively] and TIN [HR 5.81 (95% CI 2.69–12.53); P < 0.001 and HR 6.60 (95% CI 2.50–17.43); P < 0.001]. There was no difference in renal survival between the TIN group and either the NDMSc [HR 0.49 (95% CI 0.20–1.21); P = 0.19] or PGN [HR 0.57 (95% CI 0.20–1.62); P = 0.33] groups and there was also no difference in renal survival between the NDMSc and PGN groups [HR 1.19 (95% CI 0.57–2.48); P = 0.65].

Patients with severe IFTA had the worst renal survival. The risk of progressing to ESRD with severe IFTA was significantly higher compared with patients with either moderate IFTA [HR 3.01 (95% CI 1.72–5.27); P < 0.001] or mild IFTA [HR 2.10 (95% CI 1.28–3.45); P < 0.001]. There was no difference in renal survival between patients with moderate compared with mild IFTA [HR 0.74 (95% CI 0.44–1.25); P = 0.29]. Patients with severe glomerular scarring also had inferior renal survival compared with patients with mild glomerular scarring [HR 1.70 (95% CI 1.00–2.87); P = 0.03], but there was no survival benefit compared with those patients with moderate glomerular scarring [HR 1.37 (95% CI 0.81–2.33); P = 0.23].

Patients whose biopsy showed NDMSc were at lowest risk of dying compared with patients with vasculitis [HR 0.31 (95% CI 0.17–0.57); P < 0.001], PPRD [HR 0.24 (95% CI 0.11–0.52); P < 0.001], PGN [HR 0.50 (95% CI 0.30–0.85); P = 0.03] or TIN [HR 0.41 (95% CI 0.23–0.75); P = 0.008], as shown in Figure 3B. The patients with PGN also had a survival advantage over patients with PPRD [HR 0.49 (95% CI 0.24–1.00); P = 0.03], otherwise there was no significant difference between the other cohorts.

Risk of ESRD or death by histological diagnosis

The median time to either death or ESRD in patients with vasculitis was 3.04 (range 0.98–6.88) years, with the risk of reaching ESRD greater than dying without the need for RRT [HR 3.45 (95% CI 1.70–7.03); P < 0.001]. The median time for patients with a histological diagnosis of TIN to either reach ESRD or die was 8.63 (range 5.34–8.63) years. There was no difference in the risk of ESRD compared with dying without the need for RRT [HR 0.82 (95% CI 0.29–2.31); P = 0.75] in patients with TIN. The median time to RRT or death in patients with PPRD was short, at 1.27 (range 0.36–8.06) years, with no difference in the risk of ESRD over death without RRT [HR 1.32 (95% CI 0.52–3.39); P = 0.57]. Patients with PGN had a long median time to either RRT or death of 8.48 (range 5.00–8.62) years. However, they were more

Table 3. The variables associated with ESRD and death on multivariate analysis

Variable	Exp(b)	95% CI	P-value
Death			
Age at biopsy	1.07	1.02–1.12	0.0027
Serum creatinine	1.002	1.001–1.003	<0.0001
UPCR	1.0003	1.000–1.001	0.016
PPRD	2.04	1.15–3.63	0.015
Dialysis			
Serum creatinine	1.005	1.004–1.006	<0.0001
UPCR	1.001	1.000–1.001	0.0015
IFTA >50%	2.52	1.49–4.25	0.001
Non-CKD indication	2.23	1.23–3.92	0.006
PGN	0.25	0.11–0.54	0.001
TIN	0.14	0.03–0.60	0.008

likely to require RRT than die without the need for RRT [HR 3.77 (95% CI 1.32–10.82); P < 0.001]. For patients with NDMSc, the median time to either ESRD or death was not reached during follow-up. However, there did not appear to be an increased risk of ESRD over dying without the need for RRT in these patients [HR 1.90 (95% CI 0.91–3.99); P = 0.08], and their overall prognosis was good.

Multivariate analysis of patient and renal outcomes

On multivariate analysis (Table 3), clinical factors at presentation associated with the risk of progression to ESRD were serum creatinine [HR 1.005 (95% CI 1.004–1.006); P < 0.001], UPCR [HR 1.001 (95% CI 1.00–1.001); P = 0.002] and a biopsy for a non-CKD indication [HR 2.23 (95% CI 1.23–3.92); P = 0.006]. Having a histological diagnosis of PGN [HR 0.25 (95% CI 0.11–0.54); P = 0.001] or TIN [HR 0.14 (95% CI 0.03–0.60); P = 0.008] was associated with a favourable renal outcome. The histological presence of severe IFTA was associated with ESRD [HR 2.52 (95% CI 1.49–4.25); P = 0.001].

On multivariate analysis (Table 3), clinical factors at presentation associated with inferior patient survival were older age [HR 1.07 (95% CI 1.02–1.12); P = 0.003], serum creatinine [HR 1.002 (95% CI 1.001–1.003); P < 0.0001] and UPCR [HR 1.0003 (95% CI 1.00–1.001); P = 0.02]. In addition, a diagnosis of PPRD was associated with inferior patient survival [HR 2.04 (95% CI 1.15–3.63); P = 0.02].

DISCUSSION

With a greater appreciation of the role for directed therapy for glomerular disease in elderly patients, there has been a paradigm shift towards enhancing diagnosis with renal histology. While the prevalence of individual histological lesions has been well described, there remains a paucity of data addressing long-term renal and patient outcomes. The novel findings of this study relate to the lifetime risk of dialysis and death associated with different histological subtypes. Such knowledge will help in counselling elderly patients with regards to prognosis and facilitate shared decision making.

The range and relative frequency of histological lesions observed in elderly patients are different from those observed in younger patients. The predominance of vasculitis in our patient cohort is similar to findings reported in other elderly biopsy series, with pauci-immune GN often the most frequent primary diagnosis, with a reported prevalence of 17.4–31.2% [7, 8, 10]. We also found a significant proportion of cases with tubulointerstitial disease, the majority relating to TIN, and membranous nephropathy. Both lesions have also been frequently reported in other elderly case series, adding credibility to the findings of this large study [7, 8, 10]. Of note, the most frequent primary diagnoses found in our cohort are all potentially treatable with directed therapy beyond cardiovascular and glycaemic optimization, reinforcing the importance of renal biopsies in the elderly population.

Interpretation of published case series that have focused on the renal histology from elderly patients is complicated by the inconsistencies in the definition of old age [7–13]. Sixty-five years of age is the most commonly utilized definition, although cut-offs range from 60 to 80 years [7–13]. Haas *et al.* [8], who presented one of the earliest studies on patients over the age of 60 years with AKI, showed that the risk of death and ESRD was higher in patients >70 years of age, which we therefore chose as our age criterion [8]. Further consideration of the applicability of elderly biopsy studies involves ethnic disparities, which may reflect on the histology seen [7, 9–16]. Although our study has a predominance of Caucasian patients, the diversity seen is relatively large when compared with other studies [7, 12, 13, 16].

This study showed several practical prognostic findings. We showed that a histological diagnosis of PGN or TIN was associated with favourable renal outcomes, while histological evidence of severe IFTA was associated with poor renal survival. Poor function and heavy proteinuria were also associated with inferior patient survival, together with older age and a diagnosis of PPRD. When analysing the lifetime risk of dialysis over death with dialysis independence, we demonstrated that patients with PPRD and TIN were not at increased risk of RRT during their lifetime, but the median time to death was short in the former group, while the latter group had an overall good prognosis.

Only two previous studies looking at renal histology from older subjects included any detailed follow-up data. Haas *et al.* [8] showed that the 3-year patient and renal survival following a biopsy for AKI in elderly patients was 72.0 and 54.0%, respectively. The reported difference in renal and patient outcomes between that study and ours may relate to expansion of the biopsy indications to include CKD, as it is recognized that the risk of ESRD is increased in all patients with AKI [17]. In the second study, Pincon *et al.* [15] analysed the outcomes of 150 patients >70 years of age who underwent a renal biopsy and described the outcomes according to treatment. In their study, patients who received directed immunosuppression for NS had superior renal survival at 3 years. This suggests that the benefit of immunotherapeutic treatment outweighs the risk, although the untreated group may represent frailer patients who have independently a worse prognosis. The argument for the benefit of immunosuppression has also been shown in a study by Weiner *et al.* [18] of 151 patients >75 years of age with vasculitis. In their study, Weiner *et al.* [18] reported inferior survival in patients who did not receive the standard immunotherapy. Conversely to the data shown in these studies, it is well recognized that complications from immunosuppression are proportional to age [19]. Critically, given the potential growth in the need for immunotherapy in the ageing population, who may not benefit from standard-of-care treatment, evidence is needed to determine the optimal therapy for these patients [6, 19].

While there is no reported increased risk of performing biopsies in the elderly, it is still an invasive procedure and potential benefit requires consideration [20]. The first aspect to consider is whether the biopsy is likely to identify a diagnosis that would

benefit from directed therapy? Second, will determining the extent of underlying irreversible damage change management? Third, is the patient suitable to receive directed treatment, which often involves immunotherapy. Regarding determining the differential diagnosis reported in this series and others, GN, vasculitis and PPRD are more predictable in terms of serological markers and presentation, hence aiding the decision for biopsy. It is reported that ~90% of patients with ANCA-associated vasculitis have positive serology, which is consistent with the 91.4% reported in this series [21]. High serum-free light chains together with AKI are sufficient to diagnose cast nephropathy in the absence of a biopsy, while a nephrotic state in the presence of a paraprotein or serum or urinary-free light chains raises the possibility of AL amyloid in this age group [22]. While collectively the primary glomerulonephritides classically present with NS, classification still requires a biopsy. However, the advent of anti-phospholipase 2 receptor antibody (anti-PLA2R) testing may change this in the future, especially as membranous GN, which is associated with anti-PLA2R, is the most common histological diagnosis seen in elderly case series performed for NS [23].

Less predictable, however, is the relatively common diagnosis of TIN. This entity remains a significant challenge to nephrologists not only due to a lack of specific clinical features, but also to the increased risk of TIN in this age group related to polypharmacy [24, 25]. Drugs are the most common cause of TIN in the elderly, with penicillin and proton pump inhibitors being the leading causes [24, 25]. Diagnosing TIN is important, as renal outcome is dependent on therapy as well as the removal of offending drugs, and active management with steroids confers benefit. Prendecki *et al.* [25] demonstrated greater improvement in GFR and fewer patients progressing to ESRD with steroid treatment. Muriithi *et al.* [24] demonstrated the importance of the timing of treatment, with shorter delays to initiation of steroids correlating with renal recovery at 6 months. TIN may be included in the differential of all elderly patients presenting with AKI, and determining who warrants a biopsy to confirm or exclude TIN is not straightforward. The prevalence of undiagnosed TIN in the elderly is not known, and these patients may be deprived the opportunity to receive specific therapy to improve their renal outcomes.

There are several limitations to our study. Given its retrospective nature, the study is subject to confounding. Comparisons with other published case series in this field must be made with caution given the disparities in classification of indication and histology, population variance and differing thresholds for renal biopsy. Importantly, the histological categories are wide and outcomes by treatment are not reported.

However, to our knowledge, this study is the largest reported series of renal biopsies in the elderly population and the first to describe longer-term outcomes by histology. It adds to the available literature in the field of geriatric nephrology by showing that renal biopsies for unselected indications in the elderly not only provide a histological diagnosis, but also prognostic information on patient and renal survival. Hence a probing question must arise for nephrologists on whether more elderly patients could potentially benefit from a biopsy given the incidence of AKI and CKD in this population? However, for those patients who do undergo a biopsy, future studies must include ways of optimizing outcomes in this unique patient group, in whom conventional treatment may be relatively contraindicated.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS' CONTRIBUTIONS

M.W. was involved in the research idea and study design. A.N. and K.S. made contributions to the acquisition of data. A.N. and M.W. conducted the analysis and interpretation of data and performed statistical analysis. M.W., C.R., T.H.C. and C.P. were responsible for supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

None declared.

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