Q J Med 2008; **101**:215–224
doi:10.1093/qjmed/hcm142 Advance Access published on 2 February 2008

Primary glomerulonephritis: an update on renal survival and determinants of progression

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Received 21 August 2007 and in revised form 31 October 2007

Summary

Background: Few epidemiological studies have investigated the long-term outcome of primary glomerulonephritis (GN) and its determinants in the decade since angiotensin-converting enzyme inhibitors entered widespread use.
Aim: To study several traditional and less traditional risk factors for kidney disease progression in a cohort of patients with primary GN.
Design: Retrospective cohort study.
Methods: We included 536 patients with primary GN first diagnosed between 1994 and 2001: 283 IgA nephropathy (IgA), 129 membranous nephropathy (MN), and 124 focal and segmental glomerulosclerosis (FSGS). Adjusted hazard ratios (HR) or dialysis or preemptive transplantation for end-stage renal disease (ESRD) according to various characteristics were estimated with Cox proportional-hazard models.
Results: At diagnosis, mean patient age was 43 ± 17 years, 74% were men, and the mean estimated glomerular filtration rate (eGFR) was 69 ± 31 mL/mn/1.73m^2. After a mean follow-up of 7-years, 104 patients had started ESRD treatment and 14 had died before reaching ESRD. The 7-year renal survival rate was 69% for FSGS, 88% for MN, and 82% for IgAN ($p < 0.01$). In patients with FSGS, younger age was associated with a higher risk of ESRD. Baseline proteinuria, diabetes, and haemoglobin (Hb) concentration were strongly associated with shorter time to ESRD independent of baseline eGFR, but gender, hypertension and smoking were not. Adjusted HRs for ESRD were 2.6 [95% confidence interval, 1.2–5.8] for diabetes and 2.4 [1.3–4.5] for the lowest and 1.9 [1.0–3.6] for the intermediate Hb tertiles versus the highest.
Discussion: In patients with primary GN, renal survival is clearly lower for FSGS than for IgAN and MN. Independent predictors for progression were baseline diabetes and anaemia, as well as proteinuria, for all GN types, and younger age, for FSGS.

Introduction

Glomerulonephritis (GN) is the third leading cause of end-stage renal disease (ESRD) in European populations.[1] Its most frequent histological types are IgA nephropathy (IgAN), membranous nephropathy (MN) and focal and segmental glomerulosclerosis (FSGS).[2,3] In the mid-1990s angiotensin-converting enzyme inhibitors (ACEi) were shown to slow progression to ESRD in non-diabetic kidney diseases and became widely used in patients with GN.[4] It is worth looking at data on renal survival and progression to ESRD today, now that most patients receive either ACEi or angiotensin

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receptor blocking (ARB) treatments. Decline in the glomerular filtration rate (GFR) varies substantially among patients with GN.[5–7] These variations are explained only partly by the traditional risk factors, such as proteinuria,[7–9] high blood pressure[7–9] and low GF [7–9] at diagnosis. Other possible determinants for progression to ESRD remain controversial. These include male gender,[7] age,[7,10] smoking[11–13] and overweight.[14] Although diabetes is an expected risk factor for progression for non-diabetic kidney disease, the impact of its presence at the initial diagnosis of primary GN on subsequent renal function loss has not been studied. Nor has the hypothesis that anaemia may also predict progression in patients with primary GN, even though experimental data and a few studies of patients with and without diabetes so suggest.[15,16]

We therefore studied renal survival and several traditional and less traditional risk factors for progression in a cohort of 536 patients with primary IgAN, MN or FSGS, followed for a mean of 7 years. We hypothesized that these three types of GN shared common progression risk factors.

Methods

Description of the cohort

The GN-PROGRESS study is a retrospective cohort including all adult (>18 years) white patients from 11 Paris area nephrology departments who were first diagnosed with primary IgAN, MN or FSGS between January 1994 and June 2001 (see Appendix for a list of participating centres). Patients were identified from the renal biopsy files of the affiliated pathology departments, and all GNs were histologically proven. A group of nine experts (including two nephrologists and one pathologist for each histological type) reviewed the medical records of 853 patients meeting these criteria and confirmed the diagnosis and the primary nature of GN for 562. Exclusion criteria included HIV for all histological types; heroin abuse and severe reduction in kidney mass for FSGS; Henoch–Schönlein purpura, cirrhosis, arthritis and gastrointestinal inflammatory diseases for IgAN; and systemic lupus erythematosus, malignancy, virus B hepatitis and drug toxicity for MN. We also excluded 26 patients with an estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m^2 at diagnosis, i.e. chronic kidney disease stage 5 of the Kidney Disease Outcomes Quality Initiative, leaving 536 eligible cases. Between 2002 and 2004, these were all invited for an interview and a blood testing which were held at the patient convenience either at the nephrology outpatient clinic or at the dialysis or transplant centre. This was achieved in 339 of them. Attending the clinic was not feasible in 88 patients, but their medical record was accessible, 18 had died before 2002, 4 of whom after starting dialysis and 91 were lost to follow-up by the centres. A flowchart of the number of patients included and excluded in each step of data collection is shown in Figure 1.

Information

Nephrology department records provided clinical data for all patients. Baseline information at diagnosis included age, gender, body mass index (BMI), diabetes status, defined as treatment with oral anti-diabetics or insulin, systolic and diastolic blood pressure (BP), haemoglobin (Hb), serum creatinine and proteinuria (g/day or g/g creatinine). Smoking data were collected from questionnaire for patients who were interviewed and from medical records for the others. Treatment history with antihypertensive drugs, ACE inhibitors and ARBs until GN diagnosis was also recorded. GFR was estimated (eGFR) with the abbreviated MDRD equation. Hypertension was defined as systolic blood pressure (SBP) >140 mm Hg or diastolic blood pressure (DBP) >90 mm Hg or the use of antihypertensive medications. Moreover, in the subcohort of 339 interviewed patients, additional information about serum creatinine measures and GN treatment with ACEi, ARB, corticosteroid and immunosuppressive agents after diagnosis were abstracted from the medical records. Serum creatinine at the time of interview was also recorded in non-dialysed patients.

Outcome

The primary end point was the time to a first treatment for ESRD, including dialysis or preemptive transplantation. Events were identified in two ways. First, they were traced through medical records between January 2002 and March 2004; this was possible for 445 of 536 (83%) cohort patients. Linking the study database with both the 2003 national dialysis survey file and the French renal transplant waiting list on December 2004 then allowed us to identify those of the 91 untraceable patients (17%) who were treated for ESRD and to extend the follow-up of the overall cohort. A secondary composite end point was the time to either ESRD treatment or halving of eGFR. This end point was studied in the subcohort of 339 patients with serum creatinine measured between the date of renal biopsy and the interview, as mentioned above.

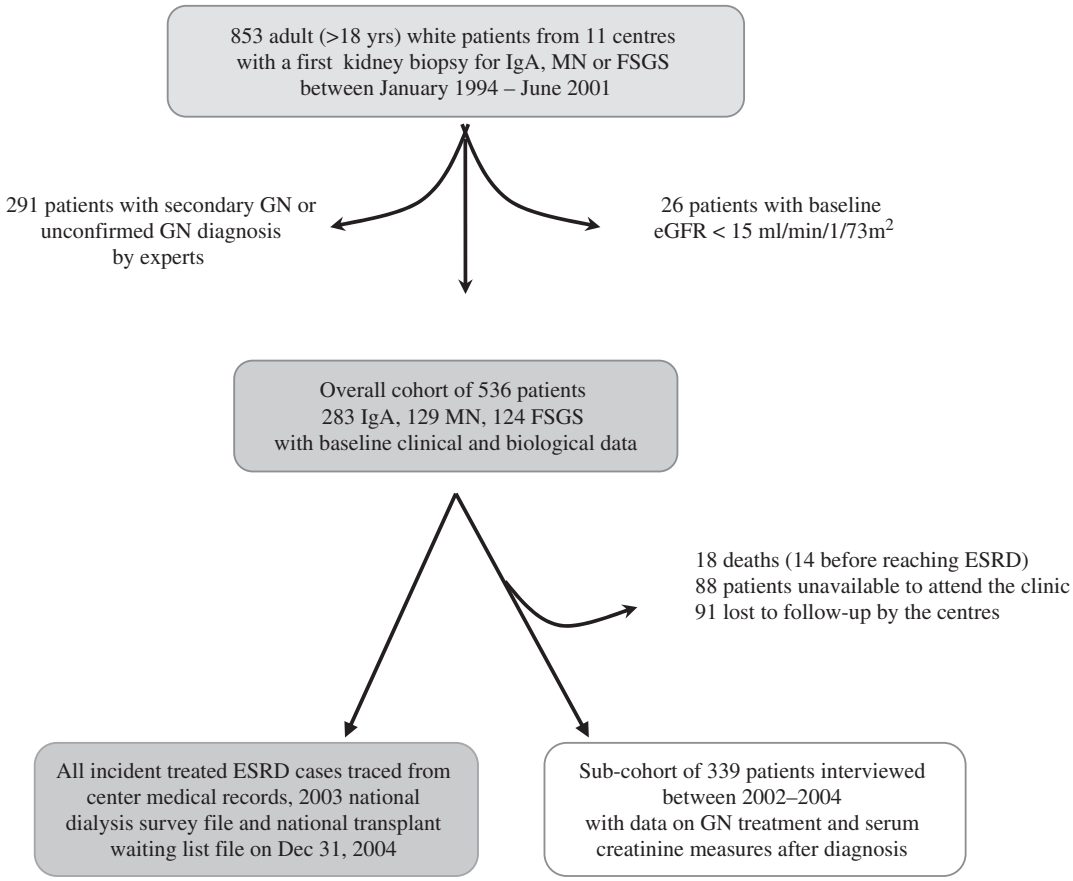

Figure 1. Flowchart of the participants in the GN-PROGRESS cohort. GN: glomerulonephritis; IgAN: IgA nephropathy; MN: membranous nephropathy; FSGS: focal and segmental glomerulosclerosis; eGFR: estimated glomerular filtration rate.

Statistical analysis

Patients' characteristics at baseline were described for the overall cohort, compared according to histological type and interview status (339 patients who were interviewed and 197 who were not). Normally distributed variables were expressed as means (SD) and compared with one-way ANOVA. Non-normally distributed variables were expressed as median and interquartile [IQ] values and compared with Mann–Whitney tests. Qualitative values were compared with Chi2. We used the Kaplan Meier method to estimate renal survival probabilities and the logrank test to compare them. In this analysis, patients who died before ESRD were censored. We also used this method to describe the incidence of ESRD according to age at diagnosis (under 40 years or 40 and older) by histologic type, hypertension, diabetes, proteinuria and Hb tertiles. The hazard ratios (HR) and 95% confidence intervals (95% CI) for ESRD according to various characteristics were studied with Cox proportional-hazard models for GN as a whole, for the overall cohort and for the subgroup of 339 patients. We first analysed the crude associations with each potential risk factor and systematically tested for possible interactions with histological type. These models analysed Hb according to gender-specific tertiles and proteinuria according to GN-specific tertiles to take into account the large differences in median values between histological types. Second, we estimated HRs adjusted for age, gender, histological type and all baseline covariates except eGFR. Finally, we also adjusted HRs for baseline eGFR. Because it was statistically significant, all these models were adjusted for the interaction term of age with histological type (Figure 3). All *P*-values were two-tailed, and values <0.05 were considered statistically significant. Analyses were performed with SAS software V 9.1 (SAS Institute, Cary, NC).

Results

Patient characteristics at baseline

IgAN was the most frequent histological type, and patients with it were the youngest of the cohort (Table 1). Overall, the cohort included three times

Table 1 Patient characteristics at baseline

	Overall cohort	Focal and segmental glomerulosclerosis	Membranous nephropathy	IgAN nephropathy	*P**	Subcohort
N	536	124	129	283		339
Age in year	43 (17)	46 (16)	54 (18)	37 (14)	<0.01	41 (16)
Men	74	67	71	77	<0.04	75
Smoking						
Never	35	27	32	39		40
Former	20	17	25	20		28
Current	28	39	24	25		32
Missing	17	17	19	16	0.03	
Body mass index (kg/m^2)						
<25	44	35	36	51		50
[25–30]	25	27	27	24		30
⩾30	14	21	17	10		15
Missing	17	17	20	15	<0.01	5
Diabetes	5	10	7	3	<0.01	5
Hypertension (>140/90 or treated)	60	74	60	53	<0.01	58
eGFR (ml/min/1.73m^2)	70 [43–91]	56 [36–83]	79 [61–95]	70 [42–92]	<0.01	67 [41–90]
⩾60	61	45	75	62		58
[30–60]	24	36	18	21		26
[15–30]	15	19	7	17	<0.01	16
Proteinuria (g/d)						
Median	2.5 [0.9–5.0]	3.7 [2–6.6]	6.0 [2.3–9]	1.2 [0.5–2.5]	<0.01	2.4 [0.9–5.2]
% >3	43	61	84	17	<0.01	
Haemoglobin (g/l)						
Men	13.8 (1.9)	14.0 (1.8)	13.5 (2)	14.0 (1.8)	NS	13.8 (2.0)
Women	12.3 (1.5)	12.6 (1.6)	12.0 (1.5)	12.3 (1.4)	NS	12.3 (1.4)
ACEi or ARB	14	18	15	11	NS	16

ACEi or ARB: angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; eGFR: estimated glomerular filtration rate; Values are mean (SD), median [interquartile range] or percent. **P*-value of the comparison between histological types.

more men than women. Smoking, obesity (BMI ⩾ 30 kg/m^2), and history of diabetes and hypertension were significantly more frequent in patients with FSGS than in those with MN and IgAN. Baseline eGFR and median proteinuria were higher in patients with MN than with IgAN or FSGS. At diagnosis, microscopic haematuria was present in 34%, 34% and 65% of the patients with FSGS, MN and IgAN, respectively. History of macroscopic haematuria was present in 15% of those with IgAN. Twenty-five percent of IgAN patients were asymptomatic at renal biopsy, i.e. 19% had proteinuria less than <0.5 g/24 h and 6% isolated microscopic haematuria. As expected, Hb levels were higher in men than in women, but they were similar across GN type.

Table 1 summarizes the baseline characteristics of the 339 patients who were interviewed. These patients had IgAN more often than their non-interviewed counterparts (57% vs. 46%), but they did not differ significantly with respect to age, gender or any of the baseline clinical or laboratory markers (data not shown).

Renal survival

During a mean follow-up of 7 years, 100 patients (18.7%) from the overall cohort started dialysis, 4 (0.7%) received a preemptive graft and 14 (2.6%) died before reaching ESRD. Renal survival differed significantly according to GN type ($P = 0.01$). Seven-year renal survival was 69% for FSGS patients, 82% for IgAN and 88% for MN (Figure 2). In the subcohort of interviewed patients, 65 (19%) started renal replacement therapy and 27 (8%) halved their eGFR, during a mean follow-up of 56 months. The percentage of treated ESRD did not differ significantly for any GN type between patients who were and were not interviewed (data not shown).

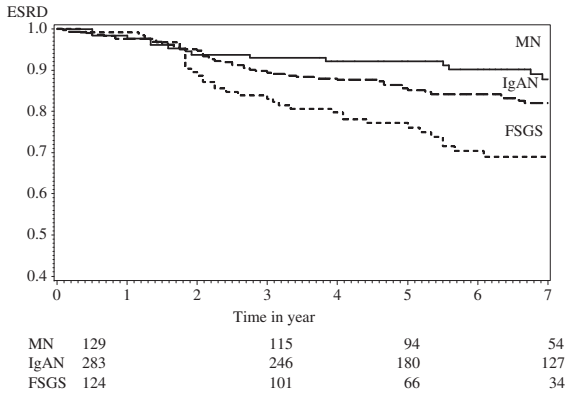

Figure 2. Renal survival by histological type in the overall cohort.

Risk factors associated with the risk of ESRD

There was a strongly significant interaction between age and histological type for the risk of ESRD: older age was associated with a higher risk for IgA patients and with a lower risk for FSGS patients (P for interaction $P=0.01$) (Figure 2 and Table 2). It is worth noting that age was not associated with nephrotic-range proteinuria or hypertension in patients with FSGS (data not shown). The ESRD incidence rate increased significantly with increasing baseline histologic-specific proteinuria tertiles and with decreasing gender-specific Hb tertiles and eGFR stages (Figure 2). In the crude analysis, the baseline characteristics most strongly related to ESRD risk were hypertension, diabetes, proteinuria, Hb level and eGFR (Table 2). Neither smoking nor BMI was related to GN progression. Neither micro- nor macroscopic haematuria was associated with ESRD risk (data not shown). Adjusting for baseline characteristics, except eGFR, tended to strengthen the association with diabetes and to weaken that with hypertension slightly. It did not, however, alter the dose–effect relations observed with proteinuria and Hb levels. Further adjustment for baseline eGFR considerably decreased the HR associated with hypertension but had a lesser impact on those related to proteinuria and Hb levels, both of which remained strongly significant. Analysis of a combined outcome variable of ESRD and death yielded similar estimates (data not shown).

In the subcohort of interviewed patients, 80% received ACE inhibitors or ARBs, i.e., 93%, 92% and 71% of those with FSGS, MN and IgAN, respectively. Corticosteroid treatment was reported by 37%, 34% and 7% of those with FSGS, MN and IgAN, respectively, and immunosuppressive treatment by 17% of those with FSGS and 25% with MN. Associations between baseline characteristics and the risk of either ESRD treatment or halving of eGFR were consistent with those for the cohort as a whole (Table 2). There was no dose–effect relation with either smoking quantity or duration (data not shown). Moreover, ACEi and ARB treatment during follow-up—for all GN cases as well as by histological type—was not significantly related to the risk of this composite event. This was also the case for steroid treatment in FSGS and MN patients, and immunosuppressive treatment in MN patients. Adjusting for these treatments did not alter any of the above associations.

Discussion

In this observational cohort of patients with primary GN, we showed that renal survival was clearly lower in those with FSGS than in those with either MN or IgAN. As expected, baseline proteinuria and eGFR were associated with the risk of ESRD, but mean proteinuria levels varied between GN types. The association of hypertension with progression to ESRD was independent of age and proteinuria, but was substantially mediated by baseline eGFR. The most original findings are that Hb level and diabetes at diagnosis were independent predictors of progression in all types, as was younger age in FSGS patients. Our hypothesis that risk factors were common to all GN types was true except for age.

The most important obstacles to studying the determinants of GN progression are the need for biopsy-proven diagnosis, the rarity of each histological type, and the relatively low incidence of ESRD. Indeed, although we considered all incident adult white patients over a 6-year period from all university and non-university nephrology centres in the Paris area, we identified only 536 eligible cases. A major strength of this study, however, is that it is based on an unselected cohort of patients with histologically well-defined primary GN, confirmed by experts, and a set of data about traditional and non-traditional risk factors for disease progression. The choice of a retrospective rather than a prospective cohort design increased the number of ESRD events, but also increased the number of patients lost to follow-up by the nephrology clinic providing their baseline characteristics, because patients in this age group frequently move away from the Paris area. Because we were able to obtain individual data about the vital and renal status for 83% of this cohort and we searched through national dialysis and transplant waiting-list databases for information about ESRD for the remaining 17% patients, selection bias should nevertheless be minimal.

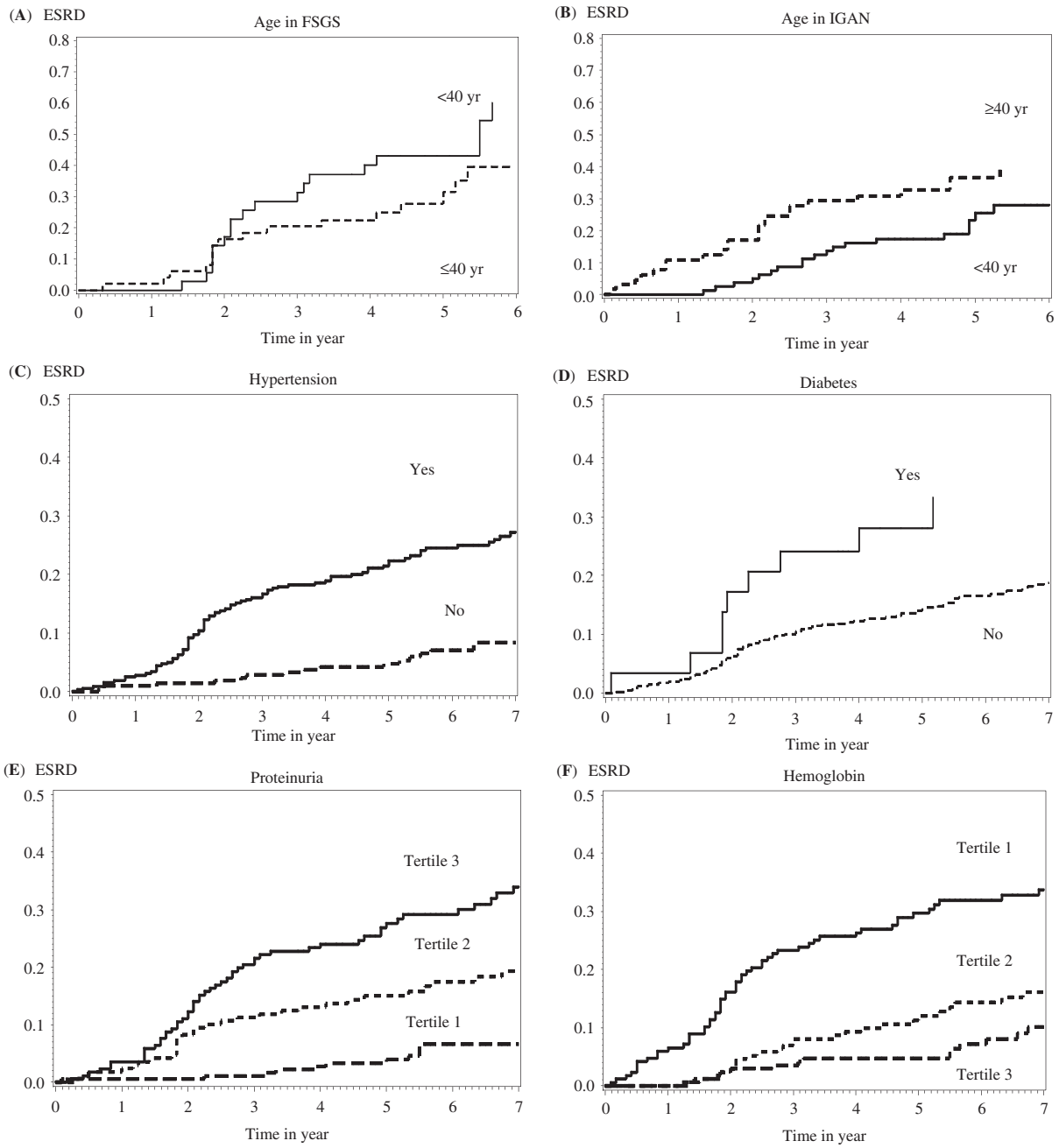

Figure 3. Risk of ESRD associated with baseline characteristics in the overall cohort (Kaplan Meier plot).
(**A**) Age $\geqslant$40 year *vs.* <40 year in FSGS (logrank $P = 0.07$) and (**B**) in IgAN (logrank $P = 0.06$).
(**C**) With and without hypertension (logrank $P < 0.01$).
(**D**) With and without diabetes (logrank $P < 0.01$).
(**E**) Median [range] of GN-specific proteinuria tertiles defined as follows: in FSGS: T1, 1.5 [0.3–2.5]; T2, 3.8 [2.7–5.0]; T3, 8.3 [5.2–20.0]; in MN, T1, 3.0 [0.1–4.2]; T2, 5.8 [4.3–7.4]; T3, 10.2 [7.5–17] and in IgAN: T1, 0.4 [0–0.6]; T2, 1.3[0.7–1.9]; T3, 3.0 [2.0–16.0] (logrank $P < 0.01$).
(**F**) Median [IQ] of gender-specific haemoglobin tertiles defined as follows in men: T1, 12.0 [10.9–12.8]; T2, 14.0 [13.7–14.4]; T3, 15.5 [15.1–16.0] and in women: T1, 10.6 [10.2–11.5]; T2, 12.4 [12.0–13.0]; T3, 13.9 [13.4–14.2] (logrank $P < 0.01$).

Comparison of our renal survival estimates with others is limited by differences between studies in inclusion criteria and in patients' personal characteristics. However, we found that renal survival was higher in patients with primary MN and IgAN than in those with FSGS. The 7-year renal survival rate of 88% observed for MN was among the highest reported: these rates range from 70% to 90%.[5,17,18]

Table 2 Hazard ratios of treated end-stage renal disease (ESRD) and of the combined outcome of ESRD or halving of eGFR associated with baseline patient characteristics

	Overall cohort ($N = 536$ pts)					Subcohort ($N = 339$ pts)		
	N	Number of treated ESRD	Crude HR (95% CI)	Adjusted for all covariates except eGFR HR (95% CI)	Fully adjusted HR (95% CI)	*N*	Number of treated ESRD or eGFR halving	Fully adjusted HR (95% CI)
GN type								
IgAN	283	53	Ref.	Ref.	Ref.	193	45	Ref.
MN	129	15	0.6 (0.3–4.0)	0.6 (0.2–3.0)	2.6 (0.3–13.0)	76	19	1.9 (0.2–22)
FSGS	124	36	1.7 (1.1–2.6)	4.4 (1.3–15.0)	7.0 (2.0–24.0)	70	28	17.0 (4.0–72.0)
Age by 10 years								
IgAN	283	–	1.3 (1.1–1.5)	1.1 (0.9–1.4)	1.1 (0.9–1.3)	193	–	1.1 (0.7–1.5)
MN	129	–	1.1 (0.8–1.5)	1.0 (0.8–1.4)	0.9 (0.6–1.2)	76	–	1.1 (0.8–1.6)
FSGS	124	–	0.8 (0.7–1.0)	0.8 (0.6–1.0)	0.7 (0.6–0.9)	70	–	0.6 (0.4–0.8)
Gender								
Women	140	27	Ref.	Ref.	Ref.	86	14	Ref.
Men	396	77	1.0 (0.7–1.6)	1.1 (0.6–1.8)	1.1 (0.6–1.8)	253	78	1.3 (0.7–2.3)
Diabetes								
No	507	95	Ref.	Ref.	Ref.	321	86	Ref.
Yes	29	9	1.6 (0.9–3)	2.7 (1.3–6)	2.6 (1.2–5.8)	18	6	3.1 (1.2–7.8)
Hypertension (>140/90 or treated)								
No	215	17	Ref.	Ref.	Ref.	140	14	Ref.
Yes	317	86	4.0 (2.4–6.8)	2.9 (1.6–5.3)	1.4 (0.8–2.7)	199	78	1.9 (0.9–4.0)
GN-specific proteinuria tertiles								
1	180	13	Ref.	Ref.	Ref.	115	10	Ref.
2	175	33	3.1 (1.6–6)	3.2 (1.5–6.7)	2.5 (1.2–5.3)	105	24	2.2 (0.9–5.4)
3	171	56	5.6 (3.0–10)	6.0 (3.1–12.3)	4.1 (2.0–8.1)	113	56	6.3 (2.7–15.0)
P for trend			<0.01	<0.01	<0.01			<0.01
Gender-specific haemoglobin tertiles								
1	167	17	3.8 (2.2–6.6)	3.9 (2.2–6.7)	2.4 (1.3–4.5)	110	44	2.0 (1.1–3.8)
2	173	27	1.6 (0.9–2.9)	2.0 (1.0–3.8)	1.9 (1.0–3.6)	109	27	1.5 (0.8–2.8)
3	169	55	Ref.	Ref.	Ref.	112	17	Ref.
P for trend			<0.01	<0.01	<0.01			<0.01
Smoking								
Never	187	36	Ref.	Ref.	Ref.	139	37	Ref.
Former	109	16	0.8 (0.4–1.4)	0.6 (0.3–1.1)	0.6 (0.3–1. 2)	82	18	0.6 (0.3–1.2)
Current	149	38	1.4 (0.9–2.2)	1.2 (0.8–1.9)	1.2 (0.7–1.9)	116	37	1.2 (0.7–2.0)
Missing	91	14	0.8 (0.4–1.5)	0.7 (0.3–1.4)	0.7 (0.4–1.5)	–	–	
Baseline ACEi or ARB								
No	463	87	Ref.	Ref.	Ref.	285	75	Ref.
Yes	71	17	1.4 (0.8–2.4)	1.1 (0.6–2)	0.9 (0.5–1.6)	54	17	0.9 (0.5–1.8)
eGFR (by 10 ml/min/ 1.73 m^2)	536	–	0.6 (0.6–0.7)	–	0.7 (0.6–0.8)	339	–	0.8 (0.7–0.9)

IgAN: IgA nephropathy; MN: membranous nephropathy; FSGS: focal and segmental glomerulosclerosis; ACEi or ARB: angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; eGFR: estimated glomerular filtration rate.

In contrast, the 68% rate for FSGS and the 82% rate for IgAN were close to the middle of the literature: in earlier studies, FSGS rates ranged from 50% to 80%[6,19] and IgAN rates from 62% to 96%.[7] Given that we cannot completely rule out some underestimation, these survival rates are low. This may be explained by the relatively low rate of corticosteroid treatment for FSGS in our series, compared with others.[9,20] They are consistent with ESRD registry data, which show a rather stable

incidence of GN as a cause of ESRD over the past decade.[1]

Some studies suggest that kidney disease progresses faster in men than in women, but evidence gathered by the K/DOQI working group was inconclusive (K/DOQI 2002). Here we found a predominance of men at diagnosis, especially for IgAN, but no association between gender and progression. Some studies indicate that in IgAN patients, older age is associated with faster progression to ESRD; after adjusting for other patient characteristics, we did not find such an association, although others have.[7] With one exception, however, the literature—including this study—does not support this association of age with progression in MN patients.[10]

In our cohort of patients with FSGS, younger age was associated with a worse prognosis. To our knowledge, this has not previously been described for primary GN. This relation between age and prognosis could not be explained by any patient characteristics. It may, however, have resulted from the selection process used to identify patients with primary FSGS. Inclusion criteria were highly specific, and patients, especially those with advanced chronic renal failure and an unclear clinical history, were excluded when there was the slightest possibility that FSGS was secondary to reduction in kidney mass. This has led to the exclusion of many elderly patients with a long history of hypertension, for whom the primary nature of FSGS was difficult to assert. Although selection bias is a likely explanation for this unexpected finding of a relation between progression and age, we cannot rule out the possibility that primary FSGS, as we defined it, truly has a worse prognosis in younger patients. It is becoming increasingly clear that FSGS is a heterogeneous entity, and the subset of FSGS occurring in young adult could be particularly severe.

As expected, baseline proteinuria was a major predictor of renal function loss and there was a significant dose–effect relation between proteinuria and both rate of progression to ESRD and eGFR decline.[7–10] The levels of proteinuria associated with progression, however, varied across histological types, and levels were much higher for MN and FSGS than for IgAN. Hypertension, another traditional risk factor for kidney disease progression, was strongly associated with the risk of ESRD, independently of other covariates except eGFR, but, in contrast with these covariates, the relation was largely explained by baseline eGFR level. Therefore, in our patient cohort, the association of hypertension at diagnosis with ESRD risk was confounded by baseline eGFR level. These findings do not contradict clinical trials showing that the better the blood pressure control after diagnosis the lower the risk for kidney disease progression, which we did not study in this observational cohort. They seem, nevertheless, inconsistent with those from a patient-level meta-analysis of non-diabetic kidney diseases showing that higher systolic blood pressure levels both at baseline and follow-up were associated with higher risk for progression even after adjusting for baseline serum creatinine concentration.[21] The authors of this study, however, did not exclude reverse causation to explain this association.

The widespread use of ACEi and ARB treatment during this period is reflected by our finding that nearly all patients with FSGS and MN and three quarters of those with IgAN received these drugs. Although this factor is, like corticosteroid and immunosuppressive treatments, important to adjust for in this kind of study, the relation with eGFR decline should not be interpreted causally, as indication bias is to be expected in observational studies.[22]

The role of diabetes in the progression of primary GN was expected, but has rarely been investigated. We report for the first time that the coexistence of diabetes and GN at diagnosis is strongly associated with the risk of ESRD, independent of other patient characteristics. Although the precise mechanisms by which diabetes mellitus induces glomerular lesions are still unclear, it is conceivable that diabetes acts as an amplifier and promotes sclerosis of already damaged glomeruli. This finding underlines the importance of treating diabetes in patients with primary GN.

Smoking is commonly accepted as a risk factor for kidney disease progression. Our negative finding is inconsistent with the positive associations we observed in a previous case–control study of patients diagnosed with the same GN types eight years earlier in the same area, as well as with those reported by Orth *et al*. and Ejerblad *et al*.[11–13] Those studies did not take into account as many potential confounders as we did here, and this may account for the apparent inconsistency. Other likely explanations include a chance finding or lack of power.

A few observational studies have reported an inverse relation between Hb level and GFR decrease in patients with either diabetic nephropathy or unspecified chronic renal failure.[16,23] A number of population-based studies also observed an association between Hb and GFR levels, but very few were longitudinal.[15] This relation has not yet been prospectively studied in patients with primary GN. We found that baseline Hb inversely predicted time to ESRD, independently of other risk factors, including baseline quantitative eGFR

and proteinuria. Because this association remained after careful adjustment for baseline eGFR, confounding by the severity of kidney disease is unlikely. Some experimental data support a causal association.[24] Specifically, hypoxia of tubular cells resulting from anaemia may play an important role in the tubulointerstitial damage associated with chronic kidney disease and may also contribute to glomerulosclerosis and tubulointerstitial damage by increasing oxidative stress.[24] Whether correction of anaemia with erythropoiesis-stimulating agent (ESA) would improve GN outcome, however, is a different question. While two small interventional trials report that high target ranges of Hb levels are associated with a slower decrease in GFR,[25,26] two recent and relatively large trials have failed to provide evidence that ESA has a renoprotective effect,[27–29] questions have been raised about their methods, however, and this effect remains the topic of debate.[27–29]

Several limitations of the study deserve comment. First, although it is based on a large cohort of primary GN cases, it may have lacked power in the analysis of some risk factors, such as smoking. Second, serum creatinine was not measured in a single laboratory and GFR was estimated with a creatinine-based equation. Although inter-laboratory calibration errors affect estimates for high values of serum creatinine only slightly and the MDRD equation performs well in French patients in the eGFR range observed, inaccuracy and bias in eGFR are likely.[30] Consequently, adjustment for eGFR may have been suboptimal. Finally, as discussed above, renal survival and deaths may have been moderately underestimated, due to a possible lack of sensitivity of the record linkage method used to identify renal events for 17% of the cohort patients.

In conclusion, this study reported that renal survival remains lower in FSGS than in other types of GN, particularly in younger FSGS patients. Beyond the traditional risk factors, anaemia and diabetes were identified as strong independent and potentially modifiable predictors of ESRD for GN as a whole. These findings have two major implications. First, diabetes should be carefully monitored and controlled in patients with primary GN. Second, further clinical trials are needed to evaluate whether correction of anaemia can improve the course of GN progression.

Acknowledgements

This study was supported by grants from the Ministry of Health (PHRC AOM 00022), the Ministry of Environment (Décision d'aide EN00D08), the Ministry of Research (Décision d'aide 01P0513) and the Biomedecine Agency (AO Recherche et Greffes 2005).

Conflict of interest: None declared.

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Appendix

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