Kidney International, Vol. 34 (1988), pp. 382–388

Prognostic indicators in patients presenting with the nephrotic syndrome

LINDA P. HUNT, COLIN D. SHORT, and NETAR P. MALLICK

The Faculty of Medicine Computational Group and The Department of Renal Medicine, Manchester Royal Infirmary, Oxford Road, Manchester, United Kingdom

Prognostic indicators in patients presenting with the nephrotic syndrome. Clinical data from 246 patients presenting with a nephrotic syndrome and biopsy-proven glomerular disorder were analyzed, using statistical survival techniques, to determine which of several variables (sex, age, plasma creatinine, diastolic blood pressure and 24-hour urinary protein loss) were associated with subsequent end-stage renal failure. The best prediction of outcome could be made at one year (N = 121); then plasma creatinine ($P < 0.001$) and heavy proteinuria (P = 0.049) were the best determinants. For a given plasma creatinine level, heavy urinary protein was associated with a worse outcome. The incidence of end-stage renal failure was greatest three to four years from the date edema first developed. Plasma creatinine and urinary protein values, collected four-monthly throughout the study period, were analyzed as time-dependent covariates. A relationship was found between the prevailing risk of renal failure and earlier heavy proteinuria ($P < 0.001$). Spontaneous complete remission of proteinuria was associated with a highly favorable outcome (P = 0.001) and normal, or impaired but stable, renal function.

The long-term outcome of patients with histopathologically-defined glomerular damage needs to be determined to enable an accurate prognosis to be made and to assess the value of therapeutic regimens. Usually prognosis has been evaluated for single histopathological groups; only occasionally have the groups been compared [1]. Even within such defined groups, however, the clinical course of individual patients is highly variable.

We decided to analyze, from our prospective series, a group of patients from across the histopathological spectrum, but with a single clinical presentation, that is, a nephrotic syndrome. In this defined cohort we have sought markers of eventual outcome.

Life tables and Kaplan-Meier estimates take account of differing follow-up periods and enable the percentage of survivors in subgroups of patients to be compared [1]. Given a clear definition of 'onset' and 'end-point', such methods can be used to study the time interval to, for example, remission of proteinuria and to any subsequent relapse [2]. The most important factors in determining a given outcome can be assessed using multivariate techniques. The Cox 'proportional hazards' regression model has been used to discern factors associated with survival on differing treatments for end-stage renal failure, for example on hemodialysis [3] or after transplantation [3, 4], and, more recently, to study factors associated with progression to renal failure in the natural history of IgA nephropathy [5, 6]. Changes in plasma creatinine were used as end-points for some analyses in a study of the natural history of a variety of glomerular pathology [7, 8]. Variables of interest were measured at a fixed point in time, for example at time of biopsy.

In this report, we explore not only variables at fixed points in time, but also use time-dependent covariates to analyze data collected prospectively at sequential follow-up attendances. We have examined the prognostic value of a selected group of clinical variables.

This study began prospectively in 1971, when one of us (NPM), with colleagues at the Manchester Royal Infirmary, decided to review and to document all such patients and to follow them on a regular outpatient basis. Patients were seen at four-monthly intervals, when clinical, biochemical and hematological data were obtained. From 1981, the three present authors have assembled all the data on computer, and we have subjected it to statistical analysis. Retrospective data were available for some patients biopsied between 1960 and 1971; where appropriate these too were included. All patients had significant proteinuria (that is, more than 1 g/24 hr). We excluded any patient requiring dialysis within one month of onset or with diabetic nephropathy. Principal findings on the 444 patients in the study have been reported [9].

In 145 patients the first evidence of disease was asymptomatic proteinuria detected at a routine medical examination. These form a highly important subgroup [9] and are the subject of a separate analysis. We concentrate here on the 246 patients whose first manifestation of renal disease was the nephrotic syndrome. Our aim was to examine survival from the date that edema first appeared until end-stage renal failure (ESRF) supervened, and to determine the prognostic value of certain clinical and pathological variables.

Methods

Patients

There were 246 patients whose disease first manifested as a nephrotic syndrome. These occurred between 1948 and 1979, the majority (94%) after 1961. Actual follow-up ranged from 11 weeks to 33 years, with a median of seven years. The male to

Received for publication August 26, 1986
and in revised form April 19, 1988

Table 1. Clinicopathological diagnostic groups

Biopsy	Male N	Male %		Female N	Female %		Both sexes N	Both sexes %
Minimal change	24	15%		9	10%		33	13%
No light microscopic change	12	8%		12	13%		24	10%
Membranous nephropathy	46	30%		21	23%		67	27%
Mesangial proliferative with immunofluorescence:								
IgA predominant	1			1			2	1%
IgM predominant	9	41	26%	8	25	28%	17	7%
Other	6			6			12	5%
Not done	25			10			35	14%
Mesangiocapillary	10	6%		11	12%		21	9%
Diffuse proliferative	5	3%		2	2%		7	3%
Focal segmental proliferative	4	3%		5	6%		9	4%
Other	14	9%		5	6%		19	8%
Total	156	100%		90	100%		246	100%

Table 2. Groupings for variables showing numbers of patients for whom data was available

Sex	Male	156 (63%)
	Female	90 (37%)
Age at onset (*years*)	less than 20	67 (27%)
	20 to 34	40 (16%)
	35 to 49	61 (25%)
	50 or more	78 (32%)
	At onset	At one year
Plasma creatinine *mmol/liter*		
less than 0.12	41 (53%)	77 (55%)
0.12 to 0.19	22 (29%)	39 (28%)
0.20 or more	14 (18%)	23 (17%)
Total	77	139
Diastolic blood pressure *mm Hg*		
less than 110	114 (83%)	155 (92%)
110 or more	24 (17%)	13 (8%)
Total	138	168
24-hour urinary protein *g*		
less than 1	0 (0%)	29 (19%)
1 to 4.99	19 (21%)	31 (21%)
5 to 9.99	26 (29%)	24 (16%)
10 or more	45 (50%)	67 (44%)
Total	90	151
Urinary protein/creatinine ratio *g/g*		
less than 4	7 (12%)	42 (34%)
4 to 7.99	23 (40%)	29 (24%)
8 or more	28 (48%)	52 (42%)
Total	58	123

female ratio was approximately 2:1, and the sexes had similar histopathological spectra (Table 1). Mean age at onset was 38 years (SD 19) for men and 36 years (SD 18) for women.

Thirty-one patients had systemic diseases (systemic lupus erythematosus 15, Henoch Schönlein purpura 3, microscopic polyarteritis 2 and amyloidosis 11).

Treatment

Diuretics and hypertensive agents were prescribed as clinically indicated. Hypertension was treated immediately it was confirmed. Thiazides were used as a first line treatment if diuretics had not been used previously. Antihypertensive agents (methyldopa and beta-blockers) were used subsequently.

From 1971, immunosuppressive agents and steroid therapy were reserved for patients with potentially responsive lesions. Of 57 patients with 'no significant change' on light microscopy, 33 patients showed a prompt and complete remission of heavy proteinuria after steroid therapy. This is referred to as minimal change nephropathy (MCN).

In earlier years, a number of other patients received immunosuppressives and/or steroids. Preliminary results do not suggest the presence of an unsuspected cohort whose disease remitted on any drug therapy. The only exception may be membranous nephropathy where, as we have reported [10], some patients benefitted from 'pulse' steroid therapy.

Variables for analysis

Plasma creatinine (mmol/liter), urinary protein loss (g/24 hr), diastolic blood pressure (mm Hg; obtained at each follow-up visit), and sex and age at onset were chosen for analysis. The ratio of the urinary protein to the urinary creatinine output (g/g over the 24 hr period) was calculated to minimize errors caused by inaccurate collection of urine.

Initially, patients were grouped according to values of these variables at the onset and at each anniversary (Table 2). Only measurements obtained within eight weeks from the relevant date were used. Our previous work [9] had suggested a 24-hour urinary protein loss of more than 5 g had significance; in this analysis we chose cut-off points of 5 and 10 g/24 hr for urinary protein. Corresponding values for the urinary protein/creatinine ratios were '4' and '8'. (These were equivalent percentiles for all available measurements in the study.) A diastolic blood pressure of 110 mm Hg, uncorrected for age and sex, was chosen to indicate 'moderate' hypertension; such levels are associated generally with increased morbidity and mortality, such as cardiovascular disease. Treatment had often been initiated at lower levels. 'Mild' hypertension, defined according to the normotensive limit for the patient's age and sex [11], and plasma albumin level (g/liter), were also considered in the multivariate analysis.

Plasma creatinine and albumin were measured using standard autoanalyzer methods, and urinary protein was measured by a turbidometric method using salicylsulphonic acid.

Preliminary statistical analysis

Kaplan-Meier survival estimates were calculated for the whole group, using ESRF, (dialysis, transplantation without prior dialysis, or death due to renal failure) as the end-point. Patients who died from other causes were censored. In a separate analysis we examined deaths, not from renal failure, but from causes which may have been related to the consequences of prolonged renal disease, such as ischemic heart disease or cerebro-vascular disease.

For ESRF, survival estimates were calculated for the subgroups of patients defined at onset and at one year (Table 2) and compared by the Mantel-Cox test [12]. Estimates of the 'hazard

rates' [13] were plotted to ensure that the statistical assumptions required for a Cox regression analysis were met.

For patients in whom a complete data set was available, Cox 'proportional hazards' regression analysis [12, 14, 15] was used to find which of the variables age, sex, plasma creatinine level, moderate hypertension, and prevailing urinary protein loss, measured either at onset or at one year, were related independently to progression to ESRF. Preliminary analysis established that urinary protein/creatinine ratio was a more reliable parameter than 24-hour urinary protein loss, and that this ratio could be considered usefully in two subgroups (<4, ≥4). A reciprocal transformation for plasma creatinine level gave a more precise parameter for analysis than the prevailing plasma level. The year of onset was included to determine whether there was a trend towards better survival over the study period, since such a finding would have rendered the data set non-homogeneous. The statistical significance of each variable in turn was assessed by deleting the variable and using the likelihood-ratio test.

Once the most important markers of renal outcome were established, they were compared with the histopathological diagnosis in the Cox regression analysis by employing a series of 'dummy' variables for the main biopsy groups.

Statistical analysis using the sequentially collected data

The sequential data collection enabled time trends to be examined for each individual. With time, the prevailing value may become a more important indicator of prognosis than the value at onset or at one year. We therefore considered time-dependent covariates.

We tested for a significant change in risk of ESRF for those patients whose proteinuria had remitted spontaneously. Patients with MCN were excluded. 'Remission' was defined as a 24-hour urinary protein level below 0.3 g, validated by a second result of less than 0.5 g. Time to first remission was noted, and a new variable was defined for each patient, giving the value '0' before remission and '1' after.

We tested then for increase in risk associated with 'heavy' or 'very heavy' proteinuria (equivalent to more than 5 or more than 10 g/day) at any time. Three 'marker states' were defined according to the current urinary protein/creatinine ratio (less than 4; 4 to 7.99; 8 or more) and risks of ESRF were compared between the states, using the method described by Gail [16]. 'Relative risks' were calculated; these were risks associated with the 'heavy' or 'very heavy' proteinuric states (ratios ≥4 and ≥8) compared with the 'best' state (<4).[1]

In this analysis, we explored whether the risk of reaching ESRF was better predicted by the marker state 4, 12 or 24 months earlier, particularly since, for the patient approaching ESRF, proteinuria may be reduced because of the fall in GFR.

Finally we incorporated plasma creatinine into the definition of marker state. Four states were defined, depending on whether the plasma creatinine level was 0.2 mmol/liter or more and whether the urinary protein/creatinine ratio was above or below 4 (Table 7).

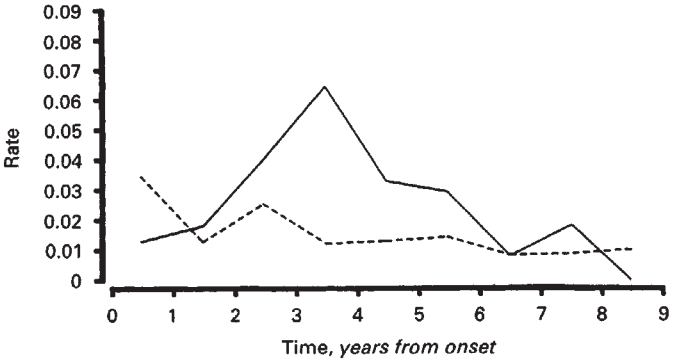

Fig. 1. *Piecewise-constant hazard rate estimates.* Numbers of ESRFs occurring in each 12 month interval divided by the total patient-years at risk. Symbols are: (——) renal deaths; (-----) other deaths.

Results

Preliminary survival analyses

Of 242 patients who had a definable date for onset of edema, 158 (65%) were alive with their own functioning kidneys when last seen, 44 (18%) progressed to ESRF, and the remainder died from other causes (ischemic heart disease 8, cerebro-vascular disease 4, malignancy 5, others 12, and cause unknown 12). Kaplan-Meier survival estimates for ESRF were 97% at two years, 85% at five years and 79% at ten years. Plots of the estimates of the hazard rates suggested a 'peak' risk of ESRF three to four years from onset (Fig. 1), but no peak was detected for 'other deaths'.

Comparisons between the subgroups are summarized in Table 3. Only two patients progressed to ESRF during the first year. An elevated plasma creatinine, either at onset or at one year, and heavy urinary protein loss persisting at one year were the factors most significantly related to eventual ESRF. A raised plasma creatinine level, however, did not necessarily imply that ESRF was inevitable, since we found many patients in whom levels rose temporarily above 0.2 mmol/liter.

Other factors associated with a worse outcome were male sex and a diastolic blood pressure of 110 mm Hg or more at onset.

Hypertension

Hypertension was difficult to assess prognostically, since it was usually treated promptly and rarely persisted. Of the 24 patients who were hypertensive (diastolic pressure 110 mm Hg or more) at onset, 'control' if defined by two successive levels below 100 mm Hg, was achieved in all but two patients after a median of 11 weeks. Levels fell spontaneously for five patients and, for the remainder, occurred after a median of six weeks therapy. The cohort with hypertension at one year were previously untreated; almost all had been normotensive at onset, and their hypertension was not associated with prognosis.

[1] To calculate the 'relative risks', we utilized the marker states for all patients at the time of each discrete ESRF event. Patients whose marker states were unknown were temporarily excluded. To estimate data at dates between follow-up attendances, we used the 'nearest' result within eight weeks. The 'numbers at risk' at each discrete ESRF event, the corresponding marker states, and the marker state of the ESRF patient were determined and this information was substituted into a log partial likelihood equation [16], which was maximized by using a library subroutine [18]. The significance of the differences between states was assessed using the likelihood ratio test. Relative risks were calculated from resulting estimates of the marker state coefficients, which we assumed to be constant over time.)

Table 3. Comparisons of renal survival in subgroups of patients

Variable	Groups compared	Significance[a]	Comments
Sex	male vs. female	NS ($P = 0.053$)	Worse survival for males
Age *years*	in Table 1	NS	Slight trend towards better survival in younger patients
Plasma creatinine *mmol/liter*	less than 0.2 vs. 0.2 or more	at onset: $P = 0.037$ at one year: $P < 0.001$	Worse survival with increased creatinine
Diastolic blood pressure *mm Hg*	less than 110 vs. 110 or more	at onset: $P = 0.037$ at one year: NS	Worse survival with increased blood pressure at onset only
Urinary protein *g/24 hr*	less than 5 vs. 5 or more	at onset: NS at one year: $P = 0.005$	Worse survival with higher levels at one year only
	less than 1 vs. 1 to 4.99	at one year: NS	
	5 to 9.99 vs. 10 or more	at one year: NS	
Urinary protein/creatinine ratio *g/g*	less than 4 vs. 4 or more	at onset: NS ($P = 0.075$) at one year: $P = 0.011$	Worse survival with higher levels at onset or at one year

[a] Significance by the Mantel-Cox test. NS, not significant.

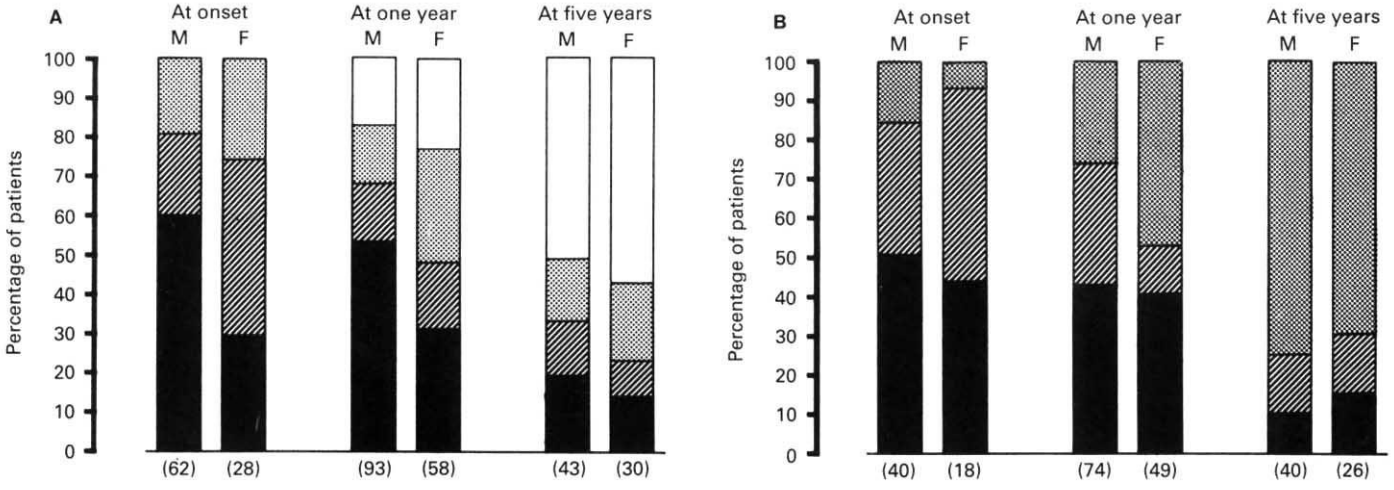

Fig. 2. *Patients grouped according to their 24-hour urinary protein output* (**A**) *and urinary protein/creatinine ratio* (**B**). Numbers of patients given in parenthesis. Abbreviations are: M, males; F, females. Symbols are: for **A**, □ < 1 g, ▨ 1–5 g, ▨ 5–10 g, ■ 10 g; for **B**, ▨ < 4 g, ▨ 4–8 g, ■ 8+ g.

Two thirds (62%) of patients were hypertensive at some time in their follow-up, but the levels did not remain high. For example, they had fallen below 110 (on two successive occasions) within four months in 83% of patients and within eight months in 91%. Levels fell spontaneously in 46% of patients and were associated with therapy in the remainder (antihypertensives ± thiazides 37%, thiazides only 17%). Half of the patients went on to have further periods of hypertension which lasted rather longer; levels had fallen in only 70% by four months, but in 89% by eight months. Spontaneous falls were less common (28%).

Longitudinal changes

The univariate analyses confirmed the importance of the variables we had chosen, but there were obvious interrelationships between the variables.

Figures 2A and B show that the percentage of patients with heavy proteinuria fell with time, and that there was a significant difference in urinary protein loss between the sexes at onset and at one year (chi-squared test, $P < 0.025$ and $P < 0.05$, respectively). This may be a reflection of body size, but at one year, differences between the urinary protein/creatinine ratios were also significant ($P < 0.025$). This correction for urinary creatinine output may adjust for body size, since, unlike urinary protein output, the ratio did not correlate significantly with weight and surface area. The fall in urinary protein loss with time was not attributable exclusively to the death (and so loss from further analysis) of patients with heavy losses, and a similar trend was observed within the five-year survivors, suggesting overall that the underlying lesions in surviving patients healed gradually.

While overall plasma creatinine levels remained steady (Fig. 3), levels were compared between the sexes after correction for weight and for surface area. Males had significantly higher levels at each anniversary from one to five years (Mann-Whitney U-test, maximum $P < 0.05$).

The relationship between prevailing heavy urinary protein loss and plasma creatinine level at onset, one and five years, is

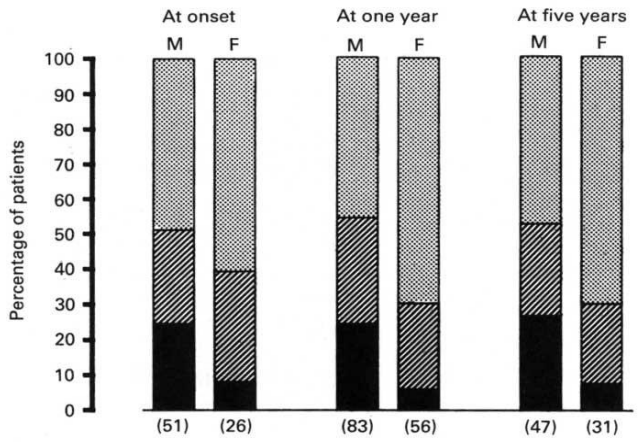

Fig. 3. *Patients grouped according to their plasma creatinine level.* Numbers of patients given in parenthesis. Abbreviations are: M, males; F, females. Symbols are: ▩ < 0.12 mmol/liter; ▨ 0.12–0.19 mmol/liter; ■ ≥ 0.2 mmol/liter.

Table 4. Relationship between prevailing urinary protein/creatinine ratio and plasma creatinine level

	Plasma creatinine level at		
	onset	one year	five years
Prevailing urinary protein/creatinine ratio			
<4	0.10[a]	0.09	0.10
	0.08–0.24 (6)	0.04–0.34 (41)	0.04–0.69 (48)
>4	0.12	0.12	0.14
	0.05–0.53 (47)	0.02–1.13 (80)	0.06–0.97 (18)
	NS[b]	$P = 0.012$	$P = 0.007$

[a] median, range, (*N*)
[b] comparison by two-tailed Mann-Whitney U-test. NS, not significant.

shown in Table 4. Plasma creatinine levels were significantly higher for those patients with persisting very heavy proteinuria (urinary protein/creatinine ratio ≥4) at one and at five years.

Multivariate analysis of survival-Cox proportional hazards regression

The data set at onset was incomplete, since this was frequently documented at an outlying hospital. Fifty-two subjects had adequate data. Of these, the 47 males were analyzed; none of the five females progressed to ESRF. Only heavy urine protein loss at onset (urinary protein/creatinine ratio ≥4) was significantly associated with progression to ESRF ($P = 0.025$).

At one year, 113 patients had complete data sets. Plasma creatinine level (after transformation) and heavy proteinuria (ratio ≥4) were the most significant, independent factors ($P < 0.001$; $P = 0.052$ respectively, Table 5A). Sex, age, and hypertension were not statistically significant. The year of onset, which ranged from 1961 to 1979 in these patients, did not influence outcome. This implies prognosis had not changed over the years of the study.

Table 5. Cox proportional hazards regression using information at one year to model renal survival

Coding for the grouped variables		
Sex	Female = 0	Male = 1
Diastolic blood pressure *mm Hg*	<110 = 0	110 or more = 1
Urinary protein/creatinine *g/g*	<4 = 0	4 or more = 1
A. $N = 113$		
Age	−0.015 SE 0.014	NS[a]
Sex	0.13 SE 0.62	NS
Plasma creatinine (reciprocal)	−0.27 SE 0.083	$P < 0.001$
Diastolic BP (grouped)	−0.85 SE 1.0	NS
Urinary protein/creatinine ratio (grouped)	1.3 SE 0.77	NS ($P = 0.052$)
Year of onset	−0.007 SE 0.063	NS
B. $N = 121$		
Plasma creatinine (reciprocal)	−0.27 SE 0.076	$P < 0.001$
Urinary protein/creatinine ratio (grouped)	1.3 SE 0.75	$P = 0.049$

[a] Coefficients with associated standard errors (SE) and significance by the likelihood ratio test. NS = not significant.

Table 6. Kaplan-Meier renal survival estimates for the seven main histopathological groups

	Number	At five years	At ten years
Minimal change	33	100%	100%
No light microscopic change	23	86%	78%
Membranous nephropathy	65	89%	87%
Mesangial proliferative	65	84%	75%
Mesangiocapillary	21	65%	57%
Diffuse proliferative	7	86%	86%
Focal segmental proliferative	9	88%	88%

An analysis at one year using only plasma creatinine and heavy proteinuria (121 patients) is shown in Table 5B. Relative risk of ESRF associated with heavy proteinuria (ratio ≥4) is exp (1.3) or 3.5.

In two separate analyses, we included 'mild' hypertension (defined according to the patients age and sex) and plasma albumin level at one year. These were not statistically significant determinants of outcome.

Biopsy

For the main clinico-pathological subgroups, Kaplan-Meier estimates at 5 and 10 years are given in Table 6. Only two groups were significantly different from the others; in MCN no patient progressed to ESRF; in mesangiocapillary disease (MCap) prognosis appeared poor. Patients with MCN and MCap disease differed from the remainder at one year: then the percentages with urinary protein/creatinine ratio above 4 and plasma creatinine level above 0.2 mmol/liter were 43% (of 14) and 7% (of 15) for MCN, 80% (of 10) and 21% (of 14) for MCap and 66% (of 92) and 19% (of 86) for the remainder. These findings were not influenced by exclusion of the patients with underlying systemic diseases.

The numbers of patients in the individual, histopathologically defined groups were too small for separate multivariate analyses. When biopsy findings were included in the Cox analysis,

Table 7. Relationship between risk of ESRF and earlier heavy proteinuria

A. Urinary protein/creatinine ratio used to define marker state
Marker state
0 = less than 4
1 = 4 to 7.99
2 = 8 or more

Lag	State '1'	State '2'	P
4 months	2.1 SE 0.62 (8)[a]	3.0 SE 0.57 (20)	<0.001
8 months	2.8 SE 0.79 (16)	3.4 SE 0.76 (30)	<0.001
1 year	1.2 SE 0.79 (3)	3.0 SE 0.62 (19)	<0.001
2 years	1.9 SE 0.72 (6)	2.7 SE 0.66 (15)	<0.001

B. Urinary protein/creatinine ratio and plasma creatinine used to define state

Marker state
0 = Plasma creatinine less than 0.2 mmol/liter
urine protein/creatinine ratio less than 4
1 = Plasma creatinine less than 0.2 mmol/liter
urine protein/creatinine ratio 4 or more
2 = Plasma creatinine 0.2 mmol/liter or more
urine protein/creatinine ratio less than 4
3 = Plasma creatinine 0.2 mmol/liter or more
urine protein/creatinine ratio 4 or more

Lag	State '1'	State '2'	State '3'	P
1 year	2.8 SE 1.1 (17)[a]	4.0 SE 1.2 (53)	4.9 SE 1.1 (129)	<0.001

[a] Coefficient for each state, with associated standard error (SE).
Relative risks in parenthesis.
Significance by likelihood ratio test.

the plasma creatinine level and heavy proteinuria together remained the more significant ($P = 0.002$ compared with $P = 0.070$). This indicates that these two clinical variables were more useful markers of outcome than the histopathological findings. Further analysis showed that, after allowing for plasma creatinine and urinary protein loss, histological diagnosis was only associated with a worse prognosis ($P = 0.038$) for the mesangiocapillary group.

Analyses with time-dependent covariates

A first complete spontaneous remission of proteinuria (to <0.3 g/24 hr) was significantly related to survival ($P < 0.001$). A negative coefficient (−2.4 SE 0.74) for remission indicated that once remission had occurred the risk of ESRF was reduced. One third of the patients who remitted had a subsequent relapse (proteinuria >1 g/24 hr), but most (93%) of these patients maintained stable plasma creatinine levels; 75% had levels within the normal range (<0.12 mmol/liter).

Table 7 documents the second analysis, which tested for increased risk of ESRF associated with 'heavy' or 'very heavy' proteinuria 4, 8, 12 or 24 months earlier. Table 7A shows the three marker states defined according to the urinary protein/creatinine ratio. The baseline for comparison was a ratio less than '4'. Positive coefficients for the other two states (4 to 7.99 and 8 or more) indicate that these protein losses were associated with increased risk of ESRF 4, 8, 12 or 24 months later. Relative risks are shown. Differences between the three states were statistically highly significant ($P < 0.001$) for each time lag.

In Table 7B, the prevailing plasma creatinine level also was taken into account. The baseline for this analysis was a ratio less than '4' together with a plasma creatinine level less than 0.2 mmol/liter. Results for a 12 month lag are shown. A high level of plasma creatinine (0.2 mmol/liter or more) was associated with an increased risk of ESRF, but heavy urinary protein loss (ratio '4' or more) was associated with increased risk, whether or not the plasma creatinine level was high. This analysis was repeated excluding patients with MCN lesions and patients with other systemic diseases, and the findings were unchanged.

Discussion

Our findings show that heavy proteinuria (equivalent to accurately measured urinary protein loss of more than 5 g/24 hr) at one year, together with a raised plasma creatinine, is associated with an increased risk of progression to ESRF. The relationship between increased plasma creatinine and ESRF is to be expected, since renal failure is determined by the level of plasma creatinine. We were unable to define a level of plasma creatinine above which ESRF was inevitable, and therefore used ESRF as the end point.

In a recent study in Copenhagen [7, 8], time intervals to defined changes in plasma creatinine state were analyzed, in addition to progression to ESRF. There are important differences from our study. First, the authors analyzed all patients with biopsy-proven glomerulonephritis, irrespective of first manifestation. Secondly 17 clinical, biochemical and histological variables were examined for their prognostic value which were determined only at the time of biopsy. In this analysis we have excluded patients with asymptomatic proteinuria. Our analysis is of patients presenting initially with the nephrotic syndrome who therefore, by definition, had no previous evidence of renal disease. Other data we have analyzed suggests that up to one half of patients who appear to present with the nephrotic syndrome may have had asymptomatic proteinuria for months or years previously [9].

The greatest risk of ESRF in the patients studied here is at three to four years after first manifestation. Variables measured close to onset, or at one year, were considered for prognosis, since the interval to biopsy was so variable [9]. Although male patients appear to have a worse outcome, they had higher plasma creatinine levels and heavier proteinuria at one year, and when these factors were adjusted (in the multivariate analysis), male sex was no longer significant. Neither was hypertension related to outcome but, as we have indicated, this may be because effective treatment was readily available and instituted.

Comparisons with other studies are difficult because we have chosen to look across the histopathological spectrum in a single center, prospective study. In the recent Copenhagen study, the authors concluded that histopathology does yield prognostic information, but only for patients with plasma creatinine level less than 2 mg/100 ml at biopsy. Other authors have suggested that some histopathological types can be distinguished fairly accurately by using clinical and laboratory findings [19]. Our study differs in approach from that of the Copenhagen workers, and our experience suggests that clinical variables have more prognostic value than the broad histopathological diagnosis.

This does not argue against the case for renal biopsy, however. A biopsy will exclude treatable causes of renal disease (for example interstitial nephritis), and certain histological changes may indicate that a good therapeutic response is likely, notably with MCN, vasculitic syndromes and possibly

membranous nephropathy. Furthermore, the development of sophisticated immunological and biochemical techniques may eventually broaden our understanding of the pathogenesis and current activity of the nephropathy.

With regular sequential follow-up, we have been able to undertake in-depth analyses, to explore the possibility that the risk of ESRF changes with time, and to examine the relationship between the prevailing measurements and prognosis. Proteinuria, for example, changes with time and may persist, remit or follow a relapsing and remitting course. We have shown an association between risk of ESRF and heavy proteinuria and raised plasma creatinine level up to two years previously. With the statistical techniques now available, and the disciplined incorporation of clinical and laboratory measurements, over extended follow-up, the prognosis of patients will become defined more accurately.

Acknowledgments

The authors gratefully acknowledge Dr. E.J. Acheson of the Renal Unit, MRI, who coordinated the collection of the data in the earlier phase of the study.

Reprint requests to Linda P. Hunt, MSc, MIS, The Faculty of Medicine Computational Group, Manchester Royal Infirmary, Oxford Road, Manchester, England, United Kingdom.

References

1. BLAINEY JD, BREWER DB, HARDWICKE J: Proteinuric glomerular disease in adults: Cumulative life tables over twenty years. *Quart J Med* 59, 230:557–567, 1986
2. NOLASCO F, CAMERON JS, HEYWOOD EF, HICKS J, OGG C, WILLIAMS DG: Adult-onset minimal change nephrotic syndrome: A long-term follow-up. *Kidney Int* 29:1215–1223, 1986
3. HUTCHINSON TA, THOMAS DC, MACGIBBON B: Predicting survival in adults with end-stage renal disease: an age equivalent index. *Ann Intern Med* 96:417–423, 1982
4. GORE SM: Graft survival after renal transplantation: Agenda for analysis. *Kidney Int* 24:516–525, 1983
5. D'AMICO G, MINETTI L, PONTICELLI C, FELLIN G, FERRARIO F, BARBANO DI BELGIOIOSO G, IMBASCIATI E, RAGNI A, BERTOLI S, FOGAZZI G, DUCA G: Prognostic indicators in idiopathic IgA mesangial nephropathy. *Quart J Med* 59, 228:363–378, 1986
6. BEUKHOF JR, KARDAUN O, SCHAAFSMA W, POORTEMA K, DONKER AJM, HOEDEMAEKER PJ, VAN DER HEM GK: Toward individual prognosis of IgA nephropathy. *Kidney Int* 29:549–556, 1986
7. BRAHM M, BALSLOV JT, BRUN C, GERSTOFT J, JORGENSEN F, JORGENSEN HE, LARSEN M, LARSEN S, LORENZEN I, LOBER M, THOMSEN AC: Prognosis in glomerulonephritis. A follow-up study of 395 consecutive, biopsy-verified cases. I Classification, renal histology and outcome. Report from a Copenhagen study group of renal diseases. *Acta Med Scand* 217:117–125, 1985
8. GERSTOFT J, BALSLOV JT, BRAHM M, BRUN C, JORGENSEN F, JORGENSEN HE, LARSEN M, LARSEN S, LORENZEN I, LOBER M, THOMSEN AC: Prognosis in glomerulonephritis. II Regression analysis of prognostic factors affecting the course of renal function and the mortality in 395 patients. Calculation of a prognostic model. Report from a Copenhagen study group of renal diseases. *Acta Med Scand* 219:179–187, 1986
9. MALLICK NP, SHORT CD, HUNT LP: How far since Ellis? The Manchester study of glomerular disease. *Nephron* 46:113–124, 1987
10. SHORT CD, SOLOMAN LR, GOKAL R, MALLICK NP: *Quart J Med* (in press)
11. *Documenta Geigy*, 7th edition. Geigy, Basle, 1970, p. 553.
12. *BMDP statistical software Chs 19.1 and 19.2*, edited by W.J. DIXON, University of California Press, London, 1983, pp. 557–594
13. KAY R: Unbiassed assessment of treatment effects on disease recurrence and survival in clinical trials. *Stat Med* 2:41–58, 1983
14. COX DR: Regression models and life tables. *J Royal Stat Soc B*, 34:187–220, 1972
15. BRESLOW N: Covariance analysis of censored survival data. *Biometrics* 30:89–99, 1974
16. GAIL MH: Evaluating serial cancer marker studies in patients at risk of recurrent disease. *Biometrics* 37:67–78, 1981
17. BRESLOW NE: Analysis of survival data under the Proportional Hazards model. *Int Stat Rev* 43:45–58, 1975
18. *Fortran subroutine library of the Numerical Algorithms Group*, Oxford, Mk 6, 1977, subroutine E04EBF
19. TOMURA S, TSUTANI K, SAKUMA A, TAKEUCHI J: Discriminant analysis in renal histological diagnosis of primary glomerular diseases. *Clin Nephrol* 23, 2:55–62, 1985