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Predicting renal survival in primary focal glomerulosclerosis from the time of presentation

Vipul C. Chitalia, J. Elisabeth Wells, Richard A. Robson, Martin Searle, and Kelvin L. Lynn

Department of Nephrology, Christchurch Hospital, and Department of Public Health and General Practice, Christchurch School of Medicine, Christchurch, New Zealand

Predicting renal survival in primary focal glomerulosclerosis from the time of presentation.

Background. To predict the risk of developing chronic renal failure in patients with primary focal glomerulosclerosis (FGS) using predictors available at the time of presentation, a retrospective analysis was performed on 111 patients who were diagnosed at Christchurch Hospital from 1965 to 1998.

Methods. The predictors of outcome included age, gender, systolic and diastolic blood pressure, serum albumin, plasma creatinine, presence of hematuria, and amount of proteinuria (all at the time of presentation). An injury score (combination of percentage of sclerosed glomeruli and proportion of tubulointerstitial fibrosis) was derived from a review of the initial kidney biopsy. Log-logistic accelerated failure time parametric models were used.

Results. The median renal survival was 16.4 years (Kaplan–Meier estimate). The best single variable model was that using the proportion of tubulointerstitial fibrosis (global chi-square 55.99, $P < 0.0001$). However, inclusion of plasma creatinine significantly improved the fit of the model (global chi-square 65.04, $P < 0.0001$). This joint model was superior to the single-variable model. Both of the models were validated using jackknifing.

Conclusion. For a patient with primary FGS, these models can be used to predict the risk of developing chronic renal failure at any time and the median renal survival, given the proportion of tubulointerstitial fibrosis and plasma creatinine at the time of presentation.

Primary focal glomerulosclerosis (FGS) constitutes 7 to 20% of glomerular lesions in children and adults presenting with proteinuria, most often with the nephrotic syndrome [1–4]. The prognosis of primary FGS is poor. Only 40% of patients with FGS survive for more than 10 years without developing end-stage renal failure [2].

Key words: FGS, chronic renal failure, sclerosed glomeruli, tubulointerstitial fibrosis.

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There are clinical and pathological indicators that can help the clinicians to predict renal failure in a patient with FGS. These are age at the time of presentation, gender, amount of proteinuria, hypertension, renal dysfunction, percentage of sclerosed glomeruli and interstitial fibrosis, location of segmental sclerosis, mean glomerular diameter and presence of vascular sclerosis, and therapeutic response to prednisone [5–8]. Most of these studies lack a quantitative model of survival, so it is not possible to estimate renal survival for an individual patient. An accurate estimation of prognosis is important in many respects. First, prognostic information can be used to inform patients about the likely outcome of their disease. Second, the prognosis of an individual patient can be used as a guide for selecting therapeutic options. An ability to predict those at "high risk" would aid the physician in selecting the patients most likely to benefit from therapies, thus minimizing the exposure to toxic immunosuppressive medications in those patients not running a high risk of developing renal insufficiency. Third, prognostic assessments are useful in designing and evaluating randomized clinical trials [9].

We studied 111 patients with primary FGS to develop a quantitative approach to predict the development of chronic renal failure from the data available at the time of presentation.

METHODS

We reviewed 165 case notes of patients diagnosed as having FGS from 1965 to 1998 at the Department of Nephrology, Christchurch Hospital, Christchurch, New Zealand. The Department of Nephrology at Christchurch Hospital is the sole provider of specialty nephrological services for a catchment area population of 0.5 million people in the South Island of New Zealand. Most of these patients were Caucasians. The clinical records of these patients were reviewed for the evidence of other diseases such as reflux nephropathy, intravenous drug

abuse, or association with other renal pathologies. These patients were excluded ($N = 34$), as were those without kidney biopsy ($N = 17$) or with inadequate kidney biopsy (total number of glomeruli less than 13, $N = 3$). Therefore, a total of 111 patients with primary FGS was analyzed. The diagnosis of FGS was made on morphologic grounds from the kidney biopsy according to the criteria of the International Study of Kidney Diseases in Children (presence of segmental and/or global glomerulosclerosis on kidney biopsy) [10].

For each patient, all of the available data were examined. The following variables, all at the time of presentation, were noted: age, gender, systolic and diastolic blood pressure, 24-hour urine protein excretion, presence of hematuria, plasma creatinine, serum cholesterol, total serum protein, and albumin.

Kidney biopsy slides with hematoxylin and eosin (H&E) stain, periodic acid-Schiff (PAS) stain, and immunofluorescence were reviewed. The following parameters were noted from each biopsy: total number of glomeruli, total number of globally sclerosed glomeruli, total number of segmentally sclerosed glomeruli, and proportion of tubulointerstitial fibrosis (IF). The percentage of renal cortex with tubulointerstitial fibrosis was determined by the standard point counting method using an ocular grid (10 mm^2 divided into 25 squares; Klarmann Rulings, Manchester, NH, USA). The percentage of tubulointerstitial fibrosis was expressed as the proportion of renal cortex involved.

An injury score was calculated for each patient from the kidney biopsy.

$$\text{Injury score} = \frac{\left(\begin{array}{c}N \text{ of segmentally} \\ \text{sclerosed glomeruli} \\ + N \text{ of globally} \\ \text{sclerosed glomeruli}\end{array}\right)}{\begin{array}{c}\text{total number} \\ \text{of glomeruli}\end{array}} + \text{IF}$$

These patients were grouped into five categories on the basis of the status of the patients when last seen. For survival analysis, renal death was the event of interest, and the death of a patient for other reasons or the end of the study period (August 1998) was counted as censoring events. The categories were as follows: category 1, renal death ($N = 49$); category 2, remission ($N = 30$); category 3, persistent deterioration of renal function till the end of study ($N = 18$); category 4, persistent proteinuria but normal renal function ($N = 9$); and category 5, nonrenal death ($N = 5$).

Definitions

For the purpose of this study, renal death was defined as a persistent rise of plasma creatinine above 0.5 mmol/liter for more than three months. Twenty-four hour proteinuria of less than 300 mg/day was considered as remission. Persistent deterioration of renal function was defined as a rise of plasma creatinine of more than 0.1 mmol/liter, but less than 0.5 mmol/liter, for more than three months. Those patients who had had no remission were grouped as persistent proteinuria. The patients who had succumbed from other than a renal cause were grouped as nonrenal deaths.

Statistical analysis

Descriptive data were expressed as mean (SD) or percentages. The overall renal survival was studied using Kaplan–Meier nonparametric life table survival analysis. A comparison among the groups of the proportion of tubulointerstitial fibrosis and plasma creatinine was done using Tarone–Ware statistics. For modeling survival, a parametric model was chosen to enable prediction for an individual patient for any specified time interval. The predictors considered for analysis were age, gender, amount of proteinuria, serum albumin, total serum protein, serum cholesterol, plasma creatinine, presence of hematuria, systolic and diastolic blood pressure (all at the time of presentation), injury score, percentage of sclerosed glomeruli, and proportion of tubulointerstitial fibrosis on kidney biopsy. An accelerated failure time model with a log logistic form was chosen after an initial exploration of the data [11]. The predictors were used individually, and then forward stepping and backward stepping were used to select predictors for a joint model. Shrinkage of the coefficients was estimated by using the heuristic method of van Houwelingen and le Cessie as described by Harrell et al [9]. Jackknifing was then used to produce shrunk coefficients, which should have greater validity for future prediction than the original coefficients. Jackknifing is a form of cross-validation [9] in which a model is fitted N times (where N is the number of patients), with one subject being omitted each time. The jackknifed estimates derived from these runs provide bias reduction, standard errors and these estimates show shrinkage so that the model obtained does not suffer from over-fitting. The main analyses were carried out using BMDP [12], but SAS [13] was used for jackknifing survival models. A computerized system for calculation of the predictors for individual patients was developed using MATHCAD [14] and Microsoft Excel [15].

RESULTS

Out of a total of 165 patients diagnosed with FGS, 111 patients with primary FGS were included for final analysis. The age at the time of kidney biopsy ranged from 16 to 70 years, and the male to female ratio was 1.62:1. Patient characteristics are shown in Table 1.

The mean time between the diagnosis and the final event was 6.9 (SD 6.84) years. The mean follow-up time

Table 1. Patient characteristics at presentation ($N = 111$)

Variable	Mean	SD	Variable	%
Age *years*	35.6	14.9	Microscopic hematuria	21
Serum albumin *g/liter*	39.3	8.37	Nephrotic range proteinuria	78
Plasma creatinine *mmol/liter*	0.13	0.07	Raised plasma creatinine >0.01 mmol/liter	48
Proteinuria *g/day*	4.92	3.99	Hypertension	47
Systolic BP *mm Hg*	145.8	20.4	Gender	
Diastolic BP *mm Hg*	88.9	9.1	Male	63
Injury score	1.0	0.41	Female	37
Sclerosed glomeruli %	55	29		
Proportion of tubulointerstitial fibrosis	0.45	0.16		
Duration of clinical disease before kidney biopsy *days*	62	34		

was 10.8 (SD 8.5) years. During the observation period, 49 patients (44%) developed renal death, and 30 patients (29%) had a remission. Eighteen patients (16.2%) experienced relentless deterioration of kidney function, and nine patients (8.1%) had persistent proteinuria with normal plasma creatinine during follow-up. There were 3 patients out of 111 (2.7%) who showed a "malignant course." They presented with proteinuria of more than 15 g/day with hypoalbuminemia (serum albumin <25 g/liter) with deterioration to end-stage renal disease within 3 to 4.8 years. Ischemic heart disease was the leading cause of nonrenal deaths. Only 28 (25%) patients out of 111 were treated with prednisone (1.0 mg/kg for 6 to 8 weeks followed by tapering depending on the response; maximum duration for the treatment was not exceeding more than 12 weeks). Six patients responded to steroids (reduction in proteinuria to <300 mg/day), and none were treated with cyclophosphamide. The therapy was individualized for every patient, but overall, the patients with gross proteinuria (>8.0 g/day), hypoalbuminemia (serum albumin < 35 g/liter) with symptomatic nephrotic syndrome, or deteriorating renal function were treated with prednisone. Sixty-one (55%) patients received angiotensin-converting enzyme inhibitors over a period of 1.4 to 9 years for non-nephrotic range proteinuria or nephrotic range proteinuria with normal serum albumin and stable renal function. The patients were regularly followed up at the intervals of three months to two years, depending on their clinical status. The duration of follow-up ranged from 2 to 25 years.

The median renal survival was 16.4 years (Fig. 1). Before looking at the predictors of survival, the relationships between predictors were examined (Table 2). Because of these relationships, it would be expected that some predictors would not be required in a composite model because their effects could be accounted for by other predictors, and an efficient and replicable model would include only one of the kidney histology variables.

A parametric model was used, as prediction is not possible with nonparametric modeling. Of the possible single predictors investigated, the best single predictor was tubulointerstitial fibrosis (Table 3). To illustrate the influence of tubulointerstitial fibrosis on renal survival, the sample was divided into three groups based on the proportion of tubulointerstitial fibrosis: group I, <0.35; group II, 0.35 to 0.52; group III, >0.52. The renal survival of the three groups is plotted using Kaplan–Meier estimates (Fig. 2). Plasma creatinine (mmol/liter) was also analyzed in a similar way after dividing the patients into three groups: group I, <0.09; group II, 0.09 to 0.14; and group III, >0.14.

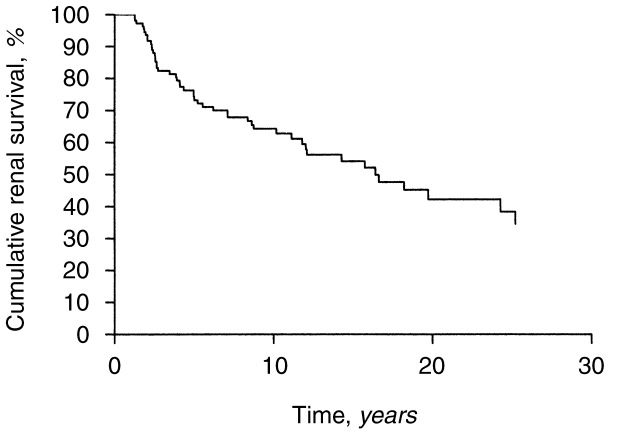

Fig. 1. Overall renal survival. The median renal survival was 16.4 years. Five- and 10-year survivals were 76% and 62%, respectively. At 5, 10, 15, 20 years, there were 72, 43, 27, 15 patients, respectively, at risk of developing renal failure.

As shown in the Table 3, all of the variables, apart from hematuria, individually predicted survival ($P < 0.05$). However, only two variables, proportion of tubulointerstitial fibrosis and plasma creatinine, were selected for the joint models. For prediction, it is important to avoid overfitting, particularly with small samples, and thus only predictors that significantly improved the fit were added to the model. The tubulointerstitial fibrosis model is the single best variable model for prediction. Including plasma creatinine also improved the fit of the model. The global chi-square for the two predictor model was 65.04 ($P < 0.0001$; shown in the **Appendix** for both of the models). Shrinkage in the joint model was only

Table 2. Correlation matrix showing relationships between predictors[a]

Predictors	Injury score	Sclerosed glomeruli %	Tubulointerstitial fibrosis	24-hour proteinuria	Serum albumin	Plasma creatinine	Systolic blood pressure	Diastolic blood pressure
Injury score	1	0.95	0.81	0.26	0.54	0.45	0.33	0.23
Sclerosed glomeruli %		1	0.57	0.20	0.44	0.41	0.25	0.20
Tubulointerstitial fibrosis			1	0.29	0.57	0.38	0.38	0.30
24 hour proteinuria				1	0.30	0.21	0.27	0.23
Serum albumin					1	0.40	0.44	0.30
Plasma creatinine						1	0.40	0.31
Systolic blood pressure							1	0.49
Diastolic blood pressure								1

[a] Only significant correlations are reported (critical $r \geq 0.2$ for $N = 111$ and $\alpha_2 = 0.05$)

Table 3. Predictors of survival

	Individual Predictors		Joint predictors	
Predictors	Global χ^2	P	Increase in global χ^2	P
Tubulointerstitial fibrosis	55.99	<0.0001	55.99	<0.0001
Plasma creatinine	24.13	<0.0001	9.05	<0.0026
Injury score	36.39	<0.0001		
Serum albumin	28.68	<0.0001		
Sclerosed glomeruli %	20.22	<0.0001		
Systolic BP	11.27	0.0008		
Diastolic BP	8.75	0.003		
Proteinuria	6.82	0.009		
Gender	5.0	0.04		
Hematuria	0.19	0.66		

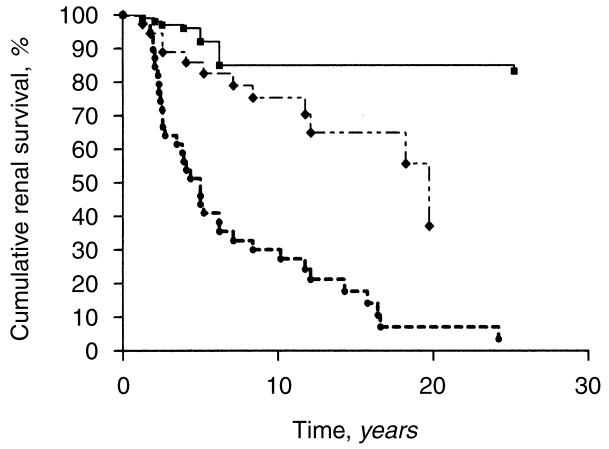

Fig. 2. Tubulointerstitial fibrosis and renal survival. The tubulointerstitial fibrosis was divided into three groups. Symbols are: (■) tubulointerstitial fibrosis <0.35 ($N = 35$); (◆) tubulointerstitial fibrosis 0.35 to 0.52 ($N = 37$); and (●) tubulointerstitial fibrosis >0.52 ($N = 39$). The difference in renal survival was significant, $P < 0.0001$ (Tarone–Ware statistics).

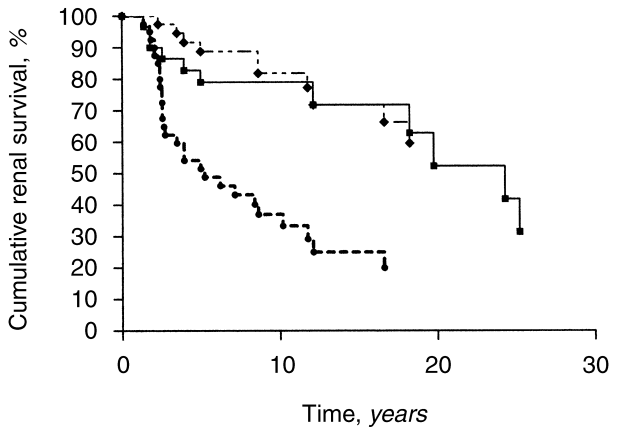

Fig. 3. Plasma creatinine (mmol/liter) and renal survival. Plasma creatinine was divided into three groups. Symbols are: (◆) plasma creatinine <0.09 ($N = 31$); (■) plasma creatinine 0.09 to 0.14 ($N = 40$); and (●) plasma creatinine >0.14 ($N = 40$). The difference in the renal survival was significant, $P < 0.0001$ (Tarone–Ware statistics).

2%. Nonetheless, jackknifing was used to shrink the coefficients in order to improve the predictive validity. As expected from the heuristic estimate of shrinkage, jackknifing produced only a small change (1.1% for tubulointerstitial fibrosis and 2.2% for plasma creatinine). The coefficients in the **Appendix** are the jackknifed coefficients (Table 4 in the Appendix section). A software program to use the survival models has been written in Microsoft Excel to make it widely usable (available on request). To illustrate the model, the predicted renal survival curves from the model (two variable) for the proportion of tubulointerstitial fibrosis from 0.1 to 0.4 and plasma creatinine (mmol/liter) from 0.1 to 0.8 are shown in Figure 4.

DISCUSSION

Primary FGS is a disease characterized by steroid-resistant nephrotic syndrome, a frequently relapsing course in 90% of the patients, renal function impairment in more than 50%, and progression to end-stage renal disease in 33% [16]. Previously, it has not been possible to predict the clinical outcome of an individual patient with primary FGS from the time of presentation [17–20]. We have developed mathematical models to predict the

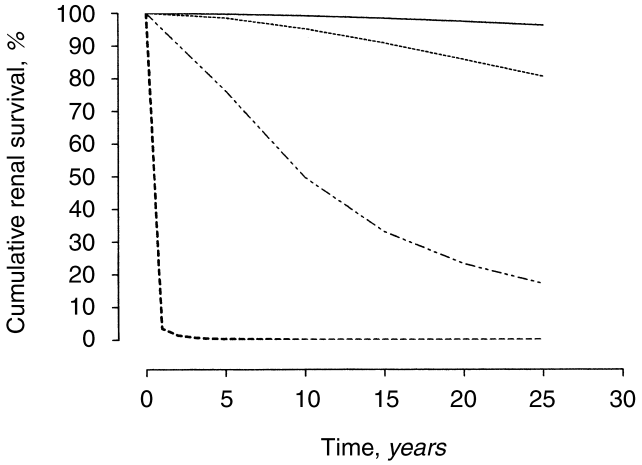

Fig. 4. Predicted renal survival curves for various values of tubulointerstitial fibrosis and plasma creatinine. Renal survival is predicted for different combinations of tubulointerstitial fibrosis and plasma creatinine (mmol/liter). Symbols are: (—) for tubulointerstitial fibrosis and plasma creatinine of 0.1 and 0.1 mmol/liter, respectively; (----) for 0.1 and 0.3 mmol/liter, respectively; (–––––) for 0.4 and 0.3 mmol/liter, respectively; and (––––) for 0.4 and 0.8 mmol/liter, respectively.

probability of developing chronic renal failure by analyzing 111 patients with primary FGS diagnosed at Christchurch Hospital from 1965 to 1998. Various clinical and histological parameters were analyzed, and two models have been developed by including the basic clinical and histological data at the time of presentation.

The median renal survival in this study during the observation period was 16.4 years; 5 and 10 renal survivals were 76% and 62%, respectively. The renal survival reported in the literature varies from a 10-year renal survival of 45% in nephrotic patients to a 91% in nonnephrotic patients to the least favorable of 25% in patients with primary FGS [18, 21]

There are several studies assessing clinical and histological features and the response to prednisone as predictors for renal survival [5–8]. Velosa et al performed renal survival analysis on 64 patients with primary FGS to ascertain factors at the time of kidney biopsy associated with progression to end-stage renal failure [22]. It was shown that patients with proteinuria (>3.5 g/24 hr), a higher initial plasma creatinine concentration, and severe tubulointerstitial damage had an accelerated course to renal failure, whereas other variables studied were not found to be associated with the time of end-stage renal disease. Shiki et al found tubulointerstitial change and mean glomerular diameter as independent risk factors among clinical and morphological predictors considered for renal outcome [6]. In a retrospective analysis performed by Schwartz et al on 81 patients with biopsy proven FGS, interstitial fibrosis was the only histological feature correlating with progression to end-stage renal disease [8]. All of these studies have indicated many variables correlating with renal outcome, but none have performed predictive renal survival analysis from the significant variables.

An attempt to predict the risk of developing renal failure in patients with primary membranous glomerulonephritis was made by Pei, Cattaran, and Greenwood by developing a mathematical model with persistent proteinuria of specified duration, creatinine clearance during that period, and slope of inverse creatinine versus time curve as variables [23]. Various models were developed using different levels of proteinuria over varying intervals of time. Persistent proteinuria was found to be the single best model for predicting chronic renal insufficiency. An approach for risk assessment of primary membranous glomerulonephritis was also proposed on the basis of these three variables. Such modeling necessitates observation of a patient for some time before ascertaining the risk of developing renal failure, which may delay initiating the therapy. The prediction was made with good accuracy; however, this model ignored the time to renal failure and merely looked at the outcome in a variable follow-up period. This means that the model fails to take account of censoring so that its estimate may be biased. Furthermore, one can predict the probability of renal failure, but the time of onset of renal failure cannot be predicted from such a model.

In this study, clinical and histological parameters as described in the literature were included for analysis. Obviously, the events that happen after the onset of disease such as the therapy, the response to it, and the behavior of different predictors, for example, control of blood pressure with the therapy over time, can change the outcome. The response to the therapy was not included in the model as a variable because the intention was to develop the model from the information (biochemical and kidney biopsy report) at the time of presentation (only a small number, 6 out of 28 patients, responded to steroid therapy). On reviewing kidney biopsies, an injury score was derived by taking into consideration sclerosed glomeruli and the proportion of interstitial fibrosis. There are a number of other histological variables described in the literature derived from morphometric analysis that are only practical in a research context [8]. Out of all of the histological predictors, interstitial damage and some times percentage of sclerosed glomeruli have emerged as independent variables correlating with renal outcome [6–8]. The clinical significance of the location of the glomerular scar (including "tip" lesion) remains controversial [7, 8]. The injury score used in this study was slightly different from that used by Raij, Azar, and Keane [24], which involved multiplying the degree of damage by the percentage of glomeruli injured by the same extent. It has been shown that the exact quantitation of the percentage of glomeruli affected and sclerosis of the glomerular tuft can be made

with only the three-dimensional morphologic analysis of electron micrographs, as sclerosed glomeruli in a given section can show more sclerosed changes in regions far from the section of examination [25]. Hence, the injury score considered in this study included only the number of sclerosed glomeruli and the proportion of interstitial fibrosis, which could be obtained from the kidney biopsy report of a patient.

Interdependency was noted among many predictors (Table 2). The high correlation was found between injury score, percentage of sclerosed glomeruli and tubulointerstitial fibrosis; injury score and serum albumin, plasma creatinine; systolic blood pressure and diastolic blood pressure, plasma creatinine, and serum albumin. These relationships explain why the final model contains only 2 out of 10 variables found to be significant predictors. All of the histopathological markers (injury score, percentage of sclerosed glomeruli, proportion of tubulointerstitial fibrosis) correlated with the renal survival to a significant extent ($P < 0.0001$), but it was the tubulointerstitial fibrosis that rendered the best predictive power to the model (Table 3). Thus, the best single variable predicting renal survival was tubulointerstitial fibrosis. The high predictive power of histological markers is not surprising, as the histological appearance represents the cumulative damage sustained by the kidney over a period of time, whereas the other clinical variables reflect the course of the disease over a short period or at a point in time. While considering the variables individually, only one other variable appears to have improved the prediction, namely plasma creatinine, even though all of the variables had a significant influence on the renal survival on their own. Integrating plasma creatinine into the tubulointerstitial fibrosis model increased the fit of the model. In this study, the amount of proteinuria per day did not feature in the final model because of its correlation with other variables.

The influence of tubulointerstitial fibrosis on survival can also be seen in Figure 2. The tubulointerstitial fibrosis was further divided into three groups, the bottom group having the least interstitial fibrosis, the middle group and the last group having more interstitial fibrosis. There was a statistically significant difference in the renal survival of patients with an tubulointerstitial fibrosis of less than 0.35 as compared with the other groups. Plasma creatinine was similarly divided into three groups (Fig. 3). It can be inferred that patients with a tubulointerstitial fibrosis of more than 0.35 and a plasma creatinine at the time of presentation of more than 0.13 mmol/liter augurs a bad prognosis.

The most stringent test of any model (and of the entire data collection system) is an external validation: the application of the "frozen" model to a new population. In this study, the models were internally validated by jackknifing, which may suffice for external validation [9].

Table 4. The coefficients in the models

Model	Intercept μ	Scale σ	Coefficients: Tubulointerstitial fibrosis	Coefficients: Plasma creatinine
Overall survival	8.6214	0.8449	—	—
Tubulointerstitial model	12.0713	0.6487	−7.1276	—
Two variable model	12.1367	0.5869	−5.8595	−5.3233

It is possible to predict renal survival from the proportion of tubulointerstitial fibrosis and plasma creatinine at the presentation. Predicting the renal survival and the risk of developing end-stage renal disease from the data at the initial presentation of the disease offers the most practical way of providing a prognosis and will help in individualizing the therapy from very beginning. In order to simplify the application for clinical purpose, these models are developed on Microsoft Excel, which can be easily used by all clinicians by entering in the values in two models (available on request).

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Reprint requests to Dr. Richard A. Robson, Department of Nephrology, Christchurch Hospital, Private Bag 4710, Christchurch 1, New Zealand.
E-mail: Richard.Robson@chmeds.ac.nz

APPENDIX

Most computer software packages use the log-linear representation of the accelerated failure time model [11]. In this formulation the survival to time t for an individual is as follows:

$$Si(t) = [1 + \exp\{(\log t - \mu - \sum \alpha_i x_i)/\sigma\}]$$

where μ is the intercept, σ is the scale parameter, and α_i is the coefficient for predictor x_i.

Note that the log is the natural log and the time is in days.

For overall survival, there are no predictors, and thus, all that needs to be entered is the time of interest.

For prediction using the tubulointerstitial fibrosis model, there is only one x, namely the proportion of tubulointerstitial fibrosis.

For prediction using the joint model, there are two x's, namely the proportion of tubulointerstitial fibrosis and plasma creatinine.

The median survival time is as follows:

$$t(50) = \exp(\mu + \sum \alpha_i x_i)$$

The coefficients in the models are given in Table 4.

For example, renal survival of a patient of FGS at 10 years (3652.5 days) will be 0.621, and thus median survival will be 15.19 years. The renal survival of same patient for the same time with tubulointerstitial fibrosis of 0.5 and plasma creatinine 0.1 mmol/liter at the time of

presentation will be 0.615 with one variable and 0.691 with two variable models. The median survival with one and two variable models will be 13.58 and 16.02, respectively.

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