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Predicting chronic renal insufficiency in idiopathic membranous glomerulonephritis

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Predicting chronic renal insufficiency in idiopathic membranous glomerulonephritis. We developed an approach in quantifying the risk of developing chronic renal insufficiency (CRI) based on a cohort of 184 patients with idiopathic membranous glomerulonephritis (IMGN), prospectively followed by the Toronto Glomerulonephritis Registry between 1974 and 1988. After a mean follow-up period of 5.8 years, 26% of patients developed CRI (defined as persistent reduction of creatinine clearance (C_{Cr}) $\leq$ 60 ml/min/1.73 m^2 for $\geq$12 months). We found that when compared to the baseline probability of the unselected patients, the severity of proteinuria at kidney biopsy added only marginally to the prediction of CRI. We introduced a special test condition: persistent proteinuria (PP) (that is, duration of proteinuria, g/day, above different cut-off levels). We examined the positive predictive value (PPV) and sensitivity (SEN) of 15 arbitrarily chosen levels of PP (that is, proteinuria $\geq$4, 6 or 8 g/day persisting for $\geq$6, 9, 12, 18 or 24 months) to select levels with optimal predictive characteristics. We found that PP $\geq$ 8 g/day for $\geq$six months was a simple and useful predictor of CRI with a PPV and SEN of 66%. To further improve our prediction, we tested the following parameters: age, sex, initial S_{Cr} and C_{Cr}, proteinuria, serum albumin, hypertension, rate of change of C_{Cr} over time, and therapy (steroids $\pm$ immunosuppressive drugs) in a multivariate analysis. Proteinuria, initial C_{Cr}, and rate of change of C_{Cr} were most important in predicting CRI. Fifteen models were then developed by including each patient's C_{Cr} at the start of PP and its rate of change during the time period selected. Two models based on PP $\geq$ 4 g/day for $\geq$18 months, or $\geq$6 g/day for $\geq$9 months significantly improved the PPV's for CRI from those based on the same levels of PP alone. Using these test conditions, we can improve the prediction of CRI from a baseline probability of 26% in unselected patients to a range of 55 to 86% in the "high-risk" patients (with SEN > 60%). Application of these predictive strategies in IMGN will be useful in managing the individual patients and in selecting patients for clinical trials by limiting the exposure of potentially toxic therapy to the "high-risk" patients.

Idiopathic membranous glomerulonephritis (IMGN) is a common form of primary glomerulopathy and an important cause of chronic renal failure related to glomerular disease [1, 2]. Its natural course is quite variable: chronic or end-stage renal failure will develop in 20 to 40% of patients [1, 3–11]; yet spontaneous complete remission also occurs in up to 35% of patients [1, 4–11, 13, 14]. Despite several recent randomized controlled trials in IMGN [12–14, 16], there remain major controversies regarding its treatment with respect to therapeutic effectiveness and acceptable toxicities [1, 15, 17–19]. An ability to predict those at "high-risk" for developing chronic renal failure would be useful since all the current treatments carry a serious risk of toxicity [1, 2, 13–15, 19].

While several prognostic factors have been identified to be associated with "poor" renal outcome, they remain qualitative [1–11, 19]. Furthermore, most studies have examined these "risk" factors at a single point in time and do not address the changing and variable course of many patients with IMGN [3–11]. Based on a prospective cohort of patients with IMGN followed by the Toronto Glomerulonephritis Registry, we have developed a quantitative approach in predicting the development of chronic renal failure in this disease.

Methods

Patient selection and data collection

The organization and the clinical activities of the Toronto Glomerulonephritis Registry have been previously detailed [20]. Since August 1974, five nephropathologists have forwarded reports of all cases of biopsy-proven glomerulonephritis to the registry. The initial clinical and laboratory data on these patients at the time of renal biopsy and all their follow-up information (prospectively collected at 2 to 6 month intervals) are entered into a computer database. This database reflects a regional experience of 18 community and university teaching hospitals in Toronto, with a population of approximately 4.5 million.

Between August 1974 and August 1987, 272 cases of membranous glomerulonephritis had been documented. Sixty-eight cases were excluded because the follow-up period was less than one year, or because of the finding of a potential secondary cause on clinical review. In the remaining 204 patients, 20 patients presented with marked renal impairment (that is, creatinine clearance (C_{Cr}) < 60 ml/min/1.73 m^2) at the time or within six months of their biopsy. Since our goal was to develop an approach to predict the development of CRI, these patients were excluded. Thus, 184 patients remaining were chosen as the database for this study.

Definitions

For the purpose of this study, chronic renal insufficiency (CRI) is defined as a creatinine clearance of less than 60 ml/min/1.73 m^2 persisting for at least 12 months. End-stage renal failure (ESRF) is defined as patients who reached the

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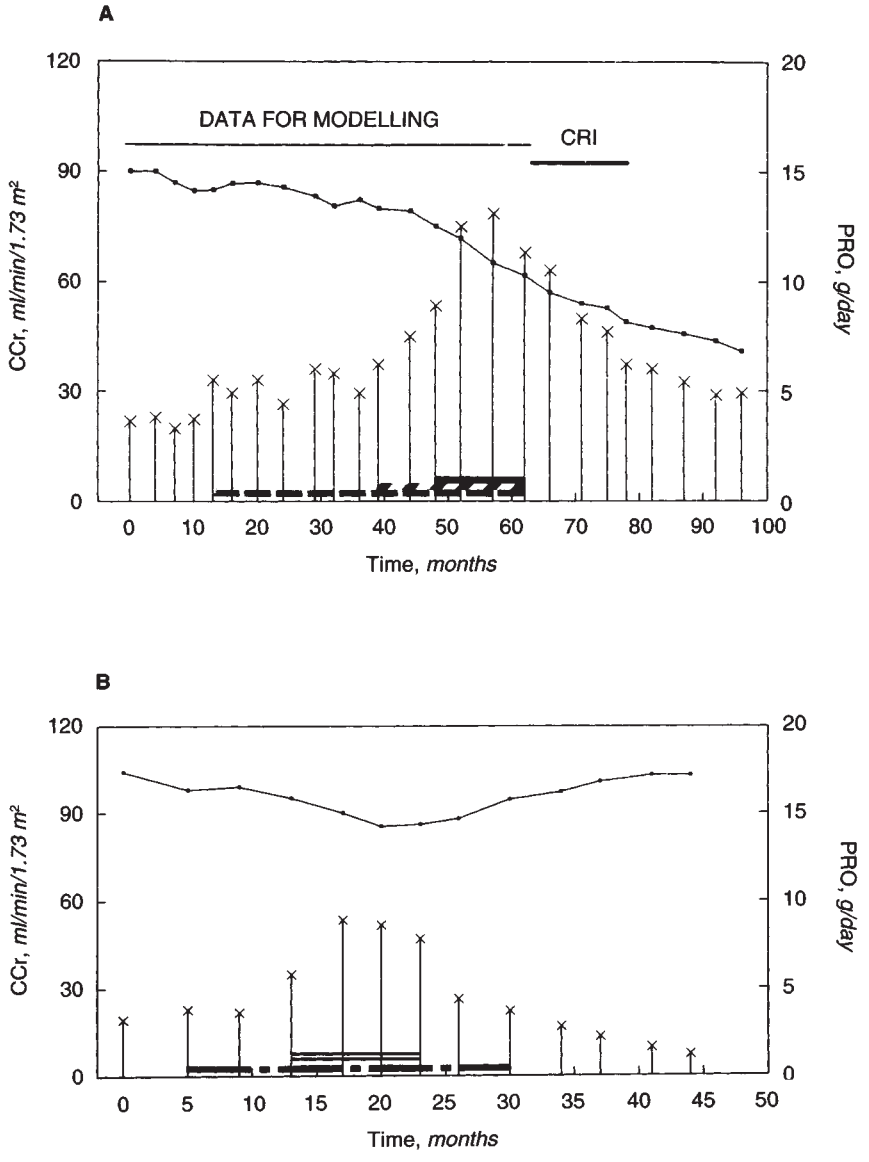

Fig. 1. *Defining the study parameters for probability modeling.* Each patient's data were examined to determine if CRI had occurred during his/her course. Once the patient was noted to have developed CRI, only the data prior to CRI were used for the modeling (**A**). Persistent proteinuria PP(≥X, ≥Y) is defined as X g/day or more of proteinuria persisting for at least Y months during a patient's course. For example, the patient in the upper panel had PP(≥8 g/day, ≥12 months) (▬▬▬▬), PP(≥6 g/day, ≥18 months) (▰▰▰▰▰▰) and PP(≥4 g/day for ≥24 months) (▬▬▬▬) during his course, whereas the patient in panel **B** only had PP(≥6 g/day, ≥6 months) (═══) and PP(≥4 g/day, ≥12 months) (▬▪▬). Symbols are: (—·— —·—) C_{Cr}; (ϒ) PRO.

stage where they required dialysis or renal transplantation. The rate of change of C_{Cr} over time (SLP) is defined as the slope of C_{Cr} versus time in ml/min/1.73 m^2 × $(year)^{-1}$. Nephrotic syndrome is defined as proteinuria of ≥3.5 g/day. Complete remission is defined as proteinuria < 300 mg/day with stable or improving C_{Cr}. Hypertension is defined as sitting blood pressure of greater than 140/95 mm Hg on two successive visits.

Development of predictive strategies for CRI

For each patient, we examined all the available data during his/her course to decide whether or not CRI had occurred. When a patient developed CRI, only data prior to the development were used for our analysis (Fig. 1, upper panel). Since the clinical and laboratory parameters of many patients with IMGN often changed during their course, we felt that assessment of risk based on one point in time was sub-optimal.

We made an assumption that within each patient the time period when he/she had the worst level of sustained proteinuria would be the most useful reference point for assessing his/her CRI risk. We introduced a special variable, persistent proteinuria (PP, defined as the duration of proteinuria, g/day, above different cut-off levels) and further determined its predictability for CRI. Fifteen arbitrary levels of PP(X, Y) were chosen, where X = proteinuria of 4, 6, or 8 g/day and Y = 6, 9, 12, 18 or 24 months of its persistence. Their positive and negative predictive values, sensitivity, specificity and accuracy for CRI were then calculated (**Appendix 1**).

To further improve our prediction, we tested the following variables in a multivariate analysis to select out predictors of CRI: age, sex, initial serum creatinine (S_{Cr}) and C_{Cr}, quantitative proteinuria, serum albumin, hypertension, slope of C_{Cr} versus time (SLP), and treatment (steroids ± other immunosuppressive drugs). The best variables independently predicting CRI were proteinuria, C_{Cr} or S_{Cr}, and SLP. Steroid ± immunosuppressive drugs did not influence either the incidence of CRI or complete remission in our patient population. Fifteen

Table 1. Patient characteristics (N = 184)

	At presentation	At last follow-up
Serum creatinine μM	93.5 ± 30	167 ± 88
C_{Cr} *ml/min/1.73 m²*	93.2 ± 25	74.5 ± 88
Proteinuria *g/day*	6.5 ± 4.3	4.1 ± 4.9
Nephrotic syndrome %	72	39
Systolic BP *mm Hg*	135 ± 21	136 ± 18
Diastolic BP *mm Hg*	83 ± 12	83 ± 10
Chronic renal insufficiency %	0	26
Complete remission %	0	26

All data are expressed as mean ± SD or percent.

models were then developed by including each patient's C_{Cr} at the start of PP and its rates of change during the time period selected (**Appendix 2**). To evaluate the performance of each model in predicting CRI, its PPV and SEN were compared to those based on the same level of PP alone.

Statistical methods

Descriptive data are expressed as mean ± SD or as percents. Positive predictive value (PPV), negative predictive value (NPV), sensitivity (SEN), specificity (SPEC) and accuracy were generated using standard definitions (**Appendix 1**) [22]. Univariate and multivariate logistic regression analyses were performed to test the clinical and laboratory predictors for CRI, and to develop the 15 specific models. Regression analyses were performed using BMDP and SAS statistical packages [21, 24].

Results

Outcomes of study patients

The mean age (±SD) of the 184 study patients at their kidney biopsy was 43 ± 17 years, and the male to female ratio was 2:1. Their mean follow-up period (±SD) was 5.8 ± 4 years. Our patient characteristics at biopsy and at the last follow-up are shown in Table 1. Over the observation period, 26% of our patients developed CRI and another 26% developed a complete remission. Fifteen of 47 patients with CRI developed ESRF during the study. None of the 47 patients with CRI had recovered his/her C_{Cr} above 60 ml/min/1.73 m² at the last follow-up. Fifty percent of our study patients were treated with a course of corticosteroids during their course, and 26 of them also received another immunosuppressive drug (such as cyclophosphamide or azathioprine).

Predicting CRI by different levels of persistent proteinuria (PP)

Proteinuria at a single point in time adds only marginally to the prediction of CRI. For example, the PPV of our patients with proteinuria ≥ 8 g/day at renal biopsy is only 42% as compared to the baseline risk of 26% in the unselected patients. Table 2 shows the test characteristics of different levels of PP in predicting CRI. Here, the PPV for each level of PP is improved when compared to the same level of proteinuria at a single time point. At higher level of PP such as PP(≥6 g/day, ≥6 months) or PP(≥8 g/day, ≥6 months), there is more than a doubling of the PPV (for example, 54–66%) from that of the unselected patients. For each level of PP, there is no significant improvement of PPV by increasing the length of its persistence beyond six months. PP(≥8 g/day, ≥6 months) is the best single level of PP predicting CRI with a PPV and SEN of 66%.

Table 2. Test characteristics of different levels of persistent proteinuria (PP) in predicting CRI

PP (≥ X g/day, ≥ Y months)	n[a]	PPV[b]	SEN	NPV	SPEC
			(Expressed as percent)		
(X = 4 at Bx)[c]	127	32	87	89	37
(X = 4, Y = 6)	92	44	85	92	62
(X = 4, Y = 9)	75	44	70	87	69
(X = 4, Y = 12)	61	44	58	84	75
(X = 4, Y = 18)	36	47	36	80	86
(X = 4, Y = 24)	23	44	21	77	91
(X = 6, at Bx)[c]	80	38	66	84	64
(X = 6, Y = 6)	65	54	75	90	78
(X = 6, Y = 9)	47	55	55	85	85
(X = 6, Y = 12)	42	55	50	83	86
(X = 6, Y = 18)	25	56	30	79	92
(X = 6, Y = 24)	11	46	11	76	96
(X = 8 at Bx)[c]	55	42	49	87	77
(X = 8, Y = 6)	47	66	66	88	88
(X = 8, Y = 9)	33	64	45	83	91
(X = 8, Y = 12)	25	62	30	79	92
(X = 8, Y = 18)	14	64	24	78	96
(X = 8, Y = 24)	4	50	4	75	99

Abbreviations are: PPV, positive predictive value; SEN, sensitivity; NPV, negative predictive value; SPEC, specificity (definitions are in Appendix 1).

[a] Number of patients satisfying the PP condition

[b] The PPV in unselected patients is 26% (that is baseline risk)

[c] Test characteristics of proteinuria at a single time point (such as at around renal biopsy)

In contrast, a patient with severe proteinuria has a low probability of progressing to CRI if the proteinuria is not persistent. For example, a patient with proteinuria ≥ 8 g/day but lasting less than six months has only a 12% probability of developing CRI (that is, NPV of 88%).

Probability modeling in predicting CRI

To further improve our prediction of CRI from that based on PP alone, a general model has been developed and is shown below:

$$R(CRI) = \frac{\exp(K_0 + K_1 \times PP + K_2 \times SLP + K_3 \times C_{Cr})}{1 + \exp(K_0 + K_1 \times PP + K_2 \times SLP + K_3 \times C_{Cr})}$$

This model has incorporated two additional measures of renal function: C_{Cr} is the creatinine clearance at the start of PP expressed in ml/min/1.73 m², and SLP (slope) is the rate of change of C_{Cr} during PP expressed in ml/min × $(1.73\ m^2)^{-1}$ × $(year)^{-1}$. PP is a categoric variable, and a value of 1 is entered if a patient satisfies the specific level of PP for the model; otherwise, a value of 0 is entered. K_1, K_2, and K_3 are coefficients for PP, SLP and C_{Cr}, respectively, and K_0 is a constant. Using the above equation, 15 specific models were generated based on the corresponding levels of PP examined above.

From each model, a R(CRI) score is generated for each patient based on his/her PP, C_{Cr} and SLP. This score reflects the risk of a patient within a numerical interval of 0 and 1, where 0 represents no risk, and 1 represents a very high risk of

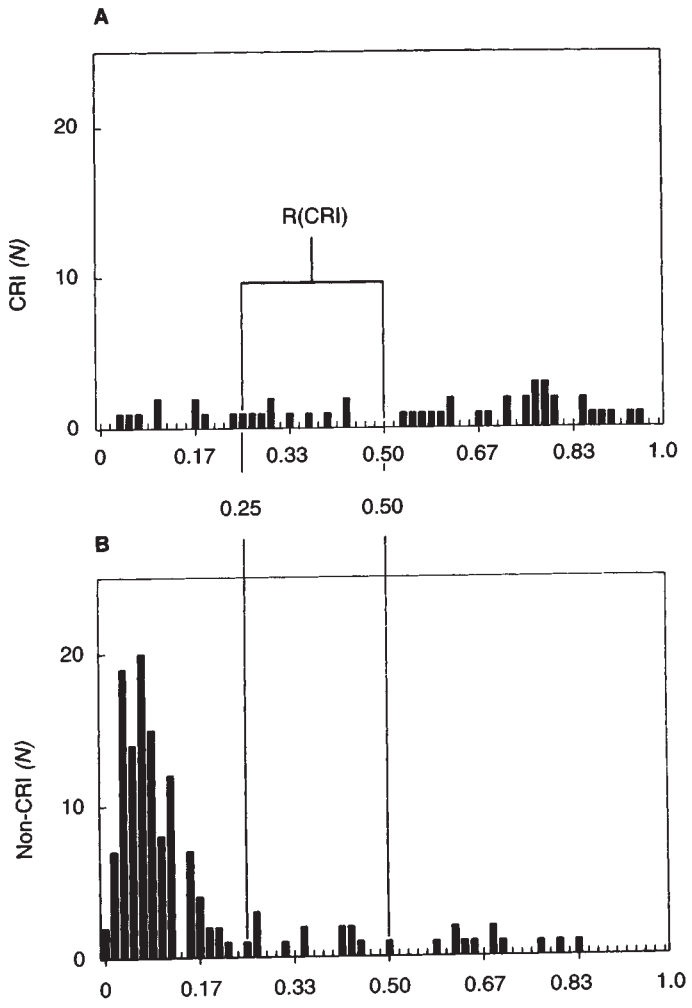

Fig. 2. *Frequency distribution of patients by their R(CRI) scores using the model based on PP(≥8 g/day for ≥6 months).* The distribution of R(CRI) scores in patients with CRI (N = 47) is shown in panel **A**, and in patients without CRI (N = 137), in panel **B**. The test characteristics of specific R(CRI) cut-offs for each model can then be defined for the prediction of CRI.

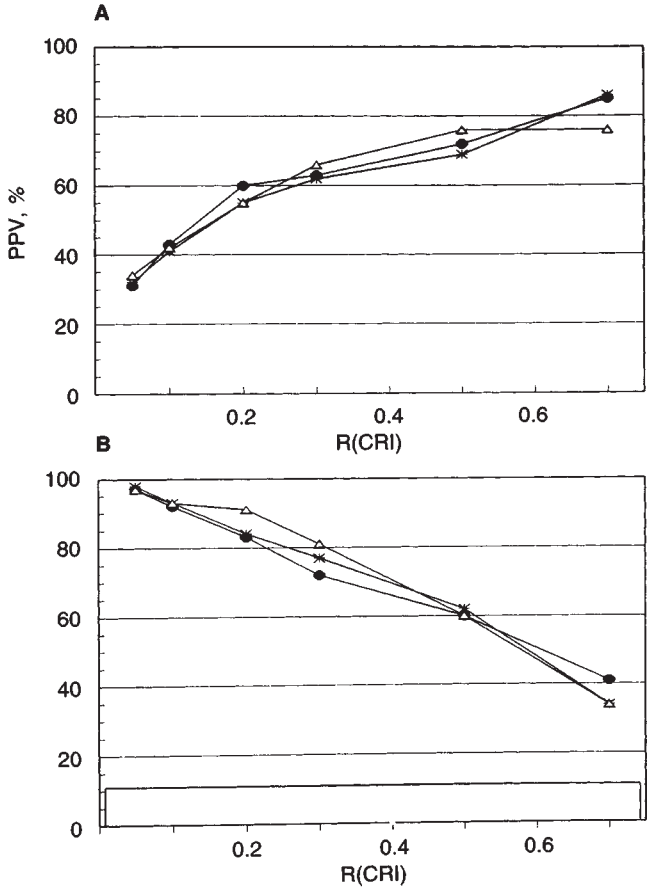

Fig. 3. *Useful models for predicting CRI in patients with IMGN.* Three models for predicting CRI based on different levels of PP and renal functional parameters are chosen for their optimal PPV (**A**) and SEN (**B**). Symbols are: (△) M (≥4 g/day, ≥18 m); (*) M (≥6 g/day, ≥9 m); (●) M (≥8 g/day, ≥6 m). The performances of these models are very similar with respect to their PPV and SEN at each R(CRI) cut-off, but they are different with respect to the duration of observation required. To achieve the same risk of CRI with lower levels of proteinuria, a longer persistence is required (see text for details).

developing CRI. To generate the corresponding predictive test characteristics for each R(CRI) score within a model, the R(CRI) scores are plotted in a frequency distribution. Using the model M(≥8 g/day for ≥6 months) as an example, the distribution of the R(CRI) scores in patients who have developed CRI is shown in the upper panel of Figure 2. Likewise, the distribution of R(CRI) scores in patients who have not developed CRI is shown in the lower panel. By selecting different cut-offs of R(CRI)'s in each model, we can evaluate the predictive characteristics of these cut-offs. When our patients are tabulated by whether they have developed CRI and by whether they have exceeded a certain R(CRI) cut-off, the test characteristics of a specific cut-off can be derived (such as 0.25 vs. 0.5) [22].

We have examined different R(CRI) cut-offs from 0.05, 0.1, 0.2, 0.3 . . . to 0.8 for their test characteristics in the above models. We selected the optimal models based on their high PPV's and SEN's. Three best models chosen whose performances are very similar are based on PP(≥4 g/day for ≥18 months), PP(≥6 g/day for ≥9 months) and PP(≥8 g/day for ≥6 months) (Fig. 3). They are different only with respect to the duration of observation required. Across all models, the R(CRI) score of 0.2 to 0.3 results in a doubling of the PPV (that is, 55–65%) from baseline (that is, 26%). An R(CRI) score of 0.5 gives an optimal performance in both PPV and SEN in these models. Conversely, an R(CRI) score of less than 0.2 in these models predicts low-risk patients for CRI (that is, <5%, or NPV > 95%). The accuracy of these models at R(CRI) scores of 0.2 to 0.7 ranges between 78 to 83%. The coefficients used in these models for PP, SLP and C_{Cr} are shown in **Appendix 2.**

Figure 4 shows the comparisons of the predictive characteristics of each of the above models (point M) with its corresponding level of PP (point P) and single time-point proteinuria at biopsy (point B). At all levels, PPV's based on single time-point proteinuria as a predictor are significantly inferior to using the corresponding level of PP or model. The top panel shows a major improvement of both PPV (from 47 to 76%) and SEN

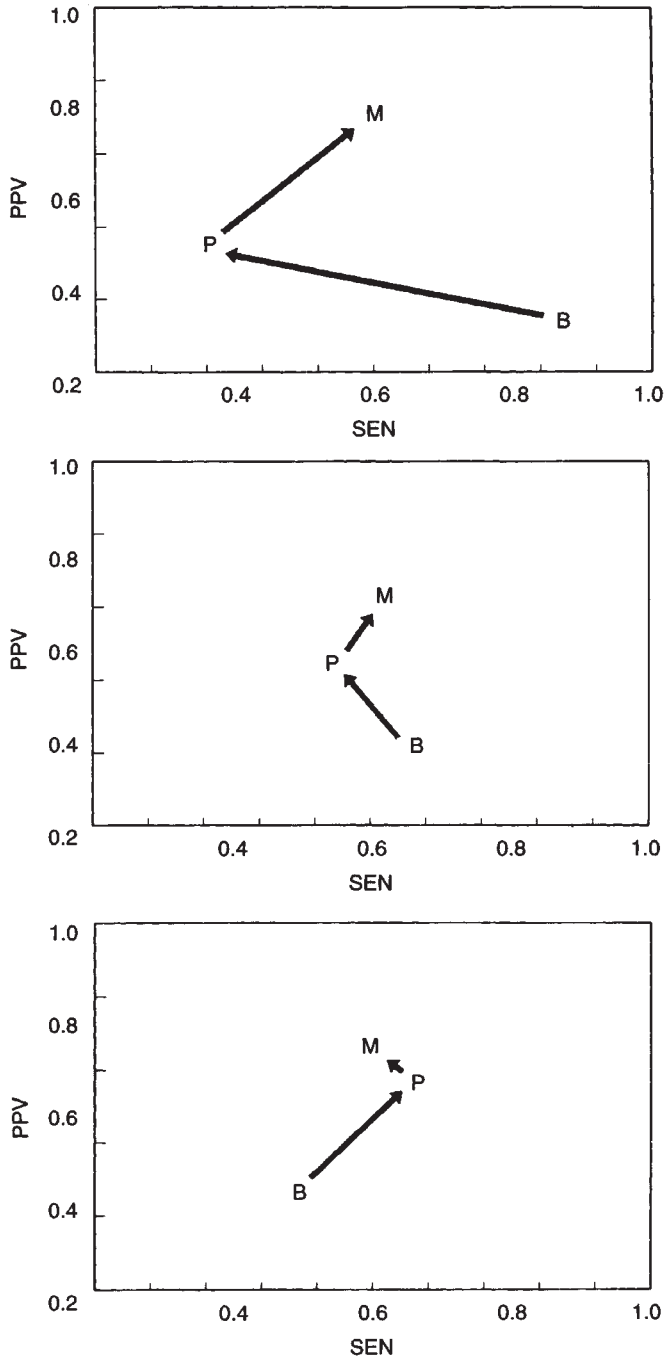

Fig. 4. *Assessing the contribution of probability modeling in predicting CRI.* The PPV and SEN for CRI based on a specific level of persistent proteinuria (PP) (point P) are compared to the full model (point M) based on a R(CRI) score of 0.5. **A** shows a dramatic improvement in both PPV and SEN by our model in patients with PP(≥4 g/day, ≥18 months). **B** shows a modest improvement by our model in patients with PP(≥6 g/day, ≥9 months). **C** shows minimal improvement by our model in patients with PP(≥8 g/day, ≥6 months). Single time-point proteinuria at biopsy (point B) of ≥4 g/day (A), ≥6 g/day (B), and ≥8 g/day (C) only improves the PPV marginally from its baseline probability (that is, 26%).

(from 36 to 60%) by our model when compared to its corresponding level of PP in patients with PP(≥4 g/day, ≥18 months). The middle panel shows a smaller improvement of PPV (from 55 to 69%) and SEN (from 55 to 62%) by our model over PP alone in patients with PP(≥6 g/day, ≥9 months). The bottom panel shows that in patients with PP(≥8 g/day, ≥6 months), there was minimal improvement by our model over PP in the PPV and a small decrease in SEN.

Once any of the persistent proteinuria test conditions are satisfied, most of the patients who are destined to developed CRI would develop this outcome within one year (median and 75th percentile time to CRI is ≤1 and 12 months, respectively; range: 0 months to 5 years).

Comments

Idiopathic membranous glomerulonephritis is a disease with a variable course. Its natural history indicates that 20 to 35% of patients will eventually undergo a complete remission, and another 20 to 40% of patients will develop chronic or endstage renal failure, while the remaining patients will have persistent proteinuria and stable renal function [1, 3–14]. Thus, at least two-thirds of patients with IMGN will have a generally benign renal course, and treatment with potentially toxic drugs would be best avoided in these patients [1, 19].

Several factors have been suggested to identify the "high-risk" patients for developing renal insufficiency in IMGN, including: male sex, old age, proteinuria, impaired renal function, and hypertension at presentation [1–4, 7–11, 19]. However, all these prognostic factors are qualitative and their application in a clinical setting remains uncertain. In this study, we present a quantitative approach in predicting the development of CRI in patients with IMGN. Multivariate analysis in our study showed that proteinuria, C_{Cr}, and its rate of change with time were the most important predictors.

We found that the severity of proteinuria at a single time-point is not very useful in predicting CRI. We made an assumption that within each patient the period when he/she has the most severe level of sustained proteinuria would be an optimal time for assessing this risk. The parameter, persistent proteinuria (PP), became the basis for our risk quantitation. Thus, PP(≥8 g/day, ≥6 months) is the single best level for predicting CRI with a PPV and SEN of 66%. Conversely, a high NPV of 88% in the same test condition means that even severe proteinuria of 8 g/day or more does not necessarily carry an adverse prognosis provided that it is not persistent for over six months. This reflects the fact that even patients with severe proteinuria do undergo spontaneous complete remission in IMGN [1, 3–14].

We propose the following approach for risk assessment: At anytime during a patient's course if persistent proteinuria ≥ 8 g/day for six months is observed, that patient is in a "high-risk" category with a 66% probability for developing CRI. Additional and more complex modeling would not change this categorization. If the patient has never exceeded this level of PP, the next lower level (that is, proteinuria ≥ 6 g/day for 9 months or more) should be checked. If this criterion is satisfied, then he/she has a 55% probability of developing CRI. This may be a sufficient threshold for treatment depending on the individual clinician. However, if a higher threshold is desired before treatment is indicated, then a more accurate prediction of CRI can be obtained by calculating the R(CRI) score using the model based on PP(≥6 g/day, ≥9 m). If a patient has neither of the above levels of PP, then PP(≥4 g/day, ≥18 months) should be checked

to see if the model based on this specific test criterion can be used to improve the prediction.

When a patient does not meet any of the above levels of PP, then any of the above models can be used to calculate a R(CRI) score by setting PP = 0, and calculating the SLP based on the interval of the worst proteinuria during the patient's course. Using this serial test strategy, we can achieve a sensitivity of greater than 80% and positive predictive value of about 70% for predicting CRI.

To use any of the models, one needs to calculate the rate of change of C_{Cr} over the chosen time period (SLP), and select the appropriate formula and coefficients from **Appendix 2**. The R(CRI) score can then be calculated by inserting the values of PP, SLP and C_{Cr}, and its corresponding PPV and SEN can be obtained from Figure 3. With this information, the clinician can then decide on whether a patient has fulfilled his/her threshold of being "high-risk" for a given treatment. For example, a R(CRI) score of 0.5 in any of the three chosen models represents a risk of developing CRI of greater than 70%.

A second application of these quantitative strategies would be for selecting "high-risk" patients for a clinical trial. For example, using any of the above three models we can select a group of patients with greater than 60% probability for developing CRI. Since the sensitivity of this serial test strategy is greater than 80%, the majority of patients who would develop CRI would be identified. The effect of selecting a "high-risk" group for CRI on the sample size required for a clinical trial can be dramatic. For example, a potentially toxic new therapy in IMGN is being tested using a randomized, placebo-controlled design. Assuming that the CRI event rate in the unselected patients is 26%, and the effect of this therapy is clinically significant if it reduces CRI rate by 50% (that is, absolute CRI rate of 13% in the treatment group). Using an $\alpha = 0.05$ (2-tailed) and $\beta = 0.2$, the sample size required in such a trial is 288 patients [23]. However, if the CRI rate in another control group with "high-risk" patients is 60%, and all other conditions are the same, the sample size required for such a trial is only 84. Thus, the number of patients exposed to the treatment arm is only 42 in the trial with the "high-risk" patients in contrast to 144 in the trial with unselected patients. The conclusions of both studies would be equally valid, but the number of patients exposed to this potentially toxic treatment would be substantially less in the latter trial.

We have developed an approach for assessing the risk of developing CRI in patients with IMGN. This approach is based on laboratory parameters well-known to be associated with an adverse renal outcome [1–3], and can be used repetitively in response to the patient's changing status. By quantifying this risk, the clinician can establish a "threshold" to select patients for a given treatment. This threshold may vary between clinicians depending on their assessment of the risks as well as the effectiveness of the treatment. Using these strategies, one can optimize the exposure of potentially toxic treatments to those patients who would be most likely to benefit from them, at the level of the individual patient or in the setting of a clinical trial.

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Appendix 1. Terms used to define a diagnostic test

Positive predictive value (PPV): Probability of having a disease in a patient with a positive test result.

Negative predictive value (NPV): Probability of not having disease in a patient with a negative test result.

Sensitivity (SEN): Probability of having a positive test result in a person with a disease (that is, "true-positive rate").

Specificity (SPEC): Probability of not having a positive test result in a patient without disease (that is, "true-negative rate").

Accuracy: The proportion of all the results of a test condition, both positive and negative, which correctly predicts the disease status.

Appendix 2. Probability modeling in IMGN

In an attempt to improve further our ability to predict CRI, we added two other variables of renal functional assessment in our patients during each of the 15 levels of PP. On every occasion where a patient fulfilled a specific level of $PP(X_i, Y_i)$, the C_{Cr} at the start of $PP(X_i, Y_i)$, and its rate of change during the same time period (SLP), were calculated. If a patient did not satisfy $PP(X_i, Y_i)$, then the C_{Cr} and SLP were calculated on the next lower level of proteinuria, $P(X_j)$ where X_j was proteinuria ≥ 3 g/day, 2 g/day or 1 g/day in descending order, and stored for the modeling at $PP(X_i, Y_i)$. If a patient never had over 1 g/day of proteinuria for six months or more, the C_{Cr} at the time of biopsy and the SLP over his/her entire course would be used. Whenever possible, each SLP calculation was based on a minimum of four data points. Fifteen models using the above database were developed, and a score, R(CRI), was generated by each model to estimate the risk of developing CRI for each patient. The positive and negative predictive values, sensitivity, specificity and accuracy for the prediction of CRI by different R(CRI) cut-offs were then determined within each model.

The logistic equation for predictive model is as follows:

$$R(CRI) = \frac{\exp(K_0 + K_1 \times PP + K_2 \times SLP + K_3 \times C_{Cr})}{1 + \exp(K_0 + K_1 \times PP + K_2 \times SLP + K_3 \times C_{Cr})}$$

where PP is PP(≥X g/day for ≥Y months): Yes = 1, No = 0; C_{Cr} is creatinine clearance at the start of the period of PP selected in ml/min/1.73 m^2; and SLP is the rate of change of C_{Cr} during PP in ml/min × $(1.73\ m^2)^{-1}$ × $(year)^{-1}$.

The coefficients for the predictive models are shown below:

	K_0	K_1	K_2	K_3
M(≥ 4 g/day for ≥ 18 months):	2.8	1.8	−0.094	−0.062
M(≥ 6 g/day for ≥ 9 months):	1.4	1.5	−0.060	−0.044
M(≥ 8 g/day for ≥ 6 months):	0.3	2.1	−0.040	−0.031

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