Identifying the ideal metric of proteinuria as a predictor of renal outcome in idiopathic glomerulonephritis

Sean J. Barbour[1,2,3], Daniel C. Cattran[4,5], Gabriela Espino-Hernandez[2], Michelle A. Hladunewich[4,5] and Heather N. Reich[4,5]

[1]Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada; [2]BC Provincial Renal Agency, Vancouver, British Columbia, Canada; [3]Centre for Health Evaluation and Outcomes Sciences, University of British Columbia, Vancouver, British Columbia, Canada; [4]Division of Nephrology, University of Toronto, Toronto, Ontario, Canada and [5]Toronto GN Registry, Toronto, Ontario, Canada

The majority of our insight about glomerulonephritis (GN) is from observational research. Because proteinuria is an important element of outcome in GN, the validity of observational analyses is dependent on the metric used to model proteinuria. Previous metrics of proteinuria included the value at baseline, the average of all values over the entire follow-up (time-averaged), the instantaneous value at each time point (time-varying), or the average of all values prior to each time point, and each of these standardized to body surface area. It was not known which of these metrics best accounts for the risk of renal outcome and should be used in GN research. To address this, we studied 1351 adult patients with IgA nephropathy, focal segmental glomerulosclerosis, and membranous nephropathy from the Toronto GN Registry. Cox regression models for the risk of end-stage renal disease or a halving of estimated glomerular filtration rate included each proteinuria metric and were compared using model fit and discrimination. Proteinuria did not need to be standardized to body surface area. Time-varying proteinuria was the best metric to account for the prognostic effects of proteinuria over time, especially in focal segmental glomerulosclerosis and IgA nephropathy over the majority of follow-up, and in membranous nephropathy earlier in the disease course. Using alternate proteinuria metrics biased analyses up to 30.3%. These findings can improve the validity and design of future observational and prediction modeling studies in GN.

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Correspondence: *Sean J. Barbour, Division of Nephrology, University of British Columbia, 5th Floor Nephrology, 2775 Laurel Street, Vancouver, British Columbia V5Z 1M9, Canada. E-mail: sean.barbour@vch.ca or Heather N. Reich, Toronto Glomerulonephritis Registry, 12 EN-228, 200 Elizabeth Street, Toronto, Ontario M5G 2C4, Canada. heather.reich@uhn.ca*

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Glomerulonephritis (GN) is a rare and relatively slowly progressive cause of kidney failure, limiting the ability to conduct clinical trials to identify new therapies and treatment goals. A large part of our understanding about the natural history, clinical outcomes, risk stratification, and treatment is therefore derived from observational research.[1] Almost 80% of recommendations from the 2012 KDIGO clinical practice guidelines for GN are based on observational data.[2] Proteinuria is one of the strongest determinants of renal prognosis in GN.[3–7] However, no consensus exists regarding the most appropriate method to quantitate and model proteinuria in observational analyses. Because different ways of modeling proteinuria may produce biased results, optimizing the method by which we account for the relationship between proteinuria and disease progression in GN would greatly improve our ability to interpret observational data and risk stratify patients to identify those at highest risk of hard renal outcomes.

Different metrics of proteinuria that have been used in GN studies include values at baseline, averaged over time, varying over time, and standardized to body surface area (BSA).[3,4,7–14] To date, there has been no comprehensive assessment of the optimal analytic method to account for the prognostic effects of proteinuria, and therefore there is no understanding of which metric of proteinuria should be used in GN research and the potential impact on study results. Time-averaged proteinuria is measured simply by averaging all proteinuria values over the duration of follow-up, and is the most commonly used method to capture longitudinal changes in proteinuria as a reflection of variation in disease activity and potentially nephrotoxic effects of long-term protein excretion. However, other more sophisticated measures have been used that capture dynamic changes of proteinuria over time, and there has never been a direct comparison of the degree to which these different metrics of proteinuria correlate with hard renal outcomes. In addition, the requirement for BSA adjustment is commonly accepted not only in the pediatric literature but has also been used in studies of adult

Table 1 | A summary of the proteinuria metrics evaluated in this study

Name	Abbreviation	Description
Proteinuria at baseline	T_0-proteinuria	Closest value within 6 months of biopsy
Time-averaged proteinuria	TA-proteinuria	The mean of all the average proteinuria values in each 6-month interval from biopsy to the end of follow-up or an outcome event
Time-varying proteinuria	TV-proteinuria	Value taken at each patient visit
Time-varying cumulative proteinuria	TVC-proteinuria	At each patient visit, it reflects the cumulative prior exposure to proteinuria by dividing the area under the proteinuria versus time curve (using the trapezoidal rule) by the total time from biopsy
Proteinuria at baseline standardized to BSA	T_0-proteinuria/1.73 m^2	Baseline proteinuria standardized to 1.73 m^2
Time-averaged proteinuria standardized to BSA	TA-proteinuria/1.73 m^2	Time-averaged proteinuria standardized to 1.73 m^2
Time-varying proteinuria standardized to BSA	TV-proteinuria/1.73 m^2	Time-varying proteinuria standardized to 1.73 m^2
Time-varying cumulative proteinuria standardized to BSA	TVC-proteinuria/1.73 m^2	Time-varying cumulative proteinuria standardized to 1.73 m^2

Abbreviation: BSA, body surface area.

populations without systematic evaluation and despite potentially large variation in body size. These are areas of substantial knowledge deficiency that need to be addressed to ensure the validity of future observational and prognostic modeling research in GN.

To address this important gap in methodological knowledge, we analyzed a large cohort of patients with idiopathic focal segmental glomerulosclerosis (FSGS), immunoglobulin A nephropathy (IgAN), and membranous nephropathy (MN) from the Toronto GN Registry. Our goal was to determine the ideal metric of proteinuria for use in GN research by identifying which proteinuria measurement accounts for the largest variability in risk of a hard renal outcome (end-stage renal disease (ESRD) or halving of estimated glomerular filtration rate (eGFR)) and best discriminates between patients who will or will not experience this outcome.

RESULTS

We considered as primary exposure variables the following metrics of proteinuria (see Table 1): baseline (T_0) proteinuria; longitudinal measures, including time-averaged, time-varying, and time-varying cumulative proteinuria (TA-proteinuria, TV-proteinuria and TVC-proteinuria respectively); and the same metrics standardized to BSA (T_0-proteinuria/1.73 m^2, TA-proteinuria/1.73 m^2, TV-proteinuria/1.73 m^2, and TVC-proteinuria/1.73 m^2). When using time-averaged proteinuria, the instantaneous risk of the renal outcome at any given time point is associated with the same (time-invariant) average of all proteinuria values over the entire course of follow-up. In contrast, the instantaneous risk of the renal outcome at any given time point is associated with the proteinuria value at that same time point when using the TV measure and is associated with the time-weighted average of all proteinuria values prior to that same time point when using the TVC measure. All comparisons between metrics of proteinuria were performed separately in the different GN subgroups.

Description of the cohort and outcome events

There were 1351 patients in the analytic cohort, including 445 with IgAN, 434 with MN, and 472 with FSGS. The derivation of the cohort is shown in Supplementary Figure S1 online, and patient characteristics at baseline and through clinical follow-up are described in Table 2. Survival without the primary outcome (50% reduction in eGFR or ESRD) in each type of GN is shown in Supplementary Figure S2 online and was more favorable in MN compared with FSGS or IgAN ($P = 0.002$), in keeping with previous studies.[4,5,7,9,13]

The need for proteinuria transformation

An assumption of Cox survival models is that the functional form of the relationship between the logarithm of the relative hazard and proteinuria is linear. For each metric of proteinuria in Table 1, there was substantial deviation from linearity, which improved with logarithmic transformation. A representative example is shown in Supplementary Figure S3 online. The univariable association between each log-transformed proteinuria metric and the primary renal outcome is shown in Supplementary Table S1 online. All measures of proteinuria at baseline and during follow-up were associated with an increased risk of the primary outcome except baseline measures of proteinuria in FSGS, which is similar to previous reports.[7,10,15,16]

Which is the optimal metric of proteinuria over time?

The first step in the analysis was to determine the optimal metric of proteinuria over time, in terms of better accounting for the variability in risk of the primary renal outcome (as assessed by Cox regression model fit using Nagelkerke's R^2 and the Akaike Information Criterion (AIC)) or improvement in discrimination between patients who did or did not develop the renal outcome 5 years after biopsy (using the change (Δ) in C-statistic, continuous net reclassification improvement (cNRI), and integrated discrimination improvement (IDI)). An increase in R^2 or a reduction in