

# Adjusting the Lens: Real World Outcomes in Nephrotic Syndrome



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[See Clinical Research on Page 449](#)

When a patient presents with nephrotic syndrome, the immediate focus is on the practicalities of performing a biopsy or not, defining the precise glomerular lesion, the determination of a specific treatment plan, and the exclusion of other serious underlying conditions. Compare this with the far more common scenario when we meet a person with progressive chronic kidney disease in whom no cause is identified and specific treatment not indicated: here we consider the patient to be at the beginning of a chronic kidney disease journey and we focus instead on slowing progression, reducing cardiovascular morbidity, and preparing for renal replacement therapy.

Our clinical focus on the immediate disease process for nephrotic syndrome may relate to existing studies concerning the management of nephrotic syndrome that focus on drug-specific effects on proteinuria with short-term follow-up. As an

example, consider the evidence related to what is considered the most benign cause of nephrotic syndrome: minimal change disease. The evidence for steroid treatment is extrapolated from several randomized controlled trials in children and from 2 studies in adults undertaken in the 1970s and 1980s.<sup>1,2</sup> The response rate to prednisolone was high, 84% and 86% at 6 months, but the broader representativeness of this evidence is limited by small sample size, limited follow-up, young age of enrolled patients, and substantial improvements in dialysis technology and availability since the trials were conducted. Similarly, further randomized controlled trials to examine the use of tacrolimus as an alternative to steroids demonstrate high response rates but with relatively small numbers, limited follow-up, and information about mortality and renal functional outcomes.<sup>3,4</sup>

This study by Anna Kolb and colleagues<sup>5</sup> shows the limitation of focus on these immediate concerns and highlights the additional importance of considering the broader prognosis of patients presenting with nephrotic syndrome. The authors linked the records of all 522 patients recorded in the Scottish Renal Biopsy Registry who

underwent a kidney biopsy for nephrotic syndrome between 2014 and 2017 to national mortality data for date and cause of death. For comparison, they determined age- and sex-specific mortality rates in the general Scottish population using publicly accessible national records. In addition, the authors linked to information regarding renal function and proteinuria, enabling them to estimate disease remission, development of acute kidney injury and of end-stage renal disease. Among the biopsied population, the sample included 327 with a primary glomerular lesion, most commonly membranous nephropathy, minimal change nephropathy, and focal segmental glomerulosclerosis, whereas 150 had a secondary cause, primarily diabetes, plasma cell dyscrasia, and systemic lupus erythematosus.

The results are sobering. During a median follow-up of 2.4 years, 21% died. People younger than 60 years with secondary nephrotic syndrome had 24 times the number of deaths compared with that expected in the age and sex standardized general population. Even for people with primary nephrotic syndrome, those older than 60 years had more than 5 times the number of deaths.

In survival modeling, age and a secondary cause of nephrotic syndrome were the strongest associations of mortality, whereas the nature of the histological lesion was less strongly associated with mortality than age, even among older people with primary causes of nephrotic syndrome.

Perhaps less surprising, overall 15% of patients progressed to end-stage kidney disease during follow-up. Among people older than 60, at 3 years, the proportion with end-stage kidney disease was 8.4% in primary nephrotic syndrome and 35.1% in secondary

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nephrotic syndrome. Among older patients with primary nephrotic syndrome, baseline glomerular filtration rate as well as membranous and mesangiocapillary lesions were associated with a higher risk of end-stage kidney disease. Overall, 29% of patients did not achieve even partial remission within 6 months of the biopsy. Even for minimal change disease, only 50% had entered complete remission by 6 months, much lower than that reported in the literature.<sup>6-8</sup>

Given the nature of routine data, there are of course limitations to the study, although these have been addressed where possible. The major issues concern the very limited information about baseline comorbidities, and relatively small numbers, particularly for models of subgroups in which many estimates have wide confidence intervals. The study is only generalizable to people who were considered well enough to undergo a kidney biopsy, and the high rates of death attributed to cardiovascular causes may reflect the characteristics of a Scottish population. Finally, there may be errors in the classification of cause of nephrotic syndrome and, as in clinical practice, it is hard to distinguish acute kidney injury from progression of kidney disease.

Nonetheless, this study is important. From an academic perspective, the prespecified protocol with explanation of deviations and open analytical code are welcome and should be widely replicated. Clinically, the study highlights the difference between renal and mortality outcomes for a routine care population and that shown among the selected population in clinical trials and disease specific cohorts. This could allow us to provide more accurate prognostic information for our patients. In addition, the paper reminds us

to focus on outcomes beyond their glomeruli. We must establish patients' priorities of care and consider adequate preparation for renal replacement therapy and advance care planning when required. In this, the situation is analogous to the management of the failing renal transplant where despite specialist nephrology follow-up patients arrive at dialysis poorly prepared.<sup>9</sup> Again, the focus on the diagnosis of the transplant pathology can blur our vision when it comes to focusing on patient-centered outcomes. The benefits of involving patient and carer groups in trial design has been taken a step forward in recent years with the SONG initiative to identify research priorities from the patient, carer, and clinician perspective in many different areas of kidney disease and this collaborative is currently undertaking this process for glomerulonephritis.<sup>S1</sup>

In addition, this paper raises important questions. *Why* is data linkage of this kind not the norm? *Why* do we struggle to determine cause of death for our patients who die away from local services? *Why* is this data surprising? While each specific cause of nephrotic syndrome is relatively rare, imagine the power of a UK-wide or international study of renal biopsy information with full linkage to treatment and biochemical data to understand features associated with renal and mortality outcomes. While we persist with randomized trials, better use of routine data could help us quantify the patients most likely to benefit from intensive immunosuppressive regimes. It is imperative that we move toward greater access to and wider use of linked data: our patients have provided the data and we must find ways to use it for maximum clinical benefit for all.

## DISCLOSURE

All the authors declared no competing interests.

## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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