ESRD Outcomes and GN Subtypes

Eric W. Young


The introduction of kidney disease registries, particularly the US Renal Data System (USRDS), launched an era of population analysis that fostered important improvements in the quality of care and outcomes for patients with ESRD. From the earliest days of population metrics, kidney disease has been classified into broad, pragmatic categories that appealed to the clinical sense of most nephrologists. Specifically, the cause of ESRD has generally been classified into the categories of diabetes, hypertension, GN, cystic diseases, and other. This basic nosology has framed the presentation of disease statistics, including incidence, prevalence, and, most especially, mortality. According to this diagnostic framework, patients with ESRD attributed to GN have a better prognosis than most other common attributed causes. For example, the adjusted 2012 mortality rate for patients with ESRD attributed to GN was 43% lower than the rate for patients with ESRD attributed to diabetes and 31% lower than the rate for patients with ESRD attributed to hypertension (1). Even more strikingly, patients with incident ESRD and GN had a 3.4-fold higher 10-year survival probability compared with patients with diabetes (1). Clinical and research views of kidney disease are grounded in statistics like these that emerged from the classification system.

Although clinicians have long recognized the heterogeneous nature of GN in the non-ESRD setting, the practice of grouping all patients with ESRD attributed to GN has not been seriously challenged. In addition to classification convenience, this acceptance partly reflects the tendency for GN to become inactive and undifferentiated as kidney failure progresses to end stage. However, the article in this issue of CJASN by O’Shaughnessy et al. (2) reminds us that GN remains heterogeneous, even when survival start time is shifted forward many years to the onset of ESRD. Using Medicare administrative claims data from the USRDS, O’Shaughnessy et al. (2) were able to classify patients with ESRD and GN into six subtypes: FSGS, IgA nephropathy (IgAN), membranous nephropathy, membranoproliferative GN, lupus nephritis (LN), and vasculitis. Large differences in mortality were found among the six GN groups. Patients with IgAN had the fewest comorbidities and the lowest mortality (after adjustment for demographics and comorbidity) followed by membranous nephropathy, FSGS, membranoproliferative GN, vasculitis, and LN. Patients with IgAN had better survival than patients with autosomal dominant polycystic kidney disease, who are often considered to have among the best prognoses among patients with ESRD. Patients with LN had the highest mortality, comparable to patients with ESRD attributed to diabetes (generally thought to be among the causes of ESRD with the highest mortality). The study by O’Shaughnessy et al. (2) clearly shows large differences in patient characteristics and mortality risk by GN subtype. The findings warrant a reconsideration of the traditional categories used to classify the cause of ESRD in population registries.

O’Shaughnessy et al. (2) used the cause of ESRD entered on the Medicare Medical Evidence registration form to classify patients by GN subtype. A relatively large number of patients were assigned to each GN subtype, facilitating a sophisticated analysis. However, this approach has known limitations. As with any clinical data, there is no assurance that the diagnosis was based on a kidney biopsy and no possibility of confirming diagnostic uniformity across sites and patients. The diagnostic coding system provides a very limited description of pathology and clinical syndrome. However, O’Shaughnessy et al. (2) made full use of the rich USRDS data sources to adjust for demographic and comorbid factors. Adjustment was applied in stages to clearly show the contribution of patient attributes to survival. Although one can never know if every important covariate was measured and entered into the statistical model, the central finding of survival heterogeneity by GN subtype was clearly revealed. Future refinements might include additional adjustment for socioeconomic characteristics (e.g., patient income or education) and disease activity at onset of ESRD. The latter could be inferred by the presence or absence of immunosuppressive treatments at the start of ESRD, which should be available in Medicare claims data for those patients with preexisting Medicare coverage who received medications through the Part D Prescription Drug Benefit. Although diagnostic refinement and additional adjustments should be pursued for explanatory purposes, there is little reason to doubt the core finding of heterogeneity in ESRD survival by GN subtype. The finding is new and important but not altogether surprising. Until now, the question had not been systematically addressed.

The study by O’Shaughnessy et al. (2) was not designed to explain the differences in outcome by GN type. The differences could be attributable to differences in the underlying biology of these inflammatory conditions. Alternatively, differential outcomes could...
be explained by exposures to immunosuppressive agents that may have been used to manage the disease, sometimes over many years. Finally, the survival differences could relate to comorbidities (possibly related to disease or treatment) that were not fully captured in the adjustment process. Several GN subtypes, notably LN and vasculitis, usually present as systemic processes that undoubtedly influence patient outcomes.

The study by O’Shaughnessy et al. (2) advocates abandonment of the current classification system for cause of ESRD in population registries. In truth, many purposes will continue to be served by the simplistic approach of grouping all GN subtypes into one category. However, any serious effort to understand population statistics for patients with ESRD attributed to GN will heretofore require parsing of the subtypes. Although it will always be difficult to assure diagnostic uniformity of biopsy interpretation in a population study, it seems likely that the ICD10 coding system will provide more diagnostic specificity in the future. ICD10 has long been used in many parts of the world and is slated for adoption in the United States starting in 2015. Compared with ICD9, ICD10 offers richer codification of histologic subtypes as well as syndrome presentation (nephrotic versus nephritic) and acute versus chronic pathology.

In a larger sense, the study by O’Shaughnessy et al. (2) illustrates the imprecision and heterogeneity of most categories used to describe the cause of ESRD. ESRD attributed to hypertension is the most striking example. The diagnosis is usually clinical; biopsy diagnosis is unusual. The degree and duration of hypertension are highly variable among patients. There is considerable overlap in severity and duration of high BP between patients who develop ESRD and those who do not. Many known causes of kidney disease could easily be misclassified as hypertension, including unrecognized ischemic nephropathy and analgesic nephropathy. More likely, some patients currently classified in the hypertension ESRD category could have a currently unrecognized etiologic contributor, such as an exposure to an environmental toxin or virus. Even for ESRD attributed to diabetes, which is generally thought to be a more secure diagnosis, there is room consider the possible contribution of other etiologic factors. Unfortunately, the most commonly attributed causes of kidney disease leading to end stage are based on descriptive phenotypes rather than defined etiologies. The study by O’Shaughnessy et al. (2) illustrates the special case of this observation applied to GN. Of course, the current classification system for GN itself is far more descriptive than etiologic.

Lumping glomerular diseases into a single encompassing category harks back to the era of Bright (3) and serves the needs of generalists and epidemiologists. The splitting of glomerular diseases into multiple, descriptive entities derives from the considerable progress that has been made by kidney specialists in understanding glomerular disease. The study by O’Shaughnessy et al. (2) nicely shows the added value of a specific GN diagnosis in population-based analyses of ESRD. When it comes to classifying and cataloging ESRD caused by GN, there is a basic role for lumping and an expanding role for splitting based on the question at hand.

Disclosures
None.

References

Published online ahead of print. Publication date available at www.cjasn.org.