Are Chronic Kidney Disease Patients Misclassified?

Newer Equation May Be More Accurate for Disease Detection and Risk Stratification

By Tracy Hampton

Glomerular filtration rate (GFR) has been the mainstay for diagnosing chronic kidney disease (CKD), and it provides a powerful tool for helping clinicians predict all-cause and cardiovascular mortality and kidney failure in patients. But what is the best equation for estimating an individual's GFR? A new meta-analysis published in the *Journal of the American Medical Association* set out to answer this question.

Comparing two equations

Although the Modification of Diet in Renal Disease (MDRD) Study equation is recommended for estimating GFR, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) recently proposed an alternative equation that applies different coefficients to the same four variables used in the MDRD Study equation: age, sex, race, and serum creatinine level.

In June 2011, only 4 percent of U.S. laboratories that reported estimated GFR used the CKD-EPI equation to do so; 92 percent still used the MDRD Study equation, while 4 percent used other equations. To comprehensively evaluate whether estimated GFR computed by the CKD-EPI equation predicts risk for adverse outcomes more accurately than the MDRD Study equation in different populations of individuals, Kunihiro Matsushita, MD, PhD, of Johns Hopkins University, in Baltimore, and his colleagues conducted a meta-analysis of data from 1.1 million adults from 25 general population cohorts, seven high-risk cohorts of vascular disease, and 13 CKD cohorts. The participants were from 40 countries or regions of Asia, Europe, North America and South America, the Middle East, and Oceania. Data transfer and analyses were conducted between March 2011 and March 2012.

Adverse outcomes included all-cause mortality (84,482 deaths from 40 cohorts), cardiovascular mortality (22,176 events from 28 cohorts), and end stage renal disease (7644 events from 21 cohorts). The goal of the analysis was to provide information to help clinicians, laboratories, and policy makers decide whether estimated GFR reporting should be based on the MDRD Study equation or the CKD-EPI equation.

Should patients be reclassified?

Estimated GFR was classified into six categories (90 or greater, 60–89, 45–59, 30–44, 15–29, and <15 mL/min/1.73 m^2) by both equations. The researchers found that approximately one-fourth of participants were reclassified to a higher estimated GFR category by the CKD-EPI equation compared with the MDRD Study equation (24.4 percent in the general population cohorts, 15.4 percent in the high-risk cohorts, and 6.6 percent in the CKD cohorts). This lowered the prevalence of CKD in all cohorts except for the elderly. Approximately 0.6 percent of participants were reclassified to a lower estimated GFR category.

Study participants who were reclassified upward had lower risks of mortality and end stage renal disease compared with those not reclassified even after adjusting for various factors. Individuals who were reclassified downward had higher risks than those who were not reclassified.

The prevalence of CKD stages 3 to 5 (<60 mL/min/1.73 m^2) was lower by the CKD-EPI equation than by the MDRD Study equation in the general population cohorts (6.3 percent vs. 8.7 percent) as well as in the high-risk cohorts (14.6 percent vs. 17.7 percent).

"Overall, the CKD-EPI creatinine-based equation more accurately classified individuals with respect to risk of mortality and end stage renal disease compared with the MDRD Study equation," the authors wrote. "Given more accurate GFR estimation, lower CKD prevalence estimates, and better risk categorization by the CKD-EPI equation without additional laboratory costs, its implementation for estimated GFR reporting could contribute to more efficient and targeted prevention and management of CKD-related outcomes."

Kamyar Kalantar-Zadeh, MD, MPH, PhD, who was not involved with the research, agreed that fewer individuals should be diagnosed with CKD.

"Many feel that an estimated GFR <60 mL/min/1.73 m^2 is too high and too imprecise of a threshold level to diagnose CKD be it with MDRD or CKD-EPI," said Kalantar-Zadeh, director of the Harold Simmons Center for Kidney Disease Research & Epidemiology within the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, in Torrance, CA. "A lower and more conservative estimated GFR such as <45 mL/min/1.73 m^2 should replace <60. It is wrong to diagnose so many elderly individuals and women with CKD and cause stigma when they really do not have the disease."

Kalantar-Zadeh and his colleague Alpesh Amin, MD, MBA, of the University of California-Irvine Medical Center, published an accompanying editorial in the same issue of *JAMA*, writing that "even though CKD staging using the more conservative CKD-EPI equation seems valid because it produces more meaningful risk profiles, it is premature to conclude that the ultimate tool for estimated GFR accuracy has been found."

They noted that inherent limitations of the MDRD equation remain essentially unchanged in the CKD-EPI equation. For example, both equations rely on creatinine as a renal filtration marker. Creatinine is a close correlate of skeletal muscle mass but also likely varies with individuals' nutritional status and how much meat they eat. "Neither MDRD nor CKD-EPI offers any adjustment for body size or muscle mass. A less muscular person or a vegetarian may have lower serum creatinine level and hence artificially better estimated GFR," said Kalantar-Zadeh.

The editorial noted that a panel of several filtration markers combined with some surrogate markers of nutritional status and body composition may provide a more accurate and clinically meaningful estimate of GFR.

Matsushita K, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate.. *JAMA* 2012; 307:1941–1951.

Kalantar-Zadeh K, Amin AN. "Toward more accurate detection and risk stratification of chronic kidney disease. *JAMA* 2012; 307:1976–1977. (editorial)