

## Staging of Chronic Kidney Disease: Time for a Course Correction

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### ABSTRACT

Awareness of chronic kidney disease (CKD) has increased in part because of the definitions and treatment guidelines set out by Kidney Disease Outcomes Quality Initiative (KDOQI); however, the staging system set forth by these guidelines has led to several problems and unforeseen consequences. Stages 1 and 2 CKD are difficult to determine using the standard Modification of Diet in Renal Disease (MDRD) estimation of GFR, and their clinical significance in the absence of other risk factors is unclear. Just because microalbuminuria in people without diabetes is a cardiovascular risk factor does not make it kidney disease. Most patients who receive a diagnosis of stage 3 CKD (GFR between 30 and 59 ml/min) are elderly people, and the vast majority of these patients will die before they reach ESRD. The staging system needs to be modified to reflect the severity and complications of CKD. It is suggested that stages 1 and 2 be eliminated and stages 3, 4, and 5, be simply termed moderate impairment, severe impairment, and kidney failure, respectively. In addition, age should be a modifying factor, especially in moderate kidney impairment. These changes would allow identification and treatment of clinically relevant disease and avoidance of what can seem exaggerated prevalence estimates.

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The increasing recognition of chronic kidney disease (CKD) in the past few years and acceptance of its abbreviation into ordinary clinical jargon stems from multiple sources. First, its most conspicuous outcome, ESRD, was increasing in the United States at alarming rates from the inception of Medicare coverage in 1972 until the late 1990s, and there still remains a very high incidence of ESRD today with 100,000 new cases per year.<sup>1</sup> Also, a reliable estimation of GFR was developed from data in the Modification of Diet in Renal Disease (MDRD) study.<sup>2</sup> Using that estimation, the prevalence of CKD is rather large in the general population.<sup>3</sup> In addition, a relation of CKD, not just ESRD, to cardiovascular disease was discovered.<sup>4</sup> Importantly, effective

therapies emerged for slowing progression of CKD.<sup>5,6</sup> Several campaigns by nonprofit organizations, government, and industry began around the turn of the century to promote CKD awareness among not just nephrologists but also people at risk and their primary care providers; however, staging of CKD embodied in the National Kidney Foundation KDOQI™ guideline published in 2002 has had a particularly large influence and at least partially underlies several of these epidemiologic analyses.<sup>7</sup>

Most readers are aware of the five stages, but they are reproduced in Table 1. The staging as it was laid out 6 years ago has had beneficial effects; however, several weaknesses and unforeseen consequences have become apparent. In the

original KDOQI publication, the general rationale for these stages was detailed in the Executive Summary<sup>7</sup>:

#### **“Why Develop a New Classification?**

*Currently, there is no uniform classification of the stages of chronic kidney disease. A review of textbooks and journal articles clearly demonstrates ambiguity and overlap in the meaning of current terms. The Work Group concluded that uniform definitions of terms and stages would improve communication between patients and providers, enhance public education, and promote dissemination of research results. In addition, it was believed that uniform definitions would enhance conduct of clinical research.*

**Why Base a New Classification System on Severity of Disease?** *Adverse outcomes of kidney disease are based on the level of kidney function and risk of loss of function in the future. Chronic kidney disease tends to worsen over time. Therefore, the risk of adverse outcomes increases over time with disease severity. Many disciplines in medicine, including related specialties of hypertension, cardiovascular disease, diabetes, and transplantation, have adopted classification systems based on severity to guide clinical interventions, research, and professional and public edu-*

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cation. Such a model is essential for any public health approach to disease.”

These views seem to us still reasonable, so what is wrong?

GFR values  $>60$  ml/min per  $1.73$  m<sup>2</sup> as estimated by the MDRD formula are generally too inaccurate for routine clinical use. Several issues contribute to this problem, including the formula's development in a large group in which all participants had depressed GFR and particular ethnic, age, and disease characteristics; for example, few Asians, few elderly, and few people with diabetes. Also, at low levels of serum creatinine (normal to high GFR), an estimation of GFR generates a very wide range of confidence intervals, a range so wide as to be useless.<sup>2</sup> A few commentators have even questioned the accuracy of estimates in the range  $<60$  ml/min per  $1.73$  m<sup>2</sup>, but we regard the estimate as just that, an estimate that is useful for clinical work in the low end of GFR if not as exact as some desire. In any case, reporting estimated GFR (eGFR)  $>60$  ml/min per  $1.73$  m<sup>2</sup> has been discouraged; however, the staging demands distinctions in this higher range. Admittedly, these problems for estimations in the near-normal and high range are most apparent since the promulgation of the system and probably in part because of it. Nevertheless, it seems to us that this weakness should be recognized and stages 1 and 2 be removed. If we cannot find them, then we should not stage them.

In addition to an eGFR, stages 1 and 2 demand the presence of “kidney damage” as a supplementary criterion.<sup>7</sup> Damage could be evidenced by several criteria; for example, biopsy and imaging, but proteinuria is the most commonly referenced data used as evidence of kidney damage. We are

uncertain of the significance of microalbuminuria in a patient with an eGFR  $>60$  ml/min per  $1.73$  m<sup>2</sup> without known kidney disease or major risk factor, especially diabetes or hypertension. Proteinuria can be transient and without pathology, for example after exercise. The staging and the epidemiology devolving from it have attempted to estimate only persistent proteinuria or, more specific, persistent albuminuria. Even persistent low-grade albuminuria in the otherwise normal person has no specific therapy. Increasing evidence suggests a cardiovascular risk to albuminuria but, again, one without current treatment.<sup>8</sup> A cardiovascular disease risk factor does not merit a diagnosis of kidney disease. Why albuminuria would have been measured in the first place in such a person except as part of an epidemiologic cohort study is a mystery of its own.

This current KDOQI staging system forms a basis for extrapolation of CKD prevalence in the general US population using sample populations, especially the National Health and Nutrition Examination Surveys (NHANES). The most recent has estimated that 13% of the adult population in the United States has CKD. This is an enormous number and for many seems inflated. The inclusion of people with eGFR  $>60$  ml/min per  $1.73$  m<sup>2</sup> but with some albuminuria (stages 1 and 2) accounted for almost 40% of the total estimate of prevalence. Except for the patient with diabetes, we have little guidance on what to do with such patients or knowledge of how many will develop complications. Thus, inclusion of such people in these population estimates expands the estimate beyond current clinical implications.

The incredibly high prevalence rate depends on inclusion of not just those

with stages 1 and 2 but also those in the range just below  $60$  ml/min per  $1.73$  m<sup>2</sup>. Because the distribution of eGFR is roughly bell shaped with a mean of  $80$  to  $90$  ml/min per  $1.73$  m<sup>2</sup>, it is obvious that more values will lie between  $50$  and  $60$  than  $40$  and  $30$ , and so forth. Thus, any arbitrary limit imposed on such a distribution will have this problem: More people at the border edge with mild impairment than down in the range of most concern with severest impairment. However, the separate phenomenon of age-related decline in GFR makes this preponderance more than mathematically unfortunate.<sup>9</sup>

With the current staging system, people who are older than  $70$  years dominate the category of moderate renal impairment; that is, GFR from  $30$  to  $59$  ml/min per  $1.73$  m<sup>2</sup> (stage 3).<sup>10</sup> Indeed, most of this group is older than  $70$  years. Because the median age of incidence for ESRD is approximately  $65$  years, the vast majority of people identified as having stage 3 CKD cannot be expected to progress to ESRD. To be sure, the additional risk for cardiovascular disease with CKD has been much noted and widely emphasized. Whether this particular cardiovascular risk factor has much meaning for the  $75$ -year-old person with an eGFR of  $59$  and no other risk factors or with controlled risk factors is unclear. What the physician should do with this risk factor is also uncertain. Age is ignored in the current staging; however, within the pool of moderate CKD, risk for ESRD depends strongly on age. Compared with the elderly, people in middle age with moderate CKD, especially if male or black, have much higher risks for ESRD and truly premature cardiovascular disease.<sup>1,11</sup>

Several other concerns can be raised

**Table 1.** Stages of CKD<sup>a</sup>

Stage	Description	GFR (ml/min per $1.73$ m <sup>2</sup> )
1	Kidney damage with normal or increased GFR	$\geq 90$
2	Kidney damage with mild decreased GFR	$60$ to $89$
3	Moderate decreased GFR	$30$ to $59$
4	Severe decreased GFR	$15$ to $29$
5	Kidney failure	$<15$ or dialysis

<sup>a</sup>CKD is defined as either kidney damage or GFR  $<60$  ml/min per  $1.73$  m<sup>2</sup> for  $\geq 3$  months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies. Reproduced from ref. 7, with permission.

with the current staging system. Disease labeling for people at little or no known risk has been raised as a hazard. The psychological weight could be untoward. The label “disease” may be unnecessarily onerous, and “impairment” might be better and just as accurate; however, we do not see this as an overriding concern but one for which the nephrologist can provide perspective to the patient and the primary care provider. Lumping many diseases into a huge category only on the basis of kidney function potentially leads to failure of diagnosis for some patients. Physicians may think they know what is happening once a label of stage 3 CKD is applied. We see this as another point that requires thoughtful nephrologic advice and guidance but does not detract from the overall value. Likewise, research into better means of altering the outcomes of CKD is not superseded by a staging label.

We emphasize that reporting eGFR with all serum creatinine values is valuable and totally separate from staging patients’ disease. In fact, such reporting is especially useful for the elderly, whose serum creatinine so poorly reflects GFR. Recognizing CKD in the elderly should benefit them even if ESRD is unlikely, because it would improve drug dosing and reduce nephrotoxin exposure. Furthermore, identification of CKD in people with high risk for ESRD, the younger and black individuals, is crucial to altering their progression and even preparing for ESRD. Less than one half of people with an eGFR below 30 ml/min/1.73 m<sup>2</sup> knew they had CKD.<sup>10</sup> Routine reporting of eGFR is a key means of identifying them and should be encouraged in all clinical laboratories.

In the past several years, staging as well as other factors have contributed to a welcome increase in awareness of CKD, but the staging system has had some unforeseeable adverse consequences. What would we do? We propose that stages 1 and 2 be eliminated.

We also think as a means of classifying, numbers, be they Roman or Arabic, always suggest more than they really deliver and should be dropped. Simply, the words originally attached to stages 3, 4, and 5 seem best: Moderate kidney impairment, severe kidney impairment, and kidney failure or ESRD, respectively. Age should be introduced as a modifying factor, especially for moderate kidney impairment.

Renal epidemiology has blossomed in recent years, providing many new insights, but we are leery about relying on the current staging system for population estimates of CKD. This approach leads to huge estimates containing large numbers of people with GFR indiscernible from normal and many elderly with moderate impairment and unproven therapeutic implication. Until trials show that such asymptomatic people benefit from a treatment or progress to ESRD, giving them a diagnosis of kidney disease seems dubious. That cardiovascular risk can attach to such minor renal findings seems clear, but that risk, to date, is not modifiable.<sup>4,11</sup> Estimates that one of eight Americans has CKD may lead the wider medical community as well as policy makers to question whether we are exaggerating out of self-interest, especially when we have little in the way of prognosis or treatment for some of these large subgroups. Kidney disease and ESRD are genuinely big enough problems that we would not want to reduce our credibility by overstating them.

## DISCLOSURES

None.

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