High Risk of Renal Failure in Under-recognized Chronic Kidney Disease: Truth or Myth?

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Taiwan has the highest incidence and prevalence of end-stage renal disease (ESRD) according to international comparisons of the United States Renal Data System report.[1] Chronic kidney disease (CKD) is a global public health challenge because of its increasing number of patients, strong association with adverse cardiovascular outcomes, and high risk of progression to ESRD.[2] Many studies have been performed to establish the role of estimated glomerular filtration rate (eGFR) screening for CKD, with or without concomitant proteinuria screening. However, the risk of renal failure in patients with "under-recognized CKD" has not been assessed. In this issue of the *Journal of the Chinese Medical Association*, Wu et al[3] are the first to report such estimates. They reported that stage 3B CKD (eGFR, 30–44 mL/min/1.73 m^2) with a normal routine clinical assessment (i.e. under-recognized CKD) and stage 5 CKD (eGFR, < 15 mL/min/1.73 m^2) have a similar risk of renal failure, which is significantly higher than the other CKD groups.

The high risk of renal failure among patients with under-recognized stage 3B CKD is surprising and may even be misleading. Prognosis associated with a given level of eGFR varies substantially based on the presence and severity of proteinuria.[4] Patients with heavy proteinuria but without overtly abnormal eGFR appear to have worse clinical outcomes than those with moderately reduced eGFR but without proteinuria as shown in a prospective cohort study based on 462,293 adults in Taiwan.[5] When stage 3 CKD is unaccompanied by other manifestations of kidney disease, such as proteinuria, it may be of little clinical consequence and is mainly a manifestation of age, sex, and race effects. In a long-term (25-year follow-up) longitudinal study of men with a high risk of cardiovascular disease (the Multiple Risk Factor Intervention Trial study),[6] it was found that an eGFR of < 60 mL/min/1.73 m^2 in the absence of "dipstick-positive" proteinuria had a positive predictive value of only 5.6% for the future development of ESRD. However, the addition of more than 1+ proteinuria to an eGFR of < 60 mL/min/1.73 m^2 substantially improved the positive predictive value to approximately 26%. The majority of patients who are destined to develop ESRD would not be detected by a screening program based on eGFR alone. The introduction of the Kidney/Dialysis Outcomes Quality Initiative (K/DOQI) classification of CKD represented a major step forward for clinicians and researchers,[7] but population-based studies suggest that the combined consideration of both parameters of kidney function, proteinuria and eGFR, may be the most effective in assessing prognosis.

Although a large cohort of 15,817 patients was screened in the present study, analytic power might still be limited and several issues need to be clarified. First, the cohort was not representative of the general population but was limited to individuals who participated in a self-pay standard medical screening program in health management centers. Some participants may already have had underlying health problems or be members of large families. CKD is known to prevail in patients with medical illness and within families. Wu et al[3] reported a prevalence rate of 10.1% of CKD stages 3–5 in this cohort, which was much higher than the 6.9% in subjects older than 20 years of age in a nationwide, randomized, stratified survey for hypertension, hyperglycemia and hyperlipidemia (the TW3H survey) by Hsu et al.[8] In addition, use of an absolute threshold of eGFR for defining stage 3 CKD (30–59 mL/min/1.73 m^2) without any adjustment for the effects of normal aging on eGFR by the K/DOQI may overestimate the prevalence of CKD.[7]

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Second, the authors failed to use more than 1 measure of urine protein in their study patients. Proteinuria may have been misclassified because of the common variability based on a single urine measurement,[9] and this may be why proteinuria was not consistent with clinically relevant outcomes in the current study.

Third, the authors did not have information on characteristics such as comorbidities, smoking and the use of medications, which may have resulted in residual confounding. Given the small numbers of patients with under-recognized stage 3B CKD and the low occurrence of dialysis observed in their study, it is likely that further adjustment for these covariables would negate the observed associations.

Finally, the follow-up in this study was relatively short to assess progression to renal failure, especially for people with high levels of baseline eGFR. The short follow-up of the study may have limited the ability to discern a significant difference in the progression to ESRD or a need for dialysis that might have developed at later time points as seen in studies with long-term follow-up. Furthermore, Wu et al[3] assessed the incidence of renal failure requiring dialysis within 2 years after standard medical screening, which may have included some participants with acute renal failure as well as those with progression of CKD. However, the authors did not separately report the rate of acute or chronic dialysis.

In the current study,[3] the hazard ratios for renal failure for patients categorized as having stage 3A CKD (eGFR, 45–59 mL/min/1.73 m^2) without proteinuria were significantly lower than those for patients with stage 3B CKD (eGFR, 30–44 mL/min/1.73 m^2). These data suggest that the effect of a low eGFR in the absence of proteinuria is not seen until the eGFR falls below the normal levels expected after adjusting for age and sex effects (approximately 45 mL/min/1.73 m^2). A reduced eGFR, particularly in the range of 30–44 mL/min/1.73 m^2, is likely to be a risk factor of cardiovascular events and progression to ESRD. However, the effect of a reduced eGFR alone, the so called "under-recognized CKD", on prognosis is questionable. In our opinion, universal eGFR-based screening would be of little value in predicting ESRD without a concomitant consideration of the presence or absence of proteinuria. It is likely that a more targeted and multiphasic approach might enhance the performance of such screening and would be more cost-effective. It is currently unknown whether or not early identification and treatment of subjects with stage 3B CKD on the basis of eGFR, but without any other manifestations of kidney disease, would reduce the subsequent risk of progression to ESRD.[10]

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