Epidemiology and Public Health Concerns of CKD in Older Adults

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CKD is increasingly common in older adults. Estimating the glomerular filtration rate can be challenging in this population, with sarcopenia affecting the accuracy of various formulae. Competing risks of death influence the risk of progression to end-stage kidney disease. In managing CKD in this population, one must take into consideration other comorbidities including assessment of geriatric syndromes. More research is still needed to guide medical management in this heterogeneous population.
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INTRODUCTION

Increasing longevity in most developing and developed countries is resulting in global aging. The United Nations projects that the global population aged 65 years and older will triple from 0.5 billion in 2010 to 1.5 billion by 2050.[1] In the United States, the number of older individuals (aged 65 years and older) will double from 40 million to 80 million over the next 30 years. Global aging has far-reaching implications for health-care systems, which will need to grapple with rapidly increasing demands for health-care services. Most of the older adults have 2 or more chronic health conditions. Syndromes such as frailty, cognitive impairment, and sensory impairment disproportionately affect older adults and result in reduced independence. Many of these issues are magnified in the CKD population. Herein, we discuss the epidemiology of CKD in older individuals and public health implications.

ESTIMATION OF GLOMERULAR FILTRATION RATE IN OLDER ADULTS

CKD is defined as a glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 or markers of kidney damage, such as albuminuria, for greater than 3 months.[2] Various creatinine-based formulae are used to estimate GFR, including the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. Few older adults were included in the development of these estimating equations, although validation of these equations using iohexol or measured creatinine clearance as the reference standard in older cohorts has generally shown that these equations are reasonably accurate.[3] The MDRD equation is less accurate at higher levels of GFR, relative to the CKD-EPI equation, although the importance of these subtle differences in clinical practice may be subject to debate. More recently, the Berlin Initiative Study (BIS) developed an equation to estimate GFR using age, gender, and serum creatinine in 600 participants aged 70 years or older.[4,5] Compared with other creatinine-based equations, the BIS equation had comparable or better accuracy, reduced bias, and improved precision. In particular, the BIS equation tends to reclassify patients to a higher estimated glomerular filtration rate (eGFR) compared with other equations. External validation of the BIS equation has been performed in European and Brazilian cohorts with comparable performance characteristics.[6]

Cystatin C is an alternate biomarker of kidney function that is less affected by muscle mass than creatinine.[7] For this reason, cystatin C has been suggested as a superior measure of kidney function in older individuals, as they are more likely to be affected by sarcopenia. Several GFR-estimating equations, including the CKD-EPI[8] and BIS equations,[9] have versions that incorporate cystatin C measurements in addition to creatinine.

EPIDEMIOLOGY OF CKD IN OLDER ADULTS

Data from the National Health and Nutrition Examination Surveys 1999 to 2004 estimate that approximately 40% of adults aged above 60 years meet the current definition for CKD using the MDRD equation to estimate GFR. Among older adults, approximately 7% have CKD Stage 1 to 2, 30% have CKD Stage 3, and 5% have CKD Stage 4 to 5.[10] Using the CKD-EPI equation, the prevalence of CKD is lower among adults aged 60 to 69 years (due to a lower percentage of adults with Stage 3 CKD), and similar among those aged $\geq$70 years.[11] Among adults aged $\geq$80 years, the prevalence of CKD using the CKD-EPI equation was $>$50% between 2005 and 2010, representing an absolute increase of more than 11% compared to the prior decade.[12]

The adjusted incident rate of treated ESRD in the United States has grown 7.1% for patients aged 75 years and older, to 1707 per million population in 2011. In contrast, incidence rates for patients aged 45 to 64 years and 65 to 74 years, are now 8.1% to 8.3% lower than in 2000, at 571 and 1307 per million, respectively.[2]

PROGNOSIS OF CKD IN OLDER ADULTS

In the absence of albuminuria or known cause of kidney disease, some question whether a low GFR in older

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persons is a true disease state. This is especially applicable to those with only a modest reduction in GFR (eg, GFR 50-60 mL/min/1.73 m^2), a large proportion of the older adult population with CKD. Indeed, some argue that age-related structural changes in the kidney can be considered a normal part of aging, especially in the absence of other electrolyte or metabolic abnormalities.[13]

To help clarify the clinical relevance of CKD in older adults, several studies have examined the prognosis of older adults with varying stages of CKD. The largest of these analyses, from Chronic Kidney Disease Prognosis Consortium, included more than 2 million adults from 46 cohort studies from general, high-risk and CKD populations.[14] In these analyses, mortality was higher with higher levels of albuminuria and lower levels of eGFR (using the creatinine CKD-EPI equation) in all age groups (Fig 1).[15] The absolute risk for mortality was higher at older age groups at all levels of albuminuria and eGFR. For albuminuria, the relative risk for mortality was consistent by age, except at higher levels of albuminuria (eg, >100 mg/g), where relative risk was slightly lower at older ages. For eGFR, interaction with age was evident across a broad range of eGFR. Among adults aged 18 to 54 years old, there was a linear relationship between lower eGFR and higher mortality risk. Among adults aged ≥54 years, a J-shaped relation between eGFR and mortality was observed. There was an increased risk of mortality as eGFR dropped below 80 mL/min, but this association was less pronounced compared to younger adults. There was also a linear increase in mortality for eGFR levels > 80 mL/min, which likely reflects sarcopenia rather than an elevated GFR. The absolute risk of ESRD was slightly lower at older vs younger age groups for albuminuria levels > 30 mg/g and eGFR levels < 45 mL/min/1.73 m^2. The relative risk for ESRD was generally similar across age groups for eGFR < 60 mL/min/1.73 m^2 or albuminuria > 30 mg/g, and no significant age interaction was detected. The finding of lower absolute risk of ESRD among older adults should be interpreted with some caution because this study considered only treated ESRD as an outcome. For example, in a Canadian population–based study, Hemmelgarn and colleagues identified patients with treated and untreated ESRD. In this study, the rate of untreated ESRD was 5 times higher in adults aged ≥85 years compared to those aged 18 to 44 years.[16]

In older adults, the competing risk of death influences whether someone progresses to ESRD. Prediction of whether older patients will progress to ESRD will inform decisions as to whether and when preparation for renal replacement therapy should take place. In a large cohort of US Veterans with CKD Stages 3 to 5, the absolute risk of death was much higher than risk of progression to ESRD in those aged >75 years of age, even in those with CKD Stage 5. Conversely, in patients younger than 45 years, the risk of progression to ESRD was greater than the risk of death, even for those with CKD Stage 2 to 3.[17] Similar findings have been observed in other populations. For example, in an Italian cohort of 1200 adults averaging 65 years of age, patients with less advanced CKD were more likely to die rather than progress to ESRD.[18] In particular, ESRD occurred more frequently than death in Stage 4 and 5 CKD, whereas the opposite was true in Stage 3 CKD. Similarly, in a cohort of approximately 3000 older adults averaging 70 years of age, the risk of death and ESRD were similar for patients with CKD 4. In this study, factors such as older age, heart failure, lower hemoglobin level, lower phosphate level, malignancy, diabetes, and male gender were associated with higher risk of death prior to ESRD.[19]

In addition to death and ESRD, acute kidney injury (AKI) is also an important consequence of CKD in older adults. The incidence of AKI increases with age and carries a high morbidity and mortality.[20,21] Older adults with CKD are more susceptible to AKI events, which in turn, may contribute to progression of CKD. Efforts to reduce the number and severity of AKI episodes may be an important component of CKD management in older adults.

CLINICAL SUMMARY

- Chronic kidney disease is increasingly common in older adults and estimating the glomerular filtration rate can be challenging in this population.
- Competing risks of death influence the risk of progression to end stage kidney disease.
- In managing chronic kidney disease in this population, one must take into consideration other comorbidities including assessment of geriatric syndromes.

CLINICAL AND PUBLIC HEALTH IMPLICATIONS OF CKD IN OLDER ADULTS

The high and increasing prevalence of CKD among older adults has several potential public health and clinical implications. One of the main issues to consider is whether all older adults with CKD benefit from nephrology care. It should be evident that there are not enough nephrologists to care for the large number of older adults with CKD. A variety of risk stratification approaches have been suggested to better target nephrology care to those at highest risk of adverse outcomes, including the incorporation of cystatin C for eGFR estimation, or the assessment of geriatric syndromes such as frailty. For example, KDIGO guidelines suggest the use of cystatin C as a confirmatory test for CKD.[22] A related issue is whether a diagnosis of CKD meaningfully changes clinical management of older adults with eGFR levels between 45 to 59 mL/min/1.73 m^2. Agents such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may slow progression of CKD especially when there is concomitant proteinuria, although few of these trials included patients older than 70 years.[23] However, such agents may predispose older patients to AKI,[21] and older patients may not survive long enough to benefit from this therapy.[24] Furthermore, some argue that given slow average rate of progression of CKD in older patients with eGFR between 45 and 59 mL/min/1.73 m^2, managing these patients