Moderately Reduced Estimated Glomerular Filtration Rate (eGFR) among Community - Dwelling Older People Associated with Increased Long Term Mortality: A Study from Low to Middle Income Country in Asia.

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Research article

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Abstract

Background: Reduced glomerular filtration rate (GFR) is regarded as a component of renal senescence; however, the full impact of chronic kidney disease (CKD) among older people is still not fully understood. This study aimed to investigate the effect of reduced GFR on all-cause mortality, and the combined effect of socioeconomic status and CKD on mortality among older Thai population.

Methods: A retrospective cohort of Thai population aged ≥60 years was enrolled from the Fourth National Health Examination Survey, and estimated GFR (eGFR) and comorbid disease data were collected. Mortality information was gathered from the National Civil Registration and Vital Statistics System. Factors associated with all-cause mortality were determined using Cox proportional hazards model.

Results: A total of 9,080 participants (mean age: 69.5 years) were included. Prevalence of CKD stage 3-5 was 53.3%. During the 2008-2015 period, the overall mortality rate among CKD was 28.9 per 1,000 person-years. The stages of CKD significantly associated with increased mortality were stages 3b, 4, and 5, as follows: HR: 1.44 (95% CI: 1.24-1.67), 2.42 (95% CI: 1.98-2.96), and HR: 6.43 (95% CI: 4.67-8.87), respectively. People with higher socioeconomic status and moderate-stage CKD had lower mortality than lower socioeconomic status moderate-stage CKD.

Conclusion: Moderate decline in eGFR was found to be independently associated with all-cause mortality in Thai elderly population. Socioeconomic disparities were also observed among older CKD. Implementation of a mass screening program to identify asymptomatic individuals would accelerate diagnosis and treatment, and this would reduce the costs of care associated with advanced-stage disease.

Introduction

Chronic kidney disease (CKD) is being increasingly recognized as a global health issue with a high burden of disease, particularly among low to middle income countries (LMICs)[1]. The prevalence of CKD was reported to significantly increase with age due to the incremental effect of traditional risk factors for CKD, such as diabetes mellitus, hypertension, and cardiovascular diseases, among older people[2]. However, the prevalence of CKD did not similarly increase in some studies conducted in high income countries. Some studies found no significant increase in the prevalence of CKD as the world transitions to an aging society[3, 4], but some studies did find and report an increasing trend[5]. One study suggested that the prevalence and burden of CKD is expected to rise with rapid urbanization and the increasing prevalence of noncommunicable diseases in LMICs[6].

The clinical significance of the new definition of CKD according to KDIGO 2012 Clinical Practice Guideline, particularly among older people, has been an issue of debate[2, 7, 8]. Previous study[9] showed a lower risk of end-stage renal disease (ESRD) in older population compared to their younger counterparts because of the slow decline in estimated GFR (eGFR). Moreover, early-stage CKD was shown to associate

with lower mortality in older adults compared to younger adults with CKD.[10] It has been suggested that the majority of older patients with CKD did not transition to ESRD, but that they died from other causes. Although the association between socioeconomic status and the prevalence of CKD is well established[11], the socioeconomic disparity in CKD with regard to mortality risk was demonstrated only in high income countries[11, 12]. Evidence specific to the clinical impact of CKD staging on mortality among older people in LMICs remains comparatively scarce.

Thailand is a middle-income country with an increasing prevalence of cardiometabolic diseases. This trend during the last decade is supported by data from recent national health examination surveys[13–15]. Increases in related risk factors and the average age of the population suggest an increasing prevalence of CKD in Thailand. Previous studies from Thailand[16, 17] reported a prevalence of CKD among older people of approximately 40%, which is substantially higher than the rate of CKD among younger population. However, those studies did not explore the impact of CKD on mortality among older population, and whether any identified association is influenced by socioeconomic status. Accordingly, the aim of this study was to investigate the effect of reduced GFR on all-cause mortality, and the combined effect of socioeconomic status and CKD on mortality among older persons in Thailand.

Materials And Methods

A retrospective cohort of elderly Thai population aged 60 years or more from the Fourth Thai National Health Examination Survey (NHES-IV) conducted during 2008–2009 were evaluated in 2016 to determine all-cause mortality. Medical comorbid disease (including eGFR), functional status, and socioeconomic status data were collected at the baseline assessment. The vital status of each participant was ascertained from the National Civil Registration and Vital Statistics System.

Data collection and measurement

Serum creatinine was measured using modified Jaffe method. Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine Eq. (1[8]). In this study, CKD was defined according to GFR category by Kidney Disease: Improving Global Outcomes (KDIGO) staging, as follows: G1, G2, G3a, G3b, G4 and G5 as GFR ≥ 60 (G1 + G2), 45–59, 30–44, 15–29, and < 15 ml/min/1.73 m^2, respectively.[19] Reduced GFR was defined as GFR less than 60 ml/min/1.73 m^2. In the present study, stages 3–5 CKD were classified as moderately to severely decreased GFR.

Diabetes was defined as fasting plasma glucose of > 7.0 mmol/L, diagnosis by a physician, or taking antidiabetic medications.[20] Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or history of using any antihypertensive medications. Body weight and height were measured using standardized procedures, and body mass index (BMI) was calculated as kg/m^2. Hypercholesterolemia was defined as total serum cholesterol > 5.2 mmol/L or use of cholesterol-

lowering medication within the previous 2 weeks. According to WHO criteria, anemia was defined as hemoglobin level < 13 g/dl in males, and < 12 gm/dl in females[21].

Data collected from the NHES-IV, including demographic, socioeconomic, and health data, such as age, gender, smoking history, medication used, and medical comorbidities, were collected from survey respondents via semi-structured interview with standardized questions. Data relating to activities of daily living (ADLs) for both basic ADLs (B-ADLs) and instrumental ADLs (I-ADLs) were also obtained by interview. Impairment in ADLs was defined as the requirement for any assistance in performing ADL-related tasks. The wealth index score was determined by assessing the number of household items owned, and then a standardized score was assigned to each participant[22]. Socioeconomic status (SES) was stratified into 5 quintiles, with the lowest quintile indicating the poorest group, and the highest quintile indicating the wealthiest group.

Mortality data was retrieved until May 2016 from the Thai Vital Registration System, Bureau of Registration Administration, Ministry of Interior, which was affirmed to be a reliable source of death statistic in Thailand.[23]

Statistical analysis

Descriptive statistics were used to compare baseline characteristics of participants. Categorical data are reported as frequency and proportion, and continuous data are given as mean ± standard deviation or median with minimum and maximum depending on the distribution of data. Analysis of variance (ANOVA) test was applied for continuous variables, while chi-square test was used for categorical variables. A *p*-value less than 0.05 was considered statistically significant. Factors associated with all-cause mortality were determined using Cox proportional hazards regression model, and the results are reported a hazard ratio (HR) and 95% confidence interval. Variables of interest were compared among CKD stages. Potential confounders of all-cause mortality included in the regression model were age, gender, current smoking status, regular analgesic use, hypertension, diabetes, hypercholesterolemia, history of stroke, and wealth index score. Statistical analyses were performed using STATA 15.0 (StataCorp LP, College Station, TX, USA).

Results

Patient demographic data and prevalence of CKD

A total of 9,080 participants with a mean age of 69.5 ± 7.0 years were included. The mean age of patients with CKD stage 3–5 was higher than that of people without CKD. The prevalence of CKD stage 3–5 in this cohort was 53.3%, and the prevalence of CKD by stage was 34.0%, 14.5%, 4.0%, and 0.8% for stage 3a, 3b, 4, and 5, respectively. The prevalence of CKD stage 3–5 increased with age, as follows: 44.2% for age group 60–69, 61.2% for age group 70–79, and 76.3% for age group 80 years or more. Comorbid diseases, including diabetes, hypertension, hypercholesterolemia, and stroke, were reported at an increasingly higher proportion as the stages of CKD increased in severity. B-ADLs and I-ADLs were both

reported to be poorer with more advanced stage of CKD. Baseline characteristics of participants by CKD stage based on GFR category are shown in Table 1.

Estimated GFR decreased with increasing age, particularly among participants with diabetes mellitus and/or hypertension. Further analysis was conducted among participants aged 85 years or older without diabetes and hypertension, and the mean eGFR was 53.4 ml/min/1.73 m^2, which corresponds with CKD stage 3 according to the current guideline.

Mortality and CKD staging

During a total follow-up time of 52,120.8 person-years, 1,505 (15.3%) participants died for an overall mortality rate of 28.9 per 1,000 person-years (95% confidence interval [CI]: 27.5–30.4). Among CKD subjects, the mortality rate increased with more advanced stage of CKD from 27.2 per 1,000 person-years (95% CI: 24.9–29.7) in CKD stage 3a to 167.3 per 1,000 person-years (95% CI: 124.1-225.6) in CKD stage 5 (Table 2). Survival curves compared among the different stages of CKD are illustrated in Fig. 1.

Factors associated with increased mortality

The factors associated with all-cause mortality from univariate and multivariable analyses are shown in Table 3. In univariate analysis, age, hypertension, diabetes, stroke, and all stages of CKD from stage 3a were significantly associated with increased mortality risk. Better socioeconomic status was shown to be a protective factor against mortality. Subsequent multivariate analysis revealed age, diabetes, and stroke to be independent risk factors for mortality. CKD stages 3b-5 were also independently associated with increased risk of mortality in a dose-response manner, as follows: hazard ratio [HR]: 1.44 (95% CI: 1.24–1.67) for stage 3b; HR: 2.42 (95% CI: 1.98–2.96) for stage 4; and, HR: 6.43 (95% CI: 4.67–8.87) for CKD stage 5. Our analysis also showed socioeconomic status to be independently associated with mortality. Specifically, the higher the wealth index, the lower the person's risk of death.

Discussion

The present study demonstrates CKD to be an important risk factor for increased mortality among older people, and the strongest association with mortality is among patients with advanced-stage CKD. Three studies have explored the effect of CKD on mortality among community-dwelling older people[24–26], and all of those studies were conducted in high income countries. CKD was identified as an independent risk factor for mortality in two of those studies[24, 26], but not in the one other study[25]. The present study confirms that CKD plays an important role in predicting mortality among older people in a middle-income country, and that relationship was shown to be statistically significant starting at CKD stage 3b and higher. The observed associations were in a dose-response manner, with stronger associations observed as the stage of CKD became higher. The observed association between CKD and mortality among the elderly is consistent with recently reported findings that older people with CKD showed higher metabolic complications, cognitive impairment, frailty, and all-cause mortality.[27, 28]

A key reason for changing the definition of CKD stemmed from reported evidence suggesting association between reduced eGFR and increased risk of death[7, 29]. However, when we specifically focused on older population at an eGFR level of 60 ml/min/1.73 m^2, which is consistent with CKD stage 3a, the association with mortality was fairly weak in younger older people, and non-significant in people aged older than 75 years. Nevertheless, this association become more apparent at lower levels of eGFR[29]. The present study also found a similar trend that lower eGFR, starting at CKD stage 3b, is associated with increased mortality. Our finding is also consistent with that from a previous study[30] that found CKD stage 3b to be significantly associated with increased mortality. This finding has important clinical implications for managing older people with multiple chronic comorbidities. Inaccurate diagnosis or staging of CKD would result in extra psychological concern for the patient, and the burden and costs of repeated assessment and potentially unnecessary treatment[7]. However, failure to identify and treat a disease would likely lead to increased morbidity and premature death. Our finding that CKD stage 3b-5 is clinically significant in older adults should heighten our attention to the need for an improved pathway of care for these patients.

Regarding the relationship between socioeconomic status and mortality among older people with CKD, the present study found the socioeconomic status of people in the 3 highest wealth quintiles to be significantly correlated with lower all-cause mortality among participants with CKD stage 3b or higher in both univariate and multivariate analysis. Lower socioeconomic status is well recognized for its association with higher prevalence of unfavorable outcomes of CKD in high income countries[11, 12]. Evidence specific to the effect of disparities in socioeconomic status on CKD patients in low to middle income countries is limited, particularly relative to the association between socioeconomic status and clinical outcomes[11]. The present study demonstrated association between lower socioeconomic status and clinical disadvantages among patients with CKD stage 3b-5 in a middle-income country setting, which is similar to the findings in high income countries. Association between socioeconomic status and CKD might be due to the fact that non-communicable diseases (NCDs), chronic inflammation, neurohormonal activation, and oxidative stress are all more prevalently observed among people with a lower socioeconomic status[12]. Moreover, lower socioeconomic status may also be associated with limited access to healthcare services and substandard living conditions that contribute to the development of CKD, disease progression, and premature mortality[12].

Limitations

This study has some mentionable limitations. First, the fact that CKD was defined via one-time serum creatinine testing without urine albumin level testing could cast some doubt over the true prevalence of CKD in our study population. However, the fact that CKD stage 3b, stage 4, and stage 5 were found to be strongly associated with increased mortality in multivariate analysis demonstrates the validity and clinical importance of the method used in our study. Second and last, we did not evaluate data specific to the progression of CKD to ESRD. This evolution is complicated by the fact that older people may die from other causes before developing and/or succumbing to ESRD. Understanding this course after adjusting

for related confounders would further improve our understanding of the relationship between CKD and mortality among older population. The strengths of this study include the large size of the study population and the fact that sampling was nationwide. Moreover, representative sampling of community-dwelling older persons was employed to estimate the prevalence of the condition. Our study also explored the association between CKD and all-cause mortality in a low to middle income country. Although a number of studies have investigated the prevalence of CKD, no studies have evaluated the impact of CKD on clinical outcomes in a low to middle income country[1].

Conclusion

Moderate decline in eGFR was found to be independently associated with all-cause mortality in community-dwelling elderly Thai population. Socioeconomic disparities were also observed among older CKD, with higher mortality observed among poorer people. Implementation of a mass screening program to identify asymptomatic individuals would accelerate diagnosis and treatment, and this would reduce the costs of care associated with advanced-stage disease.

Abbreviations

ADLs: Activities of daily living

ANOVA: Analysis of variance

BMI: Body mass index

B-ADLs: Basic activities of daily living

CI: Confidence interval

CKD: Chronic kidney disease

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

eGFR: Estimated glomerular filtration rate

ESRD: End stage renal disease

GFR: Glomerular filtration rate

HR: Hazard ratio

I-ADLs: Instrumental activities of daily living

KDIGO: Kidney Disease: Improving Global Outcomes

LMICs: Low to middle income countries

NCD: Non-communicable disease

NHES-IV: Fourth Thai National Health Examination Survey

Ref: Reference

SD: Standard deviation

SES: Socioeconomic status

Declarations

Ethics Approval and Consent to Participate

The study was approved by Institutional Review Board, Siriraj hospital, Mahidol University. All participants had signed the informed consents before included in this study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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No funding was obtained for this study.

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Contributions

All authors have participated in the conceptualization and design of the study. CC and VS analyzed data and all authors interpret the data. PS wrote the first version of the manuscript. VS and WA revised the manuscript for intellectual content. All authors critically revised and approved the final manuscript and accepted the final submitted version.

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Tables

Due to technical limitations the Tables are available as a download in the Supplementary Files.

Figures

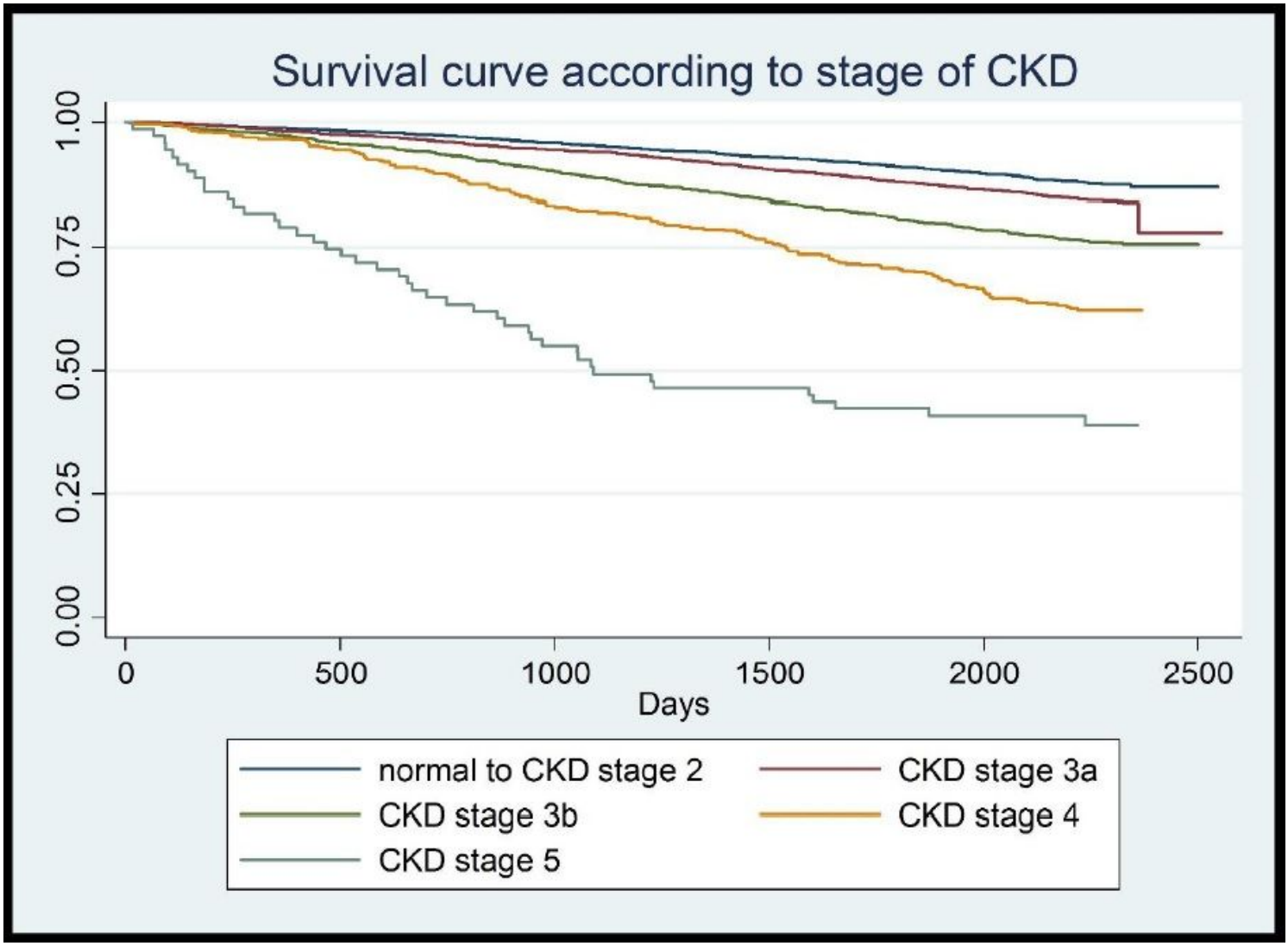

Figure 1

Survival curves compared among the different stages of chronic kidney disease (CKD)

Supplementary Files

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