Comparison of the profiles of patients defined by age-adapted and fixed threshold CKD criteria: a nationwide, cross-sectional study

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ABSTRACT

Background. Kidney function declines naturally with advancing age. Therefore an age-adapted estimated glomerular filtration rate (eGFR) threshold has been proposed instead of the fixed threshold for CKD definition. This study aims to describe and compare the profile of CKD patients defined by these two criteria in a Chinese population.

Method. We recruited adult participants with selected biochemical tests from the Chinese Physiological Constant and Health Condition survey conducted from 2007 to 2011, with the GFR estimated by the Chronic Kidney Disease Epidemiology Collaboration formula. The age-adapted threshold of eGFR is 75, 60 and 45 ml/min/1.73 m2 for the population <40 years of age, 40–64 years and >64 years, respectively. The fixed threshold is 60 ml/min/1.73 m2 for all ages.

Results. Among the recruited 23 438 participants, 480 were diagnosed with CKD by fixed threshold criteria, while 391 were diagnosed with CKD by age-adapted criteria. Patients diagnosed by fixed threshold criteria were significantly older (66.4 versus 43.4 years; \( P < .001 \)) and had a higher prevalence of all CVD risk factors compared with the non-CKD population. In contrast, age-adapted criteria defined a younger patient group and were not significantly associated with diabetes or obesity. When adjusted by age and gender, fixed-threshold–defined CKD was not significantly associated with the number of coexisting CVD risk factors, while age-adapted-defined CKD was significantly associated. We also found
that the CKD patients defined by age-adapted criteria matched well with the 2.5th percentile of eGFR in Chinese individuals. When compared with their age- and gender-matched controls, patients included by age-adapted criteria but excluded by fixed threshold criteria had a significantly higher prevalence of hypertension (23.2% versus 7.7%; \( P < .001 \)) and hyperuricaemia (25.0% versus 5.5%; \( P < .001 \)), while patients included only by the fixed threshold criteria were not significantly different in the prevalence of CVD risk factors and CKD-related disturbance except for hyperuricaemia (41.2% versus 14.0%; \( P < .001 \)).

**Conclusion.** An age-adapted criterion is more closely associated with CVD risk factors and CKD-related diseases compared with fixed threshold criteria.

**LAY SUMMARY**

Kidney function declines naturally with advancing age. Therefore an age-adapted eGFR threshold has been proposed instead of the fixed eGFR threshold for chronic kidney disease (CKD) definition. Recently there have been intense debates between fixed threshold and age-adapted criteria advocates. Using data from a nationwide, cross-sectional study including 23 438 participants, we described the declining nature of eGFR as age advances in a general Chinese population. Furthermore, we compared the profile of patients defined by these two criteria. We found that the age-adapted criteria were better associated with the occurrence of CVD risk factors and CKD-related disturbance.

**GRAPHICAL ABSTRACT**

**INTRODUCTION**

In the last decade, chronic kidney disease (CKD) has been gaining increasing attention as a leading public health problem, with high morbidity, mortality and burdens on the healthcare system [1]. The current widely accepted definition of CKD is kidney damage or an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m\(^2\) for >3 months, by the 2012 Kidney Disease: Improving Global Outcomes and the National Kidney Foundation Kidney Disease Outcomes and Quality Initiative guidelines [2–4]. However, there have been arguments that an age-adapted criterion for CKD is needed because eGFR declines with advancing age. Furthermore, the fixed threshold standard of eGFR regardless of age might lead to an overdiagnosis of CKD among the elderly population and an
underdiagnosis among young individuals [5–7]. Therefore an age-adapted eGFR threshold of 75, 60 and 45 ml/min/1.73 m² for the population <40 years of age, 40–64 years and >64 years was proposed [8].

A recent study compared the outcomes of these two different CKD criteria–defined cohorts and found a lower risk of death and kidney failure among the conventional fixed threshold criteria compared with the new age-adapted threshold [9]. The finding was not unexpected. In the last 2 decades, several cohort studies have illustrated a weak association between slightly decreased kidney function (eGFR 45–59 ml/min/1.73 m², or CKD stage 3a) and different adverse outcomes, including all-cause mortality [10–16], cardiovascular mortality [11, 17–19] and progression to end-stage renal disease (ESRD) [16, 20, 21] among the elderly population.

However, detailed profiles of the CKD patients included or excluded by these two criteria have not been studied. The profiles of these patients, such as the prevalence of intervenable CVD risk factors and life quality–determining CKD-related disturbances, may affect the medical approaches to these patients with clinical importance. Questions remain whether the ‘overdiagnosed’ elderly patients defined by the fixed threshold criteria are disease-free and do not need any medical intervention and whether the ‘underdiagnosed’ youngsters defined by the age-adapted threshold were burdened by their kidney conditions.

To address these questions, we used data from a community-based cross-sectional study to identify and characterize adults with incident CKD according to the fixed threshold and age-adapted threshold definitions. We estimated the prevalence of common cardiovascular disease (CVD) risk factors such as hypertension, diabetes, dyslipidaemia and overweight and collected the common CKD-related disturbances of hyperuricaemia, anaemia, hypocalcaemia and hyperphosphataemia among these populations. We observed the impact of age on the association between these disease profiles with two criteria of the CKD definition, illustrated the age and eGFR distribution of the CKD patients and compared the disease profiles with their age- and gender-matched non-CKD controls.

MATERIALS AND METHODS

Study population

The data used in this study are from the Chinese Physiological Constant and Health Condition survey. Details of the study are described elsewhere [22–24]; briefly, it is a population-based, cross-sectional survey conducted from 2007 to 2011. The survey used a random, multistage, stratified sampling method to obtain a nationally representative sample of the general Chinese population of six provinces, with a three-stage cluster sampling method to sample eligible subjects.

We included a total of 23 438 individuals who were >18 years of age with complete age, gender, body measurement (height and weight), blood pressure (BP) measurement and laboratory test data (serum creatinine, lipid profile, blood glucose) (Fig. 1). All the participants had completed a standard questionnaire about demographic characteristics, socio-economic data, lifestyle risk factors and their past medical history.

The protocol was approved by the Ethics Review Board of the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences. Written informed consent was signed by each participant before data collection.

Clinical and laboratory evaluation

Physical examination included measurement of weight, height and BP. BP was measured by trained medical personnel using an HEM-7000 electronic sphygmomanometer (Omron Healthcare, Muko, Japan) after the participant had rested for at least 10 minutes. The documented BP was the average value of the three-time test, while the body mass index (BMI) was calculated as body weight divided by the square of the height (kg/m²).

We collected the overnight fasting blood by venipuncture with the patient consuming a bland diet before blood testing. The blood was then centrifuged and the serum was stored at −80°C until the laboratory assay test. Serum lipids, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid (UA) and fasting blood glucose (FBG) levels were measured using an AU Series Automatic Biochemical Analyzer (Beckman Coulter, Brea, CA, USA) and Sekisui Medical (Tokyo, Japan) reagents.

The creatinine of the six subcentres in this study was detected by the creatinine oxidase method using regular automatic biochemical analyser and medical reagents for clinical detection. All the centres participated in the proficiency testing (PT) organized by the National Center for Clinical Laboratories of China and processed the appropriate control for the results qualified before and after the sample test. The laboratory of Peking Union Medical College Hospital served as the central laboratory.
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Table 1: The baseline characteristics of the study population.

| Characteristics               | Total |
|------------------------------|-------|
| Population, N                | 23 438|
| Age (years)                  | 43.8 (16.19) |
| Age group (years), n (%)      |       |
| <40                          | 10 054 (42.9) |
| 40–64                        | 10 563 (45.1) |
| >64                          | 2821 (12.0) |
| Female, n (%)                | 12 535 (53.5) |
| eGFR (CKD-EPI; ml/min/1.73 m²) | 99.45 (19.47) |
| eGFR category, n (%)         |       |
| >90                          | 16 063 (68.5) |
| 60–89                        | 6895 (29.4) |
| 30–59                        | 457 (1.9) |
| 15–29                        | 18 (0.1) |
| <15                          | 5 (0.0) |
| CVD risk factors, n (%)      |       |
| Diabetes                     | 1049 (4.5) |
| Hypertension                 | 5588 (23.8) |
| BMI ≥ 25                     | 7379 (31.8) |
| Dyslipidaemia                | 11 475 (49.4) |
| CKD-related symptoms, n (%)  |       |
| Hyperphosphataemia           | 529 (2.3) |
| Hypocalcaemia                | 545 (2.3) |
| Anaemia                      | 1242 (6.2) |
| Hyperuricaemia               | 2836 (12.1) |

Values presented as mean (SD) unless stated otherwise.

The study included 23 438 participants with a mean age of 43.8 years and 53.5% were female. The average eGFR was 99.5 ml/min/1.73 m²; 68.5% has an eGFR < 60 ml/min/1.73 m²; 29.4% had an eGFR of 60–89 ml/min/1.73 m² and 2% had an eGFR of < 60 ml/min/1.73 m². The prevalences of dyslipidaemia, overweight, hypertension and diabetes were 49.4%, 31.8%, 23.8% and 4.5%, respectively. CKD-related disturbances including hyperuricaemia (12.1%), anaemia (6.2%), hyperphosphataemia (2.3%), and hypocalcaemia (2.3%) were observed. The baseline characteristics of the study population are presented in Table 1.

A total of 480 (2.05%) participants fulfilled the criteria of fixed threshold CKD (eGFR < 60 ml/min/1.73 m² for all ages) and 391 (1.67%) participants fulfilled the criteria for age-adapted CKD (< 40 years old: eGFR < 75 ml/min/1.73 m²; 40–64 years old: eGFR < 60 ml/min/1.73 m²; > 64 years old: eGFR < 45 ml/min/1.73 m²). The baseline profiles of the CKD patients defined by these two criteria and the non-CKD population are presented in Table 2. The average age of the CKD patients defined by the fixed threshold criteria was significantly older than the non-CKD population (66.4 versus 43.4 years; P < .001), with a higher prevalence of all four CVD risk factors. In contrast, the CKD patients defined by age-adapted criteria were slightly older than the non-CKD pop-


For age and eGFR (CKD-EPI), P-values were calculated by an independent t-test. For other categorical variables, P-values were calculated by the chi-squared test.

Table 2: Comparison of disease profile between CKD and non-CKD patients diagnosed by two criteria.

| Characteristics | Fixed threshold CKD (n = 480) | Age-adapted CKD (n = 391) |
|-----------------|-------------------------------|--------------------------|
| Age (years), mean (SD) | 43.4 (15.94) | 43.8 (16.18) |
| Female, n (%) | 12.26 (53.4) | 12.30 (53.4) |
| eGFR (CKD-EPI), ml/min/1.73 m², mean (SD) | 100.46 (18.30) | 100.17 (18.73) |
| CVD risk factors, n (%) | | |
| Diabetes | 1004 (4.4) | 1024 (4.4) |
| Hypertension | 5328 (23.2) | 5427 (23.5) |
| BMI >25 | 7169 (31.5) | 7242 (31.7) |
| Dyslipidaemia | 11149 (49.0) | 11230 (49.2) |
| CKD-related disturbance, n (%) | | |
| Hyperuricaemia | 2620 (11.4) | 2684 (11.7) |
| Anaemia | 1176 (6.0) | 1206 (6.1) |
| Hyperphosphataemia | 519 (2.3) | 518 (2.3) |
| Hypocalcaemia | 532 (2.3) | 533 (2.3) |

Table 3: Association of CVD risk factor number with different CKD definitions.

| CVD risk factor count category | Fixed threshold CKD | Age-adapted CKD |
|-------------------------------|---------------------|----------------|
| Risk number ≥1 | OR 95% CI | P-value | OR 95% CI | P-value |
| CKD only | 4.367 3.272–5.967 | .001 | 1.87 1.468–2.41 | .001 |
| Adjusted | 1.112 0.817–1.546 | .512 | 1.674 1.291–2.192 | .001 |
| Risk number ≥2 | OR 95% CI | P-value | OR 95% CI | P-value |
| CKD only | 3.051 2.527–3.696 | .001 | 1.771 1.448–2.166 | .001 |
| Adjusted | 1.11 0.907–1.361 | .316 | 1.655 1.331–2.057 | .001 |
| Risk number ≥3 | OR 95% CI | P-value | OR 95% CI | P-value |
| CKD only | 3.054 2.497–3.719 | .001 | 1.947 1.520–2.467 | .001 |
| Adjusted | 1.203 0.973–1.481 | .084 | 1.757 1.353–2.260 | .001 |
| Risk number = 4 | OR 95% CI | P-value | OR 95% CI | P-value |
| CKD only | 3.113 1.877–4.857 | .001 | 2.137 1.093–3.744 | .015 |
| Adjusted | 1.053 0.626–1.762 | .835 | 1.707 0.866–3.023 | .09 |

CVD risk factor count indicates the number of positive findings among hypertension, diabetes, dyslipidaemia and BMI >25.

We further compared the prevalence of both CVD risk factors and CKD-related disturbance of CKD patients diagnosed by age-adapted criteria only or fixed threshold criteria only with age- and gender-matched non-CKD populations (Fig. 3). The preva-
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Figure 2: Age and eGFR distribution of suspected CKD and total population. (A) Estimated GFR by age in the whole population with scatter plot of suspected CKD population. (B) Venn plot of CKD patients defined by fixed threshold and age-adapted criteria.

The 'normal' value for kidney function is just one consideration for a CKD diagnosis, while another consideration is the risk of future adverse outcomes. In 2012, Hallan et al. [37] published a meta-analysis including >2 million participants, indicating a crucial conclusion that mortality and ESRD risk increased in lower eGFR populations at different ages. For those >75 years of age, the adjusted HR for all-cause mortality at an eGFR of 45 ml/min/1.73 m² versus 80 ml/min/1.73 m² was 1.35 (95% CI 1.23–1.48). The absolute risk difference was the highest among all age groups at 27.2 excess deaths per 1000 person-years. However, later in 2016, from the published data of the same paper, Delanaye et al. [5, 8] concluded that the eGFR range for the lowest HR in each age category was different. For example, among participants 18–54 years of age, the eGFR range associated with low mortality is >75 ml/min/1.73 m², but the value decreases to 45–104 ml/min/1.73 m² for those >65 years of age. We also noticed in Hallan et al.'s [37] paper that the steepest slope for increased mortality risk by eGFR decline was among participants 18–54 years of age. For this group of young participants, the mortality risk increase began to be significant immediately below an eGFR of 80 ml/min/1.73 m² and the HR for all-cause mortality rose to >1.5 at an eGFR of 60 ml/min/1.73 m². The result was consistent with our data and can be partially explained by our observation that young people with an eGFR of 60–70 ml/min/1.73 m² have a higher prevalence of CVD risk factors, especially hypertension.

Among young people <40 years of age, who generally have a lower mortality rate, the incident rate of CVD events was therefore poorly represented in prior cohort studies. We observed that an eGFR of 60–75 ml/min/1.73 m² was strongly associated with hypertension. The relationship between hypertension and kidney function is rather complex. First, hypertension is a well-recognized cause of CKD, with the risk ratio for CKD estimated to be 2.8 for a pretreatment SBP of 166–180 mmHg and 7.6 for a pretreatment SBP >180 mmHg compared with the population with a pretreatment SBP <165 mmHg [38]. In China, the per-
Figure 3: Comparison of disease profiles between patients and non-CKD controls. (A) CVD risk factors profile of patients diagnosed with age-adapted criteria alone compared with their matched non-CKD population. (B) Risk factors profile of patients diagnosed with fixed threshold criteria alone compared with their matched non-CKD population. (C) CKD-related symptoms of patients diagnosed with age-adapted criteria alone compared with their matched non-CKD population. (D) CKD-related symptoms of patients diagnosed with fixed threshold criteria alone compared with their matched non-CKD population. P-values of significance were annotated directly on the plot. P-values were calculated by chi-squared test elsewhere. The mean age of patients diagnosed by age-adapted criteria only was 33.0 years and the mean age of their matched controls was 33.1 years. The mean age of patients diagnosed by fixed threshold criteria only was 72.7 years and the mean age of their matched controls was 72.8 years.
Percentage of CKD caused by hypertension among all other causes has risen from 11.5% in 2011 to 15.9% in 2015, based on the nationwide Hospital Quality Monitoring System [39]. In contrast, decreased kidney function may also be the underlying cause of hypertension. Recently a bidirectional Mendelian randomization study showed a causal effect of better kidney function on lower BP [40]. In this study, the significantly higher prevalence of hypertension among young people with an eGFR of 60–75 ml/min/1.73 m² might indicate that hypertension, especially among young people, can be the early flag signal of impaired kidney function.

Hyperuricaemia was another closely related risk factor of CKD patients defined by either criterion. Although the idea of applying uricaemia-lowering therapies to alleviate eGFR decline among CKD patients has not been widely accepted [41–43], hyperuricaemia is common among CKD patients and paralleled the progress of CKD [44]. It might also be a sensitive indicator of early kidney function decline. There is no significant difference in hyperphosphataemia or hypocalcaemia between populations with or without CKD. Since chronic kidney disease—mineral and bone disorder more often occurs among patients with advanced CKD and severely impaired kidney function, the community-based study included mainly early-stage CKD patients.

We also observed an unexpected lower anaemia prevalence among young patients with an eGFR of 60–75 ml/min/1.73 m². In fact, these patients, both males and females, showed a higher level of blood haemoglobin compared with their age- and gender-matched controls or the normal haemoglobin reference range (male: age-adapted only group 171.3 g/l versus matched controls 158.4 g/l; female: age-adapted group 146.9 g/l versus matched controls 134.2 g/l). One possible explanation for this phenomenon is that the higher haemoglobin level in this patient group is due to their higher prevalence of hypertension [45, 46]. It has been observed in large cohorts of healthy individuals that haemoglobin level is positively associated with BP. Approximately 1 mmol/l increase in haemoglobin level predicts a 1.3 mmHg increase in SBP in males and 1.8 mmHg SBP increase in females [45]. The supplementation of erythropoietin in CKD patients may also lead to the occurrence of hypertension [47–49]. Possible mechanisms include increased responsiveness to catecholamines and angiotensin II in vascular tissue and an impaired hypoxia-induced vasodilation response [47].

To our knowledge, this is the first cross-sectional study to describe the detailed disease profile of patients included by different CKD criteria. Our findings showed that young people with an eGFR of 60–75 ml/min/1.73 m² are more likely to be ‘CKD burdened’ and elderly people with an eGFR of 45–60 ml/min/1.73 m² showed similar CVD risk factors as patients with an eGFR >60 ml/min/1.73 m², except the hyperuricaemia burden. The result was consistent with prior cohort studies [9].

Limitations

Limitations existed in this cross-sectional study and we did not enrol patients with albuminuria. In addition, urinalysis, ultrasound examination of the kidneys and other biological markers indicating existing kidney damage may provide more information but was not available in this study.

CONCLUSION

An age-adapted criterion of CKD is more closely associated with CVD risk factors and CKD-related diseases, especially among people <40 years of age and >65 years.

SUPPLEMENTARY DATA

Supplementary data are available at cj online.

ACKNOWLEDGEMENTS

The authors thank all of the participants, primary care doctors, and nurses who took part in this survey.

FUNDING

This work was partially supported by grants from the National Natural Science Foundation of China (82170709 and 81970607 to C.L.), CAMS Innovation Fund for Medical Sciences (2020-12M-C&T-A-001 and CIFMS 2021-1-12M-003 to C.L.), Capital’s Funds for Health Improvement and Research (2020-2-4018 to C.L.) and Beijing Natural Science Foundation (L202035 to C.L.). The funders had no role in the study design, data collection, analysis, decision to publish or manuscript preparation.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online Supplementary material.

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