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Estimating the glomerular filtration rate and tubular dysfunction in an elderly population with normoalbuminuria in China

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ABSTRACT

Background: The prevalence and clinical risk factors of normoalbuminuric renal impairment have not yet been investigated in elderly Chinese populations. To clarify this, we conducted survey research on an elderly Chinese community population.

Methods: A total of 691 elderly community participants were included in this study. Normoalbuminuria was defined as a urinary albumin to creatinine ratio (ACR) < 30 mg/g in morning urine. The estimated glomerular filtration rate (eGFR) and urinary alpha-1-microglobulin to creatinine ratio (MCR) were evaluated to assess normoalbuminuric kidney impairment in this elderly population.

Results: Among the whole cohort, 30.25% had albuminuria, 8.68% showed reduced eGFR and 49.78% had increased MCR. Normoalbuminuric subjects also showed a high prevalence of low eGFR and increased MCR (6.02% for reduced eGFR and 37.55% for increased MCR). Among the normoalbuminuric participants, the highest prevalence of increased MCR was found in the subjects with diabetes (50%), whereas the highest prevalence of low eGFR was found in women (8.11%). There was no significant difference in ln-MCR values between normoalbuminuric subjects with eGFR > 60 and < 60 ml/min/1.73 m^2. Age, gender, diabetes and hypertension were all independent risk factors of increased MCR. Diabetes and hypertension showed no statistical influence on decreased eGFR,whereas gender carried the highest risk for reduced eGFR.

Conclusions: Albuminuria may have limited utility as a screening marker of renal injury, as a considerable proportion of the elderly population have renal impairment despite normoalbuminuria. Rather than focusing solely on patients with diabetes or hypertension, normoalbuminuric renal impairment should be given more attention within the overall elderly population.

1. Introduction

Albuminuria is recognized as an early biochemical hallmark of kidney damage and has an important role in monitoring the progression of kidney disease and cardiovascular disease [1–3]. Numerous studies have focused on the prevalence of albuminuria in diabetic patients or the general population and assessed the clinical risk factors of albuminuria, albuminuria is highly prevalent in the general population, especially in the elderly [3–5]. Therefore, early screening strategies are strongly suggested for preventing the development of albuminuria [3]. However, recent studies have questioned the classic concept that the presence of albuminuria precedes reductions in estimated glomerular filtration rate (eGFR) [6,7]. A cross-sectional study demonstrated that approximately 36.1% of diabetic patients with low eGFR (< 60 ml/min/1.73 m^2) had no albuminuria [8]. MacIsaac et al. [9] demonstrated that 39% of individuals with type 2 diabetes had kidney impairment without albuminuria or proteinuria. Normoalbuminuric kidney impairment can be frequently observed in diabetic kidney disease phenotype in patients with low eGFR [10–12]. These research data demonstrate that renal impairment without albuminuria is common in kidney diseases.

Although numerous studies have reported the rate of renal impairment in elderly populations, most of these studies estimated kidney injury using only albuminuria [3–5]. However, albuminuria is limited in its use as a biochemical marker of renal injury because a significant percentage of individuals with renal impairment do not show albuminuria, and thus a considerable proportion of individuals with normoalbuminuric renal damage may be missed, especially the part of population with renal tubular dysfunction. Alpha-1-microglobulin is a low molecular weight protein which can be readily filtered by the

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Table 1
The descriptive data of the population included in this study.

Variable	Subjects without albuminuria(n = 482)	Subjects with albuminuria(n = 209)	P
Age (year)	67.46 ± 5.87	68.17 ± 9.49	NS
Male (%)	46.27	32.54	0.001
BMI (kg/m^2)	25.01 ± 3.62	25.23 ± 3.60	NS
SBP (mm Hg)	131.69 ± 17.45	137.83 ± 18.71	< 0.001
DBP (mm Hg)	81.71 ± 9.39	84.17 ± 10.90	0.005
Diabetes (%)	9.54	22.97	< 0.001
Hypertension (%)	55.18	70.81	< 0.001
Glucose (mmol/l)	5.02 ± 1.08	5.47 ± 1.47	< 0.001
Cholesterol (mmol/l)	5.33 ± 3.21	5.36 ± 0.99	NS
Triglyceride (mmol/l)	1.66 ± 1.09	1.97 ± 1.21	0.002
Serum creatinine (mol/l)	78.21 ± 11.44	83.72 ± 56.94	0.042
Smoking (%)	48.34	41.63	NS
eGFR (ml/ min/ 1.73 m^2)	78.18 ± 10.85	73.77 ± 13.18	< 0.001
MCR(mg/g)	12.23(7.64–19.41)	29.13(15.79–55.55)	< 0.001

NS: not significant.

glomerulus and reabsorbed by the proximal tubular. Normal urine contains very small amounts of alpha-1-microglobulin. However, in conditions causing disturbed renal tubular function, such as diabetes, the reabsorbtion of alpha-1-microglobulin is reduced [13]. Therefore, it is considered to be a marker for renal tubular dysfunction, even in the absence of clinical nephropathy [13,14]. The prevalence of kidney impairment without albuminuria in the Chinese elderly population is unclear.

2. Methods

2.1. Study population

From April to December 2018, eight hundred elderly people (> 60 y) from the suburbs of Jinhua City who received a physical examination in Jinhua Municipal Central Hospital were randomly selected for this study. The clinical characteristics of each participant, including blood pressure, height, weight, and waist circumference were measured and recorded by nurses. Descriptive information including disease history, physical activity, smoking history, and drinking were collected by a questionnaire. Fasting blood and morning urine samples were collected from each subject to analyze biochemical indicators and renal damage markers. More than one hundred people were excluded according to the following criteria: (1) primary kidney diseases; (2) insufficient clinical information; (3) unsatisfactory blood or urine sample; (4) urinary system infection. A final total of 691 participants were enrolled in this study, among whom 42.11% were male and 57.89% female. This study is approved by the ethics committee of Jinhua Municipal Central Hospital.

2.2. Measurements

All participant samples were measured in the Department of Clinical Laboratory, Jinhua Municipal Central Hospital. All fasting blood samples were centrifuged within one hour after blood collection and then assessed within three hours using a Beckman Coulter chemistry analyzer. The urine samples were collected in Eppendorf tubes and stored at −80 °C. Samples were returned to room temperature and centrifuged before analysis. Urinary alpha-1-microglobulin and albumin were measured using a Dade–Behring BNII Special Protein Analyzer. Then, the urinary albumin to creatinine ratio (ACR)and MCR were calculated. eGFR values were assessed using the CKD Epidemiology Collaboration equation.

Albuminuria was defined as ACR > 30 mg/g. Yu et al. [15] previously demonstrated that MCR > 15 mg/g was strongly suspicious of tubular dysfunction. Therefore, increased MCR was defined as MCR > 15 mg/g in this study. eGFR values lower than 60 ml/min/ 1.73 m^2were considered as low or reduced eGFR.

2.3. Statistical analysis

All analyses were performed using SPSS 19, and the figures were constructed using GraphPad Prism 5. Normally distributed data were expressed as the mean ± SD and data with skewed distributions as the median and inter-quartile range. Wilcoxon rank test and one-way analysis of variance were used to compare continuous variables with skewed and normal distributions, respectively. Categorical variables in different groups were compared using the Chi-square test. Relationships between clinical risk factors and albuminuria, low eGFR and increased MCR were evaluated using logistic regression analysis. $P < .05$ was considered to be statistically significant.

3. Results

The mean age of the participants was 67.7 ± 6.1 y, with a range of 60 to 89 y. Among the subjects, 69.75% (482) did not have albuminuria, whereas 30.25% (209) of the patients had ACR > 30 mg/g. The prevalence of diabetes and hypertension was 13.6% and 59.91%, respectively. The mean eGFR value was 76.85 ± 11.77 ml/min/1.73 m^2, and the median MCR was 14.92 mg/g in this study population. Descriptive characteristics of the participants divided into two groups according to albuminuria are shown in Table 1.

The rates of reduced eGFR and increased MCR in the cohort are listed in Table 2. The proportion of participants with low eGFR increased with higher ACR values, and the proportion of participants with increased MCR showed the same association. Subjects with ACR >

Table 2
Prevalence of reduced eGFR and increased MCR in the cohort.

	eGFR < 60% (n)	MCR > 15% (n)	eGFR < 60 and MCR > 15% (n)
Overall (n = 691)	8.68% (60)	49.78%(344)	5.50% (38)
Normoalbuminuria (n = 482)	6.02%(29)	37.55%(181)	2.28%(11)
ACR: 30–300 mg/g (n = 170)	11.18% (19)	73.53% (125)	8.82% (15)
ACR > 300 mg/g (n = 39)	30.77% (12)	97.44% (38)	30.77% (12)

Table 3
Rates of eGFR < 60 and MCR > 15 in normoalbuminuric subjects.

Subjects with normoalbuminuria	eGFR < 60% (n)	MCR > 15% (n)	eGFR < 60 and MCR > 15% (n)
Women(n = 259)	8.11% (21)	32.05% (83)	3.09% (8)
Men (n = 223)	3.59% (8)	43.95% (98)	1.34% (3)
Hypertension (n = 266)	7.14% (19)	39.85% (106)	2.63% (7)
Diabetes (n = 47)	4.35% (2)	50% (23)	2.17% (1)
Hypertension with diabetes (n = 36)	2.78% (1)	47.22% (17)	2.78% (1)
Non-hypertension and non-diabetes(n = 206)	4.37% (9)	33.50% (69)	1.94% (4)

300 mg/g had the highest prevalence of reduced eGFR (30.77%) and increased MCR (97.44%). Nonetheless, the prevalence of reduced eGFR (6.02%) and increased MCR (37.55%) were non-negligible in the individuals with normoalbuminuria.

Table 3 shows the rates of reduced eGFR and increased MCR in normal albuminuric subjects. Among the normoalbuminuric participants, individuals with diabetes had the highest percentage (50%) of MCR > 15 mg/g, whereas women showed the lowest rates. The rate of MCR > 15 mg/g in men was significantly higher than in women (43.95% vs 30.05%, P = .007). In contrast, women had the highest prevalence of reduced eGFR among the subjects with normoalbuminuria, and this rate was significantly higher than in men (8.11% vs 3.59%, P = .037). The patients with diabetes had a relatively modest prevalence of reduced eGFR. There was no significant difference in the rate of reduced eGFR between individuals with diabetes and individuals without diabetes or hypertension (4.35% vs 4.37%, P > .05).

A comparison of the MCR values converted by napierian logarithm (ln-MCR) between the subjects with different eGFR levels is shown in Fig. 1. Among the overall subjects and participants with albuminuria, the ln-MCR values increased with decreasing eGFR levels (Fig. 1A and B). In particular, the ln-MCR values of subjects with eGFR < 60 ml/min/1.73 m^2 were significantly higher than those of subjects with eGFR > 60 ml/min/1.73 m^2 (P < .05). However, there was no significant difference in ln-MCR between the normoalbuminuric individuals with different eGFR levels (P = .57).

Table 4 reveals the association between clinical risk factors and three renal impairment markers (after adjusting for confounding factors). Gender, diabetes and hypertension were the strongly independent risk factors of albuminuria and increased MCR. Females showed a 73% increased risk of albuminuria compared with males (odd ratio, OR = 1.73, P = .004). In contrast, the risk of increased MCR was significantly lower in females than that in males (OR = 0.69, P = .028). Reduced eGFR was associated with age, gender and triglycerides but not diabetes or hypertension. The risk of low eGFR was 1.66-fold higher in females compared with males (OR = 2.66, P = .004).

4. Discussion

The development of albuminuria has been considered the first biochemical marker of diabetic kidney disease, which leads to a progressive decrease in GFR and finally end-stage kidney disease [16]. However, recent data have challenged our understanding of the developmental process of renal disease. Renal impairment in the absence of albuminuria has received increasing attention. A number of studies [10,17,18] have reported the proportion of normoalbuminuric kidney impairment in patients with diabetes. Koye et al. [17] demonstrated that although the normoalbuminuric diabetic patients with reduced eGFR showed a lower risk of end-stage kidney disease compared to the diabetic patients with both reduced eGFR and albuminuria, the prevalence of normoalbuminuric eGFR loss cannot be ignored. Liyanage et al. [18] reported that even among the diabetic patients with low eGFR, a high proportion were normoalbuminuric. Penno et al. [10] demonstrated that 56% of diabetic patients with low eGFR had normal albuminuria, and kidney impairment with normoalbuminuria was identified as a strong predictor of mortality [19].

These above data show that renal impairment with normoalbuminuria has become an important component of kidney injury. Although these studies [10,17–19] focused on normoalbuminuric renal impairment in patients with diabetes, little is known regarding the prevalence of renal impairment with normal albuminuria in the general population; this is especially true for the elderly population, which also has a high risk of kidney dysfunction. Hence, in this study we used ACR, eGFR and MCR to evaluate the prevalence of normoalbuminuric renal impairment and estimate the clinical risk factors in an elderly community population in China.

Perhaps due to dietary habits (salt and sugar intake), a high

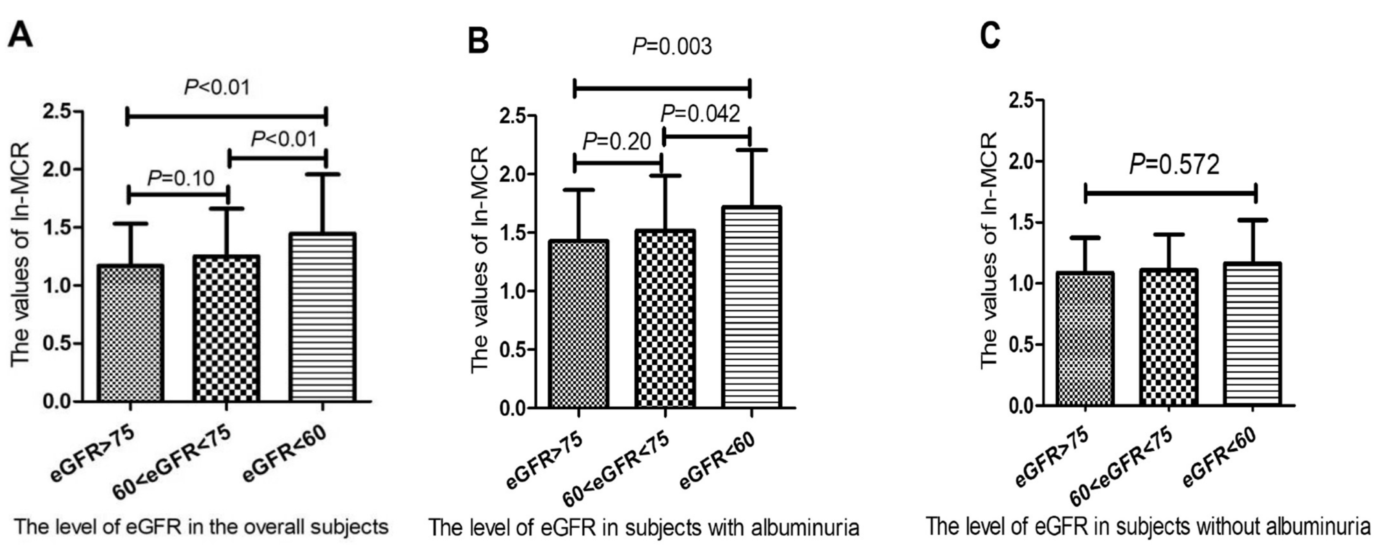

Fig. 1. Comparison of the ln-MCR values between the subjects with different eGFR levels.

Table 4
Relationship between clinical risk factors and albuminuria, reduced eGFR and increased MCR.

Clinical risk factors	Albuminuria		Reduced eGFR(< 60)		Increased MCR(> 15)	
	OR (95%CI)	*P*	*OR* (95%CI)	*P*	*OR* (95%CI)	*P*
Age	1.01 (0.98–1.04)	NS	1.13 (1.08–1.18)	< 0.001	1.04 (1.01–1.06)	0.008
Gender	1.73 (1.19–2.52)	0.004	2.66 (1.38–5.15)	0.004	0.69 (0.49–0.96)	0.028
Waist circumference	1.02 (0.99–1.06)	NS	1.03 (0.98–1.09)	NS	0.99 (0.96–1.02)	NS
BMI	0.93 (0.86–1.01)	NS	0.96 (0.84–1.09)	NS	0.96 (0.89–1.04)	NS
Diabetes	2.16 (1.35–3.46)	0.001	1.16 (0.55–2.46)	NS	1.75 (1.10–2.80)	0.019
Hypertension	1.87 (1.28–2.73)	0.001	1.72 (0.89–3.31)	NS	1.38 (1.02–1.93)	0.011
Triglyceride	1.22 (1.04–1.43)	0.014	1.27 (1.01–1.59)	0.037	1.11 (0.95–1.30)	NS
Total cholesterol	0.97 (0.90–1.04)	NS	0.95 (0.78–1.16)	NS	1.05 (0.93–1.19)	NS
Smoking	0.81 (0.57–1.15)	NS	1.23 (0.69–2.20	NS	1.29 (0.95–1.79)	NS
Physical activity	0.69 (0.48–0.98)	0.037	0.79 (0.45–1.40)	NS	0.88 (0.64–1.21)	NS

NS: not significant.

prevalence of hypertension was found in the elderly community population in this study, which was similar with the proportion of hypertension (58.96%) in other study [1]. Therefore, the proportion of participants with albuminuria was 30.25%, which was somewhat higher than that reported by other study [3]. Among the entire cohort, although both the prevalence of reduced eGFR and increased MCR were associated with higher ACR concentrations, this does not mean that the prevalence of reduced eGFR and increased MCR in the population with normal albuminuria can be ignored. Hong et al. [20] found that among diabetic patients without albuminuria in Singapore, 33.6% had abnormally increased urinary alpha-1-microglobulin levels. Similarly, approximately one-third of the participants with normoalbuminuria had elevated MCR in the present study. In addition, the rate of reduced eGFR was 6.02% and the percentage of individuals with low eGFR and increased MCR was 2.28% among the elderly population with normoalbuminuria (Table 2). Despite being lower than in diabetic patients with normal albuminuria [9], these rates in the elderly population are non-negligible.

In the subjects without albuminuria in this study, males and individuals with diabetes had a similar proportion of increased MCR. Of note, the prevalence of increased MCR in females was significantly lower than in males. This result is in accordance with previous studies. Hong et al. [20] reported that urinary alpha-1-microglobulin excretion in men was significantly higher than in women, although all subjects in that study had type 2 diabetes. Unlike increased MCR, a reduced eGFR with normal albuminuria was not as prevalent in the diabetic patients of this study; rather, females showed the highest prevalence of normoalbuminuric reduced eGFR. The prevalence in men was much lower than in women, although the underlying reason is not yet clear. Similar data was showed in the study of Liyanage et al. [18], the proportion of males among diabetic patients with eGFR < 60 ml/ min/ 1.73 m^2 was 40%, much lower than the proportion of females(60%). This may be due to significantly decreased estrogen levels in elderly women, which could lead to reduced protective effects in the vascular endothelial system. Additionally, although there were numerous individuals with low eGFR or increased MCR among these normoalbuminuric subjects, the ln-MCR values did not correlate with eGFR levels, as there was no significant relationship between the two renal impairment markers.

Associations between clinical risk factors and albuminuria, reduced eGFR and increased MCR were evaluated using logistic regression analysis. Like other studies [3,4], diabetes and hypertension were found to be the strongest risk factors for albuminuria. For increased MCR, both age and gender were independent risk factors along with diabetes and hypertension. These results are in accordance with a previous study by Hong et al. [20], although the effect of age in this study was not as dramatic as in the other study. However, the prevalence of increased MCR in this study was much higher (50% vs 33.6%) than that reported by Hong [20], which might be due to the higher average age of the population in the present study.

Females carried a higher risk of reduced eGFR than males, although the underlying reason remains unclear. Similar data were reported in a general Chinese population [21], as the proportion of males with reduced eGFR among the population was only 28.42%, much lower than that in females (71.58%). It is noteworthy that neither diabetes nor hypertension were independent risk factors for reduce eGFR. Data from Liyanage et al. [18] also found no association between reduced eGFR and diabetes duration, systolic blood pressure, diastolic blood pressure or glycemic control. Hence, regarding renal impairment, attention should not focus solely on populations with diabetes or hypertension.

5. Conclusions

The utility of albuminuria as a screening marker for renal injury is limited, as a considerable proportion of the elderly population have renal impairment despite normal albuminuria. Rather than focusing solely on populations with diabetes or hypertension, the general elderly population should be given more attention regarding normoalbuminuric renal impairment.

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