

# Association Between Frailty and Albuminuria in the Community-Dwelling Geriatric Population

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**Aim:** Elderly with frailty are more at risk of cardiovascular disease and all-cause mortality than the general population. Albuminuria is a risk factor for atherosclerosis, a major cause of frailty. We investigated the association between frailty and albuminuria in community-dwelling elderly.

**Methods:** This was a cross-sectional study for analyzing 1347 participants aged at least 65 years in the north district of Taichung, Taiwan. We defined the frailty phenotype as at least three characteristics: weight loss, exhaustion, weakness, slow walking speed, and decreased physical activity. We collected random urine and measured all participants' albumin/creatinine ratio (ACR). We analyzed the association between frailty and ACR using logistic regression with adjustments for confoundings.

**Results:** The average age of 1347 participants was  $76 \pm 7$  years, and 649 (48.2%) were male. Two hundred and forty-two (18.7) participants were robust, 853 (63.3%) participants were pre-frail, and 242 (18%) were frail. One thousand sixty-four (79%) participants had an ACR < 30 mg/g; the highest ACR was 2825 mg/g. The odds ratio of ACR was 1.12 (95% confidence interval 1.05–1.25,  $p = 0.001$ ) with adjustments for age, body mass index, estimated glomerular filtration rate, diabetes, liver function, and cholesterol.

**Conclusion:** Frailty is associated with urinary albuminuria in community-dwelling elderly, and this association is independent of traditional and non-traditional cardiovascular risk factors.

**Keywords:** frailty, albuminuria, elderly, community, albumin

## Background

Frailty is a prevalent geriatric syndrome that involves a decline of multiple systemic functions and is associated with increased all-cause mortality in the elderly.<sup>1</sup> Frailty affects 11% of community-dwelling residents in Taiwan<sup>2</sup> and 10.2% to 13.9% among inhospital patients.<sup>3</sup> Fifty percent of patients with heart failure<sup>4</sup> and twenty percent with diabetes had frailty.<sup>5-8</sup> The prevalence of frailty is expected to rise with the aging population.<sup>9</sup> Since frailty is associated with chronic disease, frailty has significant implications in clinical practice and public health.

Albuminuria is a marker of atherosclerosis<sup>10</sup> and is associated with increased all-cause mortality in patients with chronic diseases.<sup>11</sup> Atherosclerosis is linked to frailty, cognitive decline, neurodegenerative diseases, and malnutrition.<sup>12</sup> The association between albuminuria and frailty was investigated in older patients.<sup>13</sup> Low-grade albuminuria (less than 30 mg/g) is associated with frailty among community-dwelling middle-aged and older people.<sup>14</sup> The urinary albumin creatinine ratio is linked to an increased incidence of frailty using a frailty index of at least 2.5 in a longitudinal follow-up for 5.3 years.<sup>15</sup> We explore the association between urinary albumin creatinine ratio and frailty in community-dwelling elders. In this cross-sectional study, we defined frailty using a 5-item FRAIL score.<sup>16</sup>

# Methods

We conducted a population-based cross-sectional study in the North District of Taichung city residents between 2009 and 2011.<sup>17</sup> The age and sex distributions of the residents in the North District were similar to those in Taiwan. The five items of frailty include shrinking, weakness, poor endurance and energy, slowness, and low physical activity. Shrinking is an unintentional weight loss of more than 4.5 kg in one year. Weakness is the grip strength in the lowest quintile at baseline, measured by a handgrip dynamometer (TTM-110D, TTM, Tokyo, Japan) based on gender and body mass index (BMI) subgroups. Poor endurance and energy were measured using self-reports of exhaustion by two questions from the Center for Epidemiological Studies-Depression scale. Slowness was measured as the slowest quintile of the population in terms of subgroups of sex and height based on the 15 feet walking time. Low physical activity level was measured by energy expenditure using frequency, duration, and types of leisure activities reported by the participants. Participants with none of those mentioned above components were considered robust, whereas those with one or two were pre-fail, and those with more than two were frail.

Self-reported hypertension (HTN), diabetes mellitus (DM), and congestive heart failure (CHF) were recorded at enrollment. Hemoglobin (Hb), alanine transaminase (ALT), blood urea nitrogen (BUN), serum creatinine, uric acid, serum albumin, high-sensitivity c-reactive protein (hCRP), cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and urinary albumin creatinine ratio (ACR) were measured at the enrollment. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula.<sup>18</sup>

# Statistical Analysis

We reported demographic data as the mean  $\pm$  standard deviation in normally distributed or median (interquartile range) in not normally distributed continuous variables or percent frequency in categorical variables. We used Kolmogorov–Smirnov test to assess the distribution of continuous variables. The *t*-test or Mann–Whitney *U*-test were used for continuous variables according to their distribution. The Chi-square test was used for categorical variables. Because the distribution of ACR and hCRP are right-skewed, we used log-transformed ACR and hCRP in logistic regression.<sup>19</sup> We used univariate and multivariate logistic regression to analyze the association between frailty and all parameters. The odds ratio (OR) was calculated, and a *p* less than 0.05 was considered significant. All data were analyzed using a standard statistical package (R version 4.1.2 Vienna, Austria) with tableone, rms, and finalfit packages.

# Results

We enrolled 1347 participants in this study, and 649 (63.3%) were male. The average age was  $74 \pm 7$  years old. Two hundred and fifty-two (18.7%) participants were robust, 835 (63.3%) participants were pre-frail, and 242 (18%) participants were frail (Table 1). Frail participants were older and had a lower BMI. Frail participants were more likely to have DM, HTN, and CHF. In the laboratory data, frail participants had lower ALT, eGFR, serum albumin, cholesterol, higher ACR, and hCRP.

**Table 1** Characteristics of All Participants

Characteristics	Robust	Pre-Frail	Frail	p
	N = 252	N = 853	N = 242	
Age (year)	73 $\pm$ 6	74 $\pm$ 6	78 $\pm$ 7	<0.001
Male	240 (95.2)	314 (36.8)	95 (39.3)	<0.001
BMI (kg/m <sup>2</sup> )	24.5 $\pm$ 3.1	24.6 $\pm$ 3.6	23.9 $\pm$ 4.0	0.031
HTN	114 (45.2)	448 (52.5)	139 (57.4)	0.023
DM	28 (11.1)	132 (15.5)	56 (23.1)	0.001
CHF	68 (27.0)	261 (30.6)	97 (40.1)	0.004
SBP (mmHg)	140 $\pm$ 16	137 $\pm$ 17	137 $\pm$ 17	0.039

(Continued)

**Table 1** (Continued).

Characteristics	Robust	Pre-Frail	Frail	p
	N = 252	N = 853	N = 242	
DBP (mmHg)	81 ± 11	78 ± 11	74 ± 11	<0.001
Hb (g/dl)	14.5 ± 1.2	13.5 ± 1.4	13.1 ± 1.6	<0.001
ALT (IU/L)	25 ± 13	24 ± 14	21 ± 11	<0.001
BUN (mg/dl)	15 ± 5	15 ± 5	17 ± 10	<0.001
Creatinine (mg/dl)	1.0 [0.9, 1.1]	0.8 [0.7, 1.0]	0.8 [0.7, 1.1]	<0.001
eGFR (mL/min/1.73m <sup>2</sup> )	74 [64, 83]	77 [66, 88]	73 [60, 90]	0.005
Uric acid (mg/dl)	6.2 ± 1.2	5.8 ± 1.5	5.8 ± 1.7	<0.001
Albumin (g/dl)	4.3 ± 0.3	4.3 ± 0.3	4.1 ± 0.4	<0.001
hCRP (mg/dl)	0.1 [0, 0.2]	0.1 [0, 0.2]	0.2 [0.1, 0.3]	<0.001
hCRP (log-transformed, mg/dl)	-2.4 ± 1.1	-2.2 ± 1.2	-1.8 ± 1.1	<0.001
Cholesterol (mg/dl)	189 ± 33	194 ± 36	187 ± 34	0.021
Triglyceride (mg/dl)	108 ± 59	120 ± 80	114 ± 66	0.054
HDL (mg/dl)	45 ± 14	47 ± 14	47 ± 13	0.095
LDL (mg/dl)	115 ± 28	115 ± 32	111 ± 28	0.222
ACR (mg/g)	7 [4, 17]	9 [5, 22]	13 [7, 40]	<0.001
ACR (log-transformed, mg/g)	2.2 ± 1.3	2.5 ± 1.4	2.9 ± 1.5	<0.001

**Notes:** Data are presented as mean ± standard deviation or median [quartile 1, quartile 3].

**Abbreviations:** BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; CHF, congestive heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; ALT, alanine transaminase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; hCRP, high-sensitivity c-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACR, urine albumin-creatinine ratio.

ACR (log-transformed) was associated with frail (Table 2) in univariate ( $p < 0.001$ ) and multivariable logistic regression ( $p = 0.006$ ). The likelihood of being frail was increased with advancing age ( $p < 0.001$  and  $< 0.001$ ) and diabetes ( $p = 0.001$  and  $0.003$ ) in univariable and multivariable regression. Males ( $p = 0.002$  and  $< 0.001$ ) and

**Table 2** The Odds Ratio of Pre-Frailty or Frailty in Univariable and Multivariable Logistic Regression

Factors	Univariable			Multivariable		
	OR	95% CI	p	OR	95% CI	p
ACR (log-transformed, mg/g)	1.22	1.11–1.34	<0.001	1.19	1.04–1.37	0.006
Age (years)	1.10	1.08–1.13	<0.001	1.10	1.08–1.13	<0.001
Male	0.64	0.48–0.85	0.002	0.51	0.36–0.70	<0.001
BMI (kg/m <sup>2</sup> )	0.95	0.91–0.99	0.010	0.96	0.92–1.00	0.038
DM	1.78	1.26–2.49	0.001	1.69	1.12–2.51	0.003
HTN	1.30	0.99–1.73	0.064	0.98	0.71–1.36	0.918
CHF	1.58	1.18–2.10	0.002	1.27	0.92–1.74	0.113
ALT (IU/L)	0.97	0.96–0.98	<0.001	0.98	0.97–1.00	0.029
hCRP (log-transformed, mg/dl)	1.32	1.22–1.55	<0.001	1.66	1.38–2.02	<0.001
Creatinine (mg/dl)	1.18	0.94–1.45	0.079	1.14	0.84–1.53	0.070
eGFR (mL/min/1.73m <sup>2</sup> )	1.00	0.99–1.00	0.122	1.00	0.99–1.01	0.392
Cholesterol (mg/dl)	1.00	0.99–1.00	0.033	0.96	0.94–0.99	0.001
Triglyceride (mg/dl)	1.00	1.00–1.00	0.489	1.01	1.00–1.01	0.017
HDL (mg/dl)	1.00	0.99–1.01	0.722	1.03	1.01–1.06	0.010
LDL (mg/dl)	1.00	0.99–1.00	0.084	1.04	1.01–1.06	0.002

**Abbreviations:** OR, odds ratio; CI, confidence interval; ACR, urine albumin-creatinine ratio; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; CHF, congestive heart failure; ALT, alanine transaminase; hCRP, high-sensitivity c-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein.

**Table 3** Odd Ratio of Frail in Multivariable Logistic Regression

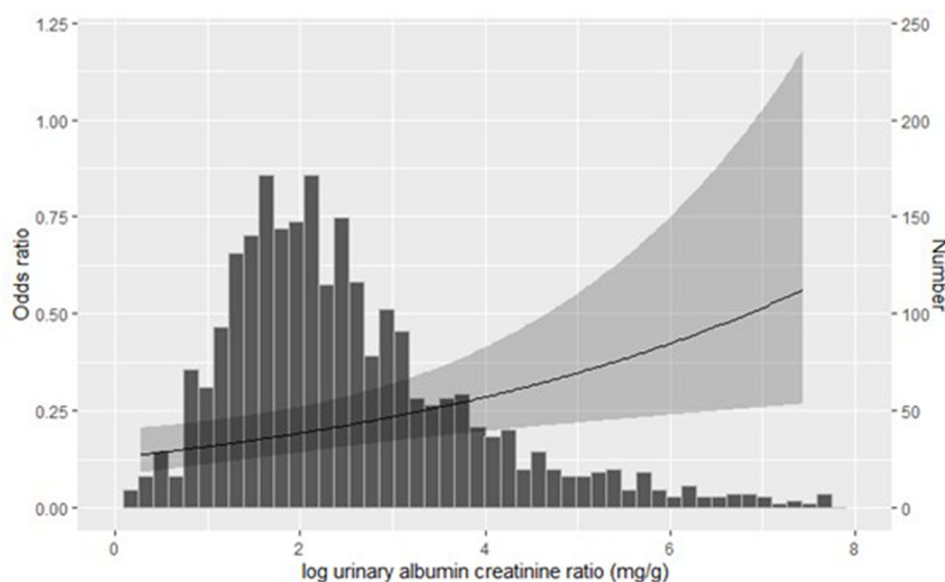
Factors	OR	95% CI	p
ACR (log-transformed, mg/g)	1.12	1.05–1.25	0.001
hCRP (log-transformed, mg/dl)	1.36	1.19–1.54	<0.001
Age (years)	1.10	1.08–1.12	<0.001
Male	0.53	0.38–0.72	<0.001
BMI (kg/m <sup>2</sup> )	0.95	0.90–0.99	0.011
DM	1.81	1.22–2.65	0.003
ALT (IU/L)	0.98	0.97–1.00	0.027
Cholesterol (mg/dl)	1.00	0.99–1.00	0.125

**Abbreviations.** OR, odds ratio; CI, confidence interval; ACR, urine albumin-creatinine ratio; hCRP, high-sensitivity c-reactive protein; BMI, body mass index; DM, diabetes mellitus; ALT, alanine transaminase.

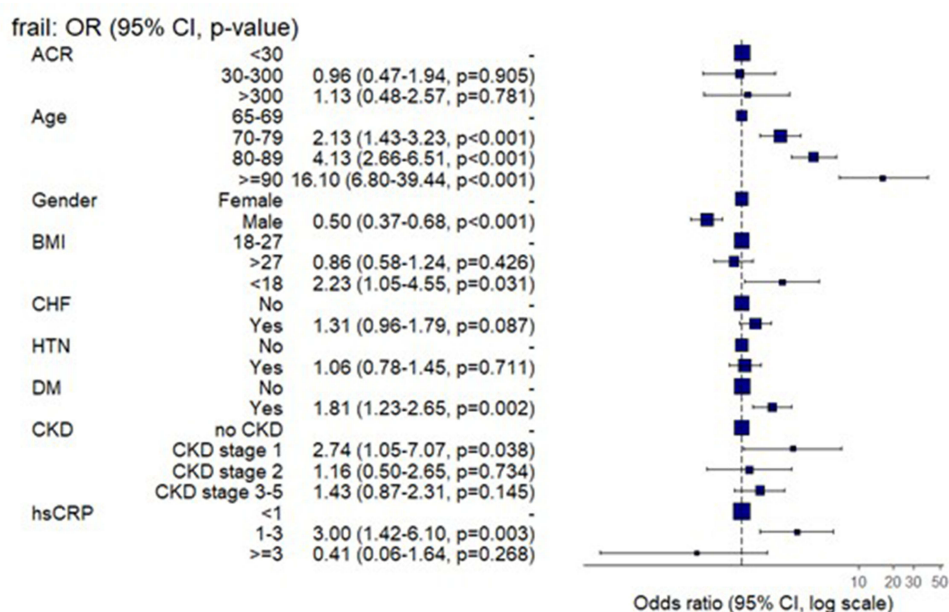
higher BMI ( $p = 0.010$  and  $0.038$ ) were associated with a lower likelihood of being frail. An increased ALT ( $p < 0.001$  and  $p = 0.029$ ) and cholesterol ( $p = 0.033$  and  $p = 0.001$ ) were associated with less likelihood of frail in univariable and multivariable regression. An increased hCRP was associated increased chance of being frail. Factors related to frail in both univariable and multiple variable regression were selected in the model (Table 3). ACR (OR 1.12, 95% CI 1.05–1.25), hCRP (OR 1.36, 95% CI 1.19–1.54), age (OR 1.10, 95% CI 1.08–1.12), male (OR 0.53, 95% CI 0.38–0.72), BMI (OR 0.95, 95% CI 0.90–0.99), diabetes (OR 1.81, 95% CI 1.22–2.65), and ALT (OR 0.98, 95% CI 0.97–1.00) were independently associated with frail.

We showed the OR of frail according to ACR in Figure 1. The OR and 95% CI of the OR were increased with the increased urinary ACR in multivariable logistic regression with adjustments for age, gender, BMI, diabetes, eGFR, hCRP and ALT. A histogram of urinary ACR (black bars) showed this distribution of ACR after log transformation.

We presented the OR and 95% CI of frail in subgroups (Figure 2) as a forest plot. The likelihood of frail was not different in participants with an ACR  $< 30$  mg/g,  $30$ – $300$  mg/g, and  $\geq 300$  mg/g. Participants older than 90 had the highest likelihood of being frail, followed by participants aged between 80 and 89 and between 70 and 79 years. The possibility



**Figure 1** Adjusted odds ratio and 95% confidence interval of frail according to urinary albumin creatinine ratio with log transformation. The black line indicates the adjusted odds ratio (OR) of frail according to the urinary albumin creatine ratio (ACR). Adjusted factors were age, gender, body mass index, diabetes, alanine transaminase, and cholesterol. The light-gray area indicates the 95% confidence interval of OR. The X-axis is the ACR with log transformation. The left Y-axis represents the adjusted OR. The right Y-axis is the number of participants. The black bar is the number of participants according to the ACR.



**Figure 2** Forest plot of odds ratio and 95% confidence interval of frail. Squares represent the odds ratio (OR) point estimate, and horizontal lines indicate the 95% confidence intervals (CI). The vertical dashed line indicates an OR of 1.0, representing no association.

**Abbreviations:** OR, odds ratio; CI, confidence interval; ACR, urine albumin-creatinine ratio; BMI, body mass index; CHF, congestive heart failure; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; hsCRP, high-sensitivity c-reactive protein.

of being frail was higher in underweight participants (BMI < 18). Diabetic participants were likelier to be frail, and the OR of frail was 1.81 (95% CI 1.23–2.65,  $p = 0.002$ ). Participants with CKD stage 1 were more likely to be frail than participants with no CKD (OR 2.74, 95% CI 1.05–7.07). The participants with an hCRP 1–3 mg/dl were more at risk of frail, and the OR of frail was 3.00 (95% CI 1.42–6.10,  $p = 0.003$ ).

## Discussions

This cross-sectional population-based study showed a linear correlation between frail and urinary ACR. The association is independent of traditional atherosclerosis risk factors such as DM, HTN, CHF, dyslipidemia and non-traditional atherosclerosis risks factors such as eGFR, and hCRP. The association of CHF and CKD is also supported by a recent study in geriatric CHF patients.<sup>20</sup> Five-item frailty score, a more comprehensive range of ACR, and community-dwelling elders are the significant characteristics that distinguish this study from the previous studies.<sup>2,13–15</sup> The increased likelihood of frail in CKD stage 1 participants supported the association of frail and ACR because an ACR > 30 mg/g is one of the CKD definitions<sup>21</sup> in participants with an eGFR > 60 mL/min/1.73m<sup>2</sup>. The previous studies focused on the association between mildly increased albuminuria and frailty.<sup>22–25</sup> The majority of our population with urine protein had an ACR between, 30–300 and >300 mg/g. Our findings supported an association of frailty and moderately/severely increased ACR in a community-based elder.

A lower eGFR is associated with frailty,<sup>26,27</sup> and mobility disability.<sup>28</sup> In this study, participants with an eGFR 30–59, 30–89, and ≥90 had a lower risk of being frail. This may provide an important clinical application that access for frailty should be considered among chronic kidney disease (CKD) patients with an eGFR < 30 (CKD stage 4). hCRP was originally a serum marker for bacterial infection and is widely used in the differential diagnosis of fever of unknown origin. Emerging research suggests that hCRP is also a marker for inflammation and atherosclerosis<sup>29</sup> and is linked to multiple clinical outcomes such as mortality and sarcopenia.<sup>30,31</sup> We also found a higher risk of frail in participants with an hCRP > 3 mg/dl compared to those with an hCRP < 1 mg/dl. The increased CRP in participants may support the association between inflammation/atherosclerosis and increased urine ACR. Most participants had an hCRP < 1 mg/dl because the study was conducted in the community.

There are some limitations of this study. First, we cannot determine the cause-and-effect relationship between ACR and frailty because of the cross-sectional study design. Second, chronic disease prevalence was low because the self-reported disease was used in this study. About 1.7% of the participants reported having CKD, but 21% were diagnosed

with CKD, according to the eGFR and ACR readings. Third, while ORs from logistic regression facilitated multivariable adjustment, they must be interpreted carefully in this cross-sectional setting. Specifically, the OR can numerically overestimate the strength of an association compared to the prevalence ratio when the outcome (frailty) is common, as it may be in this geriatric population. Therefore, our reported ORs reflect the odds of prevalent frailty and should not be interpreted as direct estimates of relative risk.

## Conclusions

Urinary albumin creatinine ratio is associated with frail in community-dwelling elderly. The association is an independent traditional atherosclerosis risk factor such as diabetes and hypertension.

## Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## Ethics Approval and Consent to Participate

The present study was approved by the institutional review board of China Medical University Hospital (DMR-97-IRB-055). Participants or their legal guardians have given their written informed consent to participate in the study before taking part. The study was conducted in accordance with the 2004 revision of the Declaration of Helsinki.

## Acknowledgments

This paper has been uploaded to ResearchSquare as a preprint: <https://www.researchsquare.com/article/rs-3142053/v1>.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This study was supported by the National Health Research Institutes of Taiwan (NHRI-EX98-9838PI) and China Medical University Hospital (DMR-113-056). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## Disclosure

The authors have no conflicts of interest to declare in this work.

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