

# Association of Walking with Survival and RRT Among Patients with CKD Stages 3–5

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## Abstract

**Background and objectives** Patients with CKD can benefit from an increase in physical activity. Walking is one of the most common exercises in patients with CKD; however, the association of walking with outcomes in patients with CKD is not clear. This study investigated the association of walking with overall mortality and RRT in patients with CKD stages 3–5.

**Design, setting, participants, & measurements** All patients with CKD stages 3–5 in the CKD program of China Medical University Hospital from June 2003 to May 2013 were enrolled. The risks of overall mortality and RRT were analyzed using competing-risks regressions.

**Results** A total of 6363 patients (average age, 70 years) during a median of 1.3 (range=0.6–2.5) years of follow-up were analyzed. There were 1341 (21.1%) patients who reported walking as their most common form of exercise. The incidence density rate of overall mortality was 2.7 per 100 person-years for walking patients and 5.4 for nonwalking ones. The incidence density rate of RRT was 22 per 100 person-years for walking patients and 32.9 for nonwalking ones. Walking, independent of patients' age, renal function, and comorbidity, was linked to lower overall mortality and lower RRT risk in the multivariate competing-risks regression. The adjusted subdistribution hazard ratio (SHR) of walking was 0.67 (95% confidence interval [95% CI], 0.53 to 0.84;  $P<0.001$ ) for overall mortality and 0.79 (95% CI, 0.73 to 0.85;  $P<0.001$ ) for the risk of RRT. The SHRs of overall mortality were 0.83, 0.72, 0.42, and 0.41 for patients walking 1–2, 3–4, 5–6, and  $\geq 7$  times per week, and the SHRs of RRT were 0.81, 0.73, 0.57, and 0.56, respectively.

**Conclusions** Walking is the most popular form of exercise in patients with CKD and is associated with lower risks of overall mortality and RRT. The benefit of walking is independent of patients' age, renal function, and comorbidity.

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## Introduction

Exercise improves cardiorespiratory fitness (1), hemodynamic reactivity (2,3), physical fitness (4,5) malnutrition-inflammation complex syndrome (6), and quality of life (7) in patients with CKD. A recent study by Wen *et al.* showed that a small amount of exercise, such as 15 minutes a day or 90 minutes a week, may reduce mortality in the general population and individuals with cardiovascular disease (8). Walking is one of the most common exercises in the general population (9) and the elderly (10); however, the effect of walking on the outcomes of patient with CKD is not clear. This study investigated the association of walking with overall mortality and RRT in patients with CKD. Because benefits of walking may be related to the frequency and duration of walking, we considered these variables in our study. Patients' walking ability may be affected by their comorbidity and renal function (11). These two factors, therefore, were also included in the analysis.

## Materials and Methods

### Patients in CKD Program

In this observational cohort study, all patients with CKD stages 3–5 in the CKD program of China

Medical University Hospital from June 2003 to May 2013 were enrolled. All patients were prospectively followed to the date of RRT (hemodialysis, peritoneal dialysis, or kidney transplantation), loss of follow-up, death, or May 2013, whichever came first. The outpatient-based CKD program enrolled all patients with CKD diagnosed by physicians of nephrology, and no exclusion criteria were applied in this program. The purpose of the CKD program was to monitor the progression of patients with CKD; laboratory measurements were performed regularly, at least four times a year. The internal review board approved the study (CMUH 102-REC3–039), and the need for informed consent was waived.

### Exercise Data

Patients reported the form, frequency, and duration of exercise in the past 3 months, with confirmation by the patient's family or caregiver. Information on patients' exercise pattern (the most common exercise, times per week, and minutes per session) was collected at enrollment. The forms of exercise included walking, hiking, jogging, dancing, and cycling. The frequency of exercise was categorized as 0, 1–2, 3–4,

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5–6, or  $\geq 7$  times per week. The duration of exercise was categorized as 0, <30 minutes, 30–60 minutes, 61–90 minutes, or >90 minutes per session. Walking was defined as walking for fitness, health, or physical recreation (12). The 64 bedridden patients were not included in the analysis.

### Clinical Variables

A history of smoking or alcohol consumption was reported by the patients at enrollment. Patients who received erythropoiesis-stimulating agent (ESA) treatment were also recorded. Underlying diseases of CKD, including diabetes mellitus (DM), chronic GN, and hypertension, had been diagnosed by the primary care physicians who enrolled the patient. Hemoglobin and creatinine were measured on enrollment into the CKD program. An eGFR was calculated using the simple Modification of Diet in Renal Disease equation ( $186 \times \text{creatinine}^{-1.154} \times \text{age}^{-0.203} \times [0.742 \text{ if female}]$ ) to define the stage of CKD (two measurements in 3 months) at enrollment. Patient's body mass index (BMI), comorbid coronary artery disease (CAD), DM, cerebrovascular accident (CVA), and any cancer in 5 years were recorded at enrollment. CAD was defined as stenosis >70% in one of the major epicardial coronary arteries, as assessed by quantitative angiography (13). DM was defined as use of insulin or a hypoglycemic agent, a fasting plasma glucose level of 126 mg/dl or greater, or a 2-hour postload plasma glucose level of 200 mg/dl or greater (14). CVA was defined as the development of an embolic, thrombotic, or hemorrhagic vascular accident or stroke with motor, sensory, or cognitive dysfunction that persisted for  $\geq 24$  hours (15).

### Statistical Analyses

Data are reported as the mean  $\pm$  SD or frequency (percentage). Testing for statistical significance was conducted using the *t* test for parametric variables, Mann-Whitney *U* test for nonparametric variables, and chi-squared test for categorical variables. Variables that were significantly different in walking patients and variables that were related to ability to perform exercise were considered as possible confounders. A subdistribution hazard ratio (SHR) and 95% confidence interval (95% CI) of the SHR of possible confounders were calculated using univariate competing-risks regression followed by multivariate competing-risks regression (16). In the competing-risks regression for overall mortality, patient death was defined as the failure event and RRT was defined as the competing event. In the competing-risks regression for RRT, RRT was defined as the failure event and patient death was defined as the competing event. All analyses were performed using Stata software, version 12 SE (Stata Corp., College Station, TX).  $P < 0.05$  was considered to represent statistically significant differences.

### Results

We analyzed 6363 patients with CKD stages 3–5 (2704 women and 3659 men), with a mean age of  $70.1 \pm 13.6$  years (Table 1). Of the 6363 patients, 552 (8.7%) patients were lost to follow-up, and the date when they were last known to be alive was recorded. In 3394 (53.3%) patients who started RRT, the dates of enrollment and RRT were

recorded. Of the 6363 patients, 2292 (36.0%) had CKD stage 3, 1287 (20.2%) had CKD stage 4, and 2784 (43.8%) had CKD stage 5. The incidence density rates were 4.6 per 100 person-years for overall mortality and 29.9 per 100 person-years for RRT. A total of 1341 (21.1%) patients reported walking as their most common exercise. The percentage of patients who reported an exercise frequency of 0 or an exercise duration of 0 was significantly higher with advancing stages of CKD. Patients' hemoglobin levels were also higher with advancing stages of CKD.

Patient age and eGFR did not significantly differ between walking and nonwalking patients (Table 2), nor did comorbid CAD and DM. The prevalence of CVA was lower in walking patients ( $P = 0.002$ ) but the prevalence of cancer was higher in walking patients ( $P = 0.04$ ) compared with the prevalence in nonwalking patients. The frequency and duration of exercise were significantly greater and hemoglobin was significantly lower in walking patients than in nonwalking ones.

Possible confounders of mortality and RRT were analyzed using univariate competing-risks regression (Table 3). The prevalence of patients with CAD, prevalence of patients with DM, prevalence of patients who smoked, prevalence of patients receiving ESA treatment, patients' BMI, and patients' eGFR did not differ between walking and nonwalking patients. These variables were considered as possible confounders because of their association with exercise, mortality, and RRT (17–21). Walking was associated with lower overall mortality (SHR, 0.65; 95% CI, 0.51 to 0.81;  $P < 0.001$ ) and RRT risk (SHR, 0.75; 95% CI, 0.69 to 0.80;  $P < 0.001$ ). Patients' age was linked to a higher overall mortality, with an SHR of 1.86 (95% CI, 1.69 to 2.04) for every 10 additional years, but was associated with lower RRT risk, with an SHR of 0.83 (95% CI, 0.81 to 0.84) for every 10 additional years. Patients' eGFR was negatively linked to overall mortality (SHR, 0.99; 95% CI, 0.98 to 0.99;  $P < 0.001$ ) and RRT (SHR, 0.98; 95% CI, 0.98 to 0.99;  $P < 0.001$ ). CAD (SHR, 1.15; 95% CI, 1.02 to 1.31;  $P = 0.028$ ) and DM (SHR, 1.20; 95% CI, 1.12 to 1.28;  $P < 0.001$ ) were associated with a higher RRT risk, whereas CVA (SHR, 1.94; 95% CI, 1.41 to 2.65;  $P < 0.001$ ) and cancer (SHR, 2.04; 95% CI, 1.52 to 2.72;  $P < 0.001$ ) were linked to a higher overall mortality. A higher frequency of exercise was associated with lower mortality (SHR, 0.83; 95% CI, 0.78 to 0.90;  $P < 0.001$ ) and lower RRT risk (SHR, 0.92; 95% CI, 0.90 to 0.94;  $P < 0.001$ ) for each category increase. Longer duration of exercise was associated with lower mortality (SHR, 0.77; 95% CI, 0.70 to 0.85;  $P < 0.001$ ) and RRT risk (SHR, 0.89; 95% CI, 0.86 to 0.92;  $P < 0.001$ ) for each category increase.

The variables with  $P < 0.05$  in univariate competing-risks regression and important confounders (3,22,23) were further analyzed using multivariate competing-risks regression (Table 4). Because walking was highly collinear with the frequency of exercise and the duration of exercise, only walking was selected in the multivariate analysis. Walking was associated with lower mortality (adjusted SHR, 0.67; 95% CI, 0.53 to 0.84;  $P < 0.001$ ) and lower RRT risk (adjusted SHR, 0.79; 95% CI, 0.73 to 0.85;  $P < 0.001$ ). Patients' age was associated with a higher mortality but lower RRT risk. The adjusted SHR of mortality was 1.88 (95% CI, 1.71 to 2.07;  $P < 0.001$ ) and the adjusted SHR of RRT was 0.83

**Table 1. Clinical characteristics of patients with CKD stages 3–5**

Characteristic	CKD 3 (n=2292)	CKD 4 (n=1287)	CKD 5 (n=2784)
Age (yr)	71±13 <sup>a,b</sup>	73±13 <sup>a,c</sup>	68±14 <sup>b,c</sup>
Men, n (%)	1585 (69) <sup>a,b</sup>	712 (55) <sup>a,c</sup>	1362 (49) <sup>b,c</sup>
BMI (kg/m <sup>2</sup> )	23.9±4.1	24.1±4.0	23.9±4.0
Mortality (per 100 person-yr)	2.5	6.8	5.4
RRT (per 100 person-yr)	24.4	20.3	40.8
Duration of follow-up (yr)	1.6 (0.9–2.1) <sup>b</sup>	1.5 (0.8–2.7) <sup>c</sup>	1.4 (0.4–2.3) <sup>b,c</sup>
<b>Comorbidity, n (%)</b>			
CAD	213 (9.3) <sup>b</sup>	95 (7.4)	162 (5.8) <sup>b</sup>
DM	799 (34.9) <sup>a,b</sup>	591 (45.9) <sup>a</sup>	1252 (45.0) <sup>b</sup>
CVA	115 (5.0) <sup>b</sup>	85 (6.6) <sup>c</sup>	106 (3.8) <sup>b,c</sup>
Cancer	127 (5.5)	99 (7.7) <sup>c</sup>	108 (3.9) <sup>c</sup>
<b>Underlying diseases, n (%)</b>			
Chronic GN	788 (34.4) <sup>a</sup>	370 (42.2) <sup>a,c</sup>	891 (32.1) <sup>a</sup>
DM	715 (31.2) <sup>a,b</sup>	543 (39.9) <sup>a</sup>	1167 (42.1) <sup>b</sup>
Hypertension	478 (20.9) <sup>b</sup>	176 (13.7)	314 (11.3) <sup>b</sup>
<b>Forms of exercise, n (%)</b>			
Walking	576 (25.1) <sup>a,b</sup>	267 (20.8) <sup>a,c</sup>	498 (17.9) <sup>b,c</sup>
Hiking	147 (6.4)	172 (13.4)	194 (7.0)
Jogging	96 (4.2)	81 (6.3)	59 (2.1)
Dancing	84 (3.7)	48 (3.7)	96 (3.4)
Cycling	94 (4.1)	93 (7.2)	64 (2.3)
<b>Frequency of exercise, n (%)</b>			
0 times/wk	1506 (65.7) <sup>a,b</sup>	941 (73.1) <sup>a,c</sup>	2157 (77.5) <sup>b,c</sup>
1–2 times/wk	81 (3.5)	45 (3.5)	79 (2.8)
3–4 times/wk	157 (6.9)	77 (6.0)	152 (5.5)
5–6 times/wk	274 (12)	138 (10.7)	257 (9.2)
≥7 times/wk	274 (12)	86 (6.7)	138 (5.0)
<b>Duration of exercise, n (%)</b>			
0 min/session	1502 (65.5) <sup>a,b</sup>	931 (72.3) <sup>a,c</sup>	2157 (77.5) <sup>b,c</sup>
<30 min/session	230 (10)	133 (10.3)	213 (7.7)
30–60 min/session	267 (11.7)	128 (10)	232 (8.3)
61–90 min/session	227 (9.9)	81 (6.3)	152 (5.5)
>90 min/session	66 (2.9)	14 (1.1)	29 (1.0)
<b>Smoking, n (%)</b>			
Current	256 (11.2)	124 (9.6)	228 (8.2)
Quit	209 (9.1)	81 (6.3)	124 (4.5)
<b>Alcohol use, n (%)</b>			
Current	113 (4.9)	41 (3.2)	70 (2.5)
Quit	146 (6.4)	56 (4.4)	112 (4.0)
Hemoglobin (g/dl)	9.2±2.3 <sup>a,b</sup>	9.9±2.4 <sup>a</sup>	10.1±2.3 <sup>b</sup>
ESA therapy, n (%)	801 (35)	449 (34.9)	922 (33.1)
eGFR (ml/min per 1.73 m <sup>2</sup> )	44.8±8.6 <sup>a,b</sup>	22.1±4.3 <sup>a,c</sup>	7.1±3.3 <sup>b,c</sup>

BMI, body mass index, CAD, coronary artery disease; DM, diabetes mellitus; CVA, cerebrovascular accident; ESA, erythropoiesis-stimulating agent.

<sup>a</sup>*P*<0.05 for CKD 4 versus CKD 3.

<sup>b</sup>*P*<0.05 for CKD 5 versus CKD 3.

<sup>c</sup>*P*<0.05 for CKD 5 versus CKD 4.

(95% CI, 0.81 to 0.85; *P*<0.001) for every 10 additional years. A higher eGFR was associated with lower overall mortality (adjusted SHR, 0.86; 95% CI, 0.82 to 0.90; *P*<0.001) and RRT risk (adjusted SHR, 0.89; 95% CI, 0.87 to 0.91; *P*<0.001) for every 10-ml/min per 1.73 m<sup>2</sup> higher eGFR. Comorbid CAD and DM were associated with a higher risk for RRT. Comorbid CVA and cancer were linked to a higher overall mortality. BMI, hemoglobin, and ESA therapy were not significantly associated with mortality or risk of RRT. The cumulative incidence of overall mortality (Figure 1A) and RRT (Figure 1B) was

significantly lower in walking patients compared with nonwalking patients in competing-risks regression with adjustments for age, eGFR, CAD, DM, CVA, and cancer.

The walking-specific dose-dependent association with patients' outcomes was further analyzed according to the frequency of walking (patients who reported a frequency of walking of 0 were the reference group). The SHR of overall mortality was 0.83 (95% CI, 0.79 to 0.89; *P*=0.04) for patients walking 1–2 times per week, 0.72 (95% CI, 0.67 to 0.82; *P*=0.002) for those walking 3–4 times per week, 0.42 (95% CI, 0.30 to 0.57; *P*<0.001) for those walking

**Table 2. Clinical characteristics of CKD patients with and without walking**

Characteristic	No Walking (n=5022)	Walking (n=1341)	P Value
Age (yr)	70.4±13.8	71.0±11.6	0.14
Men, n (%)	2876 (57.3)	783 (58.4)	0.46
BMI (kg/m <sup>2</sup> )	24.0±4.0	23.9±4.0	0.65
Median follow-up (range) (yr)	1.2 (0.6–2.0)	1.8 (1.0–3.3)	<0.001
RRT (100 person-yr)	32.9	22.0	—
Mortality (100 person-yr)	5.4	2.7	—
<b>CKD stage</b>			
3	1716 (34.2)	576 (43)	<0.001
4	1020 (20.3)	267 (19.9)	0.75
5	2285 (45.5)	498 (37.1)	<0.001
<b>Underlying diseases</b>			
Chronic GN	1660 (33.1)	390 (29.2)	<0.001
DM	1928 (38.4)	497 (37.2)	0.37
Hypertension	745 (14.9)	223 (16.7)	0.10
<b>Comorbidity</b>			
CAD	346 (7.5)	92 (6.9)	0.97
DM	2078 (41.4)	564 (42.1)	0.65
CVA	252 (5.5)	41 (3.1)	0.002
Cancer	235 (5.1)	81 (6.0)	0.04
<b>Frequency of exercise, n (%)</b>			
0	4576 (91.1)	29 (2.2)	<0.001
1–2 times/wk	61 (1.2)	144 (10.7)	<0.001
3–4 times/wk	70 (1.4)	316 (23.6)	<0.001
5–6 times/wk	141 (2.8)	528 (39.4)	<0.001
≥7 times/wk	174 (3.5)	324 (24.2)	<0.001
<b>Duration of exercise, n (%)</b>			
0	4574 (91.1)	17 (1.3)	<0.001
<30 min/session	66 (1.3)	510 (38)	<0.001
30–60 min/session	135 (2.7)	492 (36.7)	<0.001
61–90 min/session	171 (3.4)	289 (21.6)	<0.001
>90 min/session	76 (1.5)	33 (2.5)	<0.001
<b>Smoking, n (%)</b>			
Current	514 (10.2)	94 (7.0)	<0.001
Quit	304 (6.1)	110 (8.2)	<0.001
<b>Alcohol use, n (%)</b>			
Current	192 (3.8)	32 (2.4)	0.01
Quit	240 (4.8)	74 (5.5)	0.27
Hemoglobin (g/dl)	10.0±2.4	9.8±2.4	0.01
ESA, n (%)	1717 (34.2)	455 (33.9)	0.86
eGFR (ml/min per 1.72 m <sup>2</sup> )	25.3±17.6	26.0±17.8	0.20

Values expressed with a plus/minus sign are the mean±SD. BMI, body mass index; DM, diabetes mellitus; CAD, coronary artery disease; CVA, cerebrovascular accident; ESA, erythropoiesis-stimulating agent.

5–6 times per week, and 0.41 (95% CI, 0.27 to 0.62;  $P<0.001$ ) for those walking  $\geq 7$  times per week. The SHR of RRT was 0.81 (95% CI, 0.68 to 0.98;  $P=0.037$ ) for patients walking 1–2 times per week, 0.73 (95% CI, 0.63 to 0.84;  $P<0.001$ ) for those walking 3–4 times per week, 0.57 (95% CI, 0.51 to 0.63;  $P<0.001$ ) for those walking 5–6 times per week, and 0.56 (95% CI, 0.42 to 0.67;  $P<0.001$ ) for those walking  $\geq 7$  times per week.

## Discussion

This observational cohort study showed that walking was the most common exercise in patients with CKD and was associated with better clinical outcomes. The benefit of walking cannot be explained by less comorbidity in walking patients because the prevalence of patients with

CAD and patients with DM did not differ between walking and nonwalking patients (Table 2). Walking was associated with lower overall mortality and RRT in multivariate competing-risks regression that included CAD, DM, CVA, and cancer in the model (Table 4). The benefit of walking was not related to a higher renal function or younger age in walking patients. As shown in Table 2, the age and the eGFR of walking patients were not different from those of nonwalking ones. In the multivariate analysis, which included patient's age and patients' renal function in the model, walking was independently associated with lower overall mortality and risk of RRT. Moreover, the SHRs of walking were similar in univariate analysis (Table 3) and multivariate analysis (Table 4), suggesting that adding more covariates did not affect the SHR of walking. This further supported the finding that the benefit of

**Table 3. Subdistribution hazard ratio of possible prognostic factors for overall mortality and RRT in univariate competing-risks regression**

Variable	SHR for Mortality (95% CI)	SHR for RRT (95% CI)
Walking	0.65 (0.51 to 0.81)	0.75 (0.69 to 0.80)
Age (every 10 additional yr)	1.86 (1.69 to 2.04)	0.83 (0.81 to 0.84)
Male sex	1.10 (0.84 to 1.19)	0.95 (0.89 to 1.02)
BMI (every 1-kg/m <sup>2</sup> increment)	0.99 (0.97 to 1.03)	0.99 (0.98 to 1.01)
eGFR (every 10-ml/min per 1.73 m <sup>2</sup> increment)	0.99 (0.98 to 0.99)	0.98 (0.98 to 0.99)
<b>Underlying diseases<sup>a</sup></b>	0.99 (0.95 to 1.02)	0.98 (0.98 to 1.00)
CAD	1.27 (0.94 to 1.71)	1.15 (1.02 to 1.31)
DM	1.03 (0.87 to 1.23)	1.20 (1.12 to 1.28)
CVA	1.94 (1.41 to 2.65)	0.94 (0.79 to 1.11)
Cancer	2.04 (1.52 to 2.72)	0.92 (0.79 to 1.07)
Frequency of exercise (each category increase)	0.83 (0.78 to 0.90)	0.92 (0.90 to 0.94)
Duration of exercise (each category increase)	0.77 (0.70 to 0.85)	0.89 (0.86 to 0.92)
Smoking	0.64 (0.46 to 1.02)	1.09 (0.99 to 1.21)
Alcohol use	0.54 (0.32 to 0.92)	1.01 (0.87 to 1.17)
Hemoglobin (every 1-g/dl increment)	0.99 (0.96 to 1.04)	1.03 (1.02 to 1.05)
ESA therapy	0.94 (0.79 to 1.13)	0.95 (0.89 to 1.02)

SHR, subdistribution hazard ratio; CI, confidence interval; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; CVA, cerebrovascular accident; ESA, erythropoiesis-stimulating agent.

<sup>a</sup>Patients with chronic GN as a reference.

**Table 4. Subdistribution hazard ratio of possible prognostic factors for overall mortality and RRT in multivariate competing-risks regression**

Variable	Adjusted SHR (95% CI) for mortality	Adjusted SHR (95% CI) for RRT
Walking	0.67 (0.53 to 0.84)	0.79 (0.73 to 0.85)
Age (every 10 additional yr)	1.88 (1.71 to 2.07)	0.83 (0.81 to 0.85)
eGFR (every 10-ml/min per 1.73 m <sup>2</sup> increment)	0.86 (0.82 to 0.90)	0.89 (0.87 to 0.91)
BMI (every 1-kg/m <sup>2</sup> increment)	0.99 (0.96 to 1.03)	0.99 (0.98 to 1.01)
CAD	1.13 (0.84 to 1.52)	1.32 (1.16 to 1.51)
DM	1.05 (0.88 to 1.25)	1.22 (1.13 to 1.31)
CVA	1.72 (1.25 to 2.38)	0.96 (0.81 to 1.14)
Cancer	2.03 (1.50 to 2.74)	0.98 (0.83 to 1.16)
Hemoglobin (every 1-g/dl increment)	1.03 (0.99 to 1.07)	1.01 (0.99 to 1.03)
ESA therapy	0.98 (0.81 to 1.17)	0.94 (0.88 to 1.01)

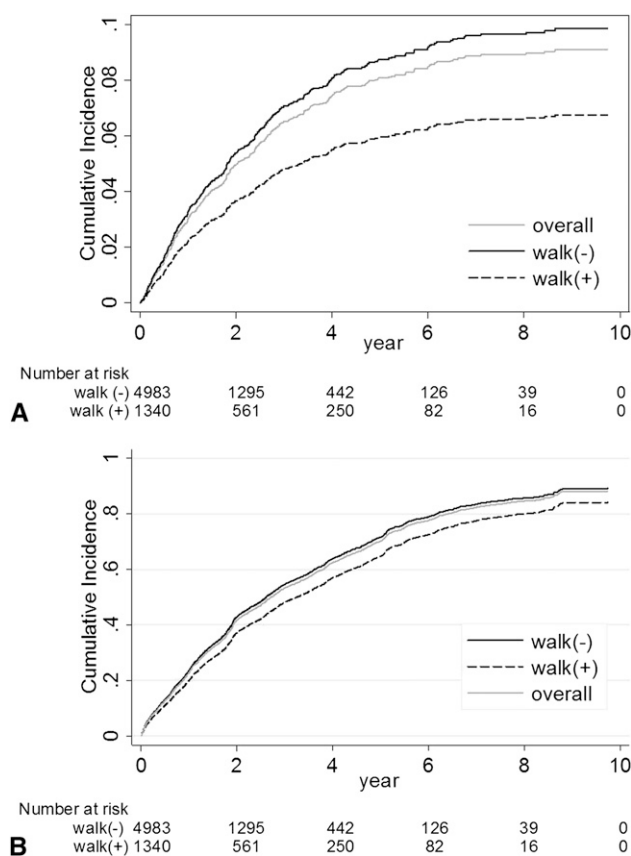
SHR, subdistribution hazard ratio; CI, confidence interval; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; CVA, cerebrovascular accident; ESA, erythropoiesis-stimulating agent.

walking was independent of patients' age, renal function, and comorbidity.

Walking was highly collinear with the frequency of exercise and the duration of exercise because walking may be easier to do at a higher frequency than other exercises. In addition, the frequency of walking was associated with better outcomes in a dose-dependent manner. The benefit of regular exercise was also observed in previous studies (3,22–25). It is possible that patients who walk regularly may be more self-driven, have better adherence (26), or have more leisure time. Having more leisure time may indicate a higher socioeconomic status, which may be linked to better outcomes (27) in walking patients. This finding was supported by the observations of other researchers that walking had a superior beneficial effect in

patients with peripheral arterial disease (28) and heart failure (29).

Advancing age was associated with higher overall mortality but lower risk of RRT. The higher risk of RRT in younger patients with CKD was consistent with our clinical observation and was supported by previous studies (17,30). In addition, patients' eGFR was negatively associated with overall mortality and RRT, also consistent with findings from earlier studies (21,23,31). Anemia is common in patients with CKD (32), and ESA treatment in anemic patients with CKD is associated with an increase of exercise tolerance (22,33). Normalized hemoglobin in patients with CKD receiving ESA treatment may decrease mortality and risk of hospitalization (19). However, we did not find a significant association between hemoglobin and



**Figure 1. | Cumulative incidence of (A) overall mortality and (B) RRT was lower in walking patients than in no walking patients in adjusted competing-risks regression.** Multivariate competing-risks regression adjusted for patients' age, eGFR, body mass index, coronary artery disease, diabetes mellitus, cerebrovascular accident, and cancer.

patients' outcomes. In univariate analysis (Table 3), higher hemoglobin was associated with higher risk of RRT. This may be explained by the fact that ESA treatment was covered by the National Health Insurance in patients with a serum creatinine >6 mg/dl, so these patients were more likely to be treated with ESA. However, we did not find a significant association between ESA treatment and better clinical outcomes.

The major strengths of the study were the large population of patients with CKD; prospective follow-up of 1.3 years; and the use of competing-risks analysis, which considered both patient death and RRT. The number of patients enrolled was adequate to observe the effect of categorized comparison of frequency and duration of exercise on patients' outcomes. It is not clear whether the frequency and duration of exercise can be increased through the instruction of caregivers or physicians to improve the outcomes of patients with CKD. This can be a potential limitation of this observational cohort study. A randomized controlled trial is needed to address this issue. Other limitations were the following: detailed information on patients' ability to walk, such as presence of claudication or walking with assistance, was not recorded; the form, frequency, and duration of exercise were recorded at enrollment; and the persistence of exercise during

follow-up was not recorded. Despite the limitations, this study clearly showed beneficial effects of walking on clinical outcomes of patients with CKD.

In conclusion, walking is the most common exercise in patients with CKD in Taiwan. Walking is associated with lower overall mortality and risk of RRT in patients with CKD not undergoing dialysis. The benefit of walking on patients' outcomes is independent of patient's age, comorbidity, and renal function. There is a dose-dependent association between clinical benefit and the frequency of walking.

#### Disclosures

None.

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