Journal of the Formosan Medical Association (2015) 114, 517–525

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

ORIGINAL ARTICLE

Low-normal serum potassium is associated with an increased risk of cardiovascular and all-cause death in community-based elderly

Ying-Ho Lai [a], Hsin-Bang Leu [b], Wen-Ting Yeh [c], Hsing-Yi Chang [d], Wen-Harn Pan [c,*]

[a] *Department of Biochemical Science and Technology, College of Life Science, National Taiwan University, Number 1, Section 4, Roosevelt Road, Taipei, Taiwan*
[b] *Healthcare and Management Center, Division of Cardiology, Department of Internal Medicine, Taipei Veterans General Hospital, Number 201, Section 2, Shih-Pai Road, Taipei, Taiwan*
[c] *Institute of Biomedical Sciences, Academia Sinica, Number 128, Section 2, Academia Road, Taipei, Taiwan*
[d] *Division of Preventive Medicine and Health Services Research, Institute of Population Health Sciences, National Health Research Institutes, Number 35, Keyan Road, Miaoli, Taiwan*

Received 12 August 2014; received in revised form 23 December 2014; accepted 6 January 2015

KEYWORDS
cardiovascular mortality;
elderly;
serum potassium

Background/Purpose: Several studies have already reported that serum potassium (SK) correlated inversely with adverse events among patients with preexisting cardiovascular disease and impaired renal function; less is known about the prognostic value of SK at the normal range in community-based elderly individuals. This study aimed to examine whether low normal SK value was associated with cardiovascular and all-cause mortalities in elderly people.
Methods: A prospective study was conducted using two independent elderly Taiwanese community cohorts that included 2065 individuals with relatively normal SK values (2.8–5.6 mmol/L). The participants were grouped as follows: low (2.8–3.4 mmol/L), low-normal SK (3.5–3.8 mmol/L), normal (3.9–4.4 mmol/L), and high-normal SK (4.5–5.6 mmol/L). Proportional hazards model was applied to compare the association between SK concentration groups and mortality.
Results: The relationship between baseline SK and all-cause and cardiovascular mortality was U-shaped, with the lowest mortality rates observed in patients with SK levels of 3.9–4.4 mmol/L. The low-normal SK group had significantly higher risks of all-cause (hazard ratio, 1.3; 95% confidence interval, 1.0–1.6) and cardiovascular mortality (hazard ratio, 1.6; 95% confidence interval, 1.1–2.3) than the normal SK group. The high-normal SK group had higher but nonsignificant risk compared to the normal group.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

* Corresponding author. Institute of Biomedical Sciences, Academia Sinica, Number 128, Section 2, Academia Road, Taipei, Taiwan.
E-mail address: pan@ibms.sinica.edu.tw (W.-H. Pan).

http://dx.doi.org/10.1016/j.jfma.2015.01.001

Conclusion: Our findings suggest that low-normal SK may be used as a marker of poor survival for elderly outpatient cares.

Introduction

Potassium homeostasis is critical to avoid adverse consequences in patients with cardiovascular disease (CVD). Normally, serum potassium (SK) level is tightly maintained between 3.5 mmol/L and 5.5 mmol/L,[1–3] and departure from normal may cause severe consequences including muscular weakness,[4] paresthesia, cardiac arrhythmias, and sudden death.[5] Although several studies have already reported that SK correlated inversely with adverse events among patients with preexisting CVD and impaired renal function,[6,7] less is known about the prognostic value of SK within the normal range and in general populations.

Walsh et al[8] have reported that there is no significant association between the SK level and adverse events among young participants. However, Wannamethee et al[9] showed that it is not the "low potassium," but the "raised potassium" that was associated with higher cardiovascular and all-cause mortality in middle-aged men, suggesting the questionable role of SK in determining future adverse events in the general population. By contrast, an earlier study has reported a negative association between potassium intake and risk of cerebrovascular events.[10,11] Our previous study showed that switching to potassium-enriched salt is beneficial for life span prolongation and CVD mortality and medical cost reduction in elderly men. The aforementioned suggests that the prognostic value of SK remains undetermined especially for the elderly.[12] However, there is a lack of adequately powered studies in the general elderly population, and this information is extremely important for geriatric care; to address this critical knowledge gap, we took advantage of two community-based elderly cohorts to examine whether the SK value within the normal range is associated with cardiovascular and all-cause mortalities in elderly people.

Participants, design, and methods

Study population

We performed the present study using two independent Taiwanese community-based elderly cohorts. One is the Elderly Nutrition and Health Survey in Taiwan (Elderly NAHSIT) performed during 1999—2000, which has complete information on 1400 participants.[13] The other is a cohort from a veteran retirement home (VRH) study, which has complete data on 665 veterans. The detailed description and design of the Elderly NAHSIT and the VRH study can be found elsewhere.[12,13] The VRH study was approved by reviewers of the National Science Council, and Elderly NAHSIT was approved by the Ethics Committees of the National Health Research Institutes and Academia Sinica in Taiwan.

Baseline measurements

Fasting venous blood samples were collected for a battery of biochemical analyses. Serum levels of potassium, sodium, glucose, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, triglycerides, uric acid, and creatinine were measured using a COBAS INTEGRA 800 (Roche, Mannheim, Germany) for the VRH study and for the Elderly NAHSIT. The body weight and height of the elderly were measured, following the same protocol. The body mass index (BMI) was calculated by dividing body weight (kg) by height square (m^2). The estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease Study equation.[14] Structured questionnaires covering sociodemographics and medical histories were administered by trained interviewers. Medical histories included hypertension medication, diabetes mellitus medication, and self-reported doctor-diagnosed heart disease, kidney disease, and stroke. Three blood pressure measurements were obtained by trained technicians, and the last two measurements were averaged and used for statistical analysis. The measurement was taken with a calibrated mercury sphygmomanometer and cuffs of the appropriate size, with the participant seated for 5—10 minutes.

In order to examine the prognostic value of low-normal and high-normal SK, individuals with SK values between 2.8 mmol/L and 5.6 mmol/L were included in this study. As there are no standardized cut-points, in this study the participants were categorized into low (2.8—3.4 mmol/L), low-normal (3.5—3.8 mmol/L), normal (3.9—4.4 mmol/L), and high-normal (4.4—5.6 mmol/L), considering this should provide a sufficient number of people in the low-normal and high-normal groups and also taking into consideration the cut-points of several previous studies, in which low SK has been defined by $\leq$3.70 mmol/L,[15] $\leq$3.90 mmol/L,[9,16,17] or $\leq$4.00 mmol/L[8,18] and high SK by $\geq$4.00 mmol/L,[16,17] $\geq$4.50 mmol/L,[15] $\geq$5.20,[8,9] or $\geq$5.50 mmol/L.[18]

Follow-up and outcome measurements

Baseline information was linked to the National Death Registry database for an 8-year follow-up. The government's confidentiality regulations were followed in the linkage process. The personal identification numbers were encrypted, and thus no privacy data from the study individuals could be identified. All-cause and cardiovascular-related deaths were coded with the International Classification of Diseases, ninth revision (ICD-9). Cardiovascular-related deaths include those caused by diabetes (ICD-9:250), hypertension (ICD-9: 401—405), ischemic heart disease (ICD-9: 410—414), heart failure (ICD-9: 428), and stroke (ICD-9: 430—438).[12]

Table 1 Baseline characteristics by serum potassium (SK) groups.

Characteristics		Low SK (2.8—3.4 mmol/L)	Low-normal SK (3.5—3.8 mmol/L)	Normal SK (3.9—4.4 mmol/L)	High-normal SK (4.5—5.6 mmol/L)	*p* for trend[a]
n (%)		51 (2.5)	252 (12.2)	1152 (55.8)	610 (29.5)	
Male		31 (60.8)	144 (57.1)	718 (62.3)	484 (79.3)	<0.001
Age, y		71.9 ± 5.8	73.0 ± 6.3	72.4 ± 5.7	73.6 ± 6.1	0.005
Body mass index, kg/m^2		25.0 ± 4.4	23.2 ± 3.7	23.8 ± 3.5	23.6 ± 0.5	0.640
Hypertension		30 (58.8)	95 (37.7)	413 (35.9)	255 (41.8)	0.914
Diabetes		7 (13.7)	21 (8.3)	138 (12.0)	87 (14.3)	0.051
Self-report heart disease		11 (21.6)	48 (19.1)	235 (20.4)	170 (27.9)	0.002
Self-report kidney disease		6 (11.8)	8 (3.2)	59 (5.1)	54 (8.9)	0.018
Self-report stroke		6 (11.8)	18 (7.1)	76 (6.6)	65 (10.7)	0.100
Serum LDL-C, mg/mL		115.0 ± 27.4	116.4 ± 41.3	123.4 ± 35.6	117.9 ± 35.4	0.972
Serum HDL-C, mg/mL		53.0 ± 16.5	52.4 ± 15.8	51.9 ± 15.2	50.6 ± 15.9	0.050
Serum cholesterol, mg/mL		195.2 ± 29.8	194.4 ± 39.9	200.4 ± 39.3	194.7 ± 40.9	0.543
Serum triglyceride, mg/mL		133.0 ± 100.4	132.9 ± 104.5	128.2 ± 110.2	122.5 ± 81.9	0.134
Serum glucose, mg/mL		116.3 ± 36.9	114.0 ± 43.8	111.6 ± 40.2	110.6 ± 44.4	0.196
Serum uric acid, mg/mL		7.25 ± 2.10	6.53 ± 2.01	6.44 ± 1.77	6.57 ± 1.75	0.464
Serum creatinine, mg/mL		1.06 ± 0.29	0.97 ± 0.29	1.01 ± 0.28	1.21 ± 0.54	<0.001
Serum sodium, mmol/L		141.4 ± 3.3	141.1 ± 3.9	141.3 ± 2.8	142.1 ± 3.9	<0.001
Systolic blood pressure, mmHg		143.0 ± 22.5	139.1 ± 21.9	136.9 ± 20.5	140.4 ± 21.6	0.397
Diastolic blood pressure, mmHg		78.7 ± 11.2	76.4 ± 12.0	76.1 ± 11.2	75.0 ± 12.1	0.011
eGFR (mL/min/1.73 m^2)		69.8 ± 17.4	76.3 ± 18.3	73.8 ± 17.9	65.3 ± 18.3	<0.001
eGFR (mL/min/1.73 m^2)	+90	5 (9.8)	38 (15.1)	125 (10.8)	32 (5.3)	<0.001[b]
	60—89	32 (62.7)	174 (69.0)	799 (69.4)	354 (58.0)	
	30—59	13 (25.5)	38 (15.1)	219 (19.0)	205 (33.6)	
	<30	1 (2.0)	2 (0.8)	9 (0.8)	19 (3.1)	

Data are presented as *n* (%) or mean ± SD.

eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

[a] *p* value was tested with the general linear model for continuous variables and logistic regression model for categorical variables for all the variables in the table except the last item.

[b] *p* value was tested with Chi-square test.

Table 2 Baseline characteristics by serum potassium status for the Elderly NAHSIT and the veteran retirement home (VRH) study.

Characteristics		Elderly NAHSIT				*p* for trend[a]	VRH study				*p* for trend[a]
		Low	Low-normal	Normal	High-normal		Low	Low-normal	Normal	High-normal	
		serum potassium concentration (mmol/L)					serum potassium concentration (mmol/L)				
		2.8–3.4	3.5–3.8	3.9–4.4	4.5–5.6		2.8–3.4	3.5–3.8	3.9–4.4	4.5–5.6	
n (%)		42 (3.0)	201 (14.4)	882 (63.0)	275 (19.6)		9 (1.4)	51 (7.7)	270 (40.6)	335 (50.4)	
Male		22 (52.4)	93 (46.3)	448 (50.8)	149 (54.2)	0.179	9 (100.0)	51 (100.0)	270 (100.0)	335 (100.0)	—
Age, y		70.7 ± 5.3	71.8 ± 5.3	71.7 ± 5.3	72.5 ± 5.4	0.038	77.4 ± 5.0	77.7 ± 7.7	74.6 ± 6.4	74.5 ± 6.5	0.011
Body mass index, kg/m^2		25.4 ± 4.5	23.3 ± 3.8	23.8 ± 3.6	23.3 ± 3.6	0.052	23.1 ± 3.8	22.4 ± 3.1	23.7 ± 3.3	23.8 ± 3.4	0.032
Hypertension,		23 (54.8)	74 (36.8)	284 (32.2)	110 (40.0)	0.591	7 (77.8)	21 (41.2)	129 (47.8)	145 (43.3)	0.223
Diabetes		7 (16.7)	17 (8.5)	93 (10.5)	48 (17.5)	0.027	0 (0.0)	4 (7.8)	45 (16.7)	39 (11.6)	0.974
Self-report heart disease		6 (14.3)	33 (16.4)	154 (17.5)	63 (22.9)	0.044	5 (55.6)	15 (29.4)	81 (30.0)	107 (31.9)	0.884
Self-report kidney disease,		5 (11.9)	5 (2.5)	20 (2.3)	14 (5.1)	0.877	1 (11.1)	3 (5.9)	39 (14.4)	40 (11.9)	0.759
Self-report stroke		5 (11.9)	11 (5.5)	33 (3.7)	12 (4.4)	0.099	1 (11.1)	7 (13.7)	43 (15.9)	53 (15.8)	0.710
Serum LDL-C, mg/mL		115.3 ± 26.8	119.1 ± 36.5	125.9 ± 33.6	123.6 ± 36.7	0.066	113.9 ± 31.9	105.7 ± 55.3	115.2 ± 40.3	113.2 ± 33.7	0.653
Serum HDL-C, mg/mL		55.8 ± 16.0	52.7 ± 14.4	53.3 ± 15.2	52.9 ± 14.8	0.588	39.7 ± 12.4	51.3 ± 20.6	47.4 ± 1 4.3	48.7 ± 16.5	0.613
Serum cholesterol, mg/mL		199.7 ± 26.7	200.7 ± 37.9	204.6 ± 38.8	203.8 ± 43.6	0.332	174.4 ± 35.9	169.7 ± 38.5	186.5 ± 37.8	187.3 ± 37.0	0.016
Serum triglyceride, mg/mL		142.9 ± 107.7	144.0 ± 111.6	127.1 ± 88.3	136.4 ± 93.3	0.367	86.8 ± 24.6	89.1 ± 50.4	132.0 ± 162.6	111.2 ± 69.4	0.943
Serum glucose, mg/mL		115.8 ± 35.4	116.4 ± 46.5	113.2 ± 38.7	120.0 ± 51.5	0.346	118.6 ± 45.4	104.4 ± 28.8	106.3 ± 44.3	102.8 ± 35.9	0.233
Serum uric acid, mg/mL		7.42 ± 2.13	6.63 ± 1.97	6.55 ± 1.77	6.85 ± 1.85	0.917	6.44 ± 1.83	6.14 ± 2.12	6.10 ± 1.74	6.34 ± 1.63	0.209
Serum creatinine, mg/mL		1.05 ± 0.31	0.93 ± 0.29	0.96 ± 0.26	1.15 ± 0.50	<0.001	1.13 ± 0.20	1.14 ± 0.26	1.18 ± 0.28	1.27 ± 0.57	0.006
Serum sodium, mmol/L		141.2 ± 2.8	141.2 ± 2.1	140.8 ± 2.0	140.3 ± 2.6	<0.001	142.1 ± 5.2	141.0 ± 7.7	142.9 ± 4.0	143.6 ± 4.1	<0.001
Systolic blood pressure, mmHg		141.6 ± 22.7	138.1 ± 21.6	135.7 ± 20.4	138.0 ± 21.6	0.525	149.7 ± 21.4	143.4 ± 22.9	140.6 ± 20.5	142.4 ± 21.5	0.936
Diastolic blood pressure, mmHg		78.9 ± 11.5	76.7 ± 11.8	76.4 ± 10.9	74.6 ± 11.2	0.007	77.6 ± 10.6	75.2 ± 12.8	75.2 ± 12.1	75.3 ± 12.8	0.884
eGFR(mL/min/1.73 m^2)		70.0 ± 18.0	77.7 ± 18.0	75.4 ± 17.7	66.3 ± 20.8	<0.001	69.1 ± 15.0	70.6 ± 18.6	68.4 ± 17.2	64.5 ± 15.9	0.001
eGFR (mL/min/1.73 m^2)	+90	4 (9.5)	35 (17.4)	108 (12.2)	21 (7.6)	<0.001[b]	1 (11.1)	3 (5.9)	17 (6.3)	11 (3.3)	0.532[b]
	60–89	26 (61.9)	140 (69.7)	632 (71.7)	151 (54.9)		6 (66.7)	34 (66.7)	167 (61.9)	203 (60.6)	
	30–59	11 (26.2)	24 (11.9)	135 (15.3)	91 (33.1)		2 (22.2)	14 (27.5)	84 (31.1)	114 (34.0)	
	<30	1 (2.4)	2 (1.0)	7 (0.8)	12 (4.4)		0 (0.0)	0 (0.0)	2 (0.7)	7 (2.1)	

Data are presented as *n* (%) or mean ± SD.

eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

[a] *p* value was tested with the general linear model for continuous variables and logistic regression model for categorical variables for all the variables in the table except the last item.

[b] *p* value was tested with Chi-square test.

Statistical analyses

The baseline characteristics of the study participants were profiled and compared between SK groups. A general linear model was carried out to test the trends for continuous variables, and a logistic regression model was conducted to test that for the proportions of the categorical variables among potassium groups. Follow-up time was calculated from the blood sampling date to the date of death or the end of the follow-up period. Survival probability was estimated and survival curves for the low and low-normal SK groups were plotted and compared to the mid-normal by using the Kaplan—Meier estimate, and the log-rank test was used to test the equality among survival curves. The Cox proportional-hazard model (PH model) was used to calculate age and multivariable-adjusted hazard ratios (HRs) across SK groups for all-cause and cardiovascular mortalities. All models were adjusted for age, body mass index; serum LDL-C, HDL-C, cholesterol, triglyceride, glucose, uric acid, creatinine, and sodium; systolic blood pressure, diastolic blood pressure, hypertension, and diabetes medication; and presence of self-reported heart disease, kidney disease, and stroke. Sex was additionally adjusted in the Elderly NAHSIT. And in combined analysis, study effect was controlled. SAS version 9.3 (SAS Inc., Cary, NC, USA) was used for data analyses.

Results

Study sample and baseline characteristics

The baseline characteristics of the 2065 study participants by strata of low, low-normal, normal, and high-normal SK levels are shown in Table 1, and similar study-specific participants' characteristics are given in Table 2. In general (Table 1), the higher the SK concentration, the higher the mean age, serum creatinine, and sodium, and the percentages of male, diabetes patients, and self-reported history of heart and kidney disease; but lower mean diastolic blood pressure and HDL-C according to the trend test. That is, people in the low-normal SK group were younger, with better kidney function and better lipid profiles, and had a lower percentage of chronic disease history. The baseline comparative results on eGFR, serum sodium, and creatinine were consistent between the two cohorts. However, the trends with SK were not the same for two cohorts for age, body mass index, diabetes, and some other disease histories.

SK level and mortality

As shown in Fig. 1, the relationship between baseline SK and all-cause or cardiovascular mortality was U-shaped, with the lowest mortality rates observed in patients with potassium levels of 3.9—4.4 mmol/L. Significant differences were observed between normal SK groups and the two low SK groups, although significance was not seen with the low SK group for CVD. The survival curves for all-cause and cardiovascular mortalities were plotted for the low, low-normal, and normal K groups using the Kaplan—Meier estimates (Fig. 2). There were significant differences among the three curves for all-cause mortality ($p < 0.001$; Fig. 2A) and for cardiovascular mortality ($p = 0.017$; Fig. 2B). The HRs for all-cause and cardiovascular mortalities comparing the low, the low-normal, and high-normal SK groups with the normal group were estimated using the Cox PH model and are presented in Table 3. Age and multiple risk factors of cardiovascular mortality were adjusted in these models. In the

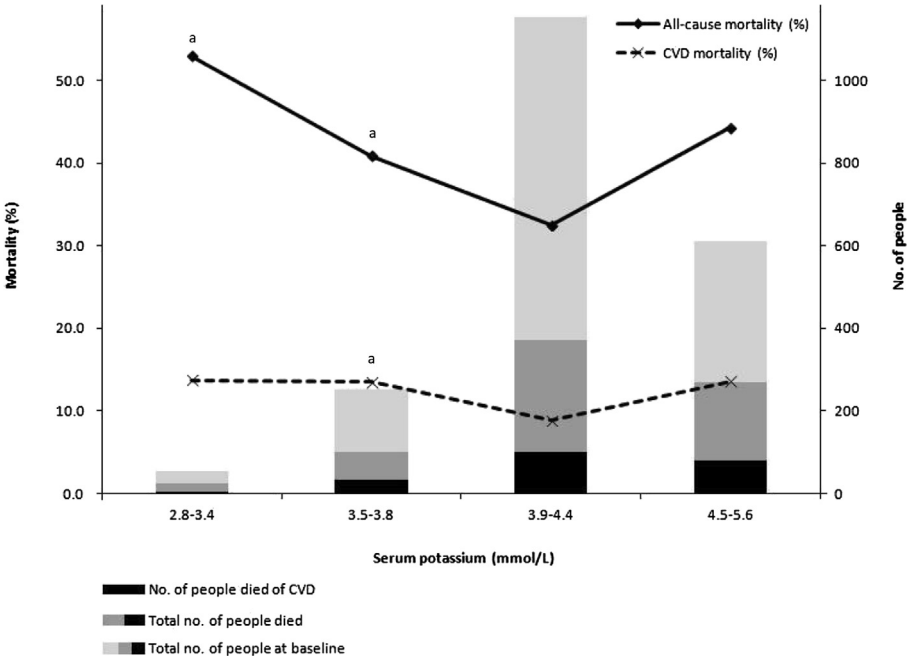

Figure 1 Distribution of baseline serum potassium levels and mortality rates by serum potassium groups. [a] Hazard ratios comparing mortality of low (2.8—3.4 mmol/L), low-normal (3.5—3.8 mmol/L), and high-normal (4.5—5.6 mmol/L) SK groups to the normal (3.9—4.4 mmol/L) SK group, estimated with Cox PH model. SK = serum potassium.

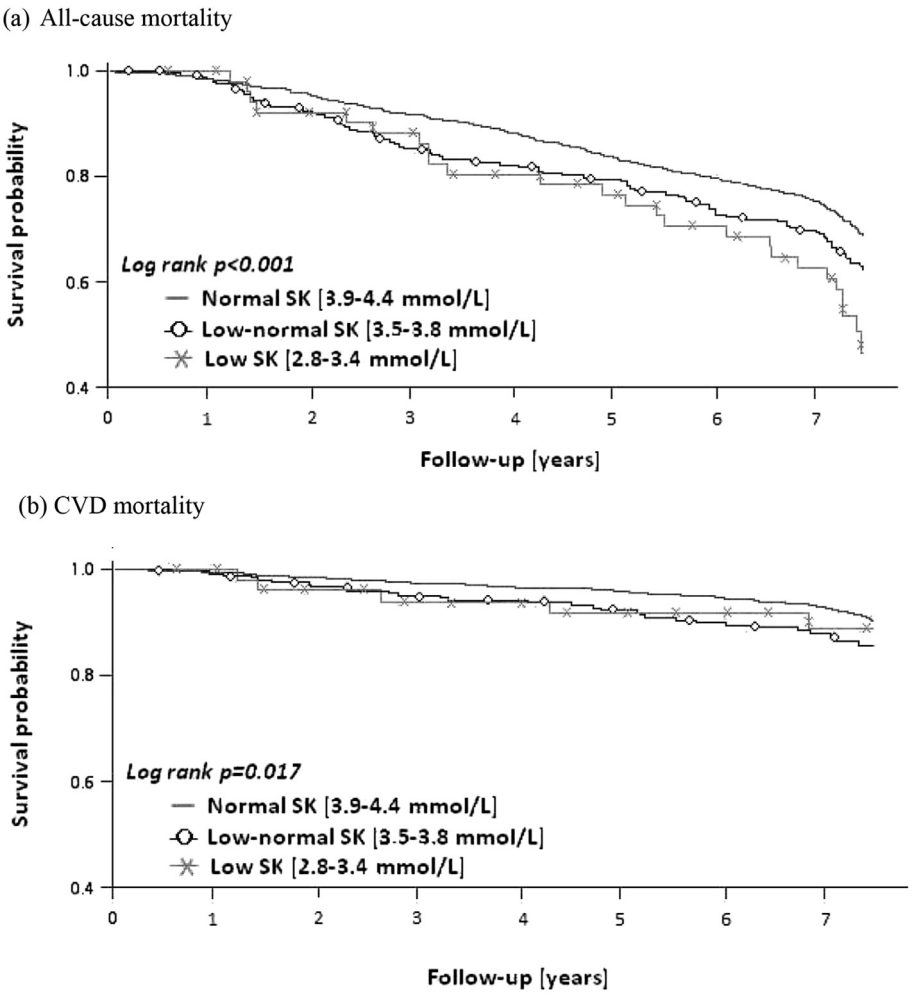

Figure 2 Survival curves for low, low-normal, and normal serum potassium groups. (a) All-cause mortality. (b) CVD mortality. [a] Survival probability was estimated, and survival curve is plotted for each serum potassium level using the Kaplan—Meier estimate. CVD = cardiovascular disease.

combined analysis, the low (1.8, 1.3—2.7) and the low-normal (1.3, 1.0—1.6) SK groups had greater risks for all-cause mortality, and so had those for CVD. However, for CVD, statistical significance was seen only in the low-normal SK group. In the Elderly NAHSIT and in the VRH study, the association between SK level and mortality is similar to that in the combined analysis, except that statistical significance was not reached in the VRH study for all-cause and cardiovascular mortalities (Table 4).

Discussion

Abnormal SK values were known to dominantly affect the cardiovascular system and have been implicated in many aspects of CVD including cardiac arrhythmia, hypertension, stroke, myocardial ischemia, and sudden cardiac death.[19] The U-shaped association between serum concentrations of potassium and cardiovascular death as well as all-cause death has been clearly demonstrated among patients with acute myocardial infarction and renal failure.[20,21] The highest mortality rate observed among those with lower potassium concentration indicated the importance of avoiding hypokalemia for patients with cardiovascular risk. Our current study for the first time demonstrated that low-normal SK level is still associated with higher risks of cardiovascular death and all-cause death among community-dwelling elderly people, which further highlights the importance of keeping the SK level higher than the lower bound of the normal range even in community-dwelling elderly.

Low SK has been associated with an increased risk of adverse events in patients with preexisting CVD and renal failure.[21—24] It may cause cellular hyperpolarity, increase resting membrane potential, and increase automaticity and excitability, leading to occurrence of cardiac arrhythmia and sudden cardiac death.[25—27] Hulting[22] showed an inverse relationship between SK and ventricular fibrillation incidence. An almost five-fold increase in ventricular fibrillation incidence was observed in acute myocardial infarction patients with an SK value <3.9 mmol/L,[22] indicating that hypokalemia may cause fatal arrhythmia and should be corrected as soon as possible in clinical practice. Furthermore, it has been reported that potassium depletion in dogs was associated with impairment of left ventricular (LV) mechanical function.[28,29] Srivastava and Young[28] later

Table 3 Multivariate-adjusted HR for all-cause and CVD mortalities by serum potassium status for Elderly NAHSIT, VRH study, and combined analysis.

Serum potassium	Elderly NAHSIT[a]		VRH study[a]		Combined analysis[b]	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
All-cause mortality						
Low SK[c]	2.4 (1.5—3.7)	<0.001	1.0 (0.4—2.5)	0.975	1.8 (1.3—2.7)	0.003
Low-normal SK[c]	1.2 (0.9—1.6)	0.150	1.4 (1.0—2.2)	0.076	1.3 (1.0, 1.6)	0.034
Normal SK[c]	1		1		1	
High-normal SK[c]	1.1 (0.9—1.4)	0.549	1.1 (0.9—1.4)	0.340	1.1 (1.0—1.4)	0.126
CVD mortality[d]						
Low SK[c]	2.3 (1.0—5.4)	0.051	0.7 (0.1—5.0)	0.682	1.6 (0.7—3.4)	0.261
Low-normal SK[c]	1.6 (1.0—2.6)	0.033	1.5 (0.7—3.4)	0.325	1.6 (1.1—2.3)	0.025
Normal SK[c]	1		1		1	
High-normal SK[c]	1.2 (0.8—1.9)	0.339	1.3 (0.8—2.1)	0.301	1.3 (1.0—1.8)	0.082

CI = confidence interval; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HF = heart failure; HR = hazard risk; ICD-9 = International Classification of Diseases, 9th revision; IHD = ischemic heart disease; LDL-C = low-density lipoprotein cholesterol; NAHSIT = Elderly Nutrition and Health Survey in Taiwan; SK = serum potassium; VRH = veteran retirement home.

[a] In VRH study, adjusted factors were age, body mass index, serum LDL-C, HDL-C, cholesterol, triglyceride, glucose, uric acid, creatinine and sodium; systolic blood pressure, diastolic blood pressure, the prevalence of hypertension, diabetes, cardiac disease, kidney dysfunction, and stroke. In Elderly NAHSIT, sex was additionally adjusted.

[b] Combined analysis included data from the VRH study and the Elderly NAHSIT. In this analysis, the study effect was adjusted.

[c] Low SK (2.8—3.4 mmol/L), low-normal SK (3.5—3.8 mmol/L), normal SK (3.9—4.4 mmol/L), and high-normal SK (4.5—5.6 mmol/L).

[d] CVD death certificates with ICD-9 codes of 250 (diabetes), 401—405 (hypertension), 410—414 (IHD), 428 (HF), or 430—438 (stroke).

proved the correlation between LV function and potassium concentration in humans, showing that moderate potassium depletion impaired the active relaxation of LV. In addition to the impaired LV function and cardiac arrhythmia caused by hypokalemia, experimental studies in animals showed that keeping a high normal potassium level may have a direct beneficial effect on the cardiovascular system, which may be independent of, but additive to, its effect on blood pressure.[30] Furthermore, experimental animal studies demonstrated that potassium has inhibitory effects on free radical formation, vascular smooth muscle proliferation, and arterial thrombosis.[31] Additionally, potassium supplement may reduce macrophage adherence to the vascular wall and thereby contribute to the reduction of vascular lesions,[32] indicating that potassium may have a beneficial effect in reducing cardiovascular events. Therefore, one may conclude that accumulating lines of evidence have indicated that an adequate potassium status can reduce blood pressure, risk of stroke, ventricular arrhythmia, and QT prolongation.[25]

Although the association between hypokalemia and increased cardiovascular death has been observed in patients with preexisting CVD and renal failure,[21—24] less is known about the prognostic value of SK at the ranges commonly encountered, especially for the elderly in the community. Our study demonstrated that low-normal SK concentration was associated with higher cardiovascular and all-cause mortality rates than the mid-normal potassium level among community-dwelling elderly people. Contrary to what has been reported previously,[21] a good proportion of our study participants have normal serum creatinine or eGFR values, indicating that maintaining an SK level higher than the lower bound of the usual normal range is also important for outpatient care. Walsh et al[8] have reported in one community-based cohort that the SK level was not associated with future risk of cardiovascular death in individuals free of CVD and not taking medications affecting potassium homeostasis. In their study, the participants were much younger (40—59 years old) than ours (mean age, 72.8 ± 5.9 years). Because a low SK level was reported to be associated with some important risk factors for CVD mortality, such as old age, more comorbidities, malnutrition, and lower BMI,[10] differences in baseline characteristics may explain the different results between these two observations. Observational studies of inverse association between potassium-rich diet and the occurrence of CVD have been reported decades ago by Khaw and Barrett-Connor,[11] who recorded a 10-mmol increase in daily potassium intake associated with a 40% reduction in the risk of stroke-associated mortality ($p < 0.001$). A recent study associating 24-hour urinary potassium excreted with cardiovascular events, using data from 101,945 persons in 17 countries, showed that higher K excretion was associated with a lower risk of death and cardiovascular events.[33] In addition, our group had previously shown that elderly men provided with potassium-enriched salt diet could live 0.3—0.9 year longer, had lower CVD mortality, and spent less on medical expenses for inpatient care than controls.[12] Taken together, managing a low-normal potassium level is critical for reducing all-cause and cardiovascular mortality in daily care practice for the elderly. Nonetheless, it is best to provide potassium through a balanced diet approach, which may ensure a reasonable dietary potassium range. In addition, the patient's SK should be carefully monitored.

Our study has several limitations. We measured SK concentration at a single point in time. Because of this, we could not account for changes in SK levels over time. However, we believe that with multiple SK measurements to increase precision, the observation may become more apparent. In addition, the sample sizes of both studies are

Table 4 Prospective studies on serum potassium level and mortality.

Authors, year	Study name	Age (y)	Studied population	*n*	Years of follow-up (y)	Serum potassium level (mmol/L)	All-cause mortality	CVD mortality
							HR (95% CI)	HR (95% CI)
Walsh et al, 2002[8]	The Framingham Heart Study	43 ± 10	General	3151	16	3.5–4.0	1.1 (0.6–2.1)	0.8 (0.4–1.5)
						4.1–5.1 (Ref)	1	1
						5.2–6.2	0.9 (0.6–1.2)	1.0 (0.7–1.3)
Fang et al, 2000[15]	NHANES I Epidemiological Follow-up Study	46.6 ± 13.9	General	2836	18	2.7–3.7	—	1.0 (0.6–1.5)
						3.8–4.4 (Ref)	—	1
						4.5–5.4	—	1.5 (1.0–2.3)
Lai et al, 2015 (this study)	Elderly NAHSIT & VRH	72.8 ± 5.9	General	2065	8	2.8–3.4	1.8 (1.2–2.7)	1.6 (0.7–3.4)
						3.5–3.8	1.3 (1.0–1.6)	1.6 (1.1–2.3)
						3.9–4.4 (Ref)	1	1
						4.5–5.6	1.1 (1.0–1.4)	1.3 (1.0–1.8)
Wannamethee et al, 1997[9]	The British Regional Heart Study	40–59	CVD (treated for hypertension)	7735	11.5	2.8–3.9 (Ref)	1	1
						4.0–4.2	1.2 (0.9–1.60)	1.5 (1.0–2.2)
						4.3–4.5	1.2 (1.0–1.6)	1.4 (1.0–1.9)
						4.6–4.8	1.4 (1.0–1.8)	1.3 (0.9–2.0)
						4.9–5.1	1.2 (0.8–1.4)	1.4 (0.8–2.4)
						5.2–6.0	1.7 (1.2–2.8)	1.5 (0.8–2.8)
Korgaonkar et al, 2010[18]	The Renal Research Institute CKD study	60.5 ± 15.4	CKD	820	0–7 (mean: 2.6)	2.5–4.0	1.9 (1.0–3.6)	—
						4.1–5.4 (Ref)	1	—
						5.5–7.0	1.8 (0.8–4.2)	—
Ahmed et al, 2007[16]	DIG trial (propensity matched)	63 ± 11	HF	2374	3.1	3.5–3.9	1.3 (1.1–1.5)	1.3 (1.1, 1.5)
						4.0–5.5 (Ref)	1	1
Bowling et al, 2010[17]	DIG trial (propensity matched)	68 ± 10	HF with CKD	1044	4.8 y	3.5–3.9	1.6 (1.3–2.0)	1.7 (1.3–2.1)
						4.0–4.9 (Ref)	1	1

not large; therefore, we had limited statistical power to study the possible moderate association between mild hypokalemia and other causes of death. Further studies with larger sample sizes are warranted to clarify the association between SK concentration and mortality in the elderly.

Conclusion

Community-dwelling elders with low-normal SK (3.5—3.8 mmol/L) had increased all-cause and cardiovascular mortality rates compared to those with mid-normal values (3.9—4.4 mmol/L) in this 8-year follow-up study. The low-normal SK status may serve as a prognostic factor of poor survival in elderly outpatient care.

Acknowledgments

The veteran retirement home (VRH) study was supported by Academic Sinica. The "Elderly Nutrition and Health Survey in Taiwan (1999—2000)" was supported by the Department of Health in Taiwan (DOH 90-TD-1090).

References

1. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Laboratory reference values. *N Engl J Med* 2004;**351**:1548—63.
2. Hyman D, Kaplan NM. The difference between serum and plasma potassium. *N Engl J Med* 1985;**313**:642.
3. Young DB. Analysis of long-term potassium regulation. *Endocr Rev* 1985;**6**:24—44.
4. Kuo SF, Huang BY, Yang NI, Lin JD. Thyrotoxic periodic paralysis in an 81-year-old diabetes patient with insulin treatment. *J Formos Med Assoc* 2012;**111**:350—1.
5. Gabow P, Peterson L. Disorders of potassium metabolism. In: Schrier RW, editor. *Renal and electrolyte disorders*. Boston, MA: Little, Brown and Co; 1980. p. 183—223.
6. Szeto CC, Chow KM, Kwan BC, Leung CB, Chung KY, Law MC, et al. Hypokalemia in Chinese peritoneal dialysis patients: prevalence and prognostic implication. *Am J Kidney Dis* 2005;**46**:128—35.
7. Torlen K, Kalantar-Zadeh K, Molnar MZ, Vashistha T, Mehrotra R. Serum potassium and cause-specific mortality in a large peritoneal dialysis cohort. *Clin J Am Soc Nephrol* 2012;**7**:1272—84.
8. Walsh CR, Larson MG, Leip EP, Vasan RS, Levy D. Serum potassium and risk of cardiovascular disease: the Framingham heart study. *Arch Intern Med* 2002;**162**:1007—12.
9. Wannamethee SG, Lever AF, Shaper AG, Whincup PH. Serum potassium, cigarette smoking, and mortality in middle-aged men. *Am J Epidemiol* 1997;**145**:598—606.
10. He FJ, MacGregor GA. Beneficial effects of potassium on human health. *Physiol Plant* 2008;**133**:725—35.
11. Khaw KT, Barrett-Connor E. Dietary potassium and stroke-associated mortality. A 12-year prospective population study. *N Engl J Med* 1987;**316**:235—40.
12. Chang HY, Hu YW, Yue CS, Wen YW, Yeh WT, Hsu LS, et al. Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. *Am J Clin Nutr* 2006;**83**:1289—96.
13. Pan WH, Hung YT, Shaw NS, Lin W, Lee SD, Chiu CF, et al. Elderly Nutrition and Health Survey in Taiwan (1999—2000): research design, methodology and content. *Asia Pac J Clin Nutr* 2005;**14**:203—10.
14. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med* 2006;**354**:2473—83.
15. Fang J, Madhavan S, Cohen H, Alderman MH. Serum potassium and cardiovascular mortality. *J Gen Intern Med* 2000;**15**:885—90.
16. Ahmed A, Zannad F, Love TE, Tallaj J, Gheorghiade M, Ekundayo OJ, et al. A propensity-matched study of the association of low serum potassium levels and mortality in chronic heart failure. *Eur Heart J* 2007;**28**:1334—43.
17. Bowling CB, Pitt B, Ahmed MI, Aban IB, Sanders PW, Mujib M, et al. Hypokalemia and outcomes in patients with chronic heart failure and chronic kidney disease: findings from propensity-matched studies. *Circ Heart Fail* 2010;**3**:253—60.
18. Korgaonkar S, Tilea A, Gillespie BW, Kiser M, Eisele G, Finkelstein F, et al. Serum potassium and outcomes in CKD: insights from the RRI-CKD cohort study. *Clin J Am Soc Nephrol* 2010;**5**:762—9.
19. Sica DA, Struthers AD, Cushman WC, Wood M, Banas Jr JS, Epstein M. Importance of potassium in cardiovascular disease. *J Clin Hypertens* 2002;**4**:198—206.
20. Xu Q, Xu F, Fan L, Xiong L, Li H, Cao S, et al. Serum potassium levels and its variability in incident peritoneal dialysis patients: associations with mortality. *PLoS One* 2014;**9**:e86750.
21. Goyal A, Spertus JA, Gosch K, Venkitachalam L, Jones PG, Van den Berghe G, et al. Serum potassium levels and mortality in acute myocardial infarction. *JAMA* 2012;**307**:157—64.
22. Hulting J. In-hospital ventricular fibrillation and its relation to serum potassium. *Acta Med Scand Suppl* 1981;**647**:109—16.
23. Madias JE, Shah B, Chintalapally G, Chalavarya G, Madias NE. Admission serum potassium in patients with acute myocardial infarction: its correlates and value as a determinant of in-hospital outcome. *Chest* 2000;**118**:904—13.
24. Nordrehaug JE, Johannessen KA, von der Lippe G. Serum potassium concentration as a risk factor of ventricular arrhythmias early in acute myocardial infarction. *Circulation* 1985;**71**:645—9.
25. Macdonald JE, Struthers AD. What is the optimal serum potassium level in cardiovascular patients? *J Am Coll Cardiol* 2004;**43**:155—61.
26. Fisch C, Knoebel SB, Feigenbaum H, Greenspan K. Potassium and the monophasic action potential, electrocardiogram, conduction and arrhythmias. *Prog Cardiovasc Dis* 1966;**8**:387—418.
27. Gettes L, Surawicz B. Effects of low and high concentrations of potassium on the simultaneously recorded Purkinje and ventricular action potentials of the perfused pig moderator band. *Circ Res* 1968;**23**:717—29.
28. Srivastava TN, Young DB. Impairment of cardiac function by moderate potassium depletion. *J Card Fail* 1995;**1**:195—200.
29. Fitzovich DE, Hamaguchi M, Tull WB, Young DB. Chronic hypokalemia and the left ventricular responses to epinephrine and preload. *J Am Coll Cardiol* 1991;**18**:1105—11.
30. Volpe M, Camargo MJ, Mueller FB, Campbell Jr WG, Sealey JE, Pecker MS, et al. Relation of plasma renin to end organ damage and to protection of K^+ feeding in stroke-prone hypertensive rats. *Hypertension* 1990;**15**:318—26.
31. Young DB, Lin H, McCabe RD. Potassium's cardiovascular protective mechanisms. *Am J Physiol* 1995;**268**:R825—37.
32. Young DB, Ma G. Vascular protective effects of potassium. *Semin Nephrol* 1999;**19**:477—86.
33. O'Donnell M, Mente A, Rangarajan S, McQueen MJ, Wang X, Liu L, et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med* 2014;**371**:612—23.