SHOCK, Vol. 52, No. 6, pp. e146–e152, 2019

VITAMIN D DEFICIENCY AND NEUROLOGIC OUTCOME AFTER SUDDEN CARDIAC ARREST

Jung-Joon Cha,[*] and Jin Wi[*†]

[*]Division of Cardiology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; and [†]Division of Cardiology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Korea

Received 28 Dec 2018; first review completed 21 Jan 2019; accepted in final form 20 Feb 2019

ABSTRACT—**Background:** Vitamin D deficiency is related to various cardiovascular diseases, including sudden cardiac arrest (SCA). This study investigated the association of vitamin D level with neurologic outcome and mortality after resuscitation from SCA. **Patients and Methods:** We enrolled patients who were successfully resuscitated from out-of-hospital cardiac arrest of presumed cardiac cause in Severance Cardiovascular Hospital as a prospective cohort registry. Baseline blood samples including pH, lactate, and vitamin D were obtained without fluid replacement just after hospital admission. Outcome was assessed by cerebral performance category (CPC) score at 1 month after SCA. Favorable outcome was defined as survival with CPC score of 1 or 2, whereas unfavorable one as death or survival with CPC scores of 3 through 5. Severe vitamin D deficiency was defined as 25(OH)D $<$10 ng/mL. **Results:** A total of 163 patients were included. Overall 96 (59%) patients had a favorable neurologic outcome, whereas 67 patients (41%) showed unfavorable outcome, including 37 (23%) mortality. Patients with unfavorable outcome were likely to be female and have initial non-shockable rhythm, longer arrest time, severe shock, diabetes, and baseline renal dysfunction. In multivariate analysis, severe vitamin D deficiency was one of the poor prognostic factors of both unfavorable neurologic outcome and mortality after SCA. **Conclusions:** Vitamin D deficiency is very prevalent and strongly associated with both unfavorable neurologic outcome and mortality in patients resuscitated from SCA.

KEYWORDS—Cerebral performance category, resuscitation, sudden cardiac arrest, vitamin D deficiency

INTRODUCTION

Each year, more than 300,000 people in the United States and a similar number in Europe experience out-of-hospital cardiac arrest (OHCA), with a survival rate of less than 10% (1, 2). Over 30,000 people in Korea also experience OHCA annually, with a survival rate of approximately 5% (3). Even in patients who initially achieve a successful return of spontaneous circulation (ROSC) after OHCA, the significant subsequent neurologic or cognitive deficits and death are common (4, 5). Hypoxic brain damage is a major cause of morbidity and mortality after sudden cardiac arrest (SCA) (6). Recovery of neurologic function is as important as survival. A patient with the significant neurologic deficits has the likelihood of poor quality of life, leading to his and his family's heavy financial and emotional burden.

Vitamin D plays a pivotal role in calcium homeostasis and bone metabolism in the body. Twenty-five hydroxyvitamin D [25(OH)D] is the predominant circulating form of vitamin D in the blood and is considered the standard measure of an individual's vitamin D status (7). Because vitamin D has beneficial pleiotropic effects through the diverse mechanisms, vitamin D deficiency has been linked to many chronic diseases (7). Vitamin D deficiency is related to various cardiovascular diseases, including hypertension, ischemic heart disease, cardiomyopathy, heart failure, and even SCA (8, 9). Recently, vitamin D deficiency has also been associated with several neuropsychiatric disorders, including Parkinson disease, Alzheimer disease, multiple sclerosis, and epilepsy (10, 11). However, the association between vitamin D level and neurologic outcome after resuscitation from SCA has never been evaluated. This study investigated the influence of vitamin D on the neurologic outcome and mortality in patients resuscitated from OHCA.

PATIENTS AND METHODS

Study population

We enrolled all consecutive patients 20 years of age or older who were successfully resuscitated from OHCA of presumed cardiac etiology between September 2012 and December 2015 at cardiac intensive care unit in Severance Cardiovascular Hospital, Seoul, Korea (38° latitude). Patients who had prior significant neurologic problems (known as pre-arrest Cerebral Performance Category 3 or 4) or confirmed acute intracranial hemorrhage or acute stroke were excluded from the analysis. Patients who had Do Not Resuscitate-order or known diseases making 1-month survival unlikely were also excluded.

Study protocol

Neurologic evaluation was assessed by the cerebral performance category (CPC) score, a 5-point scale that attempts to incorporate functional and cognitive domains to provide an assessment of brain recovery, at 1 month after the event of OHCA (12). Clinical neurologic examination, median nerve somatosensory evoked potentials, and electroencephalography were used adjunctively in patients not regaining consciousness for 72 h after discontinuation of sedation. The neurologic assessment was performed three times a day during hospitalization and after the hospital, from an outpatient clinic visit or telephone contact with patients, families, or an attending doctor if the patient was in the other hospital.

For measurement of exact initial vitamin D level, baseline blood samples were obtained just after hospital admission without any fluid replacement, and the plasma was frozen at −70°C for subsequent analysis. The vitamin D level was measured as plasma 25(OH)D concentrations in a central laboratory, on the same day, using by the radioimmunoassay method of COBRA-II AUTO-GAMMA (Packard Instrument, Md, Ramsey, Minn). Based on the initial vitamin D level, the two groups of interest were determined in terms of vitamin D deficient or those who did not meet this criterion. Therapeutic hypothermia

Address reprint requests to Jin Wi, MD, PhD, 21 Namdong-daero 774 beon-gil, Namdong-gu, Incheon 21565, Republic of Korea. E-mail:caesar@gilhospital.com; caesarspqr@naver.com

The authors report no conflicts of interest.

DOI: 10.1097/SHK.0000000000001335

TABLE 1. **Cerebral performance category (CPC) score and neurologic outcome**

CPC score		Neurologic outcome
CPC 1	Conscious and good cerebral performance or minor deficit	Favorable
CPC 2	Conscious and moderate disability	Favorable
CPC 3	Conscious and severe disability	Unfavorable
CPC 4	Coma or vegetative state (unconscious)	Unfavorable
CPC 5	Death or brain death	Unfavorable

was performed in patients who were unconscious on admission to the hospital after OHCA. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease formula.

The present study was approved by the hospital institutional review board and performed following the Declaration of Helsinki. Written informed consent was obtained from each patient or patient's legal representatives before enrollment.

Definitions

Severe vitamin D deficiency was defined as a serum concentration of 25(OH)D <10 ng/mL (13). Shockable rhythms were defined as ventricular fibrillation and pulseless ventricular tachycardia, while non-shockable rhythms were as pulseless electrical activity and asystole. Baseline renal dysfunction was defined as eGFR <60 mL/min/1.73 m^2 on admission. Severe shock is defined as sustained hypotension for > 1 h requiring high-dose vasopressor therapy (norepinephrine >30 μg/min with/without dobutamine >20 μg/kg/min) and/or mechanical circulatory support despite adequate intravascular volume. The CPC scale ranges from 1 to 5, with 1 representing conscious and good cerebral performance or minor deficit, 2 conscious and moderate disability, 3 conscious and severe disability, 4 coma or vegetative state (unconscious), and 5 death or brain death (12). Determination of brain death was decided by the Institutional Brain Death Committee. Favorable outcome was defined as survival with CPC score of 1 or 2, whereas unfavorable one as death or survival with CPC scores of 3 through 5 (Table 1). The primary endpoint was neurologic outcome assessed with CPC scale at 1 month after resuscitation from OHCA. The secondary endpoint was all-cause mortality.

Statistical analysis

Continuous data are expressed as mean ± SD and normality tests were performed for each variable to determine whether or not a data set was well modeled by normal distribution. The baseline characteristics of the two groups were compared using Student *t* test for continuous variables, and the chi-square test and Fisher exact test for categorical variables. Receiver operating characteristic (ROC) curves were used to determine the accuracy of a variable in predicting the clinical outcomes. Variables with $P < 0.10$ in the univariate analysis were entered into the multivariate logistic regression model to determine whether they were independently associated with poor neurologic outcome after SCA. Statistical significance was established at $P < 0.05$. Statistical analysis was performed by SPSS version 18.0 (SPSS Inc, Chicago, Ill).

RESULTS

Baseline characteristics of patients

Of the total of 169 patients who were successfully resuscitated from OHCA, six patients were excluded from analysis for the following reasons: prior significant neurologic problems (n = 1), acute intracranial hemorrhage (n = 1), Do Not Resuscitate-order (n = 3), and terminal-stage cancer (n = 1). Therefore, 163 patients [122 men (75%), mean age 56.3 ± 16.3 years] were included in this study. Presumed causes of cardiac arrest were 80 ischemic (49%), 61 nonischemic structural diseases (37%), and 22 ion channelopathies (14%) which included the patients who had shockable rhythm (Ventricular fibrillation, Ventricular tachycardia) at the time of sudden cardiac arrest except for both ischemic and nonischemic structural disease. Long QT syndrome, Brugada syndrome, arrhythmogenic right ventricular dysplasia, catecholaminergic polymorphic ventricular tachycardia, and idiopathic ventricular fibrillation were included in ion channelopathies. Initial shockable rhythms were observed in 102 patients (63%), and non-shockable rhythms were observed in 61 patients (37%). The mean arrest was 25.6 ± 16.6 min, and bystander CPR was performed in 110 patients (67%). Mean vitamin D level was 10.2 ± 5.3 ng/mL and severe vitamin D deficiency was diagnosed in 95 patients (58%). Therapeutic hypothermia was performed in 119 patients (90%) among 132 patients who were unconscious after OHCA. Severe shock was observed in 67 patients (41%).

At 1 month, overall 96 (59%) patients demonstrated favorable neurologic outcome: 83 patients (51%) had a CPC of 1 and 13 (8%) had a CPC of 2. Meanwhile, 67 patients (41%) showed unfavorable outcome: four (2%) had a CPC of 3, 26 (16%) had a CPC of 4, and 37 (23%) had a CPC of 5. Table 2 shows the baseline clinical characteristics of patients according to the outcome at 1 month after SCA. There were notable significant clinical differences between subjects with favorable outcome and those with unfavorable one. Patients with unfavorable outcome were more likely to be female and have initial non-shockable rhythm (55% vs. 25%, $P < 0.001$) and much longer arrest time (32.5 ± 16.8 min vs. 20.9 ± 14.8 min, $P < 0.001$). Severe shock (60% vs. 28%, $P < 0.001$), diabetes (40% vs. 19%, $P = 0.002$), and baseline renal dysfunction (72% vs. 32%, $P < 0.001$) were observed more frequently in the unfavorable outcome group. Patients with unfavorable outcome also showed lower initial arterial pH (7.04 ± 0.15 vs. 7.18 ± 0.13, $P < 0.001$) and higher lactate level (10.8 ± 4.1 mmol/L vs. 8.3 ± 4.4 mmol/L, $P < 0.001$). Vitamin D level was significantly lower in patients with unfavorable outcome (8.4 ± 4.4 ng/mL vs. 11.4 ± 5.5 ng/mL, $P < 0.001$) and in non-survivors (7.3 ± 3.8 ng/mL vs. 11.0 ± 5.4 ng/mL, $P < 0.001$). Severe vitamin D deficiency was also observed more frequently in patients with unfavorable outcome (79% vs. 44%, $P < 0.001$) and in non-survivors (89% vs. 49%, $P < 0.001$). Patients with vitamin D deficiency were likely to have initial non-shockable rhythm, severe shock, and longer arrest time (Table 3). Patients with vitamin D deficiency had significantly higher unfavorable outcome (56% vs. 21%, $P < 0.001$) and mortality rate (35% vs. 6%, $P < 0.001$).

Serum vitamin D level as a predictor of unfavorable outcome and mortality

The sensitivity and specificity of various cutoffs of serum 25(OH)D concentrations to predict the clinical outcomes were assessed using the ROC curve (Fig. 1). The vitamin D level showed an area under the ROC curve of 0.680 ($P < 0.001$), and a value <8.8 ng/mL predicted the unfavorable outcome with a sensitivity of 65% and a specificity of 68%. A value

Table 2. **Comparison of baseline characteristics according to outcome**

Variables	Total (n = 163)	Favorable (n = 96)	Unfavorable (n = 67)	*P* value
Men	122 (75%)	78 (81%)	44 (66%)	0.024
Age, yrs	56.3 ± 16.3	55.1 ± 16.0	58.0 ± 16.8	0.255
Arrest time, min	25.6 ± 16.6	20.9 ± 14.8	32.5 ± 16.8	<0.001
Bystander CPR	110 (67%)	70 (73%)	40 (60%)	0.076
Initial rhythm, shockable	102 (63%)	72 (75%)	30 (45%)	<0.001
Presumed causes of cardiac arrest				0.168
Ischemic	80 (49%)	49 (51%)	31 (46%)	0.549
Nonischemic structural diseases	61 (37%)	31 (32%)	30 (45%)	0.105
Ion channelopathies	22 (14%)	16 (17%)	6 (9%)	0.156
Severe shock	67 (41%)	27 (28%)	40 (60%)	<0.001
Therapeutic hypothermia*	119 (90%)	64 (94%)	55 (86%)	0.115
Diabetes	45 (28%)	18 (19%)	27 (40%)	0.002
Hypertension	72 (44%)	40 (42%)	32 (48%)	0.441
Baseline eGFR, mL/min/1.73 m^2	60.8 ± 26.1	66.6 ± 23.1	52.3 ± 28.0	0.001
Renal dysfunction	79 (49%)	31 (32%)	48 (72%)	<0.001
Vit D level, ng/mL	10.2 ± 5.3	11.4 ± 5.5	8.4 ± 4.4	<0.001
Vit D deficiency	95 (58%)	42 (44%)	53 (79%)	<0.001
PTH, pg/mL	117.9 ± 112.7	92.5 ± 76.5	148.3 ± 139.3	0.006
PTH >65 pg/mL	95 (58%)	50 (52%)	45 (67%)	0.063
LVEF, %	39.5 ± 19.3	41.6 ± 18.7	36.6 ± 19.9	0.101
LVEF <40%	90 (55%)	47 (49%)	43 (64%)	0.055
Initial arterial pH	7.13 ± 0.16	7.18 ± 0.13	7.04 ± 0.15	<0.001
Initial lactate, mmol/L	9.4 ± 4.4	8.3 ± 4.4	10.8 ± 4.1	<0.001

*Performed in 132 patients who were unconscious after resuscitation.
CPR indicates cardiopulmonary resuscitation; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PTH, parathyroid hormone; Vit D, vitamin D.

<10.0 ng/mL predicted the unfavorable outcome with a sensitivity of 56% and a specificity of 80%. On the other hand, the vitamin D level showed an area under the ROC curve of 0.726 ($P < 0.001$), and a value <7.7 ng/mL predicted the mortality with a sensitivity of 68% and a specificity of 68%. A value <10.0 ng/mL predicted the mortality with a sensitivity of 51% and a specificity of 90%.

Variables associated with unfavorable outcome after SCA

Multivariate logistic regression analysis revealed that severe vitamin D deficiency was strongly associated with unfavorable outcome after resuscitation from SCA (OR 2.81, 95% CI 1.11–7.11, $P = 0.029$) after adjusting for confounding variables (Table 4). Female (OR 3.61, 95% CI 1.28–10.17, $P = 0.015$), baseline renal dysfunction (OR 2.91, 95% CI

Table 3. **Comparison of baseline characteristics according to vitamin D deficiency**

Variables	Vit D deficiency (n = 95)	No vit D deficiency (n = 68)	*P* value
Men	66 (70%)	56 (82%)	0.062
Age, yrs	56.6 ± 18.2	55.9 ± 13.5	0.767
Arrest time, min	28.3 ± 17.4	21.9 ± 14.8	0.015
Bystander CPR	63 (66%)	47 (69%)	0.707
Initial rhythm, shockable	53 (56%)	49 (72%)	0.034
Presumed causes of cardiac arrest			0.130
Ischemic	46 (48%)	34 (50%)	0.842
Nonischemic structural diseases	40 (42%)	21 (31%)	0.144
Ion channelopathies	9 (10%)	13 (19%)	0.076
Severe shock	56 (59%)	11 (16%)	<0.001
Therapeutic hypothermia*	75 (89%)	44 (92%)	0.768
Diabetes	33 (35%)	12 (18%)	0.016
Hypertension	40 (42%)	32 (47%)	0.530
Baseline eGFR, mL/min/1.73 m^2	56.6 ± 27.6	66.6 ± 22.9	0.016
Renal dysfunction	56 (59%)	23 (34%)	0.002
Vit D level, ng/mL	6.6 ± 1.9	15.2 ± 4.3	<0.001
PTH, pg/mL	148.7 ± 131.9	72.6 ± 49.7	<0.001
PTH >65 pg/mL	67 (70%)	28 (42%)	0.001
LVEF, %	37.6 ± 20.0	42.2 ± 18.1	0.140
LVEF<40%	56 (59%)	34 (50%)	0.257
Initial arterial pH	7.09 ± 0.16	7.17 ± 0.15	0.001
Initial lactate, mmol/L	10.2 ± 4.5	8.2 ± 4.1	0.006

*Performed in 132 patients who were unconscious after resuscitation.
CPR indicates cardiopulmonary resuscitation; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PTH, parathyroid hormone; Vit D, vitamin D.

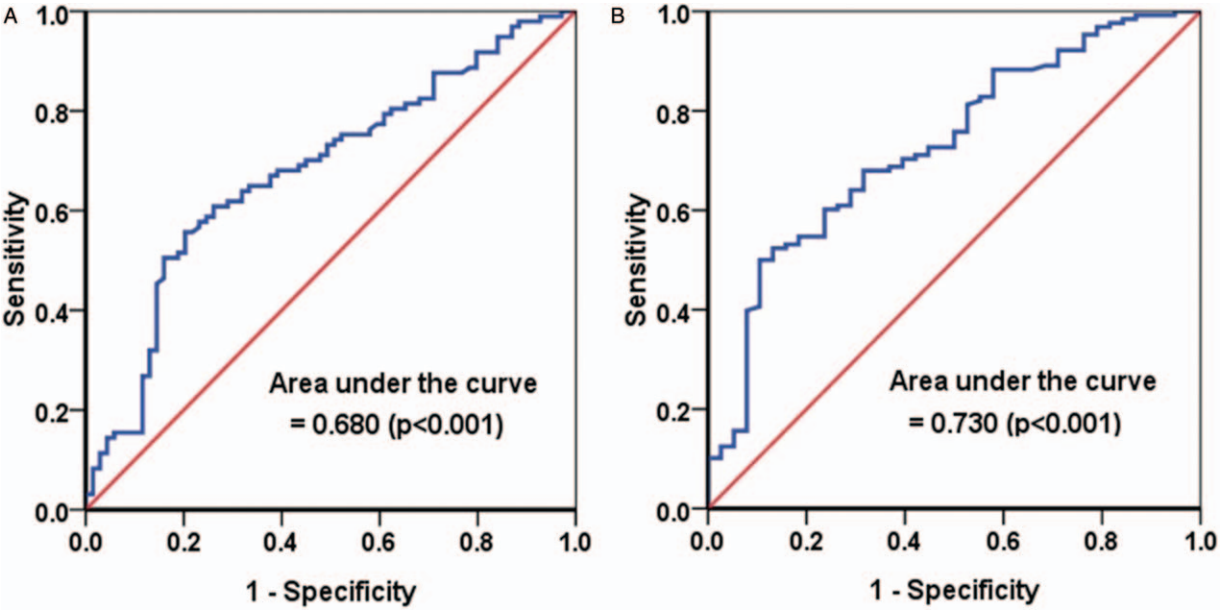

FIG. 1. **Assessment of unfavorable outcome and mortality in terms of serum 25(OH)D concentrations using the receiver operating characteristic (ROC) curve.** (A) Unfavorable outcome and (B) Mortality. 25(OH)D indicates 25 hydroxyvitamin D.

1.17–7.25, $P = 0.022$), diabetes (OR 2.91, 95% CI 1.11–7.65, $P = 0.030$), and initial arterial pH (per 0.1 increase, OR 0.56, 95% CI 0.41–0.77, $P < 0.001$) were also associated with unfavorable outcome after SCA.

Variables associated with mortality after SCA

Multivariate logistic regression analysis revealed that severe vitamin D deficiency was associated with mortality after resuscitation from SCA (OR 4.14, 95% CI 1.23–13.87, $P = 0.021$) after adjusting for confounding variables (Table 5). Baseline renal dysfunction (OR 5.80, 95% CI 1.96–17.16, $P = 0.001$) and severe shock (OR 3.58, 95% CI 1.34–9.59, $P = 0.011$) were also associated with mortality after SCA.

Changes in serum vitamin D level

To investigate changes in serum vitamin D level after OHCA, we performed an additional measurement of vitamin D with mean follow-up duration of 27.4 ± 25.1 days in the last 30 consecutive patients. The initial and follow-up mean vitamin D levels were 8.8 ± 4.0 ng/mL and 9.8 ± 4.9 ng/mL, respectively, with no statistical difference ($P = 0.058$), and demonstrated a good correlation. Of 17 patients with severe vitamin D deficiency on admission, only one patient had follow-up vitamin D level ≥ 10 ng/mL.

DISCUSSION

The major findings of the present study are that severe vitamin D deficiency is very prevalent and independently associated with both unfavorable outcome and mortality in patients resuscitated from SCA. To the best of our knowledge, this is the first evidence of such an association in this clinical setting.

Vitamin D has favorable physiologic effects on the cardiovascular system through multiple mechanisms, including

TABLE 4. **Variables associated with unfavorable outcome: multivariate logistic regression analysis**

	Univariate			Multivariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Female	2.27	1.10–4.65	0.026	3.61	1.28–10.17	0.015
Baseline renal dysfunction	5.30	2.68–10.48	<0.001	2.91	1.17–7.25	0.022
Diabetes	2.93	1.44–5.94	0.003	2.91	1.11–7.65	0.030
Vit D deficiency	4.87	2.38–9.94	<0.001	2.81	1.11–7.11	0.029
Initial arterial pH, 0.1 increase	0.50	0.38–0.65	<0.001	0.56	0.41–0.77	<0.001
Severe shock	3.79	1.96–7.33	<0.001			
Initial rhythm, non-shockable	3.70	1.90–7.21	<0.001			
LVEF<40%	1.87	0.99–3.54	0.056			
Absence of bystander CPR	1.82	0.94–3.53	0.078			
Initial lactate, mmol/L	1.14	1.06–1.23	0.001			
Arrest time, min	1.05	1.03–1.07	<0.001			
PTH	1.01	1.00–1.01	0.008			

CPR indicates cardiopulmonary resuscitation; LVEF, left ventricular ejection fraction; PTH, parathyroid hormone; Vit D, vitamin D.

Table 5. **Variables associated with mortality: multivariate logistic regression analysis**

	Univariate			Multivariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Baseline renal dysfunction	8.40	3.26–21.61	<0.001	5.80	1.96–17.16	0.001
Vit D deficiency	8.52	2.85–25.45	<0.001	4.14	1.23–13.87	0.021
Severe shock	8.40	3.52–20.04	<0.001	3.58	1.34–9.59	0.011
LVEF<40%	3.86	1.64–9.10	0.002			
Initial rhythm, non-shockable	3.81	1.77–8.18	0.001			
Diabetes	3.47	1.60–7.52	0.002			
Initial lactate, mmol/L	1.09	1.01–1.19	0.031			
Arrest time, min	1.02	1.00–1.05	0.032			
PTH, pg/mL	1.01	1.00–1.01	0.005			

LVEF indicates left ventricular ejection fraction; PTH, parathyroid hormone; Vit D, vitamin D.

protection against atherosclerosis, improvement in insulin resistance, and modulation of inflammatory processes (7, 14). Additionally, vitamin D down-regulates renin–angiotensin system and has positive inotropic effects on the heart (15, 16). The present study also showed higher prevalence of severe shock and diabetes in patients with vitamin D deficiency, consistent with previous studies. Consequently, vitamin D deficiency is associated with both mortality and various cardiovascular morbidity including hypertension, ischemic heart disease, cardiomyopathy, heart failure, and even SCA (8, 9). In the general population, vitamin D deficiency is prevalent in a significant proportion of people (7, 13). Subnormal levels of vitamin D are usually caused by poor nutrition or a lack of sun exposure. An epidemiologic study from healthy subjects showed an association between vitamin D deficiency and cardiovascular events (17). Deo et al. (18) described a high prevalence of vitamin D deficiency in SCA condition. However, there is a lack of study regarding the implications of vitamin D deficiency in SCA and its relation with the outcome and mortality has never been evaluated. Our study is the first attempt to evaluate this relation, raising interesting insights regarding the belief that vitamin D deficiency may be a risk factor for unfavorable outcome and mortality after SCA.

Vitamin D deficiency is known to be associated with unfavorable prognosis in acute ischemic stroke (19). Previous animal and clinical studies have shown that a negative correlation between vitamin D level and the infarct volume after acute ischemic stroke (20, 21). Vitamin D deficiency is also linked to poorer cognitive function and dementia (11). Vitamin D functions as a modulator in brain development and as a neuroprotectant through enhancement of endogenous antioxidant pathways, reduction of nitric oxide synthase, the regulation of neurotrophic factors expression, and the survival, development, and function of neural cells (11, 22). These processes, which enhance repair of the central nervous system by promoting axonal and dendritic sprouting and regrowth after brain injury, are critical components in recovery of brain function (23). Therefore, the decline of vitamin D-induced cognitive function and lack of neuroprotection might play a role in causing unfavorable neurologic outcome after SCA.

Vitamin D is a potent immunomodulator that modulates the immune system by regulating the monocyte or macrophage activity and reducing inflammatory cytokines and provides antioxidative mechanisms (7, 24). The pathophysiology of brain injury after SCA involves a complex cascade of molecular events, including excessive oxidative stress, oxygen-free radical production, and various inflammatory immune responses, that are triggered by ischemia and reperfusion (25, 26). Accordingly, even though patients are successfully resuscitated from SCA, neurologic or cognitive impairments are very common (4, 5). Fever control including therapeutic hypothermia is a method to prevent further brain damage by suppressing explosive immune reactions due to reperfusion injury (26, 27). In the present study, neurologic or cognitive impairments following SCA may be more prevalent due to lack of immunomodulation in patients with vitamin D deficiency.

In the present study, there was a high prevalence of severe vitamin D deficiency in patients resuscitated from OHCA. Our study was performed at a university hospital, Seoul, Korea. Vitamin D deficiency is more prevalent in Korea than in North America or Europe and becomes a serious common health problem (28, 29). Especially, the highest prevalence of vitamin D deficiency is observed in Seoul, the most industrialized city in Korea, where most people are engaged in indoor jobs with less exposure to sunlight (30). Prior studies have reported the high prevalence of vitamin D deficiency in critically ill patients (31). Krishnan et al. (32) reported that hemodilution following aggressive fluid resuscitation resulted in the reduction of serum vitamin D level in critically ill patients. In our study, however, baseline blood samples were obtained without fluid loading just after hospital admission. Moreover, the follow-up vitamin D level was not much different from the initial result and only one patient was out of deficiency in follow-up measurement among 17 patients with vitamin D deficiency on admission. Therefore, we conclude that the vitamin D level just after SCA meaningfully predicts the unfavorable outcome and mortality regardless of a patient's usual vitamin D status before SCA.

Previous studies about the effects of gender on OHCA outcomes have yielded contradictory results (33, 34). In this study, female gender was associated with higher 1-month unfavorable neurologic outcome. Baseline renal dysfunction and initial lower arterial pH were also associated with unfavorable outcome after SCA. It may indicate that greater degree of other organ failures predicts a poor neurologic outcome.

The present study had some limitations. First, it was a small-sized study conducted in a single center. Our findings need to be verified in other larger multicenter trials. Second, we used single measurements of plasma 25(OH)D concentration just after ROSC as a proxy for vitamin D status. This may not fully reflect a patient's usual vitamin D status before SCA. Third, neurologic evaluation was assessed at 1 month after the event of OHCA in this study. However, a time frame of 1 month after the event of OHCA may not reflect the best neurological outcome as some patients may continue to improve after that. Fourth, our data cannot establish a definite etiological link between vitamin deficiency and the increased risk of unfavorable neurologic outcome and mortality after SCA. Although vitamin D deficiency remained associated with unfavorable outcome and mortality after adjusting for comorbidities and potential confounding variables, one cannot rule out the possibility of vitamin D deficiency being just a risk marker instead of a risk factor. People with poor general health status may be less prone to sunlight exposure or may have an inadequate diet, leading to vitamin D deficiency. Statistical modeling may not completely be corrected for the unmeasured residual confounding factors in the multivariate analysis. Moreover, our finding that vitamin D deficiency is strongly associated with both unfavorable outcome and mortality following SCA may not translate to an effect on outcomes if vitamin D is supplemented in healthy population or people with a high risk of SCA. In addition, since there are no adequately powered studies to support that supplementation of vitamin D improves clinical outcomes in cardiovascular disease, the enrolled patients had no supplementation of vitamin D during admission. A large randomized clinical trial is needed to test the potential role of vitamin D in primary prevention or therapy in the high-risk groups of SCA.

In conclusion, through the various mechanisms of vitamin D in the cardiovascular and neurologic function and the inflammatory immune responses, the present data demonstrate that severe vitamin D deficiency is very prevalent and strongly associated with both unfavorable outcome and mortality in patients resuscitated from SCA. To the best of our knowledge, this is the first evidence of such an association in this clinical setting.

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