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The Incidence and Associated Factors of Sudden Death in Patients on Hemodialysis: 10-Year Outcome of the Q-Cohort Study

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Aim: The incidence of sudden death and its risk factors in patients on hemodialysis remain unclear. This study aimed to clarify the incidence of sudden death and its risk factors in Japanese patients on hemodialysis.

Methods: A total of 3505 patients on hemodialysis aged ≥ 18 years were followed for 10 years. Multivariate-adjusted hazard ratio (HR) with 95% confidence interval (95% CI) of each risk factor of sudden death were calculated using a Cox proportional hazards model.

Results: During the 10-year follow-up, 1735 patients died, including 227 (13%) sudden deaths. The incidence rate of sudden death was 9.13 per 1000 person-years. In multivariable-adjusted Cox analysis, male sex (HR 1.67; 95% CI 1.20–2.33), age (HR 1.44; 95% CI 1.26–1.65 per 10-year higher), the presence of diabetes (HR 2.45; 95% CI 1.82–3.29), history of cardiovascular disease (HR 1.85; 95% CI 1.38–2.46), cardiothoracic ratio (HR 1.21; 95% CI 1.07–1.39 per 5% higher), serum C-reactive protein (HR 1.11; 95% CI 1.03–1.20 per 1-mg/dL higher), and serum phosphate (HR 1.15; 95% CI 1.03–1.30 per 1-mg/dL higher) were independent predictors of sudden death. A subgroup analysis stratified by sex or age showed that lower serum corrected calcium levels, not using vitamin D receptor activators in women, and a shorter dialysis session length in men or older people (≥ 65 years) increased the risk for sudden death.

Conclusions: This study clarified the incidence of sudden death and its specific predictors in Japanese patients on hemodialysis.

Key words: Sudden death, Cardiovascular disease, End-stage kidney disease, Hemodialysis, Associated factors

Introduction/Aim

The mortality rate in patients undergoing hemodialysis remains higher compared with that in the non-dialysis population¹. Cardiovascular disease (CVD) is the most common cause of death in patients on dialysis^{2,3}. Sudden death, which is defined as sudden and unexpected natural death within a short period (generally between 1 and 24 hours) after the onset of symptoms is a serious problem. Most sudden deaths are due to CVD, such as cardiac disease, stroke, and aortic dissection, according to a previous autopsy

report⁴. A previous report showed that chronic kidney disease is an independent risk factor for sudden death⁵. According to the United States Renal Data System, sudden death is the most common cause of death in patients on hemodialysis, accounting for 28% of all deaths⁶. Another report on Japanese patients on hemodialysis showed that 16% of all deaths were due to sudden death⁷. A recent meta-analysis showed that the incidence of sudden death in patients on hemodialysis widely varies and is inconclusive⁸. Accurate evaluation of the frequency of sudden death in patients on hemodialysis based on a clear

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definition is required.

Patients on hemodialysis may be predisposed to various factors affecting the onset of sudden death compared with the general population⁹). Nevertheless, there have only been a few reports that evaluated risk factors of sudden death in patients undergoing hemodialysis¹⁰⁻¹²). Furthermore, these reports were limited to the Western population, and they had a small sample size and a short-term follow-up. We believe that the establishment of robust predictors of sudden death would be useful for better survival of patients on hemodialysis. In this study, we analyzed a 10-year follow-up data of sudden death using a large-scale cohort of patients on hemodialysis in Japan. The present study aimed to clarify the precise incidence of sudden death and its risk factors.

Methods

Study Population

The Q-Cohort Study was a multicenter, longitudinal, and observational study of patients who underwent maintenance hemodialysis in Japan. The details of this study have been previously described¹³). A total of 3598 outpatients aged 18 years or older who underwent maintenance hemodialysis at 39 dialysis facilities in Fukuoka and Saga Prefectures in the northern region of Kyushu Island were enrolled from December 2006 to December 2007. Participants were followed until December 2016. Patients without demographic data or patients whose outcomes were missing were excluded ($n=93$). The remaining 3505 patients were analyzed in this study. The study protocol was approved by the Clinical Research Ethics Committee of the Institutional Review Board at Kyushu University (Approval Number: 20-31) and was registered in the clinical trial registry (University Hospital Medical Information Network, UMIN000000556). All of the patients provided written informed consent before participation in the study. The present study was performed according to the Ethics of Clinical Research (Declaration of Helsinki). The ethics committee of all participating institutions granted approval to waive the requirement for written informed consent for the additional follow-up survey from 2011 to 2016 because of the retrospective nature of the current study.

Covariates

The details of the risk factor measurements were previously published¹³). Data of baseline characteristics and potential confounders (age, sex, dialysis vintage, presence of diabetes mellitus, history of CVD, pre-dialysis systolic blood pressure, serum levels of

albumin, ferritin, corrected calcium, phosphate, intact parathyroid hormone, total cholesterol, and C-reactive protein [CRP], Kt/V, body mass index, and use of a vitamin D receptor activator [VDRA]) were collected by reviewing medical records. History of CVD included coronary artery disease, congestive heart failure, and peripheral arterial disease, whereas stroke was excluded. The corrected serum calcium concentration was based on Payne's formula as follows: corrected calcium (mg/dL) = observed total calcium (mg/dL) + (4.0 - serum albumin concentration (g/dL))¹⁴).

Outcomes

The primary outcome was the incidence of sudden death. Sudden death was defined as a witnessed death within 24 hours after the onset of acute symptoms, and an unwitnessed unexpected death within the interval between dialysis sessions, excluding trauma, suicide, and suffocation. This definition was also referred to in a previous study¹⁵). The patients' health status was examined annually by local physicians at each dialysis facility. When patients moved to other dialysis facilities where a collaborator of this study was not present, we enquired about the information of the patients' condition by telephone or mail. Death events were collected from the patients' medical records.

Statistical Analysis

Baseline characteristics are expressed as mean \pm standard deviation or median (interquartile range) for continuous variables and as percentages for categorical variables. Statistical significance of the difference between sudden death cases and non-sudden death cases was tested using the Student's *t*-test or Mann-Whitney *U* test for continuous variables and the chi-square test for categorical variables. Multivariable-adjusted hazard ratio (HR) with 95% confidence intervals (CI) of each risk factor for sudden death were calculated using the Cox proportional hazards model. Furthermore, the total cohort was stratified by age, sex, and dialysis vintage to evaluate the interaction for the association between risk factors and sudden death. Statistical calculations were performed using JMP, version 13 software program (SAS Institute Inc. Tokyo, Japan). $P < 0.05$ was considered statistically significant.

Results

During the 10-year follow-up period, 1735 (50%) patients died from any cause. **Fig. 1** shows the causes of death of all decedents. A total of 227 deaths were attributed to sudden death, which comprised

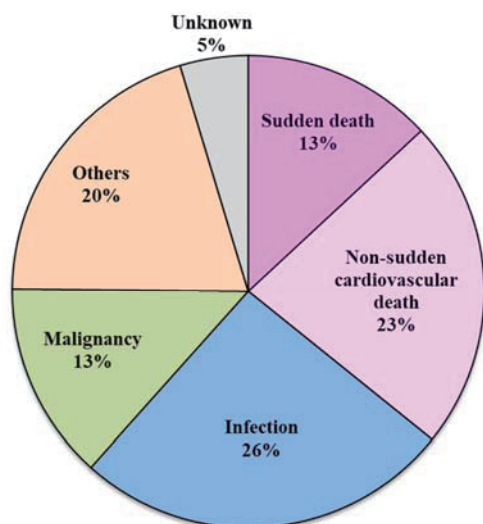


Fig. 1. Cause of death in all decedents ($n=1735$)

The rate of sudden death was 13% of all deaths.

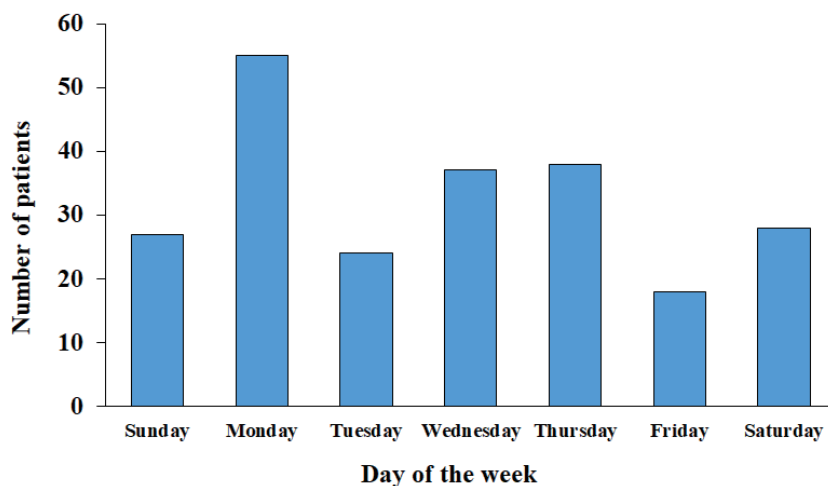


Fig. 2. Distribution of deaths according to day of the week

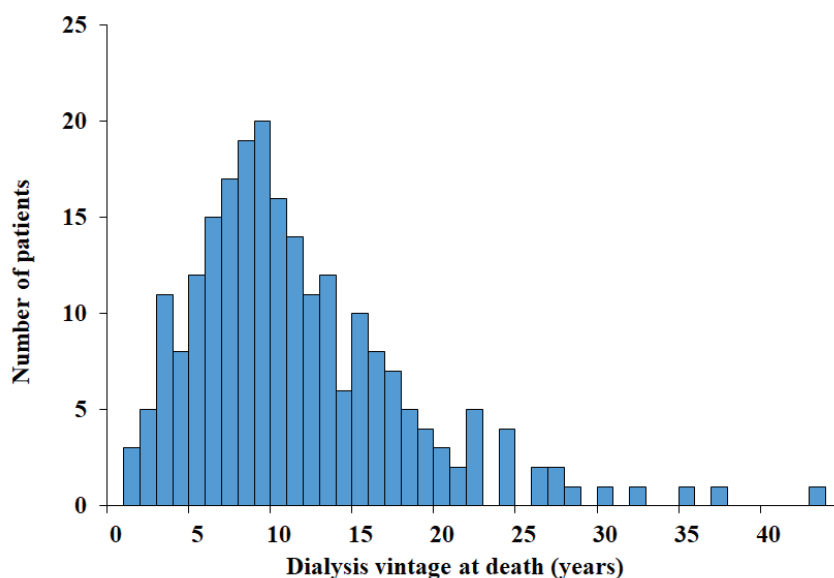


Fig. 3. Histogram of dialysis vintage at death

13% of all deaths. The incidence rate of sudden death was 9.13 per 1000 person-years. **Fig. 2** shows the distribution of sudden death by the day of the week. Sudden death is observed most frequently on Monday. The distribution of sudden death in dialysis vintage is shown in **Fig. 3**. The onset of sudden death is most common between 9 to 10 years from the start of hemodialysis. **Table 1** shows the characteristics of this study population and comparison of the characteristics of sudden death cases with non-sudden death

cases. Sudden death cases were more likely to be men ($P=0.03$) and to have a higher prevalence of diabetes ($P<0.001$) and CVD ($P<0.001$) compared with non-sudden death cases. Sudden death cases also had higher serum albumin levels ($P<0.001$), serum hemoglobin levels ($P=0.01$), and body mass index ($P=0.01$) than in non-sudden death cases. With regard to serum parameters related to chronic kidney disease-related bone-mineral disorders, sudden death cases had lower corrected calcium levels ($P<0.001$), higher

Table 1. Characteristics of the study participants, stratified by mode of death

Characteristics	All death (n = 1735)			P values
	All participants (n = 3505)	Non-sudden death (n = 1508)	Sudden death (n = 227)	
Age (years)	63.5 ± 12.8	70.4 ± 10.1	66.3 ± 10.4	<0.001*
Male (%)	59.2	60.4	67.8	0.03*
Hemodialysis vintage (years)	5.3 (2.1-11.3)	5.2 (2.2-11)	4.6 (1.7-9.9)	0.06
Presence of diabetes (%)	29.2	35.6	47.6	<0.001*
History of CVD (%)	22.4	31.2	37	0.08
Dialysis session length (hr)	4.7 ± 0.6	4.6 ± 0.6	4.7 ± 0.6	0.46
Systolic BP (mmHg)	153.0 ± 23.3	153.4 ± 24.6	155.9 ± 24.3	0.11
Cardiothoracic ratio (%)	50.5 ± 5.51	51.7 ± 5.73	51.2 ± 6.0	0.19
Hemoglobin, (g/dL)	10.5 ± 1.2	10.4 ± 1.2	10.6 ± 1.1	0.01*
Serum ferritin (ng/dL)	163 (69-303)	176 (85-337)	163 (71-281)	0.60
Serum albumin (g/dL)	3.8 ± 0.4	3.7 ± 0.5	3.9 ± 0.4	<0.001*
Serum corrected calcium (mg/dL)	9.4 ± 0.8	9.4 ± 0.8	9.2 ± 0.7	<0.001*
Serum phosphorus (mg/dL)	4.9 ± 1.2	4.7 ± 1.2	5.1 ± 1.2	<0.001*
Serum total cholesterol (mg/dL)	152 (131-178)	148 (127-173)	152 (131-178)	0.09
Serum CRP (mg/dL)	0.13 (0.06-0.3)	0.2 (0.1-0.5)	0.14 (0.08-0.36)	0.009*
Serum intact PTH (pg/mL)	106 (48-215.9)	96 (41.3-197.5)	113.6 (56-240)	0.01*
Body mass index (kg/m ²)	20.8 ± 3.1	20.8 ± 3.1	21.4 ± 2.9	0.01*
Kt/V for urea	1.57 ± 0.3	1.57 ± 0.3	1.53 ± 0.3	0.08
dose of ESA (U/week)	3,000 (1,500-4,500)	4,000 (1,500-6,000)	3,000 (1,500-4,500)	0.02*
Use of VDRA (%)	70	65.4	66.5	0.74
Use of antihypertensive agent (%)	62.5	61.3	73.6	0.002*
Use of iron supplementation (%)	37.3	37.3	38.8	0.67
Use of phosphate-binders (%)	81.1	73.2	82.8	0.008*

Data are presented as mean (standard deviation), median (interquartile range), or percentage for categorical measures.

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; BP, blood pressure; CRP, C-reactive protein; PTH, parathyroid hormone; ESA, erythropoiesis-stimulating agents; VDRA, vitamin D receptor activator

*Sudden death versus non sudden death ($P < 0.05$)

serum phosphate levels ($P < 0.001$), and higher intact parathyroid hormone levels ($P = 0.01$) than non-sudden death cases did. The dosage of erythropoiesis-stimulating agents was lower ($P = 0.02$), and the frequency of use of antihypertensive drugs ($P = 0.002$) and phosphate-binders ($P = 0.008$) was higher in sudden death cases than in non-sudden death cases.

Risk Factors Associated with the Incidence of Sudden Death

We examined the risk factors associated with sudden death at baseline (Table 2). Multivariable-adjusted Cox proportional hazards analysis showed that male sex (HR 1.67; 95% CI 1.20–2.33), age (HR 1.44; 95% CI 1.26–1.65 per 10-year higher), the presence of diabetes (HR 2.45; 95% CI 1.82–3.29), a history of CVD (HR 1.85; 95% CI 1.38–2.46), the cardiothoracic ratio (HR 1.21; 95% CI 1.07–1.39 per 5% higher), serum CRP levels (HR 1.11; 95% CI 1.03–1.20 per 1-mg/dL higher), and serum phosphate

levels (HR 1.15; 95% CI 1.03–1.30 per 1-mg/dL higher) were independently associated with the incidence of sudden death. To investigate whether there is a difference of risk factor of sudden death in the follow-up period, we have prepared a new table of multivariable Cox proportional HRs for sudden death based on a 4-year outcome (Supplemental Table 1). The risk factors for sudden death based on a 4-year outcome were substantially similar to a 10-year outcome.

Subgroup Analysis by Sex, age, and Dialysis Vintage

The results of the subgroup analysis by sex, age, and dialysis vintage are shown in Tables 3–5. In the male group, a shorter dialysis session length (<5 hours) (HR 1.43; 95% CI 1.01–2.03) was associated with sudden death, whereas lower serum corrected calcium levels (HR 1.88; 95% CI 1.36–2.63 per 1-mg/dL lower) and not using VDRA (HR 2.08; 95% CI 1.30–3.40) were significant predictors of sudden death

Table 2. Multivariable hazard ratios for sudden death

Variables	HR (95% CI)
Male	1.67 (1.20-2.33)*
Age (per 10 years higher)	1.44 (1.26-1.65)*
Presence of diabetes	2.45 (1.82-3.29)*
History of CVD	1.85 (1.38-2.46)*
Hemodialysis vintage (per 5 years higher)	1.02 (0.91-1.15)
Dialysis session length (< 5 hr)	1.19 (0.89-1.59)
Systolic BP (per 10 mmHg higher)	0.99 (0.94-1.06)
Cardiothoracic ratio (per 5% higher)	1.21 (1.07-1.39)*
Hemoglobin, (per 1 g/dL higher)	1.01 (0.90-1.14)
Serum albumin (per 1 g/dL higher)	1.23 (0.86-1.74)
Serum total cholesterol (per 10 mg/dL higher)	1.00 (0.99-1.01)
Body mass index (per 1 kg/m ² higher)	0.98 (0.93-1.03)
Serum CRP (per 1 mg/dL higher)	1.11 (1.03-1.20)*
Serum ferritin (per 10 ng/dL higher)	1.00 (0.99-1.00)
Serum intact PTH (per 10 pg/mL higher)	1.00 (0.99-1.01)
Serum corrected calcium (per 1 mg/dL lower)	1.17 (0.98-1.43)
Serum phosphorus (per 1 mg/dL higher)	1.15 (1.03-1.30)*
Kt/V (per 0.1 higher)	0.99 (0.94-1.06)
Non-use of VDRA	1.15 (0.86-1.52)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; BP, blood pressure; CRP, C-reactive protein; PTH, parathyroid hormone; ESA, erythropoiesis-stimulating agents; VDRA, vitamin D receptor activator

* $P < 0.05$

Table 3. Multivariable hazard ratios for sudden death stratified by sex

Sex (No. of Sudden Death/No. of Patients)	Male (154/2079)	Female (73/1426)	
Variables	HR (95% CI)	HR (95% CI)	p for interaction
Age (per 10-year higher)	1.46 (1.24-1.72)	1.50 (1.17-1.93)	0.94
Presence of diabetes	2.30 (1.65-3.28)	2.75 (1.57-4.81)	0.71
History of CVD	1.86 (1.31-2.61)	2.06 (1.20-3.45)	0.38
Hemodialysis vintage (per 5-year higher)	0.94 (0.80-1.10)	1.06 (0.90-1.26)	0.41
Dialysis session length (< 5 hours)	1.43 (1.01-2.02)	0.72 (0.41-1.24)	0.04*
Systolic BP (per 10 mmHg higher)	1.01 (0.94-1.10)	0.94 (0.85-1.04)	0.20
Cardiothoracic ratio (per 5% higher)	1.20 (1.01-1.42)	1.25 (1.01-1.55)	0.67
Hemoglobin, (per 1 g/dL higher)	0.99 (0.86-1.15)	1.01 (0.83-1.26)	0.93
Serum albumin (per 1 g/dL higher)	1.51 (0.99-2.30)	0.81 (0.44-1.51)	0.25
Serum total cholesterol (per 10 mg/dL higher)	1.00 (0.98-1.02)	1.01 (0.94-1.07)	0.86
Body mass index (per 1 kg/m ² higher)	0.96 (0.90-1.02)	0.99 (0.92-1.07)	0.60
Serum CRP (per 1 mg/dL higher)	1.06 (0.92-1.22)	1.11 (1.01-1.22)	0.32
Serum ferritin (per 10 ng/dL higher)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.88
Serum intact PTH (per 10 pg/mL higher)	1.00 (0.99-1.01)	1.00 (0.99-1.00)	0.89
Serum corrected calcium (per 1 mg/dL lower)	1.07 (0.85-1.33)	1.88 (1.36-2.63)	< 0.001*
Serum phosphorus (per 1 mg/dL higher)	1.17 (1.01-1.34)	1.09 (0.88-1.36)	0.35
Kt/V (per 0.1 higher)	0.98 (0.90-1.06)	1.04 (0.94-1.14)	0.19
Non-use of VDRA	0.78 (0.53-1.14)	2.08 (1.29-3.39)	< 0.001*

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; BP, blood pressure; CRP, C-reactive protein; PTH, parathyroid hormone; VDRA, vitamin D receptor activator

* P for interaction < 0.05

Table 4. Multivariable hazard ratios for sudden death stratified by age

Age (No. of Sudden Death/No. of Patients)	< 65 years (95/1827)	≥ 65 years (132/1678)	
Variables	HR (95% CI)	HR (95% CI)	<i>p</i> for interaction
Male	1.64 (0.99-2.78)	1.56 (1.01-2.44)	0.77
Presense of diabetes	4.34 (2.69-7.09)	1.69 (1.15-2.47)	0.001*
History of CVD	2.32 (1.48-3.58)	1.73 (1.19-2.50)	0.05
Hemodialysis vintage (per 5-year higher)	1.02 (0.86-1.20)	1.06 (0.91-1.25)	0.20
Dialysis session length (< 5 hours)	1.15 (0.71-1.93)	1.51 (1.03-2.21)	0.01*
Systolic BP (per 10 mmHg higher)	0.99 (0.91-1.10)	0.98 (0.91-1.07)	0.19
Cardiothoracic ratio (per 5% higher)	1.53 (1.27-1.85)	1.06 (0.88-1.26)	0.01*
Hemoglobin, (per 1 g/dL higher)	1.06 (0.89-1.27)	0.98 (0.84-1.16)	0.53
Serum albumin (per 1 g/dL higher)	1.51 (0.86-2.68)	1.13 (0.71-1.81)	0.26
Serum total cholesterol (per 10 mg/dL higher)	1.00 (0.94-1.06)	1.00 (0.99-1.01)	0.63
Body mass index (per 1 kg/m ² higher)	0.99 (0.93-1.06)	0.95 (0.89-1.02)	0.17
Serum CRP (per 1 mg/dL higher)	1.10 (0.97-1.24)	1.15 (1.03-1.29)	0.34
Serum ferritin (per 10 ng/dL higher)	1.00 (0.99-1.01)	1.00 (0.99-1.00)	0.82
Serum intact PTH (per 10 pg/mL higher)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	0.89
Serum corrected calcium (per 1 mg/dL lower)	1.31 (0.99-1.75)	1.11 (0.87-1.42)	0.11
Serum phosphorus (per 1 mg/dL higher)	1.11 (0.94-1.32)	1.13 (0.96-1.32)	0.77
Kt/V (per 0.1 higher)	1.04 (0.95-1.15)	0.97 (0.89-1.05)	0.55
Non-use of VDRA	1.03 (0.67-1.65)	1.25 (0.86-1.81)	0.56

Abbreviations: HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; BP, blood pressure; CRP, C-reactive protein; PTH, parathyroid hormone; VDRA, vitamin D receptor activator

**P* for interaction < 0.05

Table 5. Multivariable hazard ratios for sudden death stratified by dialysis vintage

Dialysis vintage (No. of Sudden Death/No. of Patients)	< 5 years (122/1682)	≥ 5 years (105/1823)	
Variables	HR (95% CI)	HR (95% CI)	<i>p</i> for interaction
Male	1.76 (1.10-2.86)	1.87 (1.13-3.13)	0.68
Age (per 10-year higher)	1.03 (1.01-1.05)	1.31 (1.10-1.57)	0.1
Presense of diabetes	2.05 (1.40-3.04)	2.94 (1.88-4.54)	0.2
History of CVD	2.04 (1.36-3.01)	1.59 (1.03-2.43)	0.85
Dialysis session length (< 5 hours)	1.39 (0.93-2.06)	1.00 (0.64-1.56)	0.81
Systolic BP (per 10 mmHg higher)	1.00 (0.92-1.09)	0.97 (0.88-1.06)	0.62
Cardiothoracic ratio (per 5% higher)	1.29 (1.07-1.55)	1.15 (0.95-1.41)	0.59
Hemoglobin, (per 1 g/dL higher)	0.96 (0.81-1.13)	1.05 (0.86-1.26)	0.81
Serum albumin (per 1 g/dL higher)	1.29 (0.81-2.08)	1.18 (0.69-2.02)	0.18
Serum total cholesterol (per 10 mg/dL higher)	1.02 (0.97-1.08)	0.99 (0.97-1.00)	0.26
Body mass index (per 1 kg/m ² higher)	1.00 (0.94-1.07)	0.93 (0.86-1.01)	0.16
Serum CRP (per 1 mg/dL higher)	0.99 (0.79-1.23)	1.17 (1.07-1.28)	0.14
Serum ferritin (per 10 ng/dL higher)	1.00 (0.99-1.01)	1.00 (0.99-1.00)	0.9
Serum intact parathyroid hormone (per 10 pg/mL higher)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	0.62
Serum corrected calcium (per 1 mg/dL lower)	1.41 (1.08-1.85)	0.96 (0.74-1.22)	0.05
Serum phosphorus (per 1 mg/dL higher)	1.17 (1.00-1.37)	1.18 (0.99-1.40)	0.5
Kt/V (per 0.1 higher)	1.02 (0.94-1.07)	0.99 (0.90-1.09)	0.83
Non-use of VDRA	1.06 (0.71-1.54)	1.22 (0.79-1.86)	0.48

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; BP, blood pressure; CRP, C-reactive protein; PTH, parathyroid hormone; VDRA, vitamin D receptor activator

**P* for interaction < 0.05

in the female group. Furthermore, the presence of diabetes (HR 4.34; 95% CI 2.69–7.09) and a high cardiothoracic ratio (HR 1.53; 95% CI 1.27–1.85 per 5% higher) were more strongly related to sudden death in the younger group than in the older group. A shorter dialysis session length (<5 hours) (HR 1.51; 95% CI 1.03–2.21) increased the risk of sudden death in the older group. **Table 5** indicates that there are no interactions of risk factors among dialysis vintage.

Discussion

Our study showed the incidence of sudden death and its risk factors in Japanese patients on hemodialysis during a 10-year, longitudinal follow-up. A total of 13% of all-cause deaths was attributed to sudden death. Additionally, we identified several independent risk factors for sudden death. Male sex, older age, the presence of diabetes, a history of CVD, a higher cardiothoracic ratio, and higher serum phosphate and CRP levels were associated with an increased risk of sudden death. To the best of our knowledge, this is the first study to evaluate the risk factors for sudden death in Asian patients on hemodialysis.

The incidence rate of sudden death observed in our cohort was approximately 25-fold higher compared with that in the Japanese general population¹⁶, and not significantly different from a previous study of Japanese patients on hemodialysis^{7, 8}. However, our rate of sudden death was lower than that in reports of patients on hemodialysis in the United States⁶ and Europe^{8, 10}. There are some explanations for the difference in incidence rates of sudden death in patients on hemodialysis among countries. First, Japanese patients on hemodialysis have a lower rate of CVD complications, which are associated with sudden death, such as coronary artery disease, congestive heart failure, and left ventricular hypertrophy, compared with Europe and the United States¹⁷. Second, the blood flow rate was lower, and the dialysis session length is longer in Japan compared with those countries¹⁸. We speculate that these conditions in daily dialysis may reduce its effect on circulatory dynamics and a shift in minerals, and thus reduce the risk of developing sudden death. Third, the rates of routine measurement of CRP levels, routine examination of chest radiographs, and yearly screening for vascular calcification are highest in Japan¹⁸. This routine evaluation of patients may lead to early treatment and prevent the onset and progression of CVD, including sudden death.

Although we have no information of the dialysis schedule (Monday, Wednesday, and Friday or Tuesday, Thursday, and Saturday), we confirmed sudden death

is observed most frequently on Monday, which is similar to a previous study¹⁹. Large weight gains or increases in serum potassium in the weekend may cause volume overload or hyperkalemia and sudden death on Monday. The onset of sudden death is most common between 9 to 10 years from the start of hemodialysis. This result was inconsistent with a previous study, which reported that the high incident rate of sudden death is found in the first year of hemodialysis²⁰, probably due to a small number of participants who are enrolled in the first year in our study.

In hemodialysis patients, sudden death could be induced by various factors such as the presence of cardiac disease, rapid fluid and electrolyte shifts, and sympathetic overactivity²¹. This study showed some risk factors for sudden death. Male sex, older age, and the presence of diabetes were also independent predictors of sudden death in our study, which is consistent with previous reports^{10–12}. These are traditional risk factors of CVD including coronary artery disease, which contributed to 60% of sudden death in the general population²². Coronary artery disease induces proarrhythmic effect and is associated with the persistence of ventricular arrhythmias during and after the treatment²⁰. Apart from these factors, a higher cardiothoracic ratio and higher levels of serum CRP and phosphate were associated with an increased risk of sudden death. Few studies have shown a direct relationship between the cardiothoracic ratio and sudden death in patients on hemodialysis. Because a higher cardiothoracic ratio reflects volume overload, cardiac dysfunction, and left ventricular hypertrophy²³, which are strong predictors of sudden death²⁴, we suggest that the cardiothoracic ratio could potentially be a convenient means of predicting sudden death. The relationship between serum CRP levels and sudden death in our study is consistent with previous studies^{10, 25}. Inflammation is associated with atherosclerotic CVD, such as coronary heart disease²⁶ and critical ischemic limb²⁷, due to the development of unstable plaque, and left ventricular hypertrophy due to the elevation of fibroblast growth factor-23 levels (FGF-23) levels²⁸, which might result in sudden death. Additionally, inflammation directly induces fatal arrhythmia because of factors such as sympathetic overactivity and myocardial fibrosis even in the absence of atherosclerosis²¹. Although a previous report showed an association between serum phosphate levels and sudden death²⁹, the mechanism has not been fully determined. Phosphate overload induces vascular, valvular, and myocardial calcification^{30, 31}, leading to the alteration of microcirculatory hemodynamics and impaired myocardial perfusion. Hyperphosphatemia also increases serum FGF-23,

which induce left ventricular hypertrophy and cardiac fibrosis³²). These structural change of vascular system and myocardium could be associated with fatal arrhythmia via localized conduction disturbance and spiral reentry³³). Moe *et al.* reported that lowering FGF-23 levels with cinacalcet was associated with a reduction of the incidence of sudden death³⁴). This study suggests that management of chronic kidney disease-related bone-mineral disorders is important for preventing sudden death.

Subgroup analysis stratified by sex showed that lower corrected serum calcium levels were independently associated with sudden death only in the female group. Most studies have suggested that lowering serum calcium concentrations leads to a risk of critical arrhythmia like torsades de pointes due to prolongation of the QT interval³⁵). In addition, hypocalcemia is related to left ventricular diastolic dysfunction³⁶), leading to sudden death. A recent study reported that hypocalcemia increased sudden cardiac arrest in the general population³⁷). However, a few studies have shown an association between hypocalcemia and sudden death in patients on hemodialysis. The reason why there was a difference between sexes regarding the association between serum calcium levels and sudden death in this study is unclear. Several studies have shown that women have a longer QT interval than men do, mainly by differences in sex hormones³⁸). Furthermore, recent studies have shown that the incidence of torsades de pointes arrhythmia due to QT prolongation is higher in women than in men³⁹). We speculate that hypocalcemia in women may increase the risk of the development of critical arrhythmia and sudden death by a sex-specific pathogenetic mechanism. Further studies are required to prove this association.

Non-use of VDRA was also a significant predictor of sudden death in the female group in our study. Vitamin D has been shown to affect electrophysiology and contractility of the heart⁴⁰), and its deficiency could be linked to arrhythmia and sudden death. A previous study suggested that vitamin D deficiency is an independent risk for sudden death in patients on hemodialysis with diabetes⁴¹) and severe secondary hyperparathyroidism⁴²). On the other hand, another study showed that patients treated with a VDRA did not have an increased risk for cardiovascular mortality, even in low serum 25-hydroxyvitamin D levels⁴³). Although a recent randomized controlled trial in Japanese hemodialysis patients suggested that oral VDRA did not reduce the risk of cardiovascular events, including sudden death⁴⁴), the proportion of sudden death among all cardiovascular events is small (18 of 188), and the effect of VDRA on different genders is

not analyzed. The association between treatment with VDRA and sudden death might be unclear. A previous study showed that supplementation of a VDRA reduced a prolonged QT interval and regressed left ventricular hypertrophy⁴⁵). Furthermore, a recent study showed that low serum 25-hydroxyvitamin D levels were associated with an increased risk for myocardial infarction⁴⁶) and cardiovascular mortality⁴⁷) in women, but not in men, probably due that sex hormones contributed to differential responsiveness to vitamin D between men and women. These results support our view that female patients on hemodialysis who are not treated with VDRA have an increased risk of sudden death. Because we cannot fully exclude the possibility of indication bias, further well-conducted clinical trials are required to confirm sex differences in the beneficial effect of VDRA.

A shorter dialysis session length (<5 hours) increased the risk of sudden death in the male and older (≥ 65 years) groups in this study. Data on the relationship between dialysis session length and sudden death is limited¹²). A shorter dialysis session length implies insufficient removal of fluid and uremic toxins, including indoxyl sulfate, which is a significant predictor of CVD⁴⁸) and requires higher ultrafiltration rates. Rapid fluid removal during hemodialysis, which is associated with increased all-cause and cardiovascular mortality⁴⁹) could contribute to hypotension, tissue ischemia, circulatory collapse, arrhythmia, and sudden death²²). Therefore, the development of sudden death being dependent on dialysis session length is not surprising. Additionally, we recently reported that a shorter dialysis session length (<5 hours) was associated with all-cause mortality, especially in older Japanese patients on hemodialysis who were ≥ 80 years old⁵⁰). Therefore, the finding that sudden death develops more frequently in populations with shorter dialysis session length (<5 hours) is unsurprising. Our findings suggest that males and older populations especially require sufficient uremic toxin removal and/or slower ultrafiltration to avoid sudden death.

There are several limitations to the present study. First, sudden death, based on our definition, included both cardiac death (e.g., arrhythmia and myocardial infarction) and non-cardiac death (e.g., cerebral hemorrhage, pulmonary embolism, and aortic dissection). Because we did not perform an autopsy in all patients, the cause of sudden death was difficult to determine. Second, we only used baseline clinical parameters to evaluate associations with sudden death and did not take into account the changes in these parameters such as the fluctuation of blood pressure or humoral factors on the onset of sudden death. Third, some parameters that could be important for understanding sudden

death were not evaluated. In particular, serum potassium levels, which could be a strong contributor of sudden death, other dialysis parameters, except for dialysis session length and Kt/V (e.g., blood flow rate and ultrafiltration rate), nutritional parameters, except albumin and body mass index, echocardiographic, and electrocardiographic data (e.g., ejection fraction, left ventricular hypertrophy, and QT interval), cardiac biomarker data, (e.g., troponins and atrial/brain natriuretic peptides), and data of commodity such as sleep apnea syndrome, which is one of the important causes of sudden death⁵¹), and medical treatment (e.g., antiplatelet agents and β -blockers) were missing. Finally, the detailed timing of sudden death (i.e., if deaths occurred in the hours before or after dialysis) is unclear. Despite these limitations, we believe that our study provides helpful information that could lead to a better understanding of sudden death in patients on maintenance hemodialysis.

Conclusion

The incidence rate of sudden death was also high in Japanese patients on hemodialysis. Therapeutic factors such as body fluid volume, serum calcium/phosphate, inflammation, dialysis session length, and use of VDRA might be important to determine the incidence of sudden death. Moreover, the effects of these risk factors on sudden death may vary, depending on age and sex. For a better understanding, future studies focusing on the effect of these factors on sudden death should be conducted.

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Conflicts of Interest

The authors report no conflicts of interest.

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Supplemental Table 1. Multivariable hazard ratios for sudden death (4-year outcome)

Variables	HR (95% CI)
Male	1.60 (0.98-2.61)
Age (per 10-year higher)	1.57 (1.26-1.96)*
Presence of diabetes	2.63 (1.66-4.17)*
History of CVD	2.14 (1.38-3.34)*
Hemodialysis vintage (per-5 year higher)	1.16 (0.98-1.38)
Dialysis session length (< 5 hr)	1.18 (0.76-1.85)
Systolic BP (per 10 mmHg higher)	1.00 (0.91-1.09)
Cardiothoracic ratio (per 5% higher)	1.29 (1.06-1.56)*
Hemoglobin, (per 1 g/dL higher)	1.14 (0.94-1.38)
Serum albumin (per 1 g/dL higher)	1.46 (0.89-2.40)
Serum total cholesterol (per 10 mg/dL higher)	0.99 (0.95-1.04)
Body mass index (per 1 kg/m ² higher)	0.98 (0.92-1.06)
Serum CRP (per 1 mg/dL higher)	1.18 (1.07-1.30)*
Serum ferritin (per 10 ng/dL higher)	1.00 (0.99-1.01)
Serum intact PTH (per 10 pg/mL higher)	1.00 (0.99-1.01)
Serum corrected calcium (per 1 mg/dL lower)	1.01 (0.77-1.34)
Serum phosphorus (per 1 mg/dL higher)	1.23 (1.03-1.46)*
Kt/V (per 0.1 higher)	1.01 (0.92-1.12)
Non-use of VDRA	0.74 (0.45-1.18)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; BP, blood pressure; CRP, C-reactive protein; PTH, parathyroid hormone; ESA, erythropoiesis-stimulating agents; VDRA, vitamin D receptor activator

* $P < 0.05$