

Prolonged Sedentary Bouts Are Critically Involved in All-Cause Mortality in Patients on Chronic Hemodialysis: A Prospective Cohort Study

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We investigated the link between prolonged sedentary bouts and all-cause mortality in patients on chronic hemodialysis, using a prospective cohort. A total of 104 outpatients on chronic hemodialysis from 2013 to 2019, aged 71.4 ± 11.4 years, were enrolled. Prolonged sedentary bouts (≥ 30 min and ≥ 60 min) (min and bouts) and relative prolonged sedentary bouts (≥ 30 min and ≥ 60 min) (%) on the patients' non-hemodialysis days were measured by a tri-accelerometer, and we also analyzed the patients' clinical parameters. The relationship between prolonged sedentary bouts and all-cause mortality was evaluated by a survival analysis and the Cox proportional hazard model. Thirty-five patients died during the follow-up period. A Kaplan-Meier analysis detected significant differences in the survival rate between two groups stratified by the median for all prolonged sedentary-bout parameters. After the adjustment for confounding factors, all of the prolonged sedentary-bout parameters were determinant factors for all-cause mortality. These results indicate that prolonged sedentary bouts on non-hemodialysis days were closely related to all-cause mortality in the patients on hemodialysis.

Key words: sedentary bout, mortality, hemodialysis, survival analysis

The number of patients on chronic hemodialysis in Japan in 2020 was reported by The Japanese Society of Dialysis Therapy to be 347,671, and a public health challenge is applying appropriate strategies (e.g., lifestyle modification and medical treatment) for patients on chronic hemodialysis (<https://docs.jsdt.or.jp/overview/file/2020/pdf/01.pdf>). The optimal management of patients on chronic hemodialysis is thus urgently required. Sedentary behavior, which is defined as any waking activity requiring an energy expenditure of 1.5 metabolic equivalents (METs) or less, is closely related

to health outcomes [1-10]. Moreover, not only total sedentary behavior but also prolonged sedentary bouts, which reflect the quality of sedentary behavior, were associated with health outcomes in several studies [11-24]. Our cross-sectional study demonstrated that total sedentary behavior (%) was closely associated with the health-related quality of life (HRQOL) of patients on chronic hemodialysis [25], and in a cohort study total sedentary behavior (%) was also an important factor for all-cause mortality [26]. We have also investigated the relationship between prolonged sedentary bouts and HRQOL in patients on chronic hemodialysis, especially

Received July 26, 2022; accepted November 1, 2022.

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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

on non-hemodialysis days, and we observed that all parameters of prolonged sedentary bouts (≥ 30 min and ≥ 60 min) (min and bouts) were closely linked to HRQOL on non-hemodialysis days, but not on hemodialysis days [27]. Although there have been several investigations of the relationship between prolonged sedentary bouts and all-cause mortality [21-24], we have found no reports regarding the relationship between prolonged sedentary bouts and all-cause mortality evaluated by a tri-accelerometer in patients on hemodialysis in Japan. We speculated that if the effects of prolonged sedentary bouts on all-cause mortality in chronic hemodialysis patients are identified, this knowledge will help develop useful strategies to maintain and improve the health of this patient population. We conducted the present prospective cohort study to evaluate the association between prolonged sedentary bouts on non-hemodialysis days and all-cause mortality in patients on chronic hemodialysis in Japan.

Patients and Methods

Patients. A total of 104 patients on chronic hemodialysis (59 men and 45 women) among 198 patients, aged 71.4 ± 11.4 years, were enrolled. They met the following criteria (Table 1, Fig. 1): (1) They were outpatients at Innoshima General Hospital, Onomichi, Japan; (2) they were registered during the 6-year period from September 30, 2013 to September 30, 2019; (3) they provided written informed consent; and (4) their clinical parameters were available and their prolonged sedentary bouts were all measured by a tri-accelerometer. All patients were followed to September 30, 2021.

Ethical approval for this study was obtained from Ethical committee of Innoshima General Hospital, Onomichi, Japan (H25-2-27, H26-1-23, H26-12-16, H27-12-25, H28-12-9, H29-12-4, H30-11-12, H31-2-25).

Table 1 Clinical characteristics of the 104 patients on chronic hemodialysis

	Mean $\pm$ SD	Minimum	Maximum
Men/Women	59/45		
Age (years)	71.4 ± 11.4	41.0	92.0
over 65 years (%)	80 (77.0)		
Height (cm)	156.0 ± 9.0	133.6	175.6
Body weight (dry weight) (kg)	54.0 ± 10.6	30.4	91.0
BMI (kg/m ²)	22.1 ± 3.6	11.3	31.5
Duration of hemodialysis (months)	73.0 ± 80.4	2.0	338.0
History of diabetes mellitus (%)	42 (40.4)		
Hypertension (%)	97 (93.2)		
Low Back Pain (%)	33 (31.7)		
Knee pain (%)	15 (14.6)		
Blood sample			
Albumin (g/dL)	3.8 ± 0.4	2.4	5.2
Blood glucose (mg/dL)	133.5 ± 42.4	82.0	302.0
Triglyceride (mg/dL)	111.9 ± 66.6	29.0	431.0
HDL cholesterol (mg/dL)	54.6 ± 16.8	19.1	108.7
Physical Activity (Non-hemodialysis days)			
Wear time (min/day)	991.3 ± 209.3	682.8	1,436.8
Sedentary behavior (min/day)	728.9 ± 257.7	304.5	1,312.5
Prolonged sedentary bouts (≥ 30 min) (min)	430.6 ± 243.6	43.8	960.3
Prolonged sedentary bouts (≥ 60 min) (min)	275.1 ± 209.6	0.0	862.0
Prolonged sedentary bouts (≥ 30 min) (bouts)	6.3 ± 3.0	0.8	14.8
Prolonged sedentary bouts (≥ 60 min) (bouts)	2.6 ± 1.7	0.0	7.6
Relative sedentary behavior (%)	71.9 ± 14.7	32.8	96.5
Relative prolonged sedentary bouts (≥ 30 min) (%)	41.6 ± 19.4	5.2	87.9
Relative prolonged sedentary bouts (≥ 60 min) (%)	25.8 ± 17.6	0.0	79.1

BMI, body mass index.

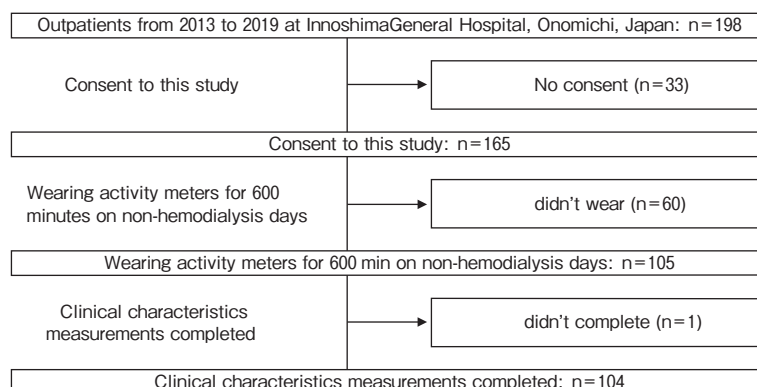


Fig. 1 Flow diagram of the study population.

Prolonged sedentary bouts. The patients' prolonged sedentary bouts were recorded by a tri-accelerometer (Active Style Pro: HJA-350IT, Omron, Kyoto, Japan), the validity and accuracy of which have been established [28-30]. As we have described [27], the subjects were asked to wear the tri-accelerometer except while sleeping and bathing for 14 consecutive days; the total non-wearing time was defined as the periods when the estimated physical activity intensity obtained from the triaxial accelerometer showed a value of 0 for >60 consecutive min. The total wearing time was defined as 24 h minus the non-wearing time.

The thresholds that we used to define prolonged sedentary bouts in the present study were ≥ 30 min (% and bout) and ≥ 60 min (% and bout), and these values plus the wearing time (min/day) and relative sedentary behavior (%) were measured as the parameters of the prolonged sedentary bouts [27].

Clinical parameters. The following clinical parameters were obtained as described [25-27]: age, height (cm), dry weight (kg), duration of hemodialysis (months), history of diabetes mellitus (yes/no), hypertension (yes/no), low back pain (yes/no), knee pain (yes/no), albumin (g/dL), blood glucose (mg/dL), triglycerides (mg/dL), and HDL cholesterol (mg/dL). Each patient's body mass index (BMI: kg/m^2) was calculated as $\text{body weight (kg)} / [\text{height (m)}]^2$. Blood examinations were performed by conventional laboratory methods. The date and cause of any deaths were obtained from the patients' medical records.

Statistical analysis. Data are expressed as the mean $\pm$ standard deviation (SD). We compared two groups stratified by the median (higher and lower groups) of the prolonged sedentary-bout parameters by

the Kaplan-Meier method. To adjust for confounding factors, *i.e.*, sex, history of diabetes mellitus, BMI, duration of hemodialysis, albumin, hypertension, low back pain and knee pain, we performed a Cox proportional hazards regression analysis, where a two-tailed p -value < 0.05 was accepted as significant. We used JMP15 Pro 15.1.0 software (SAS, Cary, NC, USA) for the statistical analyses.

Results

Table 1 summarizes the patients' clinical characteristics. The total tri-accelerometer wearing time among the 104 patients on their non-hemodialysis days was 947.3 min (median), 682.8 min (minimum), and 1436.8 min (maximum). The prolonged sedentary bouts (≥ 30 min) were $41.6 \pm 19.4\%$ and 6.3 ± 3.0 bouts, and the prolonged sedentary bouts (≥ 60 min) were $25.8 \pm 17.6\%$ and 2.6 ± 1.7 bouts. The follow-up period was 1614.8 ± 88.7 days (mean $\pm$ SD) and 1461 (745-2557) days [median (interquartile range)]. During the follow-up period, 35 patients died (pneumonia: 6, cancer: 3, renal failure: 3, sepsis: 3, sudden death: 3, cerebral infarction: 2, gastrointestinal bleeding: 2, myocardial infarction: 2, and other causes: 11).

We used the Kaplan-Meier method to compare the survival rate between the two groups stratified by the median of the prolonged sedentary-bout parameters (Fig. 2). There were significant differences in the survival rate between the two groups for all of these parameters.

To adjust for confounding factors, we evaluated the relationship between prolonged sedentary bouts and all-cause mortality by performing a Cox proportional haz-

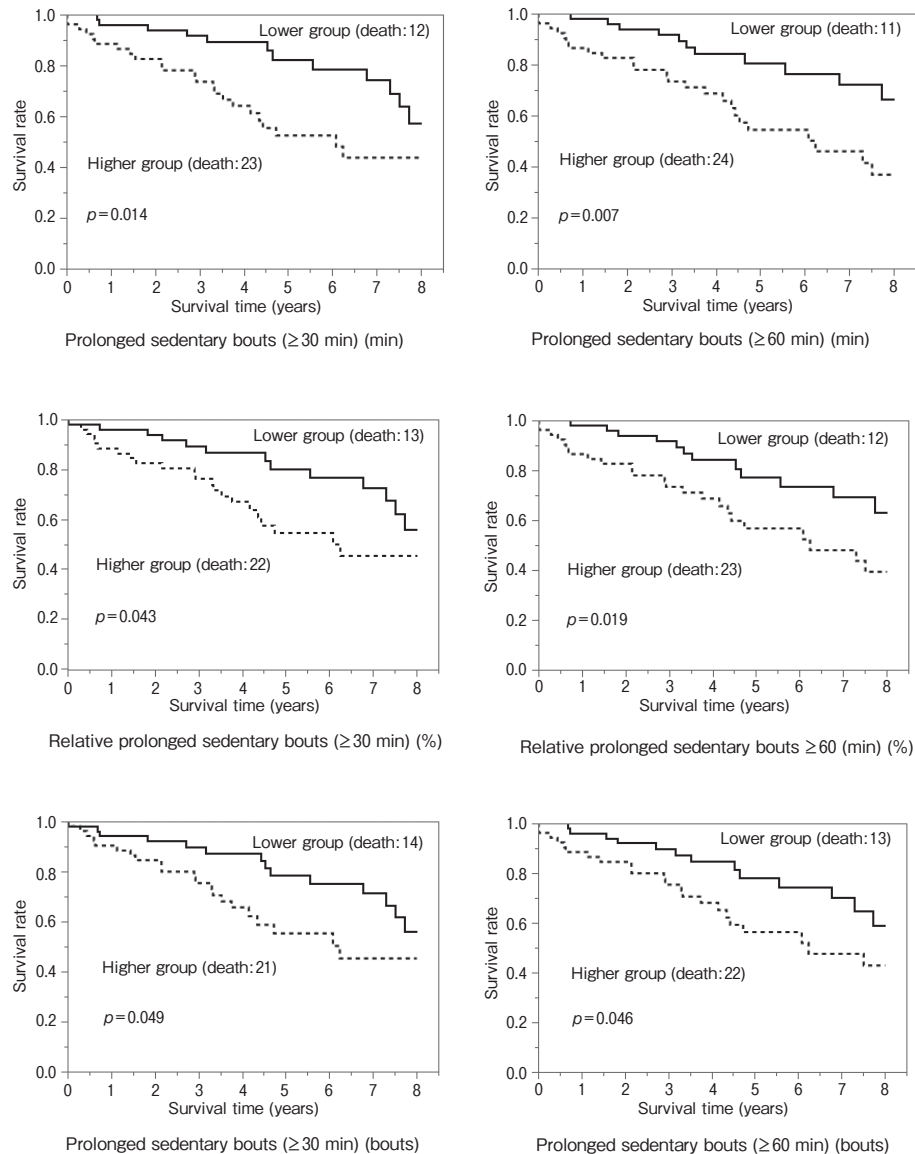


Fig. 2 Kaplan-Meier analysis of survival rates for the 104 chronic hemodialysis patients on their non-hemodialysis days.

ards regression analysis (Table 2). As noted above, 35 patients died during the follow-up period. After adjusting for age, sex, history of diabetes, BMI, duration of hemodialysis, albumin, hypertension, low back pain and knee pain, the prolonged sedentary-bout parameters were significant determinant factors for all-cause mortality in the patients on their non-hemodialysis days.

Discussion

We explored the association between prolonged sed-

entary bouts and all-cause mortality in Japanese patients on chronic hemodialysis on their non-hemodialysis days, with the use of a tri-accelerometer for each patient. The effects of prolonged sedentary bouts have been investigated in Japan [19, 20, 31-33]; for example, in their study of 1,740 community-dwelling Japanese adults, Chen *et al.* reported that half of their subjects' waking time was sedentary, and 32.7% of this time involved prolonged sedentary bouts (≥ 30 min) [31]. Shibata *et al.* noted that 297 Japanese adult subjects spent 8.8 h per day (58% of their accelerometer wearing

Table 2 Multivariate analysis of the chronic hemodialysis patients' survival rate (Cox-proportional hazard model)

Independent variables	Hazard ratio	95%CI		p-value
Relative prolonged sedentary bouts (≥ 30 min) (%)	1.03	1.00	1.05	0.0297
Age (years)	1.04	1.00	1.08	0.0368
Sex (men/women)	2.59	1.18	5.71	0.0146
History of diabetes mellitus (Yes/No)	0.75	0.35	1.62	0.4580
BMI (kg/m ²)	0.94	0.84	1.05	0.2796
Duration of hemodialysis (months)	1.00	1.00	1.01	0.2652
Albumin (g/dL)	0.72	0.28	1.78	0.4769
Hypertension	1.43	0.32	6.40	0.6244
Low back pain	1.30	0.63	2.70	0.4797
Knee pain	1.54	0.68	3.50	0.3101
Relative prolonged sedentary bouts (≥ 60 min) (%)	1.03	1.00	1.05	0.0315
Age (years)	1.04	1.00	1.08	0.0301
Sex (men/women)	2.84	1.29	6.25	0.0073
History of diabetes mellitus (Yes/No)	0.74	0.34	1.61	0.4388
BMI (kg/m ²)	0.94	0.84	1.06	0.3194
Duration of hemodialysis (months)	1.00	1.00	1.01	0.3459
Albumin (g/dL)	0.73	0.28	1.84	0.5050
Hypertension	1.57	0.35	7.01	0.5303
Low back pain	1.34	0.64	2.77	0.4402
Knee pain	1.33	0.58	3.05	0.5025
Prolonged sedentary bouts (≥ 30 min) (bouts)	1.16	1.02	1.32	0.0277
Age (years)	1.04	1.00	1.08	0.0460
Sex (men/women)	2.53	1.14	5.64	0.0189
History of diabetes mellitus (Yes/No)	0.86	0.41	1.78	0.6810
BMI (kg/m ²)	0.94	0.84	1.05	0.2792
Duration of hemodialysis (months)	1.00	1.00	1.01	0.3172
Albumin (g/dL)	0.71	0.28	1.69	0.4417
Hypertension	1.29	0.28	5.97	0.7357
Low back Pain	1.25	0.60	2.59	0.5576
Knee pain	1.65	0.74	3.65	0.2353
Prolonged sedentary bouts (≥ 60 min) (bouts)	1.35	1.07	1.70	0.0103
Age (years)	1.04	1.00	1.08	0.0767
Sex (men/women)	2.65	1.19	5.87	0.0132
History of diabetes mellitus (Yes/No)	0.75	0.35	1.62	0.4597
BMI (kg/m ²)	0.93	0.83	1.07	0.2363
Duration of hemodialysis (months)	1.00	1.00	1.00	0.5021
Albumin (g/dL)	0.77	0.30	1.93	0.5743
Hypertension	1.54	0.34	7.02	0.5588
Low back pain	1.26	0.61	2.60	0.5381
Knee pain	1.35	0.60	3.04	0.4720
Relative prolonged sedentary bouts (≥ 30 min) (min)	1.00	1.00	1.00	0.0172
Age (years)	1.04	1.00	1.08	0.0433
Sex (men/women)	2.75	1.24	6.06	0.0095
History of diabetes mellitus (Yes/No)	0.80	0.37	1.69	0.5506
BMI (kg/m ²)	0.94	0.84	1.06	0.3166
Duration of hemodialysis (months)	1.00	1.00	1.01	0.3359
Albumin (g/dL)	0.77	0.30	1.93	0.5824
Hypertension	1.29	0.29	5.83	0.7284
Low back pain	1.31	0.63	2.73	0.4664
Knee pain	1.51	0.68	3.36	0.3293
Relative prolonged sedentary bouts (≥ 60 min) (min)	1.03	1.00	1.05	0.0315
Age (years)	1.04	1.00	1.08	0.0301
Sex (men/women)	2.84	1.29	6.25	0.0073
History of diabetes mellitus (Yes/No)	0.74	0.34	1.61	0.4388
BMI (kg/m ²)	0.94	0.84	1.06	0.3194
Duration of hemodialysis (months)	1.00	1.00	1.01	0.3459
Albumin (g/dL)	0.73	0.28	1.84	0.5050
Hypertension	1.57	0.35	7.01	0.5303
Low back pain	1.34	0.64	2.77	0.4402
Knee pain	1.33	0.58	3.05	0.5025

CI, confidence interval; BMI, body mass index.

time) with 7.6 breaks per sedentary hour [32]. Other subjects' occupational activity type was related to their overall sedentary time and to patterns on working days [33], and it was reported that pre-frail and frail older adults spent more time in prolonged sedentary bouts [19]. A longitudinal analysis 430 Japanese office workers by Honda *et al.* showed that prolonged sedentary bouts were associated with a higher risk of metabolic syndrome [20].

In the present study, we evaluated prolonged sedentary bouts on the non-hemodialysis days of patients on chronic hemodialysis. The relative prolonged sedentary bouts (%) (≥ 30 min and ≥ 60 min) were approx. 41.6% and 25.8%, and prolonged sedentary bouts (≥ 30 min and ≥ 60 min) were ~ 6.3 and 2.6 ; compared to Chen *et al.*'s study, the present prolonged sedentary bouts (%) (≥ 30 min) at 41.6% were longer (32.7%), indicating that the prolonged sedentary bouts of patients on chronic hemodialysis on their non-hemodialysis days are longer than those of a healthy person.

In their examination of the relationship between prolonged sedentary bouts and all-cause mortality in 7,985 black and white adults in a cohort study, Diaz *et al.* reported that both the total sedentary time and prolonged, uninterrupted bouts were associated with all-cause mortality [21]. Dempsey *et al.* also showed that sedentary behavior in longer bout durations was associated with higher rates of cancer incidence and all-cause mortality [23]. In frail subjects, prolonged sedentary bouts and total sedentary time were associated with a higher mortality risk [24]. However, in Japan, no studies have evaluated the relationship between prolonged sedentary behavior measured by a tri-accelerometer and all-cause mortality.

Our present study explored the relationship between prolonged sedentary behavior on non-hemodialysis days and all-cause mortality in patients on chronic hemodialysis. Although increased physical activity has been shown to be beneficial for the health outcomes of patients on chronic hemodialysis [34,35], it can be difficult for patients on chronic hemodialysis to increase their physical activity—especially on hemodialysis days—because patients on hemodialysis must lie down for ≥ 3 -4 h. Considering our present findings, it may be appropriate to reduce the number of prolonged sedentary bouts on non-hemodialysis days for patients on chronic hemodialysis in clinical practice.

There are some limitations to this study. It was per-

formed at a single hospital with only Japanese patients, and the results may not be generalizable for all patients on chronic hemodialysis. In addition, the 104 patients enrolled among the 198 potential patients might have been more interested in their health. Moreover, potential disorders such as cardiovascular disease and cancer that can increase sedentary time may have affected the results. Finally, we measured prolonged sedentary behavior on only 3-4 non-hemodialysis days for each patient. Nevertheless, the results obtained herein may provide useful information to improve and maintain the health of patients on chronic hemodialysis. A higher number of patients and a multi-center study will help clarify our findings.

Acknowledgments. This research was supported in part by research grants from the Ministry of Education, Culture, Sports, Science and Technology, Japan (JSPS KAKENHI grant nos. JP 17K01851 and 20K11557).

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