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Original Paper

Utility of Regular Management of Physical Activity and Physical Function in Hemodialysis Patients

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Key Words
Disease management • Hemodialysis • Chronic kidney disease • Cardiovascular disease • Physical activity • Physical function • Exercise

Abstract
Background/Aims: Several clinical practice guidelines recommend regular assessment of physical activity and physical function as part of routine care in hemodialysis patients. However, there is no clear evidence to support these recommendations. We investigated whether the proportion of attendance at a regular program for management of physical activity and physical function can predict all-cause mortality and cardiovascular events in hemodialysis patients. ***Methods:*** This retrospective cohort study consisted of 266 hemodialysis patients participating in the management program at least once. Participants were tracked for 3 years after their first attendance at the management program to determine their attendance proportion. The main study outcomes included all-cause mortality and a composite of fatal and nonfatal cardiovascular events. ***Results:*** Median patient age was 64.5 (interquartile range, 56.8 – 72.0) years, 45% were women, and the median time on hemodialysis was 35.5 (interquartile range, 12.0 – 114.3) months at baseline. Sixty-five patients died over a median follow-up of 79 months. The incidence of cardiovascular events was 60 over a median follow-up of 68 months. Even after adjusting for any of the prognostic models, participants who attended ≤ 75% of sessions (n = 140) had higher risks of mortality (hazard ratio (HR), 1.79; 95% confidence interval (CI):

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1.00 – 3.36; *P* = 0.049) and cardiovascular events (HR, 1.84; 95% CI: 1.07 – 3.48; *P* = 0.03) than those attending > 75% of sessions (*n* = 126). ***Conclusion:*** Hemodialysis patients in whom physical activity and physical function could be assessed more regularly had better prognosis than those with only intermittent assessment.

Introduction

Patients undergoing hemodialysis have reduced levels of physical activity and physical function, [1-3] both of which are key components of frailty. A previous meta-analysis indicated a prevalence rate for frailty of 7.4% in elderly people [4]. Hemodialysis patients have an elevated prevalence of frailty, estimated to range from 30% to 40% [5, 6]. Furthermore, more than 70% of elderly patients treated with chronic hemodialysis are classified as frail [7, 8]. Although physical inactivity and decreased physical function in hemodialysis patients are associated with adverse outcomes, including mortality and hospitalization, [9-13] these are potentially modifiable conditions [14-16]. Early identification and interventions for conditions of frailty are essential to implement effective disease management strategies. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guidelines formally recommend that dialysis staff should regularly evaluate physical activity and physical function and encourage participation in regular exercise as part of routine care in patients on hemodialysis [17]. However, the evidentiary basis supporting thus recommendations remains uncertain, and it is unclear whether management strategies for physical activity and physical function are associated with long-term effects in patients undergoing hemodialysis.

The present study was performed to investigate the effects of participation in a program for regular management of physical activity and physical function on all-cause mortality and the incidences of fatal and nonfatal cardiovascular events in hemodialysis patients.

Materials and Methods

This was a retrospective observational cohort study.

Setting

This study was conducted at the Sagami Circulatory Organ Clinic, Sagamihara, Japan, which provides the physical activity and physical function management program since October 2002. The management program, which consisted mainly of routine evaluation of physical activity and physical function with provision of feedback on the results, was held once or twice each year. The purpose of the management program was to identify and modify physical inactivity and poor physical function for hemodialysis patients. All patients were encouraged every year to attend the management program by their physiotherapist or physician.

Study Population

This sample consisted of all consecutive patients who receiving hemodialysis at the clinic between October 2002 and March 2014. All the patients were undergoing maintenance hemodialysis therapy three times per week, which is the most common schedule in Japan according to the Japanese Society for Dialysis Therapy. This inclusion criteria were on hemodialysis treatment ≥3 months and capable of giving informed consent. Patients were excluded if they did not agree to participate in the study and had not attended the management program at all (Fig. 1). The study was performed according to the ethical principles of the Declaration of Helsinki and approved by the research ethics committee of Kitasato University.

Exposure Measurement: Attendance Proportion at the Management Program

The proportion of attendance at the program was defined in terms of the following: (1) whether the patient attended the program at least once, if yes (2) the participants were tracked for 3 years after their

first participation in the program, (3) Within the 3-year survey period, attendance proportion was defined as the percentage of the number of sessions actually attended by the participant divided by the number (%) of sessions available for the management program (%) (Fig. 2). To avoid survival bias and ascertainment bias, the participants who died or changed clinic within the 3-year survey period were excluded (Fig. 1).

Baseline Demographic and Clinical Factors

Baseline characteristics, including age, sex, time on hemodialysis, physical constitution (body mass index, BMI), primary kidney disease, and comorbid conditions (atherosclerotic heart disease, congestive heart failure, cerebrovascular accident/transient ischemic attack, peripheral vascular disease, dysrhythmia, and other cardiac diseases, chronic obstructive pulmonary disease, gastrointestinal bleeding, liver disease, cancer, and diabetes), were collected at entry to the study. Serum albumin levels and serum C-reactive protein levels were obtained from patient hospital charts. Comorbid conditions were quantified using a comorbidity index developed for dialysis patients consisting of primary kidney disease and the 11 comorbidities outlined above, and was calculated using the method described previously to analyze survival of hemodialysis patients [18].

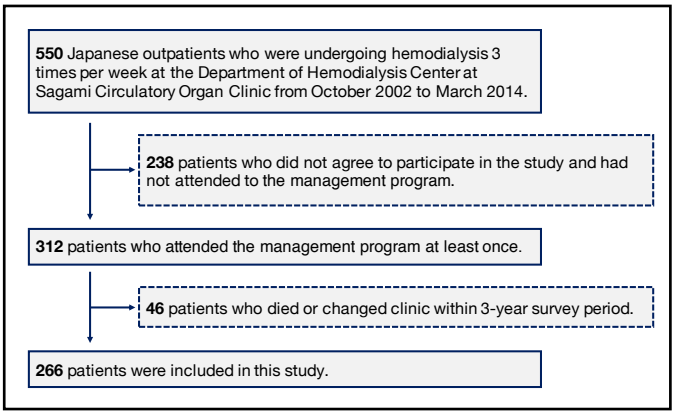

Fig. 1. Flow diagram of patient selection and exclusion process.

Physical Activity

Physical activity was measured as described previously [13]. An accelerometer (Lifecorder; Suzuken Co. Ltd., Nagoya, Japan) was used for objective assessment of baseline physical activity. The accuracy and reliability of this instrument were reported previously [19, 20]. In this study, physical activity was evaluated as the number of steps per day for a period of seven consecutive days. Measurements from a period of four consecutive non-dialysis days were analyzed.

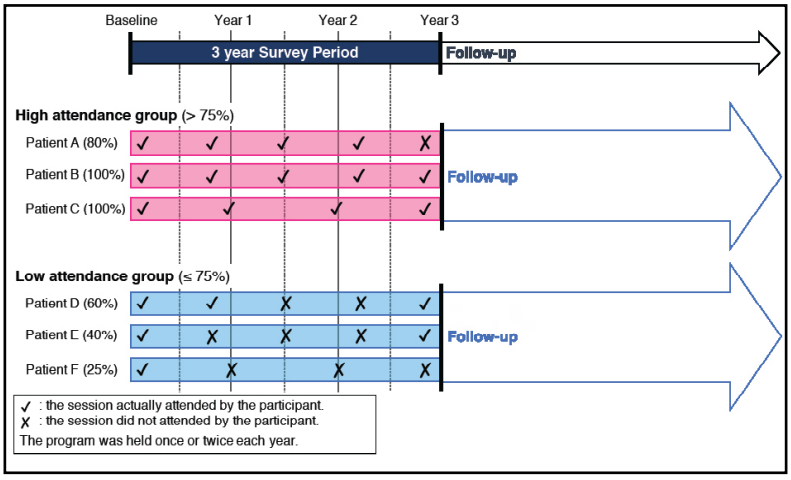

Fig. 2. Study design: timeline of survey period and follow-up. Baseline was defined as first time participants attended the management program, and participants were tracked for 3 years after obtaining baseline measurements. Within the 3-year survey period, we investigated the proportion of management program attendance, defined as the percentage of the number of sessions actually attended by the participant divided by the number of sessions available for the management program (%). As there are no established management program attendance proportion categories for hemodialysis patients, the patients were divided into the following two groups according to the median: (1) High attendance (> 75% attended) group and (2) Low attendance (≤ 75% attended) group. Analysis by Kaplan–Meier, log-rank test, and Cox proportional hazards regression analysis derived the two groups, and we set the onset event time (time 0) at the 3-year point after baseline.

Physical Function

Physical function was assessed by measuring self-selected maximum gait speed along a 10-m walkway, as described previously [21]. First, patients were asked to walk down a 10-m walking lane with an acceleration area at their usual speed to prepare for the maximum gait speed measurement. They were then instructed to walk as fast as safely possible, without running. Maximum gait speed was defined as the higher value of two attempts and expressed as the ratio of distance to time (m/s).

Outcomes

The primary study outcome was all-cause mortality, while the secondary outcome was a composite of fatal and nonfatal cardiovascular events. Cardiovascular events were defined as death from cardiovascular causes, hospital admission for nonfatal myocardial infarction, angina and heart failure. Diagnoses for primary admission were recorded using the International Classification of Disease, version 10 (ICD-10). Angina, myocardial infarction, and heart failure were defined as ICD-10 codes I20-I22 and I50. Those outcomes were assessed on the basis of death registry and medical records at the clinic. Recruitment started on October 2002, and the date of those outcomes were determined on April 2017.

Statistical Analyses

As there are no established management program attendance proportion categories have been established for hemodialysis patients, the participants were divided into two groups according to the median values: (1) High attendance (> 75% attended) group and (2) Low attendance (≤ 75% attended) group (Fig. 2 and 3). Missing values were imputed using the multivariate normal distribution with least squares imputation (Table 1). For Kaplan–Meier estimates of survival curves, the differences between groups were examined using the log-rank test. The independent prognostic effects of high management program attendance on outcomes for all participants were estimated by Cox proportional hazards regression analysis. We constructed three Cox proportional hazards regression models using pre-existing risk factors: model 1 used age, sex, BMI, serum albumin, and serum C-reactive protein as adjusting variables; model 2 included all variables from model 1 plus physical activity and maximum gait speed; and model 3 included all variables from model 2 plus comorbidity index and incidence of nonfatal cardiovascular events within 3 years.

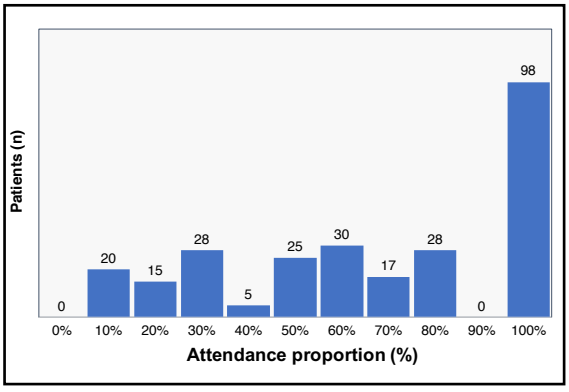

Fig. 3. Histogram: proportion of attendance at the management program.

Finally, to examine whether proportion of attendance at the management program had complementary predictive capability to baseline characteristics, we constructed receiver-operating characteristic curves for outcomes using two models: baseline characteristics only and baseline characteristics plus proportion of

Table 1. Number of missing data and multiple imputation. Values are expressed as median (interquartile range) or number (percentage) of patients. BMI, body mass index. *Incidence of nonfatal cardiovascular event within 3-year survey period

Charcteristics	Number of missing (%)		All patients (n = 266)			
			Without multiple imputation		With multiple imputation	
Age (years)	0	(0)	64.5	(56.8-72.0)	64.5	(56.8-72.0)
Female (%)	0	(0)	119	(45%)	119	(45%)
BMI (kg/m²)	98	(36.8)	20.9	(18.9-22.9)	21.1	(19.6-22.7)
Time on hemodialysis (months)	2	(0.7)	35.0	(12.0-114.8)	35.5	(12.0-114.3)
Primary kidney disease (%)						
Glomerulonephritis	0	(0)	89	(33%)	89	(33%)
Diabetes	0	(0)	112	(42%)	112	(42%)
Others	0	(0)	39	(15%)	39	(15%)
Unknown	0	(0)	20	(8%)	20	(8%)
Hypertension	0	(0)	6	(2%)	6	(2%)
Serum albumin (g/dL)	98	(36.8)	3.9	(3.7-4.1)	3.9	(3.7-4.0)
Serum C-reactive protein (mg/dL)	138	(51.9)	0.1	(0.1-0.3)	0.3	(0.1-0.5)
Comorbidity index (score)	4	(1.5)	5.0	(3.0-7.0)	5.0	(3.0-7.0)
Nonfatal cardiovascular events*(%)	0	(0)	41	(15%)	41	(15%)
Physical activity (steps)	63	(23.7)	3719	(2276-6318)	3765	(2504-5565)
Maximum gait speed (m/s)	35	(13.2)	1.47	(1.22-1.74)	1.47	(1.22-1.74)

attendance at the management program. The areas under the curves (AUCs) were compared according to the method of DeLong et al. [22]. All analyses were performed using JMP® Pro 13.2 (SAS Institute Inc., Cary, NC). All statistical tests were two sided, and $P < 0.05$ was taken to indicate statistical significance.

Results

Baseline Characteristics and Proportion of Attendance at the Management Program

We assessed the eligibility of 550 outpatients for inclusion in the present study. Of these, 238 patients refused to participate in the study and 46 participants died or changed clinic within 3 years after obtaining baseline measurements. Therefore, 266 hemodialysis patients were finally included in the present study, and more than 85% of participants were retained in the study (Fig. 1).

The patients were divided into two groups according to the median value of the proportion of attendance at the management program, as shown in Fig. 2. The baseline characteristics of the participants are shown in Table 2. Baseline characteristics and the rates of nonfatal cardiovascular events within 3 years were similar between the two groups.

Kaplan–Meier Analysis of survival and cardiovascular events

There were 65 deaths during a median follow-up of 79 months (interquartile range, 55 – 124) in the total population, consisting of 50 (35%) deaths in the Low attendance group and 15 (12%) deaths in the High attendance group at the end of follow-up. Kaplan–Meier curves followed by log-rank test showed that the rate of all-cause mortality was significantly greater in the Low attendance group than the High attendance group ($P < 0.01$) (Fig. 4A). On the other hand, 60 patients showed fatal or nonfatal cardiovascular events over a median follow-up of 68 months (interquartile range, 45 – 101), consisting of 44 (31%) patients in the Low attendance group and 16 (13%) patients in the High attendance group. Kaplan–Meier curves followed by log-rank test showed that the incidence of fatal and nonfatal cardiovascular events was significantly higher in the Low attendance group than the High attendance group ($P = 0.01$) (Fig. 4B). These findings indicated the superior survival and reduced incidence of cardiovascular events in patients with greater proportion of attendance at the management program.

Table 2. Baseline characteristics. Values are expressed as median (interquartile range) or number (percentage) of patients. BMI, body mass index. *Incidence of nonfatal cardiovascular event within 3-year survey period

Chracteristics	All (n=266)		Proportion of attendance at the management program: High attendance group (attended > 75%) (n=126)		Low attendance group (attended ≤ 75%) (n=140)	
Age (years)	64.5	(56.8 - 72.0)	63.5	(56.0 - 71.0)	65.0	(57.0 - 73.0)
Female (%)	119	(45%)	56	(44%)	63	(45%)
BMI (kg/m^2)	21.1	(19.6 - 22.7)	21.6	(19.6 - 22.7)	20.9	(19.5 - 22.5)
Time on hemodialysis (months)	35.5	(12.0 - 114.3)	27.0	(10.0 - 82.3)	45.5	(16.0 - 143.0)
Primary kidney disease (%)						
Glomerulonephritis	89	(33%)	41	(33%)	48	(34%)
Diabetes	112	(42%)	53	(42%)	59	(42%)
Others	39	(15%)	20	(16%)	19	(14%)
Unknown	20	(8%)	11	(9%)	9	(6%)
Hypertension	6	(2%)	1	(1%)	5	(4%)
Serum albumin (g/dL)	3.9	(3.7 - 4.0)	3.9	(3.7 - 4.1)	3.8	(3.7 - 4.0)
Serum C-reactive protein (mg/dL)	0.3	(0.1 - 0.5)	0.3	(0.1 - 0.5)	0.3	(0.1 - 0.5)
Comorbidity index (score)	5.0	(3.0 - 7.0)	5.0	(3.0 - 7.0)	4.5	(2.0 - 7.0)
Nonfatal cardiovascular events* (%)	41	(15%)	16	(13%)	25	(18%)
Physical activity (steps)	3765	(2504 - 5565)	3968	(2767 - 6454)	3671	(2366 - 5095)
Maximum gait speed (m/s)	1.47	(1.22 - 1.74)	1.49	(1.28 - 1.79)	1.44	(1.19 - 1.69)
Attendance proportion (%)	75	(40 - 100)	100	(100 - 100)	50	(30 - 70)

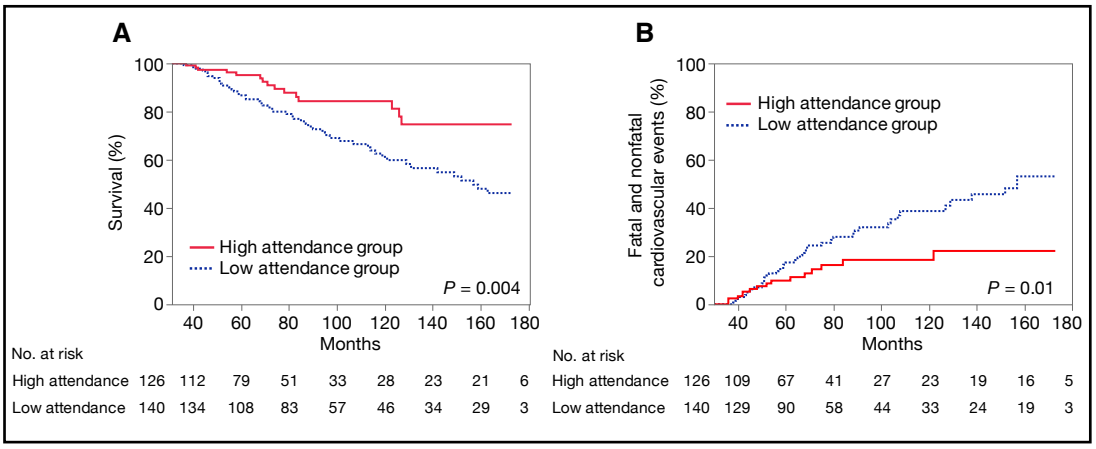

Fig. 4. Kaplan–Meier analysis of survival (A) and cardiovascular events (B) in 266 patients undergoing hemodialysis. The High attendance group (attended > 75% of all available sessions in the management program) had significantly better survival and lower incidence of cardiovascular disease than the Low attendance group (≤ 75% attendance).

Cox proportional hazards regression model for survival and cardiovascular events

Table 3 shows the results of Cox proportional hazards regression analyses of all-cause mortality and fatal and nonfatal cardiovascular events. The crude hazard ratio for all-cause mortality in the Low attendance group was 2.30 [95% confidence interval (CI): 1.33 – 4.25; $P = 0.003$] compared to the High attendance group. Even after adjusting for any of the prognostic models, the hazard ratio for all-cause mortality in the Low attendance group was 1.79 (95% CI: 1.00 – 3.36; $P = 0.049$) compared to the High attendance group. On the other hand, the crude hazard ratio for the incidence of fatal and nonfatal cardiovascular events in the Low attendance group was 2.02 (95% CI: 1.17 – 3.69; $P = 0.01$) compared to the High attendance group. Even after adjusting for any of the prognostic models, the hazard ratio for the incidence of these events in the Low attendance group was 1.84 (95% CI: 1.07 – 3.48; $P = 0.03$) compared to the High attendance group. These results indicated a significant association between proportion of attendance at the management program and adverse outcomes in hemodialysis patients independent of baseline characteristics, physical activity, physical function, and the incidence of cardiovascular events within 3 years.

Table 3. Risk of all-cause mortality and fatal and nonfatal cardiovascular events. Results reported as Hazard ratio and 95% confidence interval, from Cox proportional hazards models. *Model 1: adjusted for age, sex, body mass index (BMI), serum albumin, and serum c-reactive protein. †Model 2: adjusted for age, sex, BMI, serum albumin, serum c-reactive protein, physical activity and maximum gait speed. ‡Model 3: adjusted for age, sex, BMI, serum albumin, serum c-reactive protein, physical activity, maximum gait speed, comorbidity index, and incidence of nonfatal cardiovascular events within 3-year survey period

Outcomes	Proportion of attendance at the management program		P value
	High attendance group (attended > 75%)	Low attendance group (attended ≤ 75%)	
All-cause mortality			
Crude	reference	2.30 (1.33 - 4.25)	0.003
Model 1*	reference	2.05 (1.17 - 3.80)	0.01
Model 2†	reference	1.80 (1.00 - 3.39)	0.049
Model 3‡	reference	1.79 (1.00 - 3.36)	0.049
Fatal and nonfatal cardiovascular events			
Crude	reference	2.02 (1.17 - 3.69)	0.01
Model 1*	reference	2.02 (1.16 - 3.71)	0.01
Model 2†	reference	1.92 (1.09 - 3.55)	0.02
Model 3‡	reference	1.84 (1.07 - 3.48)	0.03

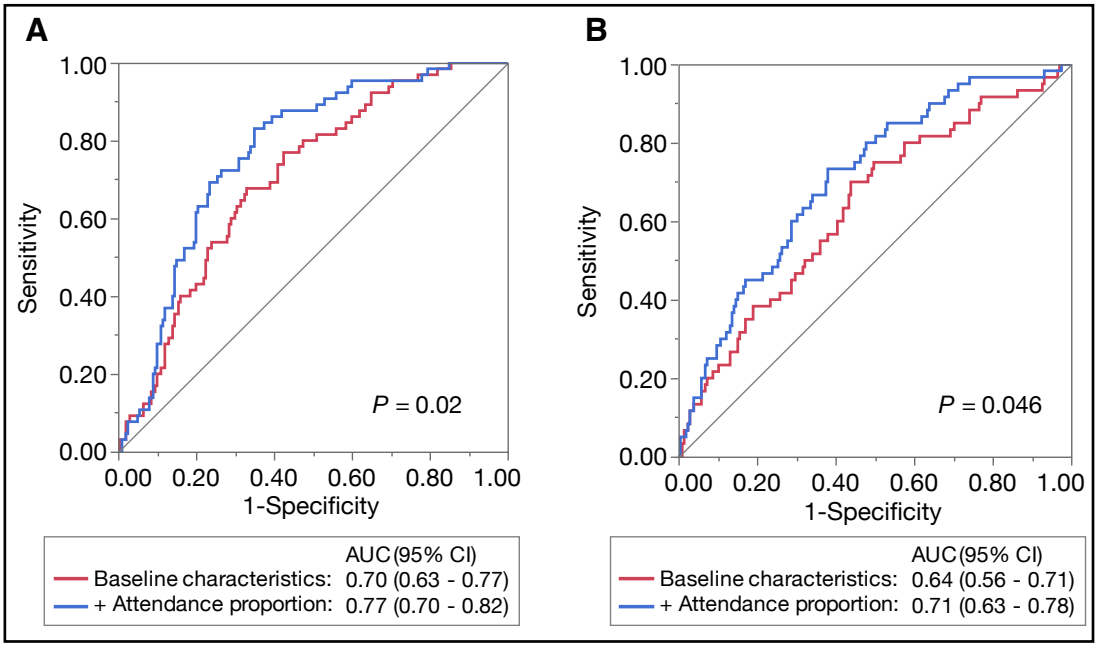

Fig. 5. Receiver-operating characteristics curves of baseline characteristics only and baseline characteristics only plus proportion of management program attendance for survival (A) and cardiovascular events (B). In both (A) and (B), the AUC was significantly better for baseline characteristics only plus proportion of management program attendance than for baseline characteristics only. Baseline characteristics, including age, sex, body mass index, serum albumin, serum C-reactive protein, physical activity, maximum gait speed, comorbidity index, and the presence of nonfatal cardiovascular events within 3 years. AUC, area under the curve; CI, confidence interval.

Complementary prognostic predictive capabilities

Receiver-operating characteristic (ROC) curve analysis was performed for the logistic regression models of baseline characteristics only and baseline characteristics plus proportion of attendance at the management program (Fig. 5). On evaluation of all-cause mortality, the AUCs on ROC curve analysis were 0.70 (95% CI: 0.63 – 0.77) for baseline characteristics only, and 0.77 (95% CI: 0.70 – 0.82) for baseline characteristics plus proportion of management program attendance. There was statistically significant difference between the AUCs of baseline characteristics only and baseline characteristics plus proportion of management program attendance ($P = 0.02$). Even when we evaluated the incidence of fatal and nonfatal cardiovascular events, the AUC was significantly better for baseline characteristics plus proportion of management program attendance [0.71 (95% CI: 0.63 – 0.78)] than for baseline characteristics only [0.64 (95% CI: 0.56 – 0.71)] ($P = 0.046$).

Discussion

Among hemodialysis patients attending a management program at least once, a lower proportion of management program attendance within the 3-year survey period was independently associated with higher risks of mortality and cardiovascular events compared to those who attended the program more regularly. We also found that the proportion of management program attendance showed complementary prognostic predictive capacity to other variables in hemodialysis patients. These results suggest that it is important for hemodialysis patients to manage physical function and physical activity regularly as part of routine care to improve their prognosis.

Chronic kidney disease is an independent risk factor for frailty, [8, 23-28] which is a predictor of injurious falls or fractures, [26] hospitalization, [8] and mortality [8, 25, 28]. Frailty among hemodialysis patients is primary characterized by physical inactivity and poor physical performance. A comprehensive meta-analysis showed that physical exercise interventions improved physical function, including muscle strength and aerobic capacity, in hemodialysis patients [14, 16]. Furthermore, wearing a pedometer, setting activity goals, use of a step diary (self-monitoring), and feedback from medical staff were shown to increase physical activity by providing motivation, reaching approximately 1000 steps per day, in hemodialysis patients [29]. In elderly patients on hemodialysis, low-intensity intradialytic exercise was shown to increase physical activity both safely and effectively [30]. These observations suggest that physical function and physical activity in hemodialysis patients can be modified, and therefore conditions of frailty should be managed as part of routine care in such patients.

Clinical geriatric practice and geriatric research involve assessment of physical performance and physical limitations to gather information on well-being and quality of life, and to determinate care needs and prognosis [31]. In aging research, measurements of physical activity and physical function are utilized as independent predictors of various adverse outcomes [32-35]. The need to assess physical activity and physical function has also been advocated in the field of nephrology research and practice [23]. Expert clinical guidelines from the Kidney Disease Improving Global Outcomes CKD Work Group or European Renal Best Practice Guideline Development Group recommend that nephrology and dialysis staff should incorporate routine assessment of functional status and encouragement of physical activity as parts of routine clinical care [17, 36]. These guidelines recommend assessment of physical activity and physical function, as physical inactivity and poor physical function have been shown to be independent predictors of adverse outcomes, and these conditions can be improved by exercise training.

Despite these guidelines [17] and a 2001 study report highlighting counseling deficits, [37] there have been no changes in practices among nephrologists [38]. Delgado and Johansen suggested that the inclusion of exercise recommendations in the guidelines was not sufficient to change practices [38]. Therefore, evidence to support these guidelines is needed. A recent multicenter clinical trial of a simple, home-based exercise program managed by dialysis staff among dialysis patients indicated meaningful physical performance benefits among those participating in exercise, [39] thus supporting the recommendations of the guidelines. However, there have been few studies assessing the impacts of exercise on mortality or major comorbidities. In addition, there was no evidence for the efficacy of operating an annual management program for assessing physical performance and encouraging regular physical activity in hemodialysis patients. To our knowledge, this is the first study to show associations between a management plan as recommended by the guidelines with mortality and cardiovascular events.

Very few studies in nephrology research and practice have used proportion of program attendance, as used in this study, as a predictive variable. On the other hand, some other studies regarding prevention, e.g., in the general sedentary population, [40] patients with cancer, [41, 42] and cardiovascular disease patients, [43-45] used the proportion of exercise-related program attendance as a predictor of outcome. In the present study, the median proportion of attendance at the management program was 75%, which was within the range reported in other studies [41, 42, 45] (Fig. 3). In cardiovascular patients, it is clear that attending a higher proportion of cardiovascular rehabilitation sessions confers greater long-term benefit than attending fewer sessions [43-45]. Our findings were consistent with those of previous studies in cardiovascular patients. In most previous studies in cardiovascular patients, cardiovascular rehabilitation program attendance was limited to those who were formally referred by their physicians. However, in the present study, all patients in the clinic were encouraged to attend the management program by their physiotherapist or physician.

Therefore, attendance patterns were investigated in a sample that was presumably unaffected by physiotherapist or physician selection bias.

In this study, the proportion of management program attendance was independently associated with higher risks of mortality and cardiovascular events, even after adjusting for physical activity and physical function, which are strong predictors of mortality and cardiovascular events in hemodialysis patients [9-13]. These results suggest that active attendance at the management program improved prognosis, regardless of the level of physical activity and physical function.

This study had some limitations. First, because it was an observational study, we were unable to adjust for all known covariates related to management program attendance. Further randomized controlled studies are needed. Second, we excluded patients who had never attended the management program. Therefore, we were unable to investigate the long-term effects in patients who did not attend the management program at all. The comorbidities in the participants may have been mild, which should be taken into consideration when generalizing our results to patients with more severe limitations. Finally, although we showed that the risks of mortality and cardiovascular events were higher in patients with lower management program attendance proportion compared to those with a higher rate of program attendance, the mechanisms underlying these observations remain to be elucidated.

Conclusion

The results of the present study showed that active attendance at a management program reduced mortality and resulted in less fatal and nonfatal cardiovascular events compared with lack of program attendance. These results support the recommendations for assessing physical activity and physical function as part of routine care in hemodialysis patients.

Acknowledgements

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Disclosure Statement

The authors have no conflicts of interest to declare.

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