

4. Maaroufi A, Fafin C, Mougel S *et al.* Patients' preferences regarding choice of end-stage renal disease treatment options. *Am J Nephrol* 2013; 37: 359–369
5. Povlsen JV, Ivarsen P. Assisted automated peritoneal dialysis (AAPD) for the functionally dependent and elderly patient. *Perit Dial Int* 2005; 25 (Suppl 3): S60–S63
6. Dimkovic N, Oreopoulos DG. Assisted peritoneal dialysis as a method of choice for elderly with end-stage renal disease. *Int Urol Nephrol* 2008; 40: 1143–1150
7. Brown EA, Wilkie M. Assisted peritoneal dialysis as an alternative to in-center hemodialysis. *Clin J Am Soc Nephrol* 2016; 11: 1522–1524
8. Franco MR, Fernandes N, Ribeiro CA *et al.* A Brazilian experience in assisted automated peritoneal dialysis: a reliable and effective home care approach. *Perit Dial Int* 2013; 33: 252–258
9. Oliver MJ, Quinn RR, Richardson EP *et al.* Home care assistance and the utilization of peritoneal Dialysis. *Kidney Int* 2007; 71: 673–678
10. Xu R, Zhuo M, Yang Z *et al.* Experiences with assisted peritoneal dialysis in China. *Perit Dial Int* 2012; 32: 94–101
11. Covic A, Bammens B, Lobbedez T *et al.* Educating end-stage renal disease patients on dialysis modality selection: clinical advice from the European Renal Best Practice (ERBP) Advisory Board. *Nephrol Dial Transplant* 2010; 25: 1757–1759
12. Bevilacqua MU, Turnbull L, Saunders S *et al.* Evaluation of a 12-month pilot of long-term and temporary assisted peritoneal dialysis. *Perit Dial Int* 2017; 37: 307–313
13. Lobbedez T, Verger C, Ryckelynck J-P *et al.* Outcome of the sub-optimal dialysis starter on peritoneal dialysis. Report from the French Language Peritoneal Dialysis Registry (RDPLF). *Nephrol Dial Transplant* 2013; 28: 1276–1283
14. Snijders T, Bosker R. *Multilevel Analysis: an Introduction to Basic and Advanced Multilevel Modeling*. London: Sage, 1999
15. Ulutas O, Farragher J, Chiu E *et al.* Functional disability in older adults maintained on peritoneal dialysis therapy. *Perit Dial Int* 2016; 36: 71–78
16. 'Tableaux de l'Économie Française'. National Institute for Statistics and Economic Studies (INSEE). <https://www.insee.fr/fr/statistiques/1906668?sommaire=1906743> (27 November 2017, date last accessed)
17. Povlsen JV, Ivarsen P. Assisted peritoneal dialysis: also for the late referred elderly patient. *Perit Dial Int* 2008; 28: 461–467
18. Kurella Tamura M, Covinsky KE, Chertow GM *et al.* Functional status of elderly adults before and after initiation of dialysis. *N Engl J Med* 2009; 361: 1539–1547
19. Belasco A, Barbosa D, Bettencourt AR *et al.* Quality of life of family caregivers of elderly patients on hemodialysis and peritoneal dialysis. *Am J Kidney Dis* 2006; 48: 955–963
20. Figueiredo AE, Bernardini J, Bowes E *et al.* A syllabus for teaching peritoneal dialysis to patients and caregivers. *Perit Dial Int* 2016; 36: 592–605
21. 'Évaluation médico-économique des stratégies de prise en charge de l'insuffisance rénale chronique terminale en France'. French Health Authority. https://www.has-sante.fr/portail/upload/docs/application/pdf/2010-10/note_cadrage_irc_t_vf.pdf (27 November 2017, date last accessed)

Received: 9.7.2017; Editorial decision: 9.11.2017

Nephrol Dial Transplant (2018) 33: 1452–1458
doi: 10.1093/ndt/gfx260
Advance Access publication 5 September 2017

Development and validation of a prediction model for loss of physical function in elderly hemodialysis patients

Shingo Fukuma^{1,2,3,4*}, Sayaka Shimizu¹, Ayumi Shintani^{2,5}, Tsukasa Kamitani^{1,2}, Tadao Akizawa⁶ and Shunichi Fukuhara^{1,2,3}

¹Department of Healthcare Epidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan, ²Research Division, Institute for Health Outcomes and Process Evaluation research (iHope International), Kyoto, Japan, ³Center for Innovative Research for Communities and Clinical Excellence (CIRC2LE), Fukushima Medical University, Fukushima, Japan, ⁴Human Health Sciences, Graduate School of Medicine, Kyoto University, Kyoto, Japan, ⁵Department of Medical Statistics, Osaka City University, Osaka, Japan and ⁶Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

*Correspondence and offprint requests to: Shingo Fukuma; E-mail: fukuma.shingo.3m@kyoto-u.ac.jp

ABSTRACT

Background. Among aging hemodialysis patients, loss of physical function has become a major issue. We developed and validated a model of predicting loss of physical function among elderly hemodialysis patients.

Methods. We conducted a cohort study involving maintenance hemodialysis patients ≥ 65 years of age from the Dialysis

Outcomes and Practice Pattern Study in Japan. The derivation cohort included 593 early phase (1996–2004) patients and the temporal validation cohort included 447 late-phase (2005–12) patients. The main outcome was the incidence of loss of physical function, defined as the 12-item Short Form Health Survey physical function score decreasing to 0 within a year. Using backward stepwise logistic regression by Akaike's Information

Criteria, six predictors (age, gender, dementia, mental health, moderate activity and ascending stairs) were selected for the final model. Points were assigned based on the regression coefficients and the total score was calculated by summing the points for each predictor.

Results. In total, 65 (11.0%) and 53 (11.9%) hemodialysis patients lost their physical function within 1 year in the derivation and validation cohorts, respectively. This model has good predictive performance quantified by both discrimination and calibration. The proportion of the loss of physical function increased sequentially through low-, middle-, and high-score categories based on the model (2.5%, 11.7% and 22.3% in the validation cohort, respectively). The loss of physical function was strongly associated with 1-year mortality [adjusted odds ratio 2.48 (95% confidence interval 1.26–4.91)].

Conclusions. We developed and validated a risk prediction model with good predictive performance for loss of physical function in elderly hemodialysis patients. Our simple prediction model may help physicians and patients make more informed decisions for healthy longevity.

Keywords: dialysis, elderly, physical function, risk prediction

INTRODUCTION

The number of older hemodialysis patients is on the rise in many countries [1, 2] and the loss of physical function among elderly patients has become a major issue [3–5]. In Japan, the average age of hemodialysis patients is now >65 years and 65% of hemodialysis patients are >65 years old [6, 7]. Physical disability is known to aggravate clinical outcomes and disrupt the daily living of hemodialysis patients [5, 8, 9]. Given the frequency of regular dialysis sessions (usually three times per week), maintenance of physical function is crucial to the continuation of regular and unaided visits to dialysis facilities. Further, a loss of physical function can result in the greater use of medical and long-term care. Therefore, from both a clinical and societal perspective, it is necessary to identify hemodialysis patients at high risk of losing physical function and requiring early intervention based on individual risk.

Previous studies have examined several risk factors for loss of physical function in elderly populations [10–15]. These studies have shown that older age and certain comorbid conditions are independently associated with physical function decline. However, given that elderly patients are likely to have multiple risk factors, their risk should be assessed multidirectionally. Early identification of patients who are at high risk for losing physical function would allow for timely intervention to protect against this loss. However, no validated risk prediction model in this area has yet been developed.

To identify patients at high risk for the loss of physical function we developed and validated a risk prediction model for the loss of physical function in elderly hemodialysis patients. To further assess the clinical importance of the loss of physical function, we also examined its influence on 1-year mortality.

MATERIALS AND METHODS

Study population

The Dialysis Outcomes and Practice Patterns Study (DOPPS) is a prospective, international, observational study of representative hemodialysis patients. In the DOPPS, representative dialysis facilities were enrolled and a random sample of hemodialysis patients were selected from each participating facility. Details of the DOPPS design have been reported previously [16].

In the present study, we used data from the DOPPS in Japan between 1996 and 2012. We included hemodialysis patients ≥ 65 years of age who had received dialysis therapy for at least 6 months. We excluded patients without baseline physical function data and those without outcome data on physical function 1 year later.

After selecting patients based on the above criteria, we defined three cohorts for three different purposes as follows: (i) derivation of the model, (ii) validation of the model and (iii) survival analysis. To develop the prediction model for the loss of physical function, we used data from the early phase of the DOPPS (Phases 1 and 2 between 1996 and 2004) and excluded patients who already had a loss of physical function at baseline. Loss of physical function was defined as a 12-item Short Form Health Survey (SF-12) physical function score of 0. For temporal validation, we used data from the late phase of the DOPPS (Phases 3 and 4 between 2005 and 2012). For this cohort as well, we also excluded patients who had a loss of physical function at baseline. For the survival analysis, we used data from all phases in our examination of the association between loss of physical function and mortality.

Outcomes

The main outcome of the prediction model was the incidence of a loss of physical function as assessed by the SF-12 physical function score [17, 18]. In the SF-12, patients are asked to describe the extent of their ability to perform two physical activities (moderate activities and ascending the stairs). Response alternatives for each item are ‘not difficult’ (2 points), ‘difficult’ (1 point) and ‘very difficult’ (0 points). The physical function score from the two items is summed and transformed into a scale of 0 to 100 points. Physical function scores were measured twice, at baseline and 1 year later. The risk of a loss of physical function was defined as a decrease in physical function score for the two items to 0 (i.e. both physical activities are very difficult) 1 year later. Previous studies have reported that a decrease in physical function is associated with poor activities of daily life independence [19, 20]. A physical function score of 0 for the SF-12 is regarded as indicative of the need for help from another person in one’s daily life.

Candidate predictors

Using the derivation cohort, we examined the following candidate predictors in accordance with previous studies [15, 21–30]: age (continuous), gender (dichotomous), dialysis vintage (continuous), blindness status (dichotomous), diabetes status (dichotomous), cardiovascular disease status (dichotomous), dementia status (dichotomous), body mass index (continuous),

mental health score (continuous), difficulty of moderate activity (three categories in a questionnaire) and difficulty of ascending stairs (three categories in a questionnaire). All of these predictors were measured at baseline. The mental health score was assessed using the SF-12 [18].

We entered 11 potential predictors in multivariate logistic regression (Supplementary Table S1). Using backward stepwise logistic regression analysis by Akaike Information Criteria (AIC), six predictors (age, gender, dementia, mental health and two items of moderate activity and ascending stairs) were selected for the final model (minimum AIC was 338.1). The continuous predictors were transformed into clinically meaningful categorical variables to develop a clinically useful scoring system. For example, age was selected and transformed into a dichotomous variable (<75 or ≥75 years) [22, 23]. Mental health score was transformed into a categorical variable according to quartile points.

Derivation of the model

Using the derivation cohort, which included patients treated in the early phase of the DOPPS (1996–2004), we conducted multivariate logistic regression including the following selected predictors: age (continuous), gender (dichotomous), dementia (dichotomous), mental health score (continuous), difficulty of moderate activity (three categories) and difficulty of ascending stairs (three categories). The categorical variables were coded as factor variables with dummy coding in the model. We conducted complete case analysis and the multivariate logistic model included 585 patients in the derivation cohort. To develop a simple prediction model, we also conducted multivariate logistic regression after categorization of continuous variables of age and mental health score. Points were assigned to each predictor based on the estimated β coefficients (coefficient-based scoring method) from the derivation cohort, with the baseline risk set at 0 points (Table 2). The points for each predictor were calculated as a ratio of the smallest positive β coefficient (0.35; β coefficient of ‘females’) and that ratio was rounded to the nearest integer. The total score was calculated by summing the points for each predictor [31]. We examined model performance in the derivation cohort. Discrimination of the model, which indicates how well a model distinguishes patients with the outcome from those without, was assessed by calculating Harrell’s C-statistic [32]. A C-statistic >0.7 and 0.8 indicates good and excellent discrimination, respectively. Calibration of the model, which indicates agreement between the observed outcomes and predictions, was assessed by comparing the observed proportion of patients with the outcome and the mean of the predicted probabilities (Table 3), known as calibration-in-the-large [31].

Validation of the model

For internal validation, we examined the model performance in the bootstrapped cohort [31]. A total of 1000 bootstrapped samples were generated from the whole cohort, including both the derivation and validation cohort. We calculated the C-statistic and calibration-in-the-large in the bootstrapped cohort as we had in the original cohort and compared the results (Table 3).

Table 1. Baseline characteristics of the derivation and validation cohorts

Variable	Derivation cohort DOPPS Phases 1 and 2 (1996–2004) (n = 593)	Validation cohort DOPPS Phases 3 and 4 (2005–12) (n = 447)	P-value*
Age, years, mean ± SD	71.6 ± 5.1	71.9 ± 5.6	0.23
Age, years, median (IQR)	71 (67–74)	71 (68–76)	
Female, n (%)	222 (37.4)	173 (37.9)	0.73
Dialysis vintage, years, mean ± SD	5.8 ± 5.3	6.3 ± 6.2	0.17
Dialysis vintage, years, median (IQR)	4.0 (1.9–8.3)	4.0 (1.5–9.0)	
Missing, n (%)	1 (0.2)	5 (1.1)	
Body mass index, kg/m ² , mean ± SD	20.5 ± 2.7	21.0 ± 2.9	0.01
Missing, n (%)	30 (5.1)	16 (3.5)	
Comorbidities, n (%)			
Diabetes	175 (29.5)	158 (34.7)	0.12
Cardiovascular disease	348 (58.6)	322 (70.6)	<0.01
COPD	12 (2.0)	19 (4.2)	0.04
Dementia	12 (2.0)	18 (4.0)	0.06
Blindness	54 (9.1)	11 (2.4)	<0.01
Serum albumin, g/dL, mean ± SD	3.8 ± 0.4	3.8 ± 0.4	0.28
<3.8, n (%)	259 (43.6)	193 (42.3)	
≥3.8, n (%)	231 (38.9)	252 (55.3)	
Missing, n (%)	104 (17.5)	11 (2.4)	
Hemoglobin, g/dL, mean ± SD	9.8 ± 1.2	10.3 ± 1.2	<0.01
<10, n (%)	335 (56.4)	170 (37.3)	
10–< 12, n (%)	221 (37.2)	250 (54.8)	
≥12, n (%)	22 (3.7)	28 (6.1)	
Missing, n (%)	16 (2.7)	8 (1.8)	
Phosphorus, mg/dL, mean ± SD	5.3 ± 1.4	5.3 ± 1.2	0.73
<3.5, n (%)	50 (8.4)	21 (4.6)	
3.5– < 6.0, n (%)	352 (59.3)	303 (66.5)	
≥6.0, n (%)	185 (31.1)	128 (28.1)	
Missing, n (%)	7 (1.2)	4 (0.9)	
Mental health score, mean ± SD	65.1 ± 25.8	63.0 ± 19.0	0.14
Mental health score, median (IQR)	50 (50–75)	60 (50–80)	
Physical function score at baseline, mean ± SD	59.4 ± 25.8	62.8 ± 25.8	0.03
Physical function score at baseline, median (IQR)	50 (50–75)	50 (50–75)	

COPD, chronic obstructive pulmonary disease.

*Derivation and validation cohorts were compared using the independent *t*-test or chi-squared test.

For temporal validation, we examined the model performance in the validation cohort, which included more recently treated patients in the late phase of the DOPPS (2005–12). We then calculated the C-statistic, calibration-in-the-large and calibration slope (Table 3).

We created calibration plots to evaluate the calibration in the derivation and validation cohort (Figure 1). The calibration plot shows consistency between the predicted probability by the

Table 2. Predictors for loss of physical function by multivariable logistic regression in the derivation cohort

Predictors	β	Points assigned	95% CI	P-value
Age ≥ 75 years	0.92	3	0.35–1.50	<0.01
Female	0.35	1	–0.21–0.92	0.22
Dementia	0.97	3	–0.45–2.39	0.18
Mental health score ^a				
≤ 50	0.56	2	–0.57–1.68	0.33
51–70	0.44	1	–0.83–1.71	0.49
71–90	–0.08	0	–1.28–1.12	0.90
>90 (reference)	–	–	–	–
Moderate activity				
Very difficult	2.51	7	1.39–3.63	<0.01
Difficult	1.24	4	0.31–2.16	<0.01
Not difficult (reference)	–	–	–	–
Ascending stairs				
Very difficult	1.41	4	0.08–2.74	0.04
Difficult	1.05	3	–0.20–2.31	0.10
Not difficult (reference)	–	–	–	–

Number of analyzed patients was 585 (complete care analysis).

C-statistic was 0.80 (95% CI 0.74–0.85).

^aThe mental health score was assessed as the SF-12 mental health score and the category was defined based on the quartiles of the scores.

prediction model and the observed probability using the loess algorithm [33]. The dashed line indicates perfect fit (reference), which has an intercept of 0 and a slope of 1.

Survival analysis

For survival analysis, we did not exclude patients who had lost physical function at baseline. The total number of patients in the survival analysis was 1376. We examined the association between baseline loss of physical function and 1-year mortality using a logistic regression model, with adjustment for age, gender, dialysis vintage, body mass index, cardiovascular disease status, diabetes status and dementia status. We calculated the adjusted odds ratios and 95% confidence intervals (CIs).

All statistical analyses were performed using STATA version 14.2 (StataCorp, College Station, TX, USA).

RESULTS

Study population

A total of 1376 maintenance hemodialysis patients ≥ 65 years of age were selected as the study population. We excluded patients with a loss of physical function at baseline ($n = 282$) and those with missing outcome data due to death during the 1-year follow-up ($n = 54$). We included 593 patients in the derivation cohort (early phase between 1996 and 2004) and 447 patients in the validation cohort (late phase between 2005 and 2012).

Table 1 shows the baseline characteristics of the derivation and validation cohorts. In both cohorts, the median age was 71 years and the median dialysis vintage was 4.0 years. The median physical function scores at baseline were similar between the two cohorts {median 50 points [interquartile range (IQR) 50–75 points]} and were lower than the respective values in the same-age (70–80 years old) Japanese general population [men: median 85 (IQR 65–95); women: median 70 (IQR 50–

Table 3. Performance of the prediction model in the derivation and validation cohorts

	Derivation cohort	Bootstrapped cohort ^c	Validation cohort
Calibration-in-the-large, %	11.0 ^a /10.9 ^b	10.7 ^a /10.8 ^b	11.9 ^a /11.9 ^b
Calibration slope	1.00 (0.87–1.13)	1.01 (0.91–1.11)	0.89 (0.61–1.16)
C-statistic (95% CI)	0.79 (0.74–0.84)	0.76 (0.72–0.80)	0.72 (0.66–0.79)

^aObserved proportion.

^bMean of predicted values.

^c1000 bootstrapped samples were generated from the whole cohort, including both the derivation and validation cohort.

85)] [34]. Many characteristics of the derivation cohort were similar to those in the validation cohort. Some characteristics were different between the derivation and validation cohort (body mass index, hemoglobin level, physical function score and prevalence of cardiovascular disease, chronic obstructive pulmonary disease and blindness). Sixty-five (11.0%) and 53 (11.9%) elderly hemodialysis patients lost physical function within 1 year in the derivation and validation cohorts, respectively.

Predictors for the loss of physical function

We examined the association between the candidate predictors and the loss of physical function in multivariate logistic regression. The associations of the categorical variables (diabetes, cardiovascular disease, dementia, blindness and two questions about baseline physical function) and continuous variables (age, dialysis vintage, body mass index and baseline mental health score) with the loss of physical function are shown in Supplementary Table S1. Using backward stepwise logistic regression analysis by AIC, we selected the predictors in the final model. The final model included age, gender, dementia status, mental health score and baseline physical function of moderate activity and ascending stairs. To improve the clinical usefulness of the prediction model (easy scoring without a calculator), age was categorized into dichotomous variables according to previous studies [2, 35] and mental health score was categorized into four categories according to quartiles. Table 2 shows the β coefficients of the predictors in the final model in the derivation cohort.

In the sensitivity analysis, we included dialysis adequacy (Kt/V) as a potential predictor. However, Kt/V was not selected for the final model based on the results of backward stepwise logistic regression analysis by AIC.

Model performance

The performance of the final model is shown in Table 3. The C-statistic, which describes the discrimination of a model, was 0.79 (95% CI 0.74–0.84) in the derivation cohort. We found similar discrimination in the bootstrapped cohort [C-statistic 0.76 (95% CI 0.72–0.80)]. The C-statistic in the validation cohort was 0.72 (95% CI 0.66–0.79).

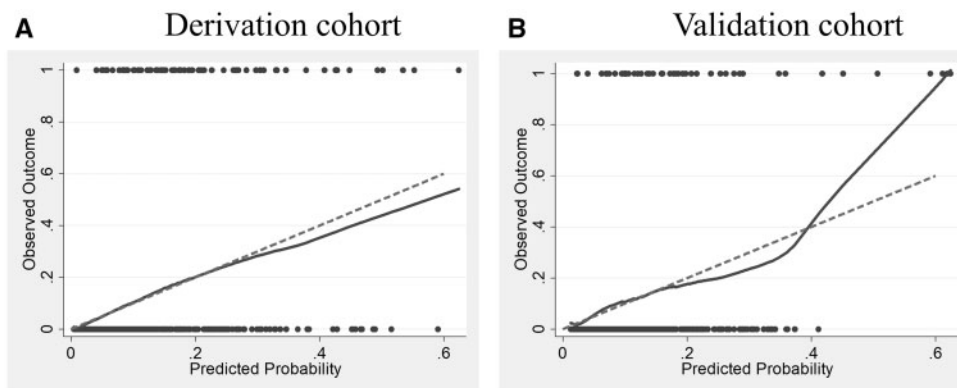


FIGURE 1: Calibration plot in the derivation and validation cohorts. The calibration plot shows consistency between the predicted probability by the prediction model and observed probability using the loss algorithm. The dashed line indicates perfect prediction (reference), which has an intercept of 0 and a slope of 1. The distribution of actual dichotomous values (0 and 1) of outcome is shown at the top and bottom of the figure.

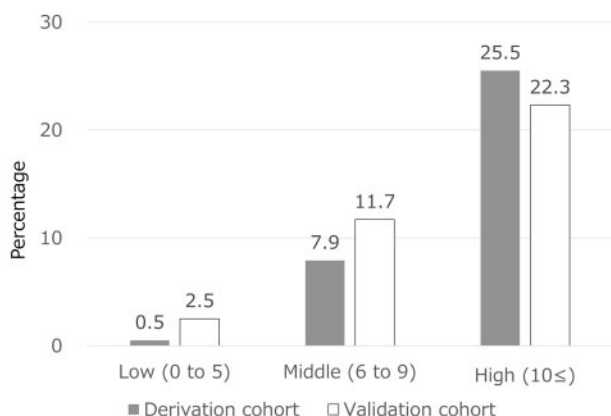


FIGURE 2: Loss of physical function by score categories showing the proportion of loss of physical function by score categories in the derivation and validation cohort. The three categories (low, middle and high) were defined based on the score tertiles.

Calibration of the model was assessed using a calibration plot, which compares the observed and predicted risks for loss of physical function (Figure 1). We also showed the calibration-in-the-large of 10.9% predicted risk compared with an 11.0% observed risk in the derivation cohort (Table 3). The calibration slope was 1.00, 1.01 and 0.89 in the derivation, bootstrapped and validation cohorts, respectively. The predicted risk was similar to the observed risk in both the bootstrapped cohort and the validation cohort. We found no systematic over- or under-prediction based on the results of the validation cohort.

Score and observed incidence of loss of physical function

The six predictors (age, gender, dementia status, mental health score, moderate activity and ascending stairs) were incorporated into the score (ranging from 0 to 20) based on the β coefficients by a multivariate logistic regression model (Table 2). Figure 2 shows the proportion of loss of physical function by score categories [low (0–5), middle (6–9) and high (≥ 10)] in the derivation and validation cohorts. We found that the observed incidence of a loss of physical function increased monotonously by score category.

Table 4. Association between baseline physical function and mortality

Physical function score at baseline	Number	Mortality, %	Odds ratio ^a	95% CI
0	282	20.6	2.48	1.26–4.91
25	224	7.1	1.04	0.47–2.29
50	408	4.2	0.66	0.31–1.40
75	229	3.5	0.57	0.23–1.42
100 (reference)	233	5.6	–	–

^aAdjusted for age, gender, dialysis vintage, body mass index, cardiovascular disease, diabetes and dementia.

Loss of physical function and mortality

Among 1376 patients, 282 (20.5%) had lost independence at baseline (i.e. baseline physical function score was 0). During the 1-year follow-up, 278 patients (20.2%) lost physical function and 112 (8.1%) died. Loss of physical function at baseline was strongly associated with 1-year mortality after adjusting for potential confounders (Table 4).

DISCUSSION

We developed and validated a risk prediction model for the loss of physical function in elderly hemodialysis patients. The developed model had good performance both in discrimination (C-statistic > 0.7 in the derivation and validation cohorts) and calibration (Figures 1 and 2). Predictors in the final model were the six variables of age, gender, dementia status, mental health score and two questions about baseline physical function, which can be measured in daily practice. To our knowledge, this is the first model for predicting the loss of physical function in elderly hemodialysis patients. We also found that the loss of physical function was common [282/1376 (20.2%) at baseline] and strongly associated with 1-year mortality in elderly hemodialysis patients. These results suggest that our newly developed prediction model may help physicians and patients make more informed decisions for healthy longevity based on patients' individual conditions.

The number of elderly hemodialysis patients is on the rise worldwide [2]. In the worldwide DOPPS, the mean age of hemodialysis patients at enrollment of each phase has

increased over time, reaching >60 years in participating countries (Europe, USA, Canada, Australia and Japan) in Phase 3 (2005–6). The Japanese Society for Dialysis Therapy (JSDT) reported that the mean age of dialysis patients was 67.5 years and >65% were >65 years of age in 2016 in Japan [7]. Among the elderly hemodialysis patients, loss of physical function is a critical issue for achieving healthy longevity. Loss of physical function makes it difficult for elderly patients to visit the dialysis clinic regularly by themselves and thereby leads to a loss of independence and greater use of medical and social resources. For patients and their families, individualized information on the risk of a loss of physical function may be useful for ensuring that patients enjoy a healthy life during dialysis therapy. For physicians, stratifying patients by risk may be useful for developing individualized and intensive treatment regimens to prevent the loss of independence [31]. For policymakers, predicting the societal burden due to the loss of physical function in such populations may be useful for planning a sustainable, long-term care system.

No model for predicting the loss of physical function in elderly hemodialysis patients has yet been developed. Although age-related loss of physical function is well known, physical function may vary substantially, even among similarly aged elderly people [10]. The present findings support the notion that the risk of loss of physical function must be assessed individually using a prediction model that includes multiple risk factors. In our model, we included a number of established risk factors that were examined as independent predictors of a loss of physical function [10–13, 15, 26–30]. One study identified an association between chronic disease and physical function [13]. The physical function scores in hemodialysis patients were significantly lower than those among patients with other chronic diseases, such as cardiovascular disease, diabetes, and mental illnesses. Hemodialysis patients are more likely to have multiple morbidities and are at a higher risk for loss of physical function than other populations. Given that our prediction model was specifically developed for use in the high-risk population of elderly hemodialysis patients, we hope the model will prove clinically relevant. Baseline physical function, mental illness and dementia may be associated with a loss of physical function through decreased physical activity [27, 28]. The findings from another study suggested that dementia might occur prior to physical function loss [26, 29]. Given that our results were consistent with those findings, we believe that the predictors in our final model are clinically comprehensible.

The clinical relevance of stratifying patients by risk of a loss of physical function was further confirmed by the association between loss of physical function and mortality. We found that loss of physical function at baseline was strongly associated with 1-year mortality in elderly hemodialysis patients. These results are consistent with previous studies [5, 36]. Loss of physical function may be a sign of overall declining health in elderly patients.

The major strength of this study is our analysis of a representative population of elderly hemodialysis patients from the DOPPS in Japan. The DOPPS selected representative hemodialysis patients in each country via a stratified random sampling

approach [16]. Developing a prediction model using a representative sample improves the model's generalizability. Because the DOPPS in Japan has maintained its basic protocol for a long time (since 1996), we were able to conduct temporal validation using a late-phase cohort. We confirmed that the developed model was generalizable to more recent patients (both discrimination and calibration were good in the validation cohort) even though we found differences in some characteristics between the derivation and validation cohorts. Second, we conducted this study in Japan, whose population is aging more rapidly than in other countries. As previously mentioned, the mean age of hemodialysis patients is increasing globally. Results from an already aging population will help physicians and policymakers in other countries prepare for aging in their own countries in the near future. Third, we were able to examine the changes in the physical function score, because the DOPPS has collected physical function scores annually using the SF-12. The SF-12 is a validated self-reported questionnaire for measuring health-related quality of life and is widely used in many clinical studies [17, 18].

However, despite these strengths, several limitations to the present study also warrant mention. First, there is no agreed-upon definition of loss of physical function based on the SF-12 physical function score. However, the SF-12 physical function domain contains two items, 'moderate activity' and 'ascending the stairs'. If a patient responds that both items are 'very difficult', they are defined as having a loss of physical function. This definition is clinically sensible, and the association with 1-year mortality adds clinical meaning to the definition. Second, we only used the data available from the DOPPS. For example, DOPPS only measured physical function and mental health on a subjective (self-reported) scale. We were therefore unable to examine physiological indicators of physical function and mental health assessment by physicians. However, self-reported measures may be clinically useful because they reflect the patient's abilities in daily life. In addition, all predictors in the final model are easy to measure without any special devices, and risk estimation using our simple model can be easily accomplished in routine clinical practice. Third, the model has not been validated outside Japan. Thus its generalizability should be assessed in a future study.

In conclusion, we developed and validated the first prediction model for loss of physical function in elderly hemodialysis patients. Our simple prediction model, which includes only six predictors, can be easily used by patients, physicians and policymakers to make more informed decisions and more easily achieve healthy longevity. Further research is needed to validate the model in other populations and to examine the impact of implementing the model in clinical practice.

SUPPLEMENTARY DATA

Supplementary data are available online at <http://ndt.oxfordjournals.org>

CONFLICT OF INTEREST STATEMENT

S.F., T.A. and S.F. have acted as scientific advisors to Kyowa Hakko Kirin. T.A. reports personal fees from Bayer Health

Care, Astellas, JT Corporation, Torii Pharma, Ono Pharma, Kissei Pharma and Chugai Pharma outside the submitted work. The remaining authors have no conflicts of interest to declare. S.S. and A.S. declare that they have no relevant financial interests.

FUNDING

The DOPPS Program is supported by Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare and Vifor Fresenius Medical Care Renal Pharma. Additional support for specific projects and countries is provided by Keryx Biopharmaceuticals, Merck Sharp & Dohme, Proteon Therapeutics, Relypsa and F. Hoffmann-LaRoche; in Canada by Amgen, BHC Medical, Janssen, Takeda and the Kidney Foundation of Canada (for logistics support); in Germany by Hexal, Deutsche Gesellschaft für Nephrologie, Shire and the WiNe Institute; and for the Peritoneal DOPPS in Japan by the Japanese Society for Peritoneal Dialysis. All support is provided without restrictions on publications.

REFERENCES

- Jager KJ, van Dijk PCW, Dekker FW *et al.* The epidemic of aging in renal replacement therapy: an update on elderly patients and their outcomes. *Clin Nephrol* 2003; 60: 352–360
- Canaud B, Tong L, Tentori F *et al.* Clinical practices and outcomes in elderly hemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clin J Am Soc Nephrol* 2011; 6: 1651–1662
- Painter P. Physical functioning in end-stage renal disease patients: update 2005. *Hemodial Int* 2005; 9: 218–235
- Altintepe L, Levendoglu F, Okudan N *et al.* Physical disability, psychological status, and health-related quality of life in older hemodialysis patients and age-matched controls. *Hemodial Int* 2006; 10: 260–266
- Jassal SV, Karaboyas A, Comment LA *et al.* Functional dependence and mortality in the International Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2016; 67: 283–292
- Hanafusa N, Nakai S, Iseki K *et al.* Japanese society for dialysis therapy renal data registry—a window through which we can view the details of Japanese dialysis population. *Kidney Int Suppl* 2015; 5: 15–22
- The Japanese Society for Dialysis Therapy Annual Report. 2015. <http://docs.jsdt.or.jp/overview/index2016.html>.
- Hung MC, Sung JM, Chang YT *et al.* Estimation of physical functional disabilities and long-term care needs for patients under maintenance hemodialysis. *Med Care* 2014; 52: 63–70
- Bossola M, Di Stasio E, Antocicco M *et al.* Functional impairment is associated with an increased risk of mortality in patients on chronic hemodialysis. *BMC Nephrol* 2016; 17: 72
- Beckett LA, Brock DB, Lemke JH *et al.* Analysis of change in self-reported physical function among older persons in four population studies. *Am J Epidemiol* 1996; 143: 766–778
- Penninx BWJH. Depressive symptoms and physical decline in community-dwelling older persons. *JAMA* 1998; 279: 1720
- Achat H, Kawachi I, Spiro A *et al.* Optimism and depression as predictors of physical and mental health functioning: the normative aging study. *Ann Behav Med* 2000; 22: 127–130
- Mittal SK, Ahern L, Flaster E *et al.* Self-assessed physical and mental function of haemodialysis patients. *Nephrol Dial Transplant* 2001; 16: 1387–1394
- Newman AB, Gottdiener JS, McBurnie MA *et al.* Associations of subclinical cardiovascular disease with frailty. *J Gerontol A Biol Sci Med Sci* 2001; 56: M158–M166
- Clegg A, Young J, Iliffe S *et al.* Frailty in elderly people. *Lancet* 2013; 381: 752–762
- Young EW, Goodkin DA, Mapes DL *et al.* The Dialysis Outcomes and Practice Patterns Study (DOPPS): an international hemodialysis study. *Kidney Int* 2000; 57: S74–S81
- Ware JE Jr, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30: 473–483
- Ware JE Jr, Kosinski M, Keller SD. A 12-item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; 34: 220–233
- Gill TM, Williams CS, Mendes de Leon CF *et al.* The role of change in physical performance in determining risk for dependence in activities of daily living among nondisabled community-living elderly persons. *J Clin Epidemiol* 1997; 50: 765–772
- Vaughan L, Leng X, La Monte MJ *et al.* Functional independence in late-life: maintaining physical functioning in older adulthood predicts daily life function after age 80. *J Gerontol A Biol Sci Med Sci* 2016; 71(Suppl 1): S79–S86
- Stuck AE, Walthert JM, Nikolaus T *et al.* Risk factors for functional status decline in community-living elderly people: a systematic literature review. *Soc Sci Med* 1999; 48: 445–469
- Covinsky KE, Palmer RM, Fortinsky RH *et al.* Loss of independence in activities of daily living in older adults hospitalized with medical illnesses: increased vulnerability with age. *J Am Geriatr Soc* 2003; 51: 451–458
- Arnau A, Espauella J, Serrarols M *et al.* Risk factors for functional decline in a population aged 75 years and older without total dependence: A one-year follow-up. *Arch Gerontol Geriatr* 2016; 65: 239–247
- Greiner PA, Snowdon DA, Schmitt FA. The loss of independence in activities of daily living: the role of low normal cognitive function in elderly nuns. *Am J Public Health* 1996; 86: 62–66
- Hays JC, Saunders WB, Flint EP *et al.* Social support and depression as risk factors for loss of physical function in late life. *Aging Ment Health* 1997; 1: 209–220
- Sauvaget C, Yamada M, Fujiwara S *et al.* Dementia as a predictor of functional disability: a four-year follow-up study. *Gerontology* 2002; 48: 226–233
- Kaplan MS, Newsom JT, McFarland BH *et al.* Demographic and psychosocial correlates of physical activity in late life. *Am J Prev Med* 2001; 21: 306–312
- Burton LC, Shapiro S, German PS. Determinants of physical activity initiation and maintenance among community-dwelling older persons. *Prev Med* 1999; 29: 422–430
- Hartley P, Gibbins N, Saunders A *et al.* The association between cognitive impairment and functional outcome in hospitalised older patients: a systematic review and meta-analysis. *Age Ageing* 2017; 46: 559–567
- Seidel D, Jagger C, Brayne C *et al.* Recovery in instrumental activities of daily living (IADLs): findings from the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Age Ageing* 2009; 38: 663–668
- Steyerberg E. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*. New York: Springer Science & Business Media, 2008
- Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996; 15: 361–387
- Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. New York: Springer, 2001
- Fukuhara S, Suzukamo Y. *Manual of SF-36v2 Japanese version*. Kyoto: Institute for Health Outcomes & Process Evaluation Research, 2004
- Glaudet F, Hottelart C, Allard J *et al.* The clinical status and survival in elderly dialysis: example of the oldest region of France. *BMC Nephrol* 2013; 14: 131
- Knight EL, Ofstun N, Teng M *et al.* The association between mental health, physical function, and hemodialysis mortality. *Kidney Int* 2003; 63: 1843–1851

Received: 4.4.2017; Editorial decision: 13.7.2017