




BMJ Open Association between facility-level adherence to phosphorus management guidelines and mortality in haemodialysis patients: a prospective cohort study

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ABSTRACT

Objectives To examine the association between facility-level adherence to phosphorus management guidelines and mortality among patients with haemodialysis, and to explore the facility-related factors associated with facility-level guideline adherence.

Design Prospective cohort study.

Setting The Dialysis Outcomes and Practice Pattern Study, which included 57 representative dialysis facilities in Japan between 2012 and 2015.

Participants A total of 2054 adult patients who received maintenance haemodialysis were included. We defined exposure according to the following four categories, depending on whether facility-level target ranges of serum phosphorus concentration adhered to the Japanese clinical practice guidelines: adherence group (lower limit ≥ 3.5 mg/dL and upper limit ≤ 6.0 mg/dL), low-target group (lower limit < 3.5 and upper limit ≤ 6.0), wide-target group (lower limit < 3.5 and upper limit > 6.0) and high-target group (lower limit ≥ 3.5 and upper limit > 6.0).

Primary outcome measure The primary outcome was the patient all-cause mortality rate.

Results The mortality rate among the patients was 7.3 per 100 person-years; 27 facilities (47%) set targets according to the guidelines. HRs for mortality with reference to the adherence group were 1.04 (95% CI 0.76 to 1.43) in the low-target group, 1.11 (95% CI 0.68 to 1.81) in the wide-target group and 1.95 (95% CI 1.12 to 3.38) in the high-target group. Involvement of dieticians in dialysis treatment was associated with facility-level guideline adherence (OR 4.51; 95% CI 1.15 to 17.7).

Conclusions A higher facility-level target range for phosphorus was associated with increased patient mortality. Among facilities that set the target according to the guidelines, dieticians tended to be involved in dialysis care. These findings suggest the importance of reviewing facilities' treatment policies in relation to updated guidelines and the need to work with relevant professionals.

INTRODUCTION

Clinical practice guidelines (CPGs) play an important role in reducing inappropriate

Strengths and limitations of this study

- A major strength of this study is that we analysed a large sample of representative dialysis facilities in Japan; therefore, we could examine facility-level factors.
- The measurement of exposure and facility-level treatment policy had high validity, as the data were collected prospectively to prevent recall bias.
- The facility-level treatment policy reported by facility directors might not represent an aggregate opinion in each facility.

variations in clinical practice, thereby improving the quality of care and decreasing healthcare expenditures.¹⁻⁶ In recent years, many clinical societies have shown high interest in CPGs, and have developed and published CPGs in various clinical areas. CPGs are widely used in quality management and healthcare policy. However, adherence to CPGs differs considerably, with several studies reporting that adherence percentages varied from 10% to 80%.^{7,8} The impact of CPGs is dependent on their acceptance by clinicians in daily practice. Accordingly, research into whether clinicians practice according to the guidelines has received scientific and political interest.⁹

Dialysis treatment is one of the representative clinical areas for which CPGs have been generated worldwide.^{10,11} There are many treatment goals in this area, among which the treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD) has received considerable attention from nephrologists. In particular, serum phosphorus control is a major target that has been associated with prognosis.^{12,13}

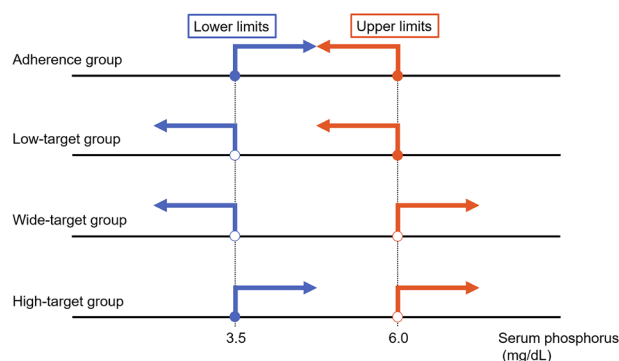


Figure 1 Definition of the exposure. Adherence group, lower limit of serum phosphorus value (LL) ≥ 3.5 mg/dL and upper limit of serum phosphorus value (UL) ≤ 6.0 mg/dL; low-target group, < 3.5 mg/dL and UL ≤ 6.0 mg/dL; wide-target group, < 3.5 mg/dL and UL > 6.0 mg/dL; high-target group, ≥ 3.5 mg/dL and UL > 6.0 mg/dL. LL, lower limits; UL, upper limits.

Although almost the same treatment targets for phosphorus have been set in CPGs for phosphorus management worldwide, it is unknown whether institutional treatment policies that do not adhere to the CKD-MBD guidelines affect patient outcomes. Also, the recommendations in CPGs are not absolute, and the CPGs take into account that treatment policies will vary depending on the condition of individual patients. However, it is unclear whether differences between recommendations in CPGs and facility-level treatment policies affect patient outcomes.

The treatment policy for phosphorus management at each facility may be an appropriate indicator for assessing guideline adherence, as it can synthetically reflect CPG accessibility, attitudes of healthcare professionals and usability of medical resources.^{7 9 14–21} Furthermore, the facility characteristics associated with phosphorus management policies have not been identified.

We, therefore, examined the association between guideline adherence regarding the facility-level target range of serum phosphorus and mortality in dialysis patients, and explored the facility-related factors associated with facility-level guideline adherence.

METHODS

Study design and participants

This was a cohort study using data from the Dialysis Outcomes and Practice Pattern Study (DOPPS) in Japan. The DOPPS was a prospective cohort study of patients enrolled randomly from a representative sample of dialysis facilities within each participating country. All participants in the DOPPS provided written informed consent prior to study enrolment. We conducted this study in compliance with the Declaration of Helsinki. This study was approved by Kyoto University Graduate School and Faculty of Medicine Kyoto University Hospital

Ethics Committee. Detailed information on the design of DOPPS has been provided elsewhere.^{22 23}

Our cohort study used data from the Japanese DOPPS (J-DOPPS) phase V conducted from 1 June 2012 to 31 May 2015. We included patients receiving maintenance haemodialysis (HD) who were older than 18 years. We excluded patients who had been receiving dialysis therapy for less than 90 days because mineral metabolism markers fluctuate more dramatically near the beginning of dialysis therapy and may not represent patterns of steady-state bone mineral dynamics. Additionally, patients with any missing data were excluded.

Definition of exposure

The exposure was the facility-level target range of serum phosphorus concentration set by each facility where patients were receiving dialysis. Facility directors reported lower limits (LL) and upper limits (UL) of serum phosphorus targets at baseline and then every 4 months during the study period. We defined the exposure according to the following four categories (figure 1), depending on whether the baseline LL and UL ranges adhered to the CPG for the management of CKD-MBD published by the Japanese Society for Dialysis Therapy in April 2012.^{24 25} This CPG recommended a serum phosphorus target range from 3.5 to 6.0 mg/dL.

- ▶ Adherence group: both LL and UL adhered to the values in the CPG (LL: ≥ 3.5 mg/dL, UL: ≤ 6.0 mg/dL).
- ▶ Low-target group: LL fell below and UL adhered the values in the CPG (LL: < 3.5 mg/dL, UL: ≤ 6.0 mg/dL).
- ▶ Wide-target group: LL fell below and UL exceeded the values in the CPG (LL: < 3.5 mg/dL, UL: > 6.0 mg/dL).
- ▶ High-target group: LL adhered to and UL exceeded the values in the CPG (LL: ≥ 3.5 mg/dL, UL: > 6.0 mg/dL).

Outcomes

The primary outcome was the all-cause mortality rate, indicated by HRs. The secondary outcome was major adverse cardiovascular events (MACEs), including acute myocardial infarction, stroke and all-cause mortality.²⁶ The survival period was calculated from patient enrolment to death. Survival at the end of the observation period (31 May 2015) was censored.

Covariates

Data collected at baseline consisted of age, gender, HD vintage (years), serum albumin (g/dL), serum phosphorus (< 3.5 mg/dL, 3.5–6.0 mg/dL, > 6.0 mg/dL),²⁴ corrected serum calcium (< 8.4 mg/dL, 8.4–10.0 mg/dL, > 10.0 mg/dL),²⁴ intact parathyroid hormone (PTH) (< 60 pg/mL, 60–240 pg/mL, > 240 pg/mL),²⁴ history of diabetes mellitus, history of liver disease, history of hypertension, history of heart disease (coronary heart disease, coronary artery disease, angina, myocardial infarction, bypass surgery and coronary angioplasty), history of stroke or transient ischaemic attack (TIA), history of

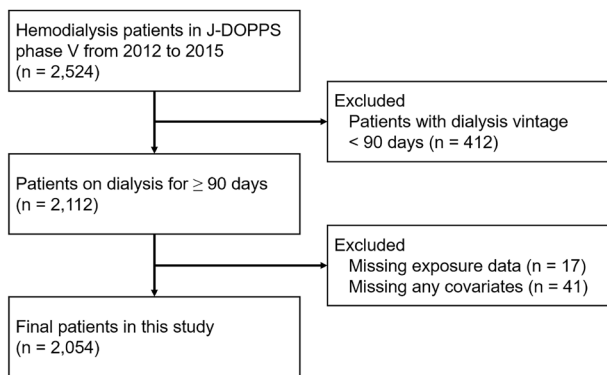


Figure 2 Selection process for study population. J-DOPPS, Japanese Dialysis Outcomes and Practice Pattern Study.

cancer, treatment time on dialysis per day (<211 min, 211–240 min, >240 min)²⁷ and CKD-MBD-related medications (phosphate binder, oral vitamin D receptor activator (VDRA), intravenous VDRA and cinacalcet). Corrected serum calcium was calculated as measured calcium concentration (mg/dL) + (4-serum albumin (g/dL)) when serum albumin was under 4.0 g/mL.^{24 28}

To investigate facility-level factors related to guideline adherence, we assessed facility size, organisation type (private or public), consultation time per week, presence of nocturnal dialysis programmes, and whether dietitians, nurses certified in dialysis nursing and/or certified social workers were involved in dialysis treatment. Facility size was divided into three groups according to the number of HD patients: fewer than 100 patients, 100–150 patients and more than 150 patients. Consultation time was defined as consultation hours per week, classified as less than 40 hours, 40–60 hours and more than 60 hours per week. Nocturnal dialysis denoted that a facility offered HD treatment at night while patients slept.

Statistical analysis

The baseline characteristics were summarised for all patients and for patients categorised in the four exposure groups. Continuous variables were described as means and SD, and categorical variables were represented as counts and percentages (%). Differences in the distribution of patient characteristics at baseline among the four groups were assessed using one-way analysis of variance for continuous variables and the χ^2 test for categorical variables. Also, we described the individual changes of serum phosphorus during the study period by exposures. Observation time and number of deaths and MACEs within the follow-up period were also summarised. The event-free survival rate for all-cause mortality and MACEs according to the categorised groups was described by the Kaplan-Meier method and compared using the log-rank test.

The primary analysis evaluated the association between the facility-level target range and mortality. We evaluated a mixed-effects Cox regression model with random intercept to account for potential differences among

dialysis facilities. This analysis was adjusted for patient-level covariates: age, gender, HD vintage, serum albumin, serum phosphorus, corrected serum calcium and comorbidities (diabetes mellitus, liver disease, hypertension, heart disease, stroke or TIA, and cancer). Unadjusted and adjusted HRs and 95% CIs were estimated using the survival model. To assess the proportionality assumption of the survival model, we examined Schoenfeld residuals. The secondary analysis was used the same model and adjusted variables for investigating the association between the facility-level target range and MACEs.

The exploratory analysis examined the facility-level factors that were associated with facility-level guideline adherence. First, facility characteristics were described by frequencies and percentages. Second, we conducted univariate logistic regression analyses using a binary outcome: adherence group or not. Explanatory variables were facility size, organisation type, consultation time, availability of nocturnal dialysis, availability of dietitian and availability of certified social worker. Third, the variables that met the criterion $p < 0.2$ in univariate analyses were entered into the final multivariate logistic regression model. ORs and 95% CIs were estimated and tested for statistical significance.

All statistical analyses were performed using STATA V.16.1 (StataCorp). Two-tailed p values of less than 0.05 were considered statistically significant, except for the univariate regressions of the explanatory analysis, as noted earlier.

Patient and public involvement

There was no patient and public involvement.

RESULTS

Patient flow

A total of 2524 patients participated in the study between 2012 and 2015. Patients were excluded if their history of dialysis was less than 90 days ($n = 412$) or in case of missing essential data (facility with missing exposure data: $n = 17$, patients with missing covariates: $n = 41$), resulting in 2054 patients included in our analysis (figure 2).

Facility treatment policy

In this study, 47% of facilities (27/57 facilities) adhered to the CPG for CKD-MBD; this adherence group included 941 (46%) patients. There were 729 (35%) patients in the low-target group (21 facilities), 212 (10%) in the wide-target group (5 facilities) and 172 (8.4%) in the high-target group (4 facilities). The minimum-maximum target ranges of phosphorus among these non-adherence groups, as reported by each facility's director, were 2.0–6.0 mg/dL in the low-target group, 2.0–6.5 mg/dL in the wide-target group and 3.5–7.0 mg/dL in the high-target group. Most facilities (44/57 facilities) did not change their target ranges from baseline to final measurement.



Patient characteristics

Patient baseline characteristics are summarised in [table 1](#). Considering all patients, the mean age was 65.5 years (SD=12.4), and 65% of patients were men. The high-target group had a mean age 2 years lower than that of the other groups. The serum albumin value in the high-target group was higher (3.9 g/dL) than that in the other three groups (average 3.7 g/dL). Regarding patient-level serum phosphorus, the adherence, low-target, and wide-target groups were in the range of serum phosphorus recommended by the CPG for CKD-MBD for approximately 60%–70% of patients. In contrast, less than 50% of the high-target group patients had phosphorus levels in accordance with the recommendation. The change of serum phosphorus by the groups during the study was presented in online supplemental figure 1. Over 70% of patients in the adherence group had serum calcium in the range 8.4–10.0 mg/dL, while the other groups had approximately 50%–60% of patients in that range. The group with the higher UL target also had higher levels of intact PTH. In all groups, most patients had a treatment time of 211–240 min. The high-target group had more patients with less than 211 min and more than 240 min compared with the other three groups. Regarding comorbidities, heart disease in the wide-target and high-target groups was proportionally less common than in the other groups. The high-target group was less likely to use prescription drugs related to CKD-MBD than were the other three groups.

Facility-level target ranges of phosphorus and patient outcomes

In terms of all-cause mortality, 329 (16%) patients died during the observation period. The median follow-up period was 2.97 years (IQR: 1.33–3.00). The mortality rate among all patients was 7.3 per 100 person-years. The mortality rate of the adherence group (6.9 per 100 person-years) was lower than that of the other three categories: 7.7 in the low-target group, 7.5 in the wide-target group and 7.5 in the high-target group per 100 person-years ([table 1](#)). The results of the Kaplan-Meier method and the log-rank test were presented in online supplemental materials (online supplemental figures 2 and 3).

With reference to the adherence group, the adjusted HRs (95% CIs) for all-cause mortality were 1.04 (0.76 to 1.43; $p=0.79$) for the low-target group and 1.11 (0.68 to 1.81; $p=0.68$) for the wide-target group. The high-target group was significantly associated with greater mortality (adjusted HR=1.95, 95% CI 1.12 to 3.38, $p=0.018$; [figure 3](#)). Plots of Schoenfeld residuals were consistent with proportionally. In terms of MACEs, this result was consistent with the result of mortality. The detailed results of the analyses were in online supplemental materials (online supplemental tables 1 and 2).

Facility characteristics

Of the 57 eligible facilities, 27 (47%) facilities set the institutional target according to the CPG for CKD-MBD,

while 30 facilities did not ([table 2](#)). Of 24 large facilities (>150 HD patients), most adhered to the CPG (48%; 13/27 facilities). In contrast, the number of small facilities (<100 HD patients) in the adherence group (19%) was less than half compared with the non-adherence group (40%). Consultation hours per week were higher in the adherence facilities than in the non-adherence facilities; 67% of facilities that adhered to the CPG provided over 60 hours of consultation, while this percentage was 33% among facilities that did not adhere to the CPG. Regarding healthcare professionals caring for HD patients, a greater percentage of facilities with dieticians and certified social workers belonged to the adherence group than the non-adherence group (81% vs 50%, and 52% vs 33%, respectively); the pattern reversed for nurses certified in dialysis nursing (0% vs 13%).

Facility factors associated with facility-level guideline adherence

In univariate logistic regression analyses, four factors were selected as candidates for the final model: facility size, consultation hours, presence of dietician, and presence of certified social worker. In the multivariate logistic regression analysis, the association between dietician presence and facility-level guideline adherence was statistically significant (adjusted OR 4.51, 95% CI 1.15 to 17.7, $p=0.031$; [table 3](#)). The c-statistic (95% CI) of the final model was 0.77 (0.65 to 0.89).

DISCUSSION

This study evaluated whether facility-level adherence to guidelines for the target range of phosphorus was associated with mortality in Japanese dialysis patients, and investigated facility-related factors associated with guideline adherence. Approximately 47% of facilities adopted treatment policies consistent with the CPG for phosphorus management. Our results showed a significant association between facility-level guideline adherence regarding target ranges of serum phosphorus and patient mortality; facilities with higher target ranges demonstrated higher mortality rates. Moreover, involving dieticians in the treatment of dialysis patients was associated with facility-level guideline adherence to target ranges for phosphorus.

Our findings help to understand the effects of facility-level guideline adherence on patient mortality. Overall, patients' actual serum phosphorus values showed trends similar to the corresponding facility target ranges. Compared with the adherence group, the low-target group exhibited a large proportion of cases with serum phosphorus below 3.5 mg/dL, the wide-target group had a higher percentage of cases with values <3.5 mg/dL or >6.0 mg/dL, and approximately half of the patients in the high-target group demonstrated values >6.0 mg/dL. Previous studies showed an association between patient-level serum phosphorus measured at baseline and all-cause mortality.^{12 13} Patients' serum phosphorus levels below 3.5 mg/dL and above 6.5 mg/dL were significantly

Table 1 Participant baseline characteristics and mortality

	Total (n=2054)		Adherence group (n=941)		Low-target group (n=729)		Wide-target group (n=212)		High-target group (n=172)		P value
	No facility=57	(12.4)	No facility=27	(12.3)	No facility=21	(12.2)	No facility=5	(12.8)	No facility=4	(12.6)	
Age (years), mean (SD)	65.5	(12.4)	65.3	(12.3)	66.5	(12.2)	65.1	(12.8)	63.1	(12.6)	0.001
Men, n (%)	1328	(65)	604	(64)	462	(63)	144	(68)	118	(69)	0.43
Haemodialysis vintage (years), mean (SD)	7.3	(7.6)	7.9	(8.0)	6.5	(6.8)	7.3	(7.7)	6.9	(7.6)	0.003
Albumin (g/dL), mean (SD)	3.7	(0.4)	3.7	(0.4)	3.6	(0.4)	3.7	(0.4)	3.9	(0.3)	<0.001
Phosphorus (mg/dL), mean (SD)	5.4	(1.4)	5.3	(1.3)	5.2	(1.4)	5.6	(1.4)	5.9	(1.6)	<0.001
<3.5 mg/dL, n (%)	116	(5.7)	38	(4.0)	60	(8.2)	10	(4.7)	8	(4.7)	<0.001
3.5–6.0 mg/dL, n (%)	1329	(65)	635	(67)	489	(67)	124	(58)	81	(47)	
>6.0 mg/dL, n (%)	609	(30)	268	(28)	180	(25)	78	(37)	83	(48)	
Calcium (mg/dL), mean (SD)	9.2	(0.7)	9.2	(0.7)	9.2	(0.7)	9.1	(0.8)	9.1	(0.9)	0.11
<8.4 mg/dL, n (%)	225	(11)	91	(9.7)	76	(10)	24	(11)	34	(20)	<0.001
8.4–10.0 mg/dL, n (%)	1322	(64)	690	(73)	436	(60)	103	(49)	93	(54)	
>10.0 mg/dL, n (%)	507	(25)	160	(17)	217	(30)	85	(40)	45	(26)	
Intact PTH (pg/mL), mean (SD)	155	(144)	153	(130)	153	(163)	165	(116)	178	(155)	0.35
<60 pg/mL, n (%)	356	(17)	176	(19)	140	(19)	24	(11)	16	(9.3)	<0.001
60–240 pg/dL, n (%)	958	(47)	448	(48)	364	(50)	88	(42)	58	(34)	
>240 pg/mL, n (%)	740	(36)	317	(34)	225	(31)	100	(47)	98	(57)	
Comorbidities, n (%)											
Diabetes mellitus	800	(39)	371	(39)	286	(39)	71	(33)	72	(42)	0.34
Liver disease	195	(9.5)	98	(10)	61	(8.4)	18	(8.5)	18	(10)	0.49
Hypertension	1599	(78)	740	(79)	565	(78)	167	(79)	127	(74)	0.55
Heart disease	535	(26)	254	(27)	210	(29)	39	(18)	32	(19)	0.002
Stroke/TIA	237	(12)	95	(10)	100	(14)	25	(12)	17	(9.9)	0.12
Cancer	227	(11)	107	(11)	80	(11)	29	(14)	11	(6.4)	0.15
Treatment time on dialysis (min/day), n (%)											
<211	375	(18)	171	(18)	129	(18)	35	(17)	40	(23)	<0.001
211–240	1088	(53)	478	(51)	396	(54)	143	(67)	71	(41)	
>240	591	(29)	292	(31)	204	(28)	34	(16)	61	(35)	
Medications, n (%)											
Phosphate binders	1516	(74)	718	(76)	529	(73)	159	(75)	110	(64)	0.006
Oral VDRA	713	(35)	352	(37)	255	(35)	61	(29)	45	(26)	0.009

Continued

Table 1 Continued

	Total (n=2054)		Adherence group (n=941)		Low-target group (n=729)		Wide-target group (n=212)		High-target group (n=172)		P value
	No facility=57	No facility=27	No facility=21	No facility=5	No facility=4	No facility=21	No facility=5	No facility=4	No facility=4		
Intravenous VDRA	623 (30)	293 (31)	209 (29)	73 (34)	48 (28)	0.63					
Cinacalcet	369 (18)	176 (19)	118 (16)	50 (24)	25 (15)	0.10					
MACEs, n (%)	354 (17)	157 (17)	130 (18)	38 (18)	29 (17)	0.93					
Death, n (%)	329 (16)	145 (15)	121 (17)	35 (17)	28 (16)	0.92					
Mortality rate (per 100 person-year)	7.3	6.9	7.7	7.5	7.5	0.83					

Adherence group, LL of serum phosphorus value (LL) ≥ 3.5 mg/dL and UL of serum phosphorus value (UL) ≤ 6.0 mg/dL; low-target group, LL < 3.5 mg/dL and UL ≤ 6.0 mg/dL; wide-target group, LL < 3.5 mg/dL and UL > 6.0 mg/dL; high-target group, LL ≥ 3.5 mg/dL and UL > 6.0 mg/dL. Calcium was albumin-corrected value: calcium + (4.0-albumin) when albumin is less than 4.0 g/dL.

Heart disease included coronary heart disease, coronary artery disease, angina, myocardial infarction, bypass surgery and coronary angioplasty.

LL, lower limits; MACEs, major adverse cardiovascular events; PTH, parathyroid hormone; TIA, transient ischaemic attack; UL, upper limits; VDRA, vitamin D receptor activator.

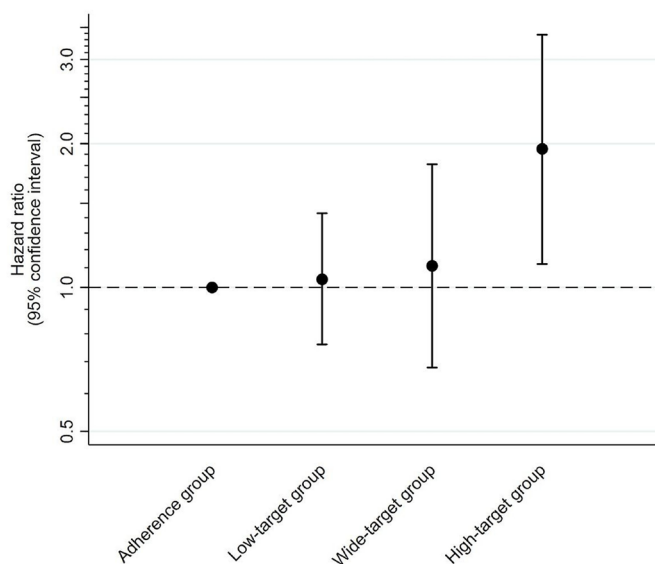


Figure 3 Mortality hazard associated with facility-level target ranges of serum phosphorus. Adherence group, lower limit of serum phosphorus value (LL) ≥ 3.5 mg/dL and upper limit of serum phosphorus value (UL) ≤ 6.0 mg/dL; low-target group, < 3.5 mg/dL and UL ≤ 6.0 mg/dL; wide-target group, < 3.5 mg/dL and UL > 6.0 mg/dL; high-target group, ≥ 3.5 mg/dL and UL > 6.0 mg/dL; adjusted for age, gender, haemodialysis vintage, serum albumin, serum phosphorus, corrected calcium and comorbidities (diabetes mellitus, liver disease, hypertension, heart disease, stroke or transient ischaemic attack and cancer). LL, lower limits; UL, upper limits.

associated with a higher risk of death.¹² Moreover, according to previous research and clinical evidence, phosphorus levels in dialysis patients tend to rise, and approximately 90% of persons in the present and previous studies exhibited values greater than 3.5 mg/dL. Therefore, clinically, the emphasis for most patients is on lowering serum phosphorus rather than raising it. Regarding the UL, the low-target and wide-target groups (maximum UL: 6.0 mg/dL in low-target group and 6.5 mg/dL in wide-target group) demonstrated almost the same levels as the adherence group, and facility directors in these three groups may have similar treatment policies to keep serum phosphorus levels in HD patients below the adequate UL. This could explain why only the high-target group showed an association with increased mortality.

In this study, we assessed the facility target range of phosphorus, which represented a facility treatment policy, and adjusted baseline patient-level phosphorus data. This result indicated that the facility treatment policy for phosphorus management could affect individual patient outcomes, even when excluding the effect of individual phosphorus status. The exposure in this study may, therefore, include not only the concept of phosphorus management but also the concept of various treatment policies from many clinical perspectives. These components might include the management of other clinical items, such as renal anaemia, dialysis adequacy, vascular

Table 2 Facility characteristics

	All facilities (n=57)		Guideline adherence				
			Adherence (n=27)		Non-adherence (n=30)		P value
Facility scale (HD patients), n (%)							
<100	17	(30)	5	(19)	12	(40)	0.21
100–150	16	(28)	9	(33)	7	(23)	
≥150	24	(42)	13	(48)	11	(37)	
Organisation type, n (%)							
Private	48	(84)	22	(81)	26	(87)	0.59
Public	9	(16)	5	(19)	4	(13)	
Consultation hours per week, n (%)							
<40	11	(19)	4	(15)	7	(23)	0.038
40–60	18	(32)	5	(19)	13	(43)	
≥60	28	(49)	18	(67)	10	(33)	
Nocturnal dialysis programmes, n (%)	34	(60)	18	(67)	16	(53)	0.31
Dietician, n (%)	37	(65)	22	(81)	15	(50)	0.013
Certified nurse in dialysis nursing, n (%)	4	(7.0)	0	(0)	4	(13)	0.049
Certified social worker, n (%)	24	(42)	14	(52)	10	(33)	0.16

Dietician, certified nurse in dialysis nursing and certified social worker were defined as whether the facility had at least one such person in charge of HD patients.
HD, haemodialysis.

access and comorbidity, as well as patient education. Facilities that set the same target ranges of phosphorus as those indicated in the CPG may tend to offer high-quality care to patients. Therefore, even if individual-level effects at baseline were detected, there was an association between facility treatment policy and mortality. That is, this association between exposure and mortality in our study may indicate the composite effects of institutional treatment strategies.

There could be several reasons why dialysis facilities did not set their targets according to the CPG. First, some physicians were sceptical about guidelines and related evidence; they thought, for example, that the guidelines were too rigid to apply to individual patients, and not appropriate for translation to typical patients with different demographic characteristics.^{15–17,29} Generally, the practice of evidence-based medicine is described as ‘the integration of best research evidence with clinical expertise and patient values.’³⁰ This does not mean that medical staff blindly provide uniform treatment to all patients based on CPGs. A previous systematic review reported the two main reasons for intentional non-adherence to guidelines were contraindications and patients’ preferences.³¹ The main strategies for phosphate control are diet restrictions and dose adjustment of phosphate binders, which could harm some patients. For example, strict diet restrictions could worsen nutritional status, while increasing phosphate binders may lead to polypharmacy or constipation. Physicians who consider these potential harms could accept a less strict phosphorus target. Our findings that patients in the high-target group were less likely to take phosphate

binders support this idea. Moreover, CPGs may not be fully known to physicians although the CPG for CKD-MBD is available on an open-access website.

Additionally, this study indicated that facilities where the treatment policy was consistent with the CPG recommendation were more likely to involve dieticians in patients’ treatment. Dieticians specialise not only in phosphorus management but also in many other aspects of nutrition management, including renal-disease-related intake restriction of salt, potassium and water, and comorbidities such as diabetes mellitus and hyperlipidaemia. The facilities where dieticians are involved might offer multifaceted patient education. Further research is needed in other clinical fields, since it is possible that facility-level guideline adherence may be associated with the presence of relevant healthcare professionals.

Strengths and limitations

The first strength of the current study was its design.³² The measurement of exposure had high validity, as we collected the exposure data prospectively to prevent recall bias. The second advantage was the sample size. This study included a relatively large population and numerous dialysis centres. Therefore, we were able to evaluate facility-level factors. The third strength was the sampling method of the J-DOPPS, which was representative of most Japanese dialysis settings.³²

There were several limitations to our study. First, facility-level target ranges of phosphorus at baseline were used to define the exposure categories in this study; however, patients may have transferred into different categories

**Table 3** Facility factors associated with facility-level guideline adherence

	Univariate model			Multivariate model		
	OR	95% CI	P value	OR	95% CI	P value
Facility scale (HD patients)						
<100	Reference			Reference		
100–150	3.09	0.73 to 13.0	0.12	1.48	0.29 to 7.62	0.64
≥150	2.84	0.76 to 10.6	0.12	1.02	0.19 to 5.46	0.98
Organisation type						
Private	Reference					
Public	1.48	0.35 to 6.19	0.59			
Consultation hours per week						
<40	Reference			Reference		
40–60	0.67	0.14 to 3.35	0.63	0.55	0.08 to 3.62	0.54
≥60	3.15	0.74 to 13.4	0.12	2.88	0.60 to 13.9	0.19
Nocturnal dialysis programmes						
None	Reference					
Offered	1.75	0.60 to 5.13	0.31			
Dietician						
Absent	Reference			Reference		
Present	4.40	1.32 to 14.7	0.016	4.51	1.15 to 17.7	0.031
Certified social worker						
Absent	Reference			Reference		
Present	2.15	0.74 to 6.28	0.16	1.67	0.48 to 5.82	0.42

Dietician and certified social worker were defined as whether the facility had at least one such person in charge of HD patients. C-statistic of the final model was 0.77 (95% CI 0.65 to 0.89).

HD, haemodialysis.

during the study period. Further, as the facility treatment policy and patient data were collected at different times, misclassification might have also occurred. However, we confirmed that the facility target ranges changed minimally, and that measurement times differed only slightly throughout the observation period. Second, the facility treatment policy might not be an aggregate opinion in each facility. This is because the facility-level target range of phosphorus was reported by one facility director; if there were multiple doctors in a centre, there might not have necessarily been consensus on the target range. Third, our findings did not imply that setting facility treatment targets according to CPGs will directly reduce mortality. Fourth, the adjustment of unknown confounding factors associated with the relationships we investigated was not possible, which is a general limitation of observational studies. Finally, it may be difficult to generalise our findings to other areas or guidelines, as the present study did not investigate other types of CPGs or countries.

CONCLUSION

Our findings demonstrated that approximately half of the dialysis centres in Japan set target ranges according to the CPG for phosphorus management. We found an

association between a higher target range of serum phosphorus and patient mortality. Our results also suggested that the presence of a healthcare professional involved with the facility-level treatment policy was associated with facility-level guideline adherence. These results suggest that facility directors and healthcare providers should refer to updated CPGs when evaluating treatment policies in their facilities. Furthermore, physicians and other healthcare professionals who are relevant to facility treatment policies may play a key role in guideline adherence.

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Contributors TI conceived and designed the study. SS, SF, and YY supervised the conduct of the study. TI collected and analysed the data and drafted the manuscript. SS, TH, YM, SF, and YY reviewed and made substantial contributions to earlier drafts. All authors have read and approved the final version of the manuscript.

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Competing interests SF has acted as a scientific advisor to Kyowa Kirin. TI, SS, TH, YM and YY have no relevant financial interests.

Patient consent for publication Not required.

Ethics approval All participants in the study provided written informed consent prior to study enrolment. This study was approved by Kyoto University Graduate School and Faculty of Medicine Kyoto University Hospital Ethics Committee (approval number R1301).

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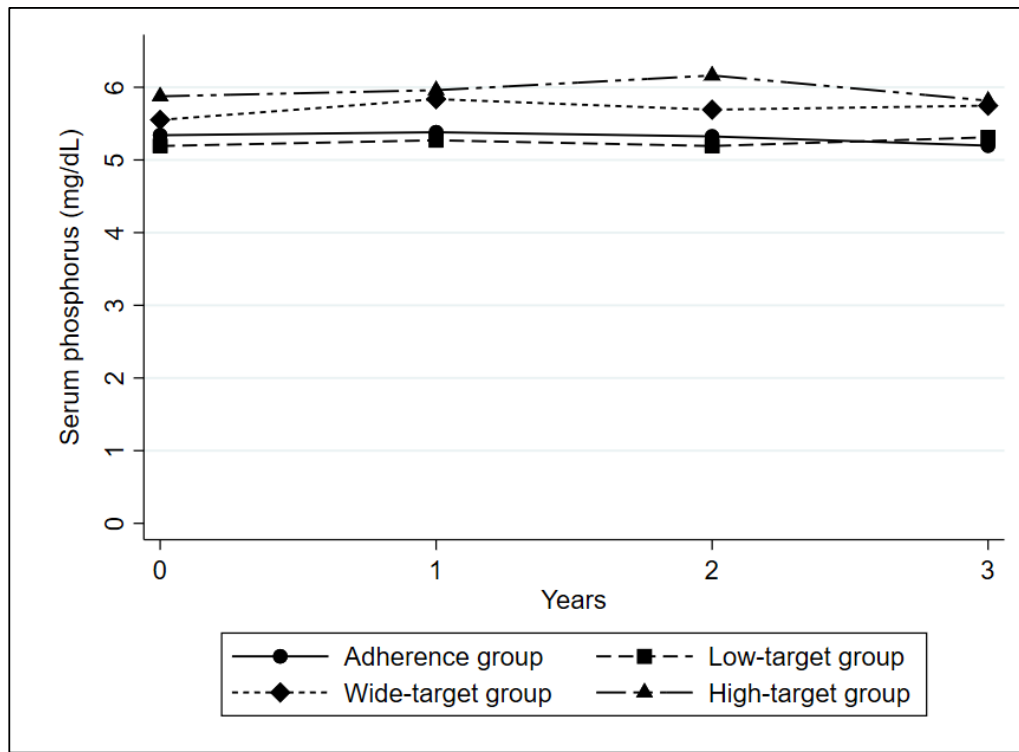
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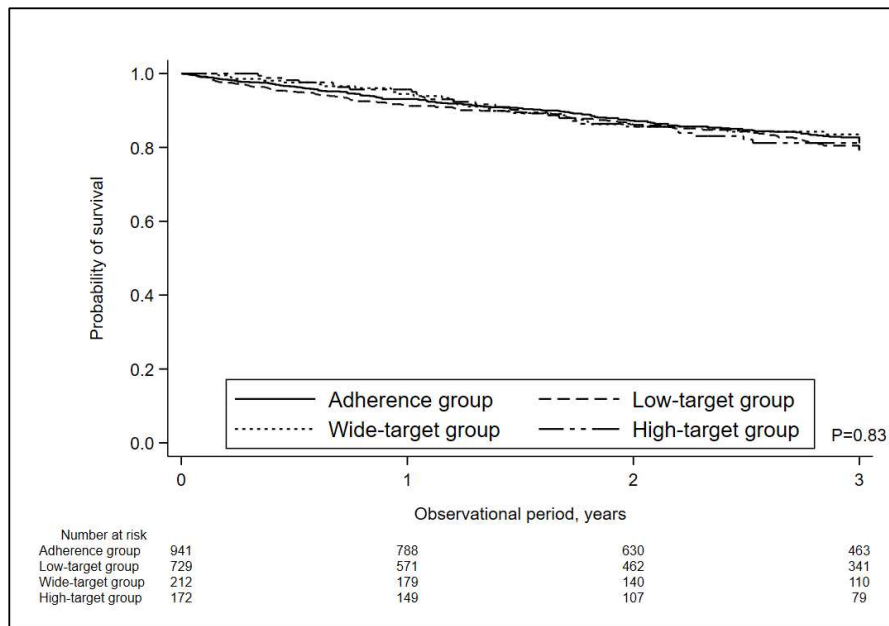
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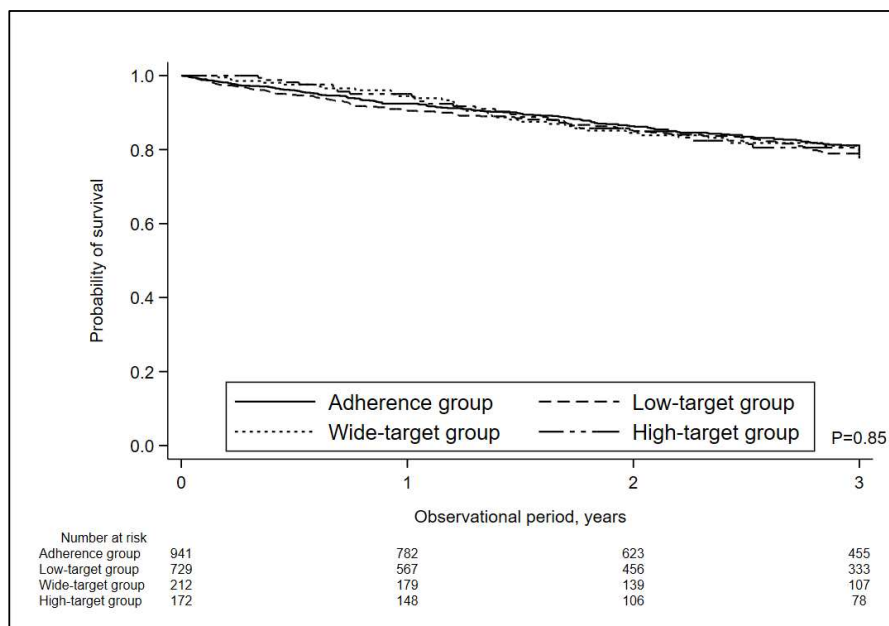
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Supplementary Figure S1. Change of serum phosphorus concentration by exposure groups throughout the study.



Supplementary Figure S2. Event-free survival rate for all-cause mortality.



Supplementary Figure S3. Event-free survival rate for MACEs. MACEs included acute myocardial infarction, stroke, and all-cause mortality. MACEs, major adverse cardiovascular events.

Supplementary Table S1. Association between facility-level target ranges of phosphorous and all-cause mortality.

	Unadjusted HR	95% CI	P-value	Adjusted HR	95% CI	P-value
Facility-level target						
Adherence group	1.00	Reference		1.00	Reference	
Low-target group	1.12	(0.88 to 1.42)	0.36	1.04	(0.76 to 1.43)	0.79
Wide-target group	1.07	(0.74 to 1.55)	0.71	1.11	(0.68 to 1.81)	0.68
High-target group	1.09	(0.72 to 1.63)	0.69	1.95	(1.12 to 3.38)	0.018
Age				1.06	(1.04 to 1.07)	< 0.001
Men				1.46	(1.14 to 1.86)	0.003
Dialysis vintage				1.02	(1.01 to 1.04)	0.005
Serum albumin				0.58	(0.51 to 0.67)	< 0.001
Serum phosphorus				0.82	(0.65 to 1.02)	0.63
Corrected serum calcium				0.95	(0.76 to 1.18)	0.073
Diabetes mellitus				1.55	(1.21 to 1.97)	< 0.001
Liver disease				1.09	(0.77 to 1.54)	0.62
Hypertension				0.85	(0.63 to 1.13)	0.25
Heart disease				1.23	(0.97 to 1.56)	0.091
Stroke or TIA				1.16	(0.86 to 1.58)	0.33
Cancer				1.35	(1.01 to 1.82)	0.046

Adherence group, lower limit of serum phosphorus value (LL) \geq 3.5 mg/dL and upper limit of serum phosphorus value (UL) \leq 6.0 mg/dL; Low-target group, LL $<$ 3.5 mg/dL and UL \leq 6.0 mg/dL; Wide-target group, LL $<$ 3.5 mg/dL and UL $>$ 6.0 mg/dL; High-target group, LL \geq 3.5 mg/dL and UL $>$ 6.0 mg/dL. Heart disease included coronary heart disease, coronary artery disease, angina, myocardial infarction, bypass surgery, and coronary angioplasty. HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack.

Supplementary Table S2. Association between facility-level target ranges of phosphorous and MACEs

	Unadjusted HR	95% CI	P-value	Adjusted HR	95% CI	P-value
Facility-level target						
Adherence group	1.00	Reference		1.00	Reference	
Low-target group	1.11	(0.88 to 1.40)	0.38	1.06	(0.79 to 1.42)	0.71
Wide-target group	1.08	(0.76 to 1.54)	0.68	1.15	(0.73 to 1.81)	0.56
High-target group	1.04	(0.70 to 1.54)	0.86	1.85	(1.10 to 3.11)	0.020
Age				1.05	(1.04 to 1.06)	< 0.001
Men				1.50	(1.18 to 1.90)	0.001
Dialysis vintage				1.02	(1.01 to 1.04)	0.005
Serum albumin				0.59	(0.52 to 0.67)	< 0.001
Serum phosphorus				0.83	(0.67 to 1.03)	0.093
Corrected serum calcium				0.93	(0.76 to 1.14)	0.48
Diabetes mellitus				1.52	(1.20 to 1.92)	< 0.001
Liver disease				1.05	(0.75 to 1.47)	0.76
Hypertension				0.89	(0.68 to 1.18)	0.42
Heart disease				1.24	(0.98 to 1.56)	0.071
Stroke or TIA				1.14	(0.85 to 1.54)	0.38
Cancer				1.30	(0.97 to 1.74)	0.075

Adherence group, lower limit of serum phosphorus value (LL) \geq 3.5 mg/dL and upper limit of serum phosphorus value (UL) \leq 6.0 mg/dL; Low-target group, LL < 3.5 mg/dL and UL \leq 6.0 mg/dL; Wide-target group, LL < 3.5 mg/dL and UL > 6.0 mg/dL; High-target group, LL \geq 3.5 mg/dL and UL > 6.0 mg/dL. Heart disease included coronary heart disease, coronary artery disease, angina, myocardial infarction, bypass surgery, and coronary angioplasty. MACEs included acute myocardial infarction, stroke, and all-cause mortality. MACEs, major adverse cardiovascular events. HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack.