

Hospitalization for Patients on Combination Therapy With Peritoneal Dialysis and Hemodialysis Compared With Hemodialysis



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Introduction: Combination therapy with peritoneal dialysis and hemodialysis (PD+HD) is widely used for PD patients with decreased residual kidney function in Japan; however, hospitalization for this combined dialysis has not been investigated so far. We compared the risk of hospitalization for PD+HD with that for HD.

Methods: A multicenter, prospective observational study was conducted on 42 PD+HD and 42 HD patients matched for age and diabetic nephropathy. The main outcome measure was the cumulative incidence of hospitalization for any cause assessed with the Kaplan-Meier method. Hospitalization rates (the number of admissions per 100 patient-years) associated with dialysis modality were also calculated. The impact of dialysis modality on time to hospitalization was analyzed using the Cox proportional hazard model.

Results: There was no significant difference between groups in terms of age, sex, dialysis vintage, diabetic nephropathy, and comorbidities. The cumulative incidence of hospitalization did not significantly differ between the groups (log-rank test, $P = 0.36$). Although total hospitalization rates were 66.0 in PD+HD and 59.2 in HD, hospitalization rates for the sum of PD-related infections (a composite of catheter-related infection and peritonitis) and vascular access troubles were 21.7 in PD+HD and 7.2 in HD. On univariate Cox proportional hazard analysis, dialysis modality had no significant impact on time to hospitalization.

Conclusion: The risk of hospitalization was not significantly different between PD+HD and HD, although PD+HD patients had a higher risk of dialysis access-related complications than HD patients.

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KEYWORDS: cardiovascular event; combined dialysis; end-stage renal disease (ESRD); PD+HD; residual kidney function (RKF); survival

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See Commentary on Page 389

Residual kidney function (RKF) is an irreplaceable property for patients with end-stage renal disease (ESRD). RKF provides better body fluid control and greater solute clearance, and even influences the requirements of dialysis frequency.¹ The loss of RKF is

strongly associated with mortality and morbidity in patients with ESRD.^{2–6} PD is better to preserve RKF as compared with HD.^{7,8} However, a previous study reported that PD patients depended on RKF more strongly than HD patients for achieving adequate dialysis, and PD patients were susceptible to fluid overload and solute accumulation after RKF decline.⁹ Although the prognosis of PD was similar or better than that of HD in the early phase of dialysis,^{10–14} patients' long-term prognosis became worse than that of HD patients.¹⁰ Therefore, in many regions, PD patients with decreased RKF are transferred to full-dose HD even if they wish to further continue PD.

Combination therapy with 5 or 6 days of PD and once-weekly HD (PD+HD) is a widely used dialysis option for

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patients with decreased RKF in Japan, to increase dialysis doses and fluid removal.¹⁵ In 2014, there were 1913 PD+HD patients in Japan, and its proportion was 20.7% of all Japanese PD patients.¹⁶ Among Japanese PD patients who have lost RKF, those who do not want to continue PD will be transferred to full-dose HD, and those who wish to continue PD will be transferred to PD+HD. If PD patients demonstrate underdialysis, we recommend switching them to HD or PD+HD. Previous studies on PD+HD reported improvements in uremic symptoms, hypertension, anemia, left ventricular hypertrophy, and peritoneal function,^{17–21} but clinical outcomes have yet to be prospectively investigated.

Hospitalization is an important outcome measure providing insights into the morbidity, quality of life, and the cost of treatment among dialysis patients.²² Previous studies have shown no difference in total hospitalization rates between PD and HD.^{23–26} However, there have been no reports on the risk of hospitalization in PD+HD patients.

The aim of the present study was to compare the risk of hospitalization for PD+HD patients with that for HD patients.

METHODS

Patients

In the multicenter prospective cohort study, clinically stable patients with ESRD on PD+HD (5 or 6 days of PD with once-weekly HD) or HD (3 sessions per week) who had been dialyzed for more than 3 months were recruited from 6 facilities and followed between 2012 and 2016. Forty-two PD+HD patients were matched with 42 HD patients with 1:1 matching for age and diabetic nephropathy among the entire cohort (Figure 1), in which we previously investigated health-related quality of life among PD+HD, HD, and PD patients.²⁷ The exclusion criteria of the study were as follows: patients younger than 20 years; those who changed their dialysis modality or were hospitalized within 1 month; those without a decision-making ability due to cognitive impairment; those with severe frailty or a life expectancy of less than 6 months. PD+HD patients receiving 2 or more HD sessions per week and HD patients receiving other than 3 HD sessions per week were also excluded.

We collected information on baseline characteristics, blood tests, echocardiogram, and clinical outcomes, such as hospitalization, death, and cardiovascular event. According to clinical practice, blood tests were performed for PD+HD patients on the day of the monthly visit, and were conducted before the initial HD session of a week for HD patients. In PD+HD patients, blood tests were performed 5.3 ± 1.4 days after the last HD session.

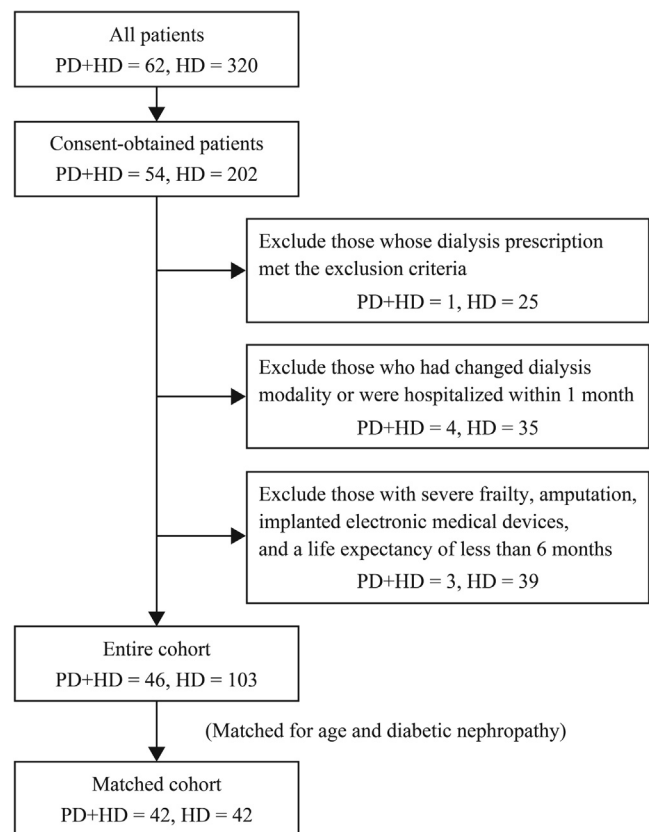


Figure 1. Patient flow in the study. HD, hemodialysis; PD+HD, combination therapy with peritoneal dialysis and hemodialysis.

The present study was approved by the Ethics Committee at each participating facility, and all participants provided written informed consent before enrollment.

Outcome Measures

The primary outcome measure was the cumulative incidence of hospitalization for any cause in the matched cohort. Secondary outcome measures included hospitalization rates, hazard ratio (HR) for time to hospitalization, and the cumulative incidence of death from any cause and the composite cardiovascular event (a composite of cardiac sudden death, myocardial infarction, stroke, or hospitalization for heart failure) in the matched cohort.

Statistical Analysis

Values were described as n (%), mean \pm SD, or median (interquartile range). Continuous variables between 2 groups were compared using the Student t test or Wilcoxon rank sum test, whereas categorical variables were compared using the χ^2 test or Fisher exact test, as appropriate.

The cumulative incidence of hospitalization, death, and the composite cardiovascular event was described using the Kaplan-Meier method with censoring for renal transplantations or loss to follow-up, and were

Table 1. Baseline characteristics of participants

Measures	Entire			Matched		
	PD+HD (n = 46)	HD (n = 103)	P value	PD+HD (n = 42)	HD (n = 42)	P value
Age (yr)	59.6 ± 10.8	62.7 ± 13.8	0.18	58.6 ± 10.5	58.7 ± 10.4	0.97
Female	10 (21.7)	21 (20.4)	0.85	10 (23.8)	10 (23.8)	1.00
Body mass index (kg/m ²)	24.0 ± 4.2	23.3 ± 4.6	0.38	24.0 ± 4.3	24.1 ± 4.9	0.87
Dialysis vintage (yr)	5.8 ± 3.1	5.5 ± 4.6	0.69	5.9 ± 3.0	5.4 ± 3.5	0.47
Diabetic nephropathy	16 (34.8)	31 (30.1)	0.57	15 (35.7)	15 (35.7)	1.00
Systolic blood pressure (mm Hg)	143 ± 24	150 ± 25	0.11	143 ± 25	149 ± 21	0.17
Daily urine volume (ml)	0 (0–9)	50 (0–300)	<0.01	0 (0–9)	28 (0–312)	<0.01
History of disease						
Ischemic heart disease	5 (10.9)	18 (17.5)	0.34	5 (11.9)	4 (9.5)	1.00
Peripheral artery disease	1 (2.2)	6 (5.8)	0.30	1 (2.4)	3 (7.1)	0.62
Stroke	5 (11.9)	6 (5.8)	0.32	5 (11.9)	2 (4.8)	0.43
Cancer (complete resection)	4 (9.5)	11 (10.7)	1.00	4 (9.5)	6 (14.3)	0.74
Gastrointestinal ulcer	3 (7.1)	9 (8.7)	0.75	3 (7.1)	4 (9.5)	1.00
Hepatitis or cirrhosis	2 (4.8)	5 (4.9)	1.00	2 (4.8)	2 (4.8)	1.00
Current smoker	10 (23.8)	21 (20.4)	0.83	10 (23.8)	11 (26.2)	1.00
Medication						
Number of antihypertensives	1.0 ± 1.2	1.8 ± 1.5	<0.01	0.9 ± 1.2	2.0 ± 1.4	<0.01
Antiplatelet	17 (37.0)	62 (60.2)	0.01	15 (35.7)	23 (54.8)	0.12
Anticoagulant	0 (0)	3 (2.9)	0.55	0 (0)	1 (2.4)	1.00
Blood test						
Creatinine (mg/dl)	12.7 ± 2.9	11.8 ± 2.8	0.055	12.8 ± 3.0	12.5 ± 2.6	0.61
Hemoglobin (g/dl)	11.8 ± 1.3	10.7 ± 0.9	<0.01	11.8 ± 1.4	10.9 ± 0.9	<0.01
Albumin (g/dl)	3.8 ± 0.5	3.8 ± 0.3	0.51	3.8 ± 0.4	3.9 ± 0.3	0.28
Phosphate (mg/dl)	5.1 ± 1.5	5.3 ± 1.2	0.29	4.9 ± 1.4	5.8 ± 1.3	<0.01
C-reactive protein (mg/dl)	0.2 (0.1–0.6)	0.1 (0.1–0.3)	<0.01	0.2 (0.1–0.5)	0.1 (0.0–0.3)	0.06
Brain natriuretic peptide (pg/dl)	90 (27–175)	167 (90–354)	<0.01	87 (27–182)	131 (74–247)	0.04
Echocardiogram						
LV ejection fraction (%)	62.9 ± 10.5	64.0 ± 11.1	0.57	62.4 ± 10.6	63.4 ± 11.9	0.66
LV mass index (g/m ²)	110 ± 32	112 ± 38	0.74	110 ± 33	112 ± 33	0.84
Types of vascular access						
Arteriovenous fistula	46 (100)	98 (95.2)	0.32	42 (100)	40 (95.2)	0.49
Arteriovenous graft	0 (0)	5 (4.9)		0 (0)	2 (4.8)	
PD condition						
Automated PD	37 (80.4)	—	—	36 (85.7)	—	—
2.5% glucose dialysate	32 (69.6)	—	—	28 (66.7)	—	—
Icodextrin	4 (8.7)	—	—	3 (7.1)	—	—
Daily UF volume by PD (kg)	0.7 ± 0.3	—	—	0.7 ± 0.3	—	—
HD condition						
Time of 1 HD session (h)	4.2 ± 0.6	4.1 ± 0.3	0.06	4.3 ± 0.5	4.1 ± 0.4	0.20
Quantity of blood (ml/min)	200 ± 34	208 ± 30	0.16	199 ± 35	213 ± 27	0.08
Dialyzer membrane area (m ²)	1.8 ± 0.3	1.9 ± 0.3	0.33	1.8 ± 0.3	1.9 ± 0.2	0.06
UF volume by 1 HD session (kg)	2.0 ± 1.0	2.3 ± 1.1	0.12	2.1 ± 1.0	2.6 ± 1.1	0.02

HD, hemodialysis; LV, left ventricular; PD, peritoneal dialysis; PD+HD, combination therapy with peritoneal dialysis and hemodialysis; UF, ultrafiltration. Data are shown as n (%), mean ± SD, or median (interquartile range), as appropriate.

statistically tested with the log-rank test. Hospitalization rates were calculated as the number of admissions per 100 patient-years. The impact of dialysis modality on time to hospitalization was analyzed by univariate Cox proportional hazard model using a dummy variable and described as unadjusted HR with 95% confidential interval. For death and cardiovascular event, Cox proportional hazard analysis was not performed because of the very small number of these events.

All statistical tests were 2 sided at a significance level of 5%. All statistical analyses were performed using JMP 13.0.0 (SAS Institute Inc., Cary, NC).

Sensitivity Analysis

A sensitivity analysis on entire cohort was performed to evaluate the effect of missing data through matching process. Hospitalization rates for the entire cohort were calculated as complete case analysis. Adjusted HR of dialysis modality on the entire cohort was calculated using multivariate Cox proportional hazard model adjusting for age and diabetic nephropathy (factors for matching).

RESULTS

Baseline characteristics for the matched cohort were well balanced between the groups (Table 1). In the

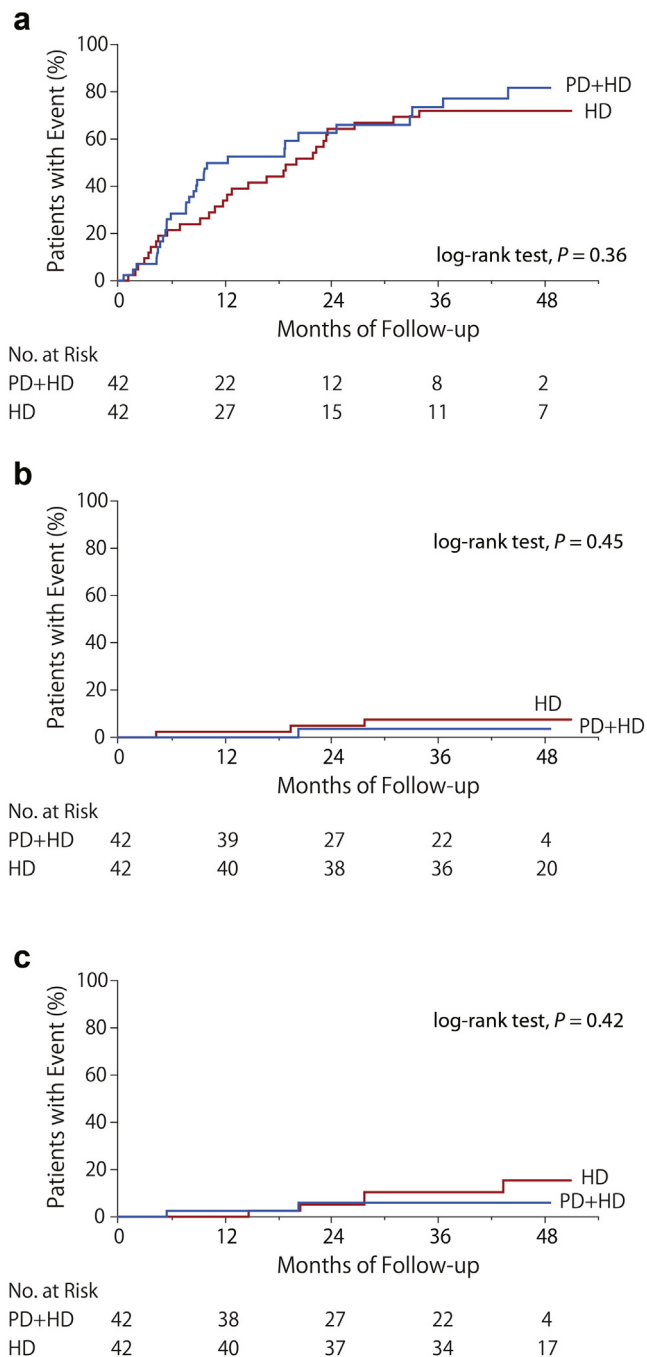


Figure 2. Kaplan-Meier estimates of the probability of outcomes among combination therapy with peritoneal dialysis and hemodialysis (PD+HD) and hemodialysis (HD) patients. The cumulative incidence of (a) hospitalization for any cause (primary outcome), (b) death from any cause, and (c) the composite cardiovascular event (a composite of cardiac sudden death, myocardial infarction, stroke, or hospitalization for heart failure), according to treatment groups in matched cohort. P values from the log-rank test are not adjusted for multiple comparisons.

matched cohort, 37 of 42 PD+HD patients (88%) were transferred from PD because of fluid overload and/or insufficient solute clearance, and 5 (12%) were transferred from HD because they wished to reduce the frequency of HD based on their lifestyles. The total

dialysis vintage was comparable between PD+HD and HD, and the duration of combined dialysis was 1.9 (0.4–4.4) years in PD+HD patients. The median daily urine volume was 0 ml (0–9 ml) in PD+HD and 28 ml (0–312 ml) in HD. No significant differences were observed in age, sex, diabetic nephropathy, the history of comorbid diseases, smoking status, and types of vascular access (VA). Although blood pressure in PD+HD patients was similar to that in HD patients, the number of antihypertensives in PD+HD patients was fewer than in HD patients. The prescription of oral antiplatelet and anticoagulant drugs was less common in PD+HD patients than in HD patients. Based on blood tests, both groups achieved the target hemoglobin (10 to 12 g/dl) and phosphate levels (3.5 to 6.0 mg/dl) recommended by the Japanese guidelines.^{28,29} Most PD+HD patients were treated with automated PD and used 2.5% glucose dialysate, but a few used icodextrin. Regarding dialysis prescription in each HD session, no clinically relevant differences were noted between the groups.

For the matched cohort, the median follow-up period was 3.1 years (2.0–4.0 years). According to the Kaplan-Meier estimates, no significant differences were observed in the cumulative incidence of hospitalization for any cause between the groups (Figure 2a). A total of 30 (71.4%) PD+HD and 29 (69.0%) HD patients were hospitalized, and total hospitalization rates (per 100 patient-years) were 66.0 in PD+HD and 59.2 in HD (Table 2). Univariate Cox proportional hazard analysis

Table 2. Hospitalization rates associated with dialysis modality

Events	Entire		Matched	
	PD+HD ($n = 46$)	HD ($n = 103$)	PD+HD ($n = 42$)	HD ($n = 42$)
Number of patients with event, n (%)	34 (73.9)	65 (63.1)	30 (71.4)	29 (69.0)
Cardiovascular disease	14.5	25.6	16.0	15.2
Dialysis access-related complications	22.2	6.5	21.7	7.2
PD catheter-related infection ^a	12.8	—	11.3	—
Peritonitis	6.0	—	6.6	—
VA occlusion/stenosis	3.4	4.9	3.8	4.3
VA infection	0.0	1.5	0.0	2.9
Elective PD catheter removal for transfer to HD	4.3	—	4.7	—
Infection except for dialysis access-related complications	1.7	6.8	1.9	9.4
Diabetic gangrene	2.6	2.8	2.8	1.4
Gastrointestinal bleeding	0.9	2.2	0.0	2.9
Cancer	2.6	3.7	2.8	2.2
Overhydration	3.4	0.3	3.8	0.7
Others	16.2	15.4	12.3	20.2
Total	68.2	63.3	66.0	59.2

HD, hemodialysis; PD, peritoneal dialysis; PD+HD, combination therapy with peritoneal dialysis and hemodialysis; VA, vascular access.

^aA composite of exit-site infection and tunnel infection.

Hospitalization rates were described as the number of admissions per 100 patient-years.

showed that dialysis modality had no significant impact on time to hospitalization (unadjusted HR: 1.27; 95% confidence interval: 0.76–2.13; $P = 0.36$). For the entire cohort, total hospitalization rates were similar to that for the matched cohort in both groups (Table 2). On multivariate Cox proportional hazard analysis on the entire cohort, dialysis modality still did not affect time to hospitalization after adjustment for age and diabetic nephropathy (adjusted HR: 1.40; 95% confidence interval: 0.83–2.37; $P = 0.20$).

The leading cause of hospitalization in both groups was cardiovascular disease, and hospitalization rates were similar between the groups (Table 2). In PD+HD patients, the hospitalization rate for PD-related infections (a composite of catheter-related infection and peritonitis) was 17.9 per 100 patient-years, including 11.3 for PD catheter-related infection (exit-site infection and tunnel infection), and 6.6 for peritonitis. Rates of hospitalization for VA troubles (a composite of VA occlusion/stenosis and VA infection) were 3.8 in PD+HD and 7.2 in HD per 100 patient-years. Hospitalization rates for the sum of PD-related infections and VA troubles were 21.7 in PD+HD and 7.2 in HD. Infections except for dialysis access-related complications and gastrointestinal bleeding occurred more frequently in HD patients than in PD+HD patients. These features were also observed in the entire cohort.

During the observation period, only 1 (2.4%) PD+HD and 3 (7.1%) HD patients died, and the composite cardiovascular event occurred in 2 (4.8%) PD+HD and 5 (11.9%) HD patients. According to the Kaplan-Meier estimates, no significant differences were observed in the cumulative incidence of death or the composite cardiovascular event between the groups (Figure 2b and c). Nine (21.4%) PD+HD patients were transferred to HD, whereas none of the HD patients changed their dialysis modality until death. Renal transplantation was undertaken in 2 PD+HD patients (4.8%).

There was a clinically suspected case of encapsulating peritoneal sclerosis in a 71-year-old female patient who was treated by PD for 6.4 years and PD+HD for a subsequent 6.5 years. After transferring from PD+HD to HD, the patient developed ileus twice in 4 years, and oral corticosteroids were prescribed.

DISCUSSION

The present study demonstrated that the cumulative incidence of hospitalization for any cause for PD+HD did not significantly differ from that for HD during the median follow-up period of 3.1 years. Total hospitalization rates for PD+HD were also similar to that for HD, whereas hospitalization rates for dialysis

access-related complications were higher in PD+HD patients than in HD patients.

Because PD+HD requires both PD catheter and VA, they potentially have an increased risk of dialysis access-related complications. Indeed, the hospitalization rate for the sum of PD-related infections and VA troubles in PD+HD was 3 times higher than that in HD patients. This may concur with a recent analysis by Lafrance *et al.*,³⁰ in which PD patients had a higher risk of dialysis access-related hospitalization than HD patients. In our study, most patients with VA occlusion/stenosis were treated on an outpatient basis by percutaneous transluminal angioplasty. In contrast, PD+HD patients were always hospitalized in case of peritonitis, although a recent guideline stated that some patients with peritonitis could be treated as outpatients.³¹ These treatment policies for PD-related infections may have affected high hospitalization rates for dialysis access-related complications in PD+HD patients. Because the “re-training” of PD procedures could reduce the incidence of peritonitis in PD patients,^{32,33} continuous education and training to improve patient self-care may be useful for reducing the dialysis access-related hospitalization of PD+HD.

In this study, gastrointestinal bleeding occurred more commonly in HD patients than in PD+HD patients. Because HD patients were more likely to take antiplatelet drugs and were more frequently administered heparin during HD sessions than PD+HD patients, oral antiplatelet, anticoagulant, and intradialytic heparin use may have influenced gastrointestinal bleeding in HD patients.

We could not draw any conclusion on the risk of mortality and cardiovascular event for PD+HD as compared with that for HD. The cumulative incidence of death or the composite cardiovascular event and hospitalization rates for cardiovascular reasons were comparable between PD+HD and HD; however, the number of these events were too small to perform further statistical analysis. Larger and longer studies are needed to investigate death and cardiovascular events in Japanese PD+HD patients.

The appropriate treatment period for PD+HD is unknown. In our study, the mean dialysis history of PD+HD patients was 5.9 ± 3.0 years at baseline, and the median observation period was 3.0 (1.1–3.8) years. A clinically suspected encapsulating peritoneal sclerosis was observed in a patient with 12.9 years of PD history; however, limited information is currently available on the long-term prognosis of PD+HD patients.

Better preservation of RKF by incremental HD or PD is a recent topic related to precision medicine in ESRD,^{1,34,35} although there are few reports on precision medicine in patients with ESRD with decreased RKF.

Recently, we reported that PD+HD may have a similar profile of health-related quality of life to PD and have an advantage in role and social participation as compared with HD.²⁷ PD and HD combination may be an individualized dialysis modality and a treatment of choice in patients with ESRD with decreased RKF who prefer PD lifestyles for social, economic, or geographic reasons.

The small sample size and the short follow-up period were the major limitations in the present study; however, the number of hospitalizations was not small. Patient and treatment selection bias were inevitable; in particular, there may be a survivor effect in PD+HD patients. Conversely, however, our treatment policy might have been overprotective for PD+HD patients, as all patients with peritonitis were hospitalized. Although these biases cannot be fully removed, consistency between the results on the matched cohort and entire cohort may strengthen the credibility of our findings. Furthermore, because dialysis access problems are more common in the early phase of dialysis, our study may underestimate the risk of hospitalization due to dialysis access complications. In addition, it was not possible to compare dialysis doses between the groups because a common measure has not yet been established. However, blood pressure, blood tests, and echocardiogram suggested that markers of dialysis adequacy, such as body fluid, anemia, phosphate, and nutritional status, were well in both groups. Some blood test data, such as hemoglobin and brain natriuretic peptide, in the PD+HD group were better than data in the HD group, but these results may have been substantially affected by the different time-point of the tests. Finally, our present findings are generalizable only in PD+HD patients who transferred from PD or HD after RKF decline.

In conclusion, the present study suggests that the risk of hospitalization was not significantly different between PD+HD and HD, although PD+HD patients had an increased risk of dialysis access-related complications compared with HD patients. Future studies are still needed to clarify the long-term prognosis of PD+HD, such as death and cardiovascular events.

DISCLOSURE

All the authors declared no competing interests.

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