

Risk Factors for Early Peritoneal Dialysis Discontinuation: Importance of Heart Failure

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Background: The number of patients on peritoneal dialysis (PD) in our hospital has increased during the past 5 years, but the number discontinuing PD has also increased. The purpose of this study was to identify the risk factors for PD discontinuation by analyzing the association between technical survival period (defined as the duration of PD) and various clinical factors.

Methods: We retrospectively investigated 87 patients who were started on PD at our hospital and attended regularly from April 2015 to March 2020, and we analyzed the association between technical survival period and various clinical factors. We also looked for associations between technical survival period and hospitalizations for heart failure, peritonitis, and exit-site infections among patients undergoing PD.

Results: The patients using renin-angiotensin-aldosterone system inhibitors (RASi) ($P = 0.0218$), those with left ventricular ejection fraction (LVEF) $> 50\%$ ($P = 0.0194$) when they started PD, and those with estimated glomerular filtration rate (eGFR) ≥ 6 (mL/min/1.73 m²) ($P = 0.0013$) at the initiation of PD showed significantly longer technical survival period, and those who were hospitalized for heart failure had significantly shorter period ($P = 0.0008$).

Conclusion: Treatment of RASi, LVEF $> 50\%$ and eGFR ≥ 6 mL/min/1.73 m² when the initiation of PD and better volume control to prevent ultrafiltration failure and heart failure may improve technical survival period in patients undergoing PD. (J Nippon Med Sch 2022; 89: 72–80)

Key words: peritoneal dialysis, technical survival, heart failure, ultrafiltration failure, renin-angiotensin-aldosterone system inhibitors

Introduction

The number of chronic dialysis patients in Japan was 334,505 at the end of 2017, but only 2.7% of these were on peritoneal dialysis (PD)¹. Worldwide, by contrast, the number of patients on PD is increasing, and is now approaching 11% of all patients on dialysis². In the United States of America, 10.1% of patients receiving renal replacement therapy (RRT) undergo PD³. PD is also a more commonly used modality of RRT in Asia; in Hong Kong, for example, 73% of patients who require RRT undergo PD⁴. Since Japan is bucking the international trend in terms of PD deployment, efforts should be considered to achieve an optimal rate of PD usage in this country.

One of the major reasons for the lower rate of PD usage in Japan is that many medical staff, including doctors, incorrectly believe that PD causes more problems than hemodialysis. Since April 2015, we have been making efforts at our hospital to wean the medical staff off their bias against PD and thereby achieve a more proper rate of usage of this modality. As a result, the number of patients on PD at our hospital has increased during the past 5 years, but the number discontinuing PD (including early drop-out) has also increased. The purpose of this study, therefore, was to identify the risk factors causing patients to discontinue PD, especially in the early stages. To do this, we investigated the association between tech-

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nical survival period (defined as the duration of PD) and various clinical factors.

Methods

Participants and Study Design

In this single center, retrospective cohort study, we investigated 87 patients who were started on PD at Nippon Medical School Hospital and attended regularly between April 2015 and March 2020. We defined that we discontinued to follow up the participants at the time of PD cessation or the end of the study period in this study, and we referred to the patients on combination therapy, undergoing PD and hemodialysis periodically, as the patients undergoing PD. Information was collected on each patient's sex, age, primary disease, body mass index (BMI), current and former smoking, a renin-angiotensin-aldosterone system inhibitor (RASi) use, diverticulosis, diuretic use, vitamin D (Vit D) supplementation, malignant tumors, cardiovascular disease (CVD), hemoglobin (Hb), estimated glomerular filtration rate (eGFR) at the start of PD, serum potassium (K), serum albumin, C-reactive protein, dialysate creatinine to plasma creatinine ratio (D/P ratio), dialysate glucose to initial dialysate glucose ratio (D/D ratio), duration of PD, Left ventricular ejection fraction (LVEF), Automated PD, and Combination therapy with hemodialysis. In addition, we collected information on any hospitalizations among these patients for heart failure, peritonitis, or exit-site infections (ESI) while they were undergoing PD.

All patients used the automated connecting and disconnecting device with ultraviolet light on PD.

Analysis about Technical Survival Period in All Patients

We investigated survival analysis about the technical survival period during the observational period in all of the patients in Mantel-Cox log-rank test; we defined the end point as the discontinuation of PD.

Causes of PD Cessation and Comparison between the Patients Ceased by Ultrafiltration Failure and Peritonitis

We investigated the causes of PD cessation in participants. In addition, we compare between the patients ceased by ultrafiltration failure and peritonitis in Mantel-Cox log-rank test, because the two causes were common causes of PD cessation.

Clinical Factors at the Introduction of PD and Technical Survival Period

We analyzed the association between the technical survival period and the following 10 factors in Mantel-Cox

log-rank test: LVEF, smoking, sex, diabetes, diverticulosis, CVD, eGFR, RASi use, diuretic use, and Vit D supplementation at the time of PD initiation.

Clinical Events during PD and Technical Survival Period

We also analyzed survival analysis about the association between technical survival period and any hospitalizations among the patients for heart failure, peritonitis, or ESI while they were undergoing PD in Mantel-Cox log-rank test; we defined the end point as the discontinuation of PD.

Statistical Analysis

All laboratory values are presented as means \pm standard deviation. Continuous variables were compared with the unpaired t-test, and survival analysis was performed on longitudinal data to address its multiplicity. Fisher's exact test was used for various inter-group comparisons. The Mantel-Cox log-rank test was used to compare survival curves. *P* values < 0.05 were considered statistically significant for all analyses performed. All statistical analyses were performed with Prism[®] software version 8 (GraphPad Software, La Jolla, CA, USA).

Statement of Ethics

The study protocol was approved by the Ethics Committee of Nippon Medical School Hospital (B-2020-198) and designed in accordance with the Declaration of Helsinki.

Results

Basic Characteristics of Participants

Table 1 shows the baseline characteristics of the 87 patients (65 men, 22 women) recruited for this study. Their most common primary disease was diabetic nephropathy (41 cases), and the second-most common was nephrosclerosis (21 cases). Hypertension was the most common complication (83 cases), followed by diabetes mellitus (51 cases).

Technical Survival Period in All Participants

Figure 1 shows the results of the survival analysis about technical survival period in all patients: median survival time was 31 months. A total of 40 patients discontinued PD over the 5-year period covered by this study. Of these, half had dropped out by around 15 months, with a lower rate after 20 months (**Fig. 2A**).

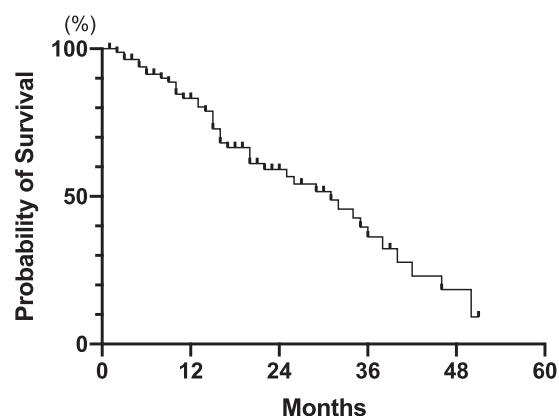
Causes of PD Cessation and Comparison between the Patients Ceased by Ultrafiltration Failure and Peritonitis

As shown in **Table 2**, the most common cause of discontinuation was ultrafiltration failure (37.5%), followed

Table 1 Baseline characteristics of the patients

	total, n	87
Female, n (%)	22 (25.3)	
Age (years)	62.5 ± 14.5	
BMI (kg/m ²)	23.9 ± 4.0	
Smoking, n (%)	52 (59.8)	
Diabetes, n (%)	51 (58.6)	
RASi, n (%)	49 (56.3)	
Diuretics (%)	43 (49.4)	
Vit D supplement at PD initiation, n (%)	20 (23.0)	
Malignant tumor, n (%)	16 (18.4)	
CVD, n (%)	12 (13.8)	
Diverticulosis, n (%)	34 (39.0)	
Hb (g/dL)	9.97 ± 1.16	
eGFR at PD initiation (mL/ min/1.73 m ²)	7.17 ± 3.45	
Serum K (mEq/L)	4.52 ± 0.64	
Serum Alb (g/dL)	3.35 ± 0.62	
CRP (mg/dL)	0.47 ± 0.87	
D/P ratio	0.68 ± 0.15	
D/D ratio	0.38 ± 0.10	
Duration of PD (months)	19.01 ± 12.73	
Left ventricular ejection fraction (%)	65.28 ± 9.88	
Automated PD, n (%)	53 (60.9)	
Combination therapy with hemodialysis, n (%)	11 (12.6)	

BMI: body mass index, RASi: renin-angiotensin-aldosterone system inhibitor, Vit D: vitamin D, PD: peritoneal dialysis, CVD: cardiovascular disease, Hb: hemoglobin, eGFR: estimated glomerular filtration rate, K: potassium, Alb: albumin, CRP: C-reactive protein, D/P ratio; dialysate creatinine to plasma creatinine ratio, D/D ratio; dialysate glucose to initial dialysate glucose ratio.



Patients at risk
All patients 87 59 25 12 5 0

Fig. 1 Rates of technical survival in all participants

by peritonitis (10%). The mean technical survival period in the patients who discontinued PD because of ultrafiltration failure was 15.94 ± 10.83 months; the mean technical survival period for those discontinuing because of peritonitis was longer at 21.31 ± 14.10 months. However, the difference was not statistically significant as calcu-

lated with the Mantel-Cox log-rank test ($P = 0.2290$) (Fig. 2B).

Clinical Factors at the Introduction of PD and Technical Survival Period

The technical survival period of the patients using RASi ($P = 0.0218$) when they started PD and the patients LVEF $> 50\%$ ($P = 0.0194$) were significantly longer (Fig. 3A and B), but no statistically significant differences in technical survival were found for the other 7 factors (smoking, sex, diabetes mellitus, diverticulosis, CVD, diuretic use, and Vit D supplementation) (Fig. 3C-I). In addition, the technical survival period of the patients with $eGFR \geq 6$ mL/min/1.73 m² ($P = 0.0013$) at the initiation of PD was significantly longer (Fig. 3J).

Clinical Events during PD and Technical Survival

Technical survival period in the patients hospitalized for heart failure was significantly shorter ($p = 0.0008$) (Fig. 4), but hospitalizations for peritonitis and ESI resulted in no significant differences in technical survival period (Fig. 5, 6).

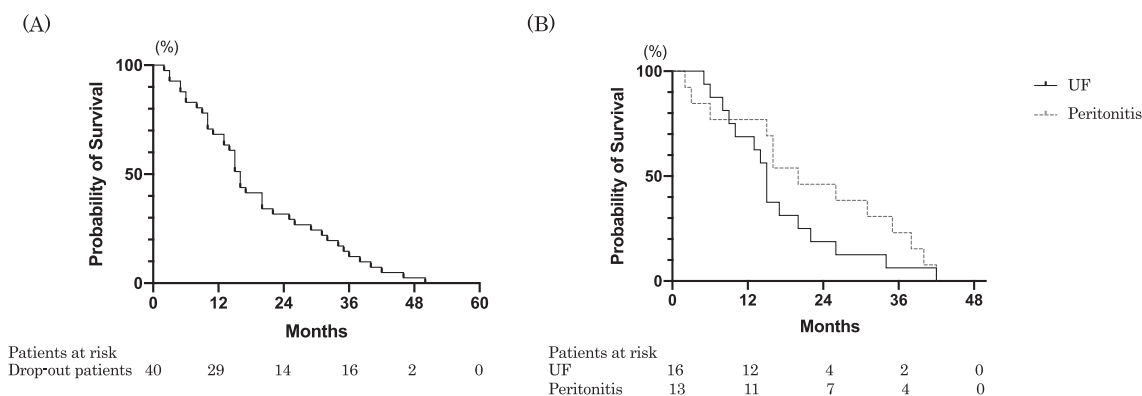


Fig. 2

(A). Rates of technical survival in patients discontinuing peritoneal dialysis

(B). Rates of technical survival in patients discontinuing peritoneal dialysis because of ultrafiltration failure and peritonitis

UF: ultrafiltration failure

Table 2 Causes of peritoneal dialysis discontinuation

total, n	cause of death	40
Ultrafiltration failure, n (%)		15 (37.5)
Peritonitis, n (%)		4 (10.0)
Exit-site infection, n (%)		3 (7.5)
Transplantation, n (%)		3 (7.5)
Death, n (%)		9 (22.5)
	Malignancy	2
	Senility	2
	Heart failure	1
	Peritonitis	1
	Undetermined	3
Others, n (%)		6 (15)

Discussion

PD has advantages over hemodialysis in terms of cardiovascular and residual renal function, and it is also reported to be more cost-effective⁵. Nevertheless, PD is still the minor modality in Japan because of bias against it among medical staff. A major reason for this bias is concern about encapsulating peritoneal sclerosis (EPS), one of the most serious complications found in patients on PD. EPS was certainly a serious cause for concern in the 1990s, but the number of patients with EPS has decreased and their prognosis has improved thanks to improved dialysates and PD devices⁶, and it has been reported that there is no longer any evidence that PD should be avoided because of the risk of EPS⁷.

A previous study gave technical survival rates at 1 year and 3 years of 96.7% and 84.5%, respectively⁸, and researchers in Hong Kong reported a rate of 96.8% at 1 year⁹. Although this study could not indicate exact survival rate at 1 and 3 years because our study had many

censoring patients in early periods, our median survival time, 31 months might be short compared with the other reports. Therefore, we thought that our management of patients on PD may have to improve from these results. To improve the technical survival periods in patients on PD in our hospital, we analyze the other results in this study, although the results had some limitations such as many patients censored in early periods.

Many studies have indicated that the major cause of PD discontinuation is peritonitis⁸⁻¹², but in our study, ultrafiltration failure was the major cause, accounting for 37.5% of cases, which was considerably higher than the number of discontinuations caused by peritonitis (10%). The mean of technical survival period for patients discontinuing PD because of ultrafiltration failure was shorter than in those who discontinued because of peritonitis. Although we could not suggest clearly because but the difference was not statistically significant, the result may indicate that the number of the patients ceased PD by ultrafiltration failure in our hospital was able to reduce more because the number may be more than the other facilities; this result might account to some extent for the shorter technical survival period found in our study than in previous studies. Half of our patients who discontinued PD did so within the first 15 months, and the rate of discontinuation declined after 20 months. This suggests that the first 15 months are crucial if we are to improve the retention rate and technical survival period of patients on PD in our hospital.

Although it has been reported that patients with diabetes mellitus have a shorter technical survival period than those without¹², diabetes mellitus was not found to be a significant risk factor for shortened technical survival pe-

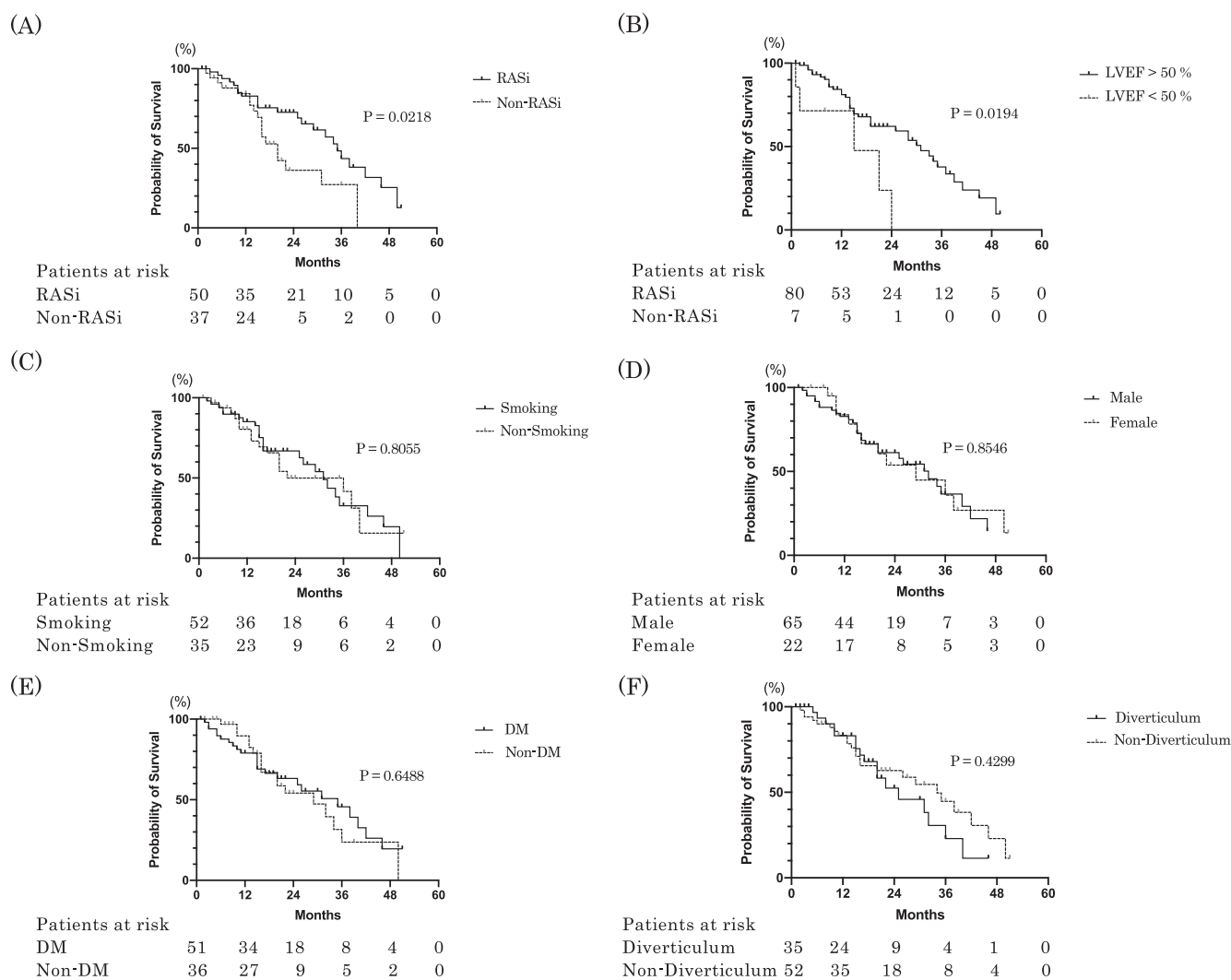


Fig. 3

- (A). Rates of technical survival in patients taking/not taking renin-angiotensin-aldosterone system inhibitors at peritoneal dialysis initiation
RASi: taking renin-angiotensin-aldosterone system inhibitors at peritoneal dialysis initiation, Non-RASi: not taking renin-angiotensin-aldosterone system inhibitors at peritoneal dialysis initiation
- (B). Rates of technical survival in patients according left ventricular ejection fraction at peritoneal dialysis initiation
LVEF; left ventricular ejection fraction
- (C). Rates of technical survival in current and former smokers, and in those that never smoked
Smoking: current or former smoker at peritoneal dialysis initiation, Non-Smoking: never smoked prior to peritoneal dialysis initiation
- (D). Rates of technical survival according to sex
- (E). Rates of technical survival in patients with/without diabetes mellitus
DM: with diabetes mellitus, Non-DM: without diabetes mellitus
- (F). Rates of technical survival in patients with/without diverticula
Diverticula: with diverticula, Non-Diverticula: without diverticula

riod in our study. The result may indicate that the other factors such as heart failure affected more than diabetes mellitus in this study compared with the previous reports, although we could not explain clearly by only this result.

Our study revealed a significantly longer technical survival period in patients using RASi when they started

PD. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) do not decrease the number of cardiovascular events in patients on dialysis, but ARBs may generally protect against cardiovascular events, including heart failure¹³. Our results showed that hospitalization for heart failure was a significant risk factor for short technical survival period, but because the

Heart Failure is a Risk Factor in Peritoneal Dialysis

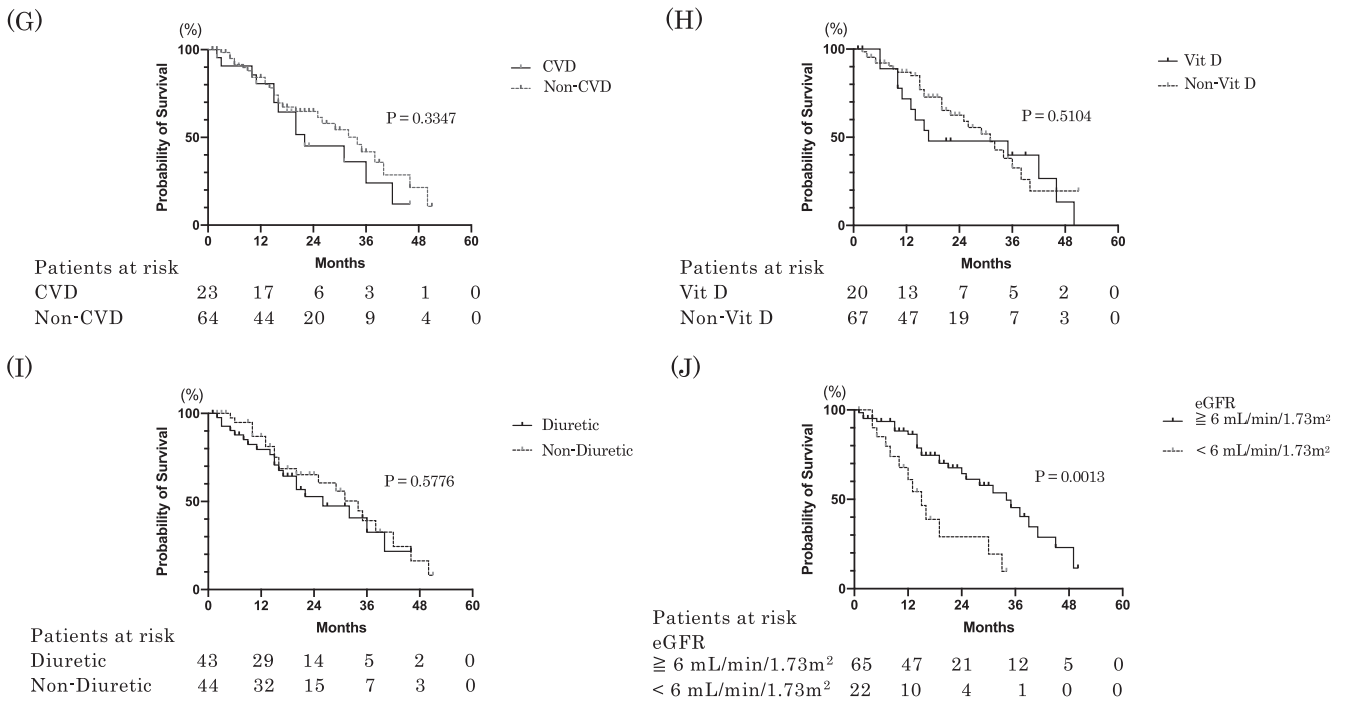


Fig. 3

- (G). Rates of technical survival in patients with/without cardiovascular disease at peritoneal dialysis initiation
CVD: with cardiovascular disease at peritoneal dialysis initiation, Non-CVD: without cardiovascular disease at peritoneal dialysis initiation
- (H). Rates of technical survival in patients with/without vitamin D supplementation at peritoneal dialysis initiation
Vit D: with vitamin D supplementation at peritoneal dialysis initiation, Non-Vit D: without vitamin D supplementation at peritoneal dialysis initiation
- (I). Rates of technical survival in patients taking/not taking diuretics at peritoneal dialysis initiation
Diuretics: Taking diuretics at peritoneal dialysis initiation, Non-Diuretics: not taking diuretics at peritoneal dialysis initiation
- (J). Rates of technical survival in patients according estimated glomerular filtration rate at peritoneal dialysis initiation
eGFR; estimated glomerular filtration rate.

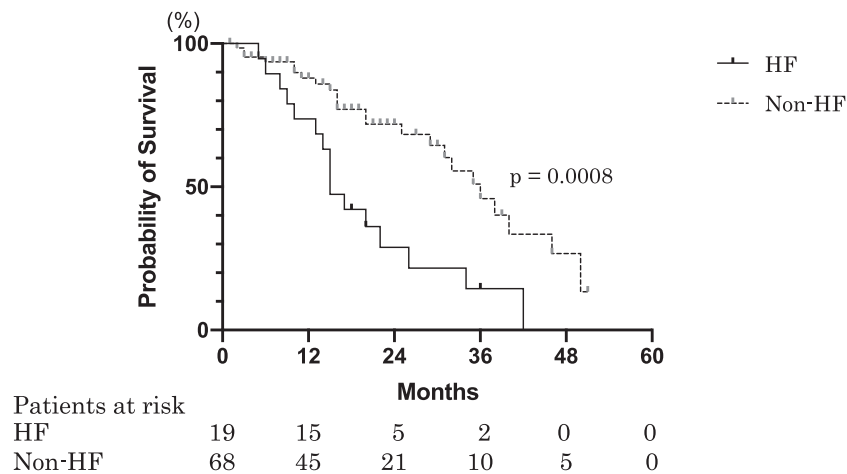
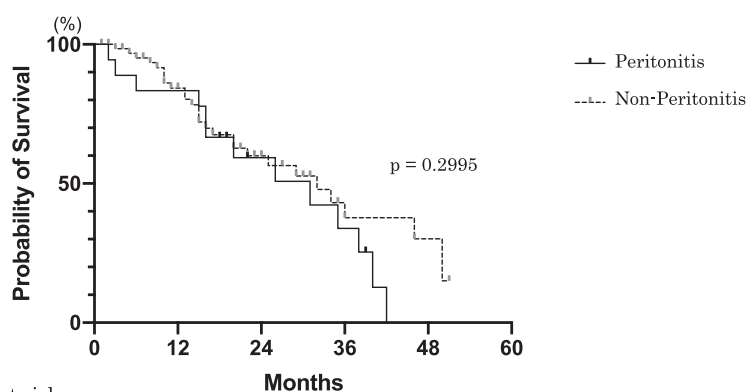
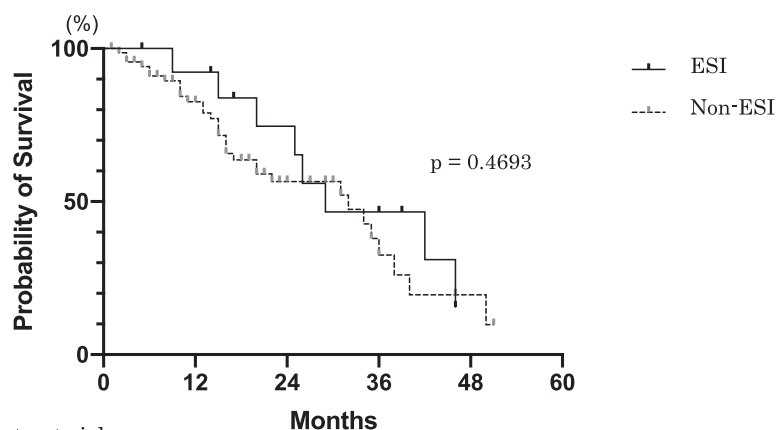


Fig. 4 Rates of technical survival in patients hospitalized for heart failure while on peritoneal dialysis
HF: patients hospitalized for heart failure while on peritoneal dialysis, Non-HF: patients not hospitalized for heart failure while on peritoneal dialysis



Patients at risk	0	12	24	36	48	60
Peritonitis	18	16	8	5	0	0
Non-Peritonitis	69	44	18	8	5	0

Fig. 5 Rates of technical survival in patients hospitalized for peritonitis while on peritoneal dialysis
 Peritonitis: patients hospitalized for peritonitis while on peritoneal dialysis, Non-Peritonitis: patients not hospitalized for peritonitis while on peritoneal dialysis



Patients at risk	0	12	24	36	48	60
ESI	17	13	9	5	2	0
Non-ESI	73	47	17	7	3	0

Fig. 6 Rates of technical survival in patients hospitalized for exit-site infections while on peritoneal dialysis
 ESI: patients hospitalized for exit-site infections while on peritoneal dialysis, Non-ESI: patients not hospitalized for exit-site infections while on peritoneal dialysis

number of patients taking RASi who were hospitalized for heart failure was exactly the same as the number not taking RASi, it was not clear whether RASi use decreased the need of hospitalization for heart failure. However, it is possible that RASi use by patients when they started PD affected heart failure not requiring hospitalization, thereby improving technical survival period in such patients. It has also been reported that ACEi and ARBs help prevent mortality in patients on PD¹⁴, so it is possible that RASi use is effective for patients on PD in terms of technical survival period. In addition, the technical survival period of the patients with LVEF > 50% at

the initiation of PD was significant longer in this study. The result might indicate that higher LVEF at the initiation of PD was associated with the technical survival period of the patients ceased by ultrafiltration failure was shorter than the other report described above. The patients with lower LVEF had higher risk of heart failure. Therefore, we might have to manage the patients with lower LVEF at the initiation of PD more carefully about ultrafiltration failure, although the concrete mechanism was unclear in this study.

In this analysis about the technical survival periods of

study, we compared the patients with $eGFR < 6 \text{ mL/min/1.73 m}^2$ with the other patients, because Japanese Society for Dialysis Therapy recommends the initiation of peritoneal dialysis before $eGFR < 6 \text{ mL/min/1.73 m}^2$ ¹⁵. The technical survival periods of patients with $eGFR < 6 \text{ mL/min/1.73 m}^2$ at the initiation of PD was significant shorter in this study. In terms of technical survival period of patients undergoing PD, the residual renal function is one of the most important factors, because the residual renal function is associated with urinary volume which is associated with volume control closely. Therefore, as the result in this study, the higher $eGFR$ at the initiation of PD might have some advantages in terms of technical survival period of patients on PD. However, the proven management to keep residual renal function in patients on PD does not exist, currently. In addition, actually, it is difficult that we choose the exact proper period of initiation PD in each patient required renal replacement therapy including PD.

PD-related peritonitis is one of the most common complications in patients on PD, and it is associated with increased mortality and PD discontinuation^{8-12,16-18}. ESI is also a common complication of PD-related peritonitis^{18,19}. The association between technical survival period and hospitalizations for peritonitis and ESI in this study found no significant association for either complication. We treat PD-related peritonitis and ESI according to the guidelines published by the International Society for Peritoneal Dialysis^{18,19}, which might have affected those results. Nevertheless, 10% of the patients who discontinued PD during the course of the study did so as a result of peritonitis, so we are aware of the need to improve methods to predict and prevent peritonitis and ESI in order to improve technical survival.

More patients on PD are hospitalized for cardiovascular disease (including heart failure) than for infections (including peritonitis), and cardiovascular disease is the most common cause of death in patients on dialysis²⁰. Ultrafiltration failure, which can cause heart failure in patients on PD, is one of the major reasons for PD discontinuation and transfer to hemodialysis²¹. The prevalence of heart failure is estimated to be around 35% in patients on PD, and volume control is essential to improve the prognosis of such patients^{22,23}. The results in this study also indicates that controlling heart failure during PD is key to improving technical survival duration. Because ultrafiltration failure-which can trigger heart failure-was also the major cause of PD discontinuation in this study, we can conclude that, in our hospital at least, prevention

of ultrafiltration failure and better control of heart failure are the keys to improving technical survival period in patients on PD. Although we could not explain the mechanism and reasons by these results in this study, the improvement in management of ultrafiltration failure might associate with the improvement the rates of technical survival at the first 15 months. We need the further study about ultrafiltration failure in patients on PD in our hospital to improve the technical survival period.

Limitation

This study has certain limitations. First, the number of participants was limited and be insufficient to allow robust statistical analysis, because this study conducted at a single center. Second, the observation period was only 5 years. Third, this study included many censoring patients in early periods. Those limitations may have caused various biases in this study. Therefore, further large-scale, prospective studies are required to confirm the results of this study.

Conclusion

In this study, technical survival period was significantly longer in patients taking RASi, patients with $LVEF > 50\%$ when they started PD, and patients with $eGFR \geq 6 \text{ mL/min/1.73 m}^2$ at the initiation of PD was significantly longer. And hospitalization for heart failure was a significant risk factor for shorter technical survival period in patients on PD. Volume control to prevent heart failure may increase technical survival period in patients undergoing PD.

Data Availability: All data generated or analyzed during this study are available from the corresponding author on request.

Consent: All participants signed written informed consent forms, which included information about the research. Confidentiality of information and anonymity were also considered in this study.

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Authors' Contributions: KT drafted the first manuscript. KT, YSu, AH, TK and YSa managed the patients. YSa coordinated the data analysis and helped with writing the manuscript. All authors participated in discussions and read and approved the final manuscript.

Conflict of Interest: The authors have no conflicts of interest to declare.

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