ORIGINAL ARTICLE

The Survival and Associated Factors for Patients on Peritoneal Dialysis With History of Admission From Volume Overload

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ABSTRACT

Introduction: Patients with peritoneal dialysis (PD) who develop volume overload (VO) have high risks of dropout from death or advancement to hemodialysis. We aimed to determine the mortality rates, associated factors, and patient survival rates of PD patients who had history of admission from VO. **Methods:** We reviewed data of PD patients who were registered in the Database of Peritoneal dialysis in EXcel (DPEX) from January 2008 to December 2018. They were followed until death or the end of June 2020. Patients with at least 18 years of age and history of admission from VO were classified into two groups. Group A had a history of VO after starting PD. Group B had a history of VO before and after starting PD. The mortality rates were calculated. Patient survival and associated factors were evaluated by Kaplan-Meier and multiple cox regression, respectively. **Results:** 1,882 patients had history of admission from VO. The overall mortality rate was 28.9 per 100 person-years. The mortality rates in group A and group B were 25.4 and 41.7 per 100 person-years, respectively. Patients in group A had lower age, fewer comorbidities, longer dialysis vintage, and better patient survival than those in group B. Factors related to worsening patient survival were increased age, diabetes, and comorbidities. **Conclusion:** Patients with history of admission from VO before and after the start of PD had higher mortality rates than those with history of admission from VO after PD. Increased age, diabetes, and comorbidities were the associated factors of patient survival.
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Keywords: Dialysis, kidney replacement therapy, patient survival, peritoneal dialysis, volume overload

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INTRODUCTION

The presence of volume overload is associated with poor outcomes in dialysis patients. Previous studies showed that it was an independent predictor of mortality in patients with hemodialysis (HD), and peritoneal dialysis (PD) (1-7). Patients with volume overload tend to have arterial stiffness, hypertension, left ventricular hypertrophy, decreased left ventricular ejection fraction, and heart failure which lead to cardiovascular death (8). Volume overload in patients with PD is associated with a decrease in technique survival, increase risks of peritonitis from enteric organisms, and a negative impact to the quality of life (9-12). Factors associated with volume overload in these patients which were previously determined are increased age, gender, diabetes, higher systolic blood pressure (SBP), poor nutritional status, and use of hypertonic PD solutions (3, 13).

There are three main healthcare schemes to cover the Thai population (14). They are the civil servant medical health care scheme (CSMBS), social security health care scheme (SSS), and universal health coverage scheme (UHC). The majority of Thai patients with end-stage kidney disease (ESKD) are under UHC. PD First policy was used as the main modality of dialysis to ESKD patients covered by UHC since January 2008 before changing to a shared decision-making policy in February 2022. Although using the PD First policy, patients with PD

could permanently transfer to HD and be reimbursed by the National Health Security Office (NHSO) under the UHC. The types of PD solutions in the period of the PD First policy were limited to glucose-based PD solutions and the modality of PD was restricted to continuous ambulatory PD (CAPD) exchanges. This is a limitation to correct volume overload which results from a fast peritoneal solute transfer rate (PSTR). This study aims to investigate the mortality rates, patient survival, and associated factors in patients with PD who had history of admission due to volume overload during the PD First policy. The results would be beneficial to the UHC to consider adding other PD modalities in the health coverage scheme to improve outcomes in patients who could not transfer to HD.

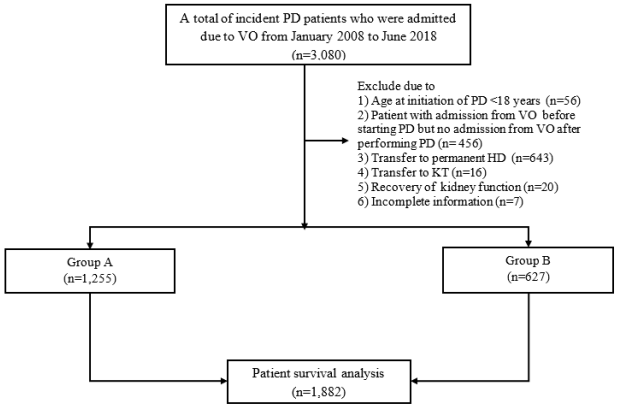
MATERIALS AND METHODS

Study population

This retrospective cohort study was conducted from the dates of the incident in PD patients who were voluntarily registered in the Database of Peritoneal Dialysis in the EXcel (DPEX) program (15). The patients who had history of admission from volume overload after starting PD were reviewed. The inclusion criteria for these patients for analysis were the age of at least 18 years and starting PD from January 2008 to December 2018. Patients who were transferred to permanent HD, kidney transplantation (KT), had recovery of kidney function, and incomplete information were excluded from the study. Figure 1 shows the flow of the study population. There were 21,709 PD patients registered in the DPEX database from 2008 to 2018. The number of incident PD patients who had history of admission from volume overload after starting PD and met the inclusion criteria was 1,882 (8.7%) cases. They were separated into two groups. Group A was the patients who had history of admission from volume overload after starting PD but did not have history of admission from volume overload prior to starting PD. Group B was the patients who had history of admission from volume overload before and after starting PD. The number of patients in group A and group B was 1,255 (5.8%) and 627 (2.9%) cases, respectively.

Data collection and variables

The demographic data of patients was demonstrated in age at the start of PD, gender, educational levels, types of reimbursement from health care coverage scheme, causes ESKD, comorbidities, serum creatinine (SCr), and estimated glomerular filtration rate (eGFR) at the time of initiating PD, and their time on PD therapy. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation was used to calculate the eGFR (16). The comorbidities were classified as diabetes, cerebrovascular disease, cardiovascular disease, liver disease, gastrointestinal disease, cancer, and airway disease according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes.



Group A: patients with history of admission from volume overload after start peritoneal dialysis

Group B: patients with history of admission from volume overload before and after start peritoneal dialysis

Abbreviations: VO, volume overload; PD, Peritoneal dialysis; HD, Hemodialysis; KT, Kidney transplantation

Figure 1: Flow of study population

Definition and Outcome

The primary outcome was all-cause mortality while patients performed PD. All participants were followed from the date of initiated PD until the date of death during performing PD or the date of censor at the end of June 2020. The admission from volume overload was identified by using various combinations of ICD-10 codes for fluid overload, pulmonary edema, and pleural effusion which were diagnosed at discharge.

Statistical Analysis

All analyses were done with STATA version 15 (StataCorp, College Station, TX). The categorical variables were demonstrated in numbers and percentages. The continuous variables were presented in mean with standard deviation (SD), and median with interquartile range (IQR). The 95% confidence interval (95%CI) was analyzed based on the normal approximation to the binomial distribution. The Mann-Whitney test was applied to compare quantitative variables between groups. The Chi-square test was used to compare qualitative variables, as appropriate. The mortality rates per100 person-years since initiating PD and its 95% CI were calculated based on the Poisson distribution assumption. Patient survival was analyzed by using the Kaplan-Meier method. The associated factors of all-cause mortality were investigated by a multivariate Cox proportional-hazard model which we included all the significant variables in a backward manner from the univariate analysis, and/or those variables considered clinically relevant according to the current literature. A p-value of less than 0.05 was accepted as statistically significant.

Ethical clearance

This study was approved by the Institutional Review Committee for Research in Human Subjects at Khon

Kaen University and Srinakharinwirot University No. SWUEC-481/2563X.

RESULTS

Patient characteristics, mortality rate, and patient survival

Table I shows the characteristics of patients who were enrolled in the study. The median (IQR) of age at starting PD was 55.6 (46.7-64.1) years. Patients in group B had higher age at the starting PD than those in group A [58.7 (50.8-66.0) vs 54.0 (44.5-62.7), respectively]. Most of the patients had an educational level in primary school or were illiterate. The percentage of patients who were reimbursed from the NHSO under the UHC was more than 90%. This was higher in group B (95.2%) than in group A (91.0%). The most common cause of ESKD was diabetic nephropathy which was 52.3% in group A and 56.1% in group B. The percentages of patients with comorbidities in diabetes, cerebrovascular disease, cardiovascular diseases, liver disease, gastrointestinal disease, cancer, and airway disease were higher in group B than in group A. Patients in group A had SCr levels higher than those in group B. The time on PD therapy of patients in group A was longer than those in group B. The time of observations in 1,882 patients was 5,535.3 person-years. 1,599 patients died during the observational period. The overall mortality rate was 28.9 per 100 person-years. The time of observations in group A was 4,347.1 person-years and the number of patients with death was 1,104 cases. The time of observations in group B was 1,188.3 person-years and the number of patients with death was 495 cases. The mortality rate in group A was 25.4 per 100 person-years while it was 41.7 per 100 person-years in group B (Table II).

Figure 2 shows the patient survival of those with history of admission from volume overload comparing between group A and group B. Patients in group A had better survival than those in group B. The 1-, 3-, 5-, and 10-year survival rates of patients in group A were 87.5% (95%CI: 85.6-89.3), 51.4% (95%CI: 48.6-54.2), 27.5% (95%CI: 24.9-30.0), and 3.4% (95%CI: 24.9-30.0), respectively. The 1-,3-, and 5-year survival rates of patients in group B were 68.5% (95%CI: 64.8-72.0), 31.7% (95%CI: 27.8-35.8), and 7.7% (95%CI: 5.2-11.0), respectively. In addition, we performed analysis by including patients who transferred to permanent HD and reclassified into group A1 and group B1 according to the history of admission from volume overload. We found that patients in group B1 had lower numbers and rates of transfer to permanent HD than those in group A1.

We conducted further analysis on the group of incident PD patients with a history of admission due to volume overload before PD started but not after and defined them as group C. We found that this group had better survival and lower mortality rate than group A and group B.

Table I: Characteristics of PD patients with history of admission from volume overload

Characteristics	Overall (n=1,882)	Group A (n=1,255)	Group B (n=627)	P-value
Age at start PD in year (IQR)	55.6 (46.7-64.1)	54.0 (44.5-62.7)	58.7 (50.8-66.0)	<0.001[a]
Sex (number, %)				0.922[b]
Male	934 (49.6%)	624 (49.7%)	310 (49.4%)	
Female	948 (50.4%)	631 (50.3%)	317 (50.6%)	
Education (number, %)				0.003[b]
Illiterate and primary school	1,530 (81.3%)	999 (79.6%)	531 (84.7%)	
Secondary school	310 (16.5%)	220 (17.5%)	90 (14.4%)	
Collage or higher	42 (2.2%)	36 (2.9%)	36 (2.9%)	
Health Scheme (number, %)				0.002[b]
UHC	1,739 (92.4%)	1,142 (91.0%)	597 (95.2%)	
CSMBS	102 (5.4%)	78 (6.2%)	24 (3.8%)	
Others	41 (2.2%)	35 (2.8%)	6 (1.0%)	
Cause of ESKD (number, %)				
Diabetic Nephropathy	1,009 (53.6%)	657 (52.3%)	352 (56.1%)	0.066[b]
Analgesic nephropathy	168 (8.9%)	90 (7.2%)	78 (12.4%)	<0.001[b]
Hypertension	482 (25.6%)	325 (25.9%)	157 (25.0%)	0.366[b]
Obstructive nephropathy	21 (1.2%)	20 (1.6%)	1 (0.2%)	0.002[b]
Others	55 (2.9%)	42 (3.4%)	13 (2.1%)	0.078[b]
Unknown	147 (7.8%)	121 (9.6%)	26 (4.2%)	<0.001[b]
Comorbidity (number, %)				
Diabetes	417 (22.1%)	235 (18.7%)	182 (29.2%)	<0.001[b]
Cerebrovascular disease	434 (23.1%)	187 (14.9%)	247 (39.4%)	<0.001[b]
Cardiovascular disease	446 (23.7%)	206 (16.4%)	240 (38.3%)	<0.001[b]
Liver disease	79 (4.2%)	33 (2.6%)	46 (7.3%)	<0.001[b]
Gastrointestinal disease	76 (4.0%)	32 (2.6%)	44 (7.0%)	<0.001[b]
Cancer	14 (0.7%)	9 (0.7%)	5 (0.8%)	1.000[b]
Airway disease	108 (5.7%)	68 (5.4%)	40 (6.4%)	0.402[b]
Laboratory parameter (IQR)				
eGFR ml/min/1.73m^2	4.7 (3.3-6.7)	4.5 (3.2-6.4)	5.1 (3.5-7.5)	<0.001[a]
Creatinine mg/dL	9.9 (7.0-13.4)	10.0 (7.4-14.0)	9 (6.4-12.3)	<0.001[a]
Dialysis vintage in year (IQR)	2.5 (1.3-4.0)	3.0 (1.6-4.9)	1.9 (0.7-2.7)	<0.001[a]

Note: [a]Mann-Whitney test for compare non-parametric value between group; [b]Chi-square test for compare proportion between group
Abbreviation: CSMBS, civil servant medical benefit scheme; ESKD, end stage kidney disease; eGFR, estimated glomerular filtration rate; PD, peritoneal dialysis; UHC, universal health coverage scheme
Group A: history of admission from volume overload after start peritoneal dialysis
Group B: history of admission from volume overload before and after start peritoneal dialysis

Factors associated with mortality

Figure 3 shows the associated factors of patient survival in PD patients with history of admission from volume overload. Increased age at the start of PD, diabetes, cerebrovascular disease, gastrointestinal disease, eGFR at the time of initiating PD, and having history of admission from volume overload before and after starting PD were the factors associated with increased risks of mortality in all PD patients with history of admission from volume overload after starting PD. After controlling for the effect of covariate factors, multivariable analysis showed a significance with lower survival in patients with a

Table II: Mortality rates of patients with history of admission from volume overload

Patient with volume overload	Number of patients	Person-years	Death, N	Death per 100 person-years	95% CI
Overall	1,882	5,535.3	1,599	28.9	27.5-30.3
Group of patients					
Group A	1,255	4,347.1	1,104	25.4	23.9-26.9
Group B	627	1,188.3	495	41.7	38.1-45.4

Abbrevation 95% CI, 95% confidence interval
Group A: patients with history of admission from volume overload after start peritoneal dialysis
Group B: patients with history of admission from volume overload before and after start peritoneal dialysis

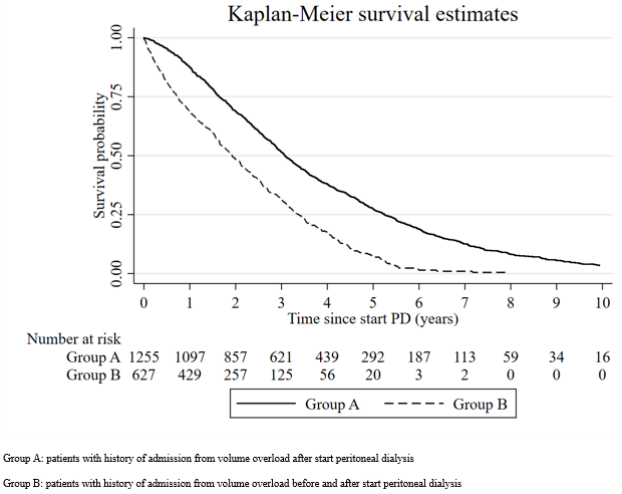


Figure 2: Patient survival with history of admission from volume overload comparing between group A and group B

history of admission due to volume overload prior to and after starting PD (Group B) (HR: 1.70; 95%CI: 1.51-1.91). This is in comparison to the patients with a history of admission due to volume overload after starting PD only (group A). The associated factors of mortality in patients with group A were increased age at the start of PD, diabetes, cerebrovascular disease, gastrointestinal disease, and eGFR at the time of initiating PD. The associated factors of mortality in patients with group B were increased age, liver disease, and cancer.

Figure 4 shows the number of PD patients with diabetes and the number of comorbidities and the hazard ratio of mortalities in those with history of admission from volume overload after starting PD. The percentages of patients with diabetes plus comorbidities were higher in group B than in group A (Figure 4A). Patients who had diabetes and three or more comorbidities had a higher adjusted risk of mortality than those with diabetes and two comorbidities [1.61 fold (95% CI: 1.27-2.09) vs 1.31 (95% CI: 1.12-1.53), respectively] (Figure 4B).

The data on cardiovascular death and also other causes of death were not available in our data set therefore we could not perform the Cox regression model to investigate the effect of volume overload on cardiovascular or other causes of death.

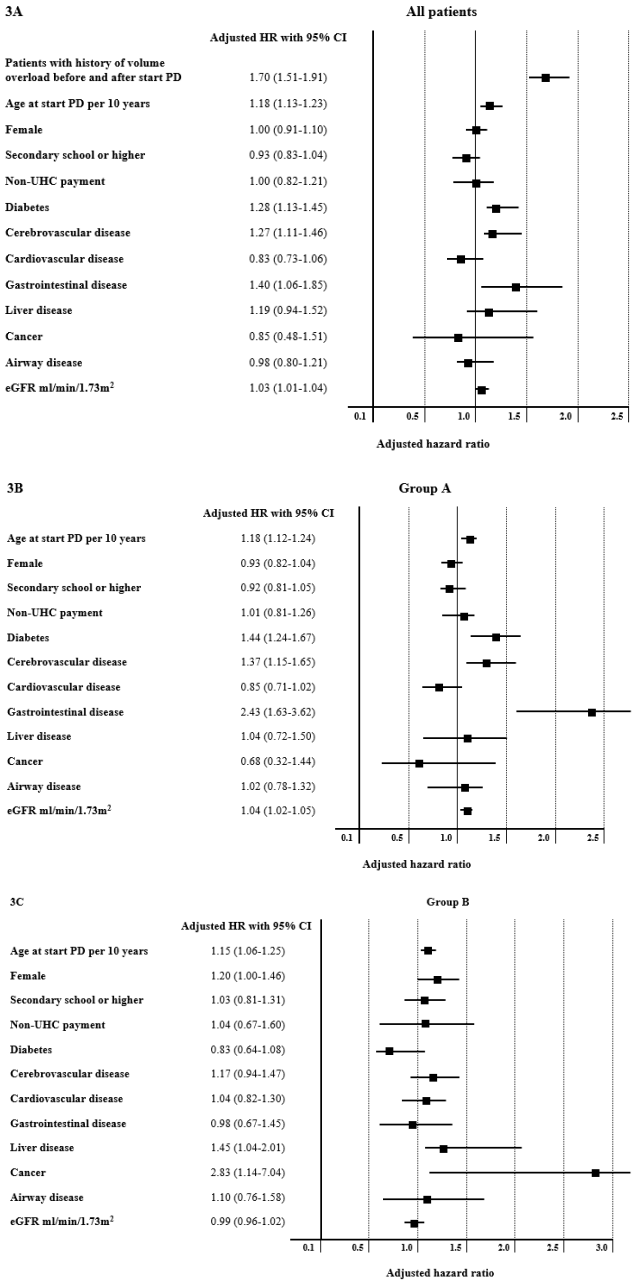


Figure 3: Associated factors of patient survival in PD patients with history of admission from volume overload (A: all patients; B: patients in group A; C: patients in group B). Abbreviations: eGFR, estimated glomerular filtration rate; HR: Hazard ratio, CI: Confidence interval; PD: peritoneal dialysis; UHC, universal health coverage scheme. Group A: history of admission from volume overload after start peritoneal dialysis. Group B: history of admission from volume overload before and after start peritoneal dialysis

DISCUSSION

Our study shows the adverse effect of volume overload on patient survival. Patients with PD who had history of admission from volume overload before and after starting PD had worse patient survival rates compared to those who developed volume overload after starting PD. The mortality rate of PD patients who had volume overload before and after starting PD was higher than those who had volume overload after starting PD. Factors associated with all-cause mortality were increased age

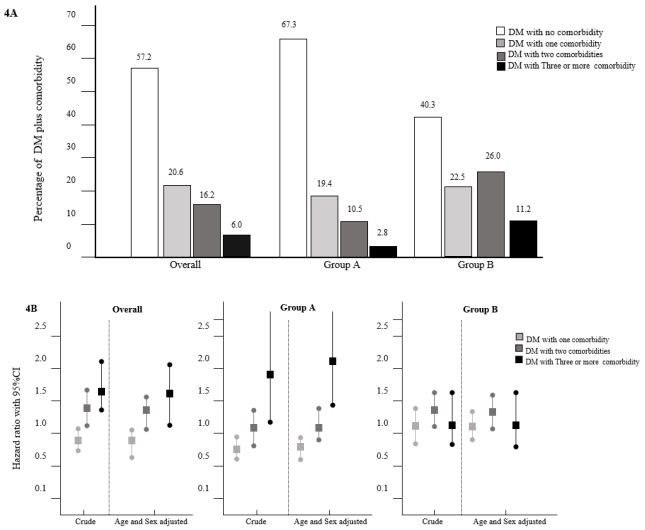


Figure 4: Hazard ratio of death among PD patient with a history of admission due to VO according to DM plus comorbidity

at starting PD, diabetes, and comorbidities.

Previous studies demonstrated that volume overload was common in patients with PD (3, 17-19). Patients with volume overload had increased risks of death or transfer to HD (3, 11). These previous studies used the Body Composition Monitor (BCM) measurements to determine volume overload (3, 11, 17-19). Our study determined volume overload from history of admission in patients with PD because the BCM measurements were not available in most PD centers and were not in routine practice. In addition, we want to emphasize the consequence of volume overload in symptomatic patients. Patients who need hospitalizations due to volume overload mean that they have significant severity. The modifiable causes of volume overload should be investigated and corrected (20). A previous study has shown that the appropriate management to control volume overload resulted in improvement in cardiac functions and decreased rehospitalization related to volume overload (21).

Our study shows that factors associated with all-cause mortality in patients with history of admission due to volume overload after starting PD were increased age, diabetes, and comorbidities which were the same factors associated with survival in patients with PD (22, 23). The higher risk of death in patients with volume overload prior to and after starting PD compared to those with volume overload after starting PD only in our study was similar to the results in a previously published study (11). The patients in group B had more advanced age at the time of starting PD, a higher percentage of diabetes and many other comorbidities, education level in illiterate and primary school, and UHC compared to those in group A suggests that the causes of volume overload were complex. The difference in baseline demographic characteristics of patients in group A and group B was the additional explanation for the difference in mortality between groups. These comorbidities and/or social conditions were barriers that were not suitable for HD as shown in the supplemental data that patients in group B1 had a lower rate of transfer to HD than those in group A1. Therefore, vigorous management and a multidisciplinary approach to control volume overload are required in these patients to prolong their survival. The modifiable comorbidities should be identified early and treated. Dietary counseling should be routinely provided to patients until they are able to restrict sodium intake. Diuretics should be adjusted in patients with residual kidney function to get more urine volume. The PD prescriptions should be optimized to match with types of peritoneal membrane and avoid hyperglycemia to get sufficient peritoneal fluid removal. The volume status should be closely monitored to ensure that they are in normal hydration.

The International Society of Peritoneal Dialysis (ISPD) recommends that evaluation of the peritoneal membrane should be performed at the time of starting PD and monitored during PD therapy (24). The function of the peritoneal membrane can change over time during dialysis treatment (24). We could not analyze the types of the peritoneal membrane as most of the patients did not have data from the peritoneal equilibration test (PET). We propose that the inappropriate PD prescriptions to the types of the peritoneal membrane may be an important cause of volume overload, especially in patients with history of volume overload after starting PD. The ISPD recommends that PET should be repeated to determine peritoneal function in patients who have problems with volume overload and those not maintain well-being (24). The types of peritoneal membrane function will provide the plan of modality transfer to automated peritoneal dialysis (APD) as the NHSO allows APD to be reimbursed in patients under the UHC after the policy changed to shared decision-making in February 2022. The current situation of dialysis in Thailand is found that most incident ESKD patients choose HD as the first dialysis modality. We predict that it will be the paradigm shift from failed PD and transferred to HD during the PD First policy to failed HD and transferred to PD. PD will be the last dialysis modality for these patients. The reimbursement for PD solutions should not be restricted to glucose-based PD fluid to preserve the peritoneal membrane and avoid metabolic syndrome to improve clinical outcomes (25, 26).

We have acknowledged the major limitations of our study. First, we could not define key clinical information, such as residual kidney function, dialysate glucose exposure, diuretics use, and peritoneal membrane transporter status. These were important factors related to volume control in PD patients. Second, we could not determine risk factors and effects between comorbidities and volume overload because we could not identify the time of first diagnosis of comorbidities. Third, we did not have data on residual kidney function, dietary sodium intake, and nutritional status. These factors are

the causes and effects of volume overload and mortality. Even though our study had limitations, it had strength according to it was the nationwide scale and reflected the real-world practice in Thailand. From epidemiological viewpoints, the results can be useful for not only local patients but also Asian PD populations.

We demonstratethe high mortality in PD patients with volume overload which is associated with advanced age, diabetes, and multiple comorbidities. The results have beneficial to suggestion that these patients need close monitoring and intensive management from PD centers. They require more frequent adjustment of PD prescriptions which may be changed to other PD modalities advancing from continuous ambulatory PD.

CONCLUSION

The volume overload before and/or after starting PD was associated with high mortality. Factors related to death in patients with volume overload were increased age, diabetes, and comorbidities.

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