Risk Factors of First Peritonitis Episode in Thai CAPD Patients

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Background: *Peritonitis is a major complication of continuous ambulatory peritoneal dialysis (CAPD) patients. Information on the specific risk of peritonitis is important in reducing this common complication.*
Material and Method: *A single center, retrospective cohort study was done to assess time to first peritonitis event and risk factors in Thai CAPD population.*
Results: *Between January 1995 and December 2005, 322 incident CAPD patients were recruited for the present study. During the study period of 4,281 patient-months, 198 episodes of first peritonitis were recorded. The median peritonitis-free time was 13.7 months. A Cox regression model showed that an increase in level of baseline albumin and hematocrit by 1 g/dL and 1% would decrease risk of peritonitis by 27% and 3%, respectively (hazard ratio (95%CI): 0.73 (0.59-0.91) and 0.97 (0.94-1.00)). A neutral effect of self and caregiver performer was observed in the present study.*
Conclusion: *The present study confirmed the susceptibility of hypoalbuminemia and anemia to peritonitis. Awareness of particular risk groups should be achieved to prevent peritonitis.*

Keywords: *Continuous ambulatory peritoneal dialysis, First peritonitis episode, Risk factors*

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Continuous ambulatory peritoneal dialysis (CAPD) is one of the treatment modalities for end stage renal disease patients. This mode of treatment needs fewer resources compared to hemodialysis[1]. From the patients' point of view, CAPD may be suitable for rural people who have limited access to hemodialysis centers.

Peritonitis is a leading cause of mortality (about 0.8%-12.5%) and technique failure (30-40%) in CAPD patient[2]. At present, the acceptable incidence of PD-related peritonitis is not more than 0.67 episodes per case per year[3]. One of the successes of a CAPD program is a low peritonitis rate. Information on risk factors associated with increased risk of peritonitis in the patients is therefore important in reducing this complication.

Factors previously found to influence peritonitis were body mass index (BMI), diabetic kidney disease and baseline serum albumin. Previous studies have shown that higher BMI is associated with a shorter time to first peritonitis episode and episodes of peritonitis per case per year are significantly higher among patients with higher BMI[2]. However, due to the lower prevalence of obesity in the Thai population, it remains to be seen whether these data can be extrapolated to Thai patients.

Diabetic kidney disease CAPD patients have been shown to be more susceptible to peritonitis. Guo et al found that diabetes tended to have a slightly lower CAPD technique success than non-diabetic patients, however the difference did not reach statistical significance[4]. Cueto-Manzano et al reported both peritoni-

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tis and diabetes as predictors of CAPD technique failure in a 12-year cohort study in Mexico. However they did not report any association between these two factors and peritonitis[5].

Baseline serum albumin has also been associated with the susceptibility to peritonitis. The CANUSA Peritoneal Dialysis Study Group[6] found that a decreased serum albumin concentration at baseline was associated with increased risk of technique failure, although this was not specifically ascribed to peritonitis. Chow et al observed a significant increase in risk of developing peritonitis with a decrease in baseline serum albumin in a Chinese population[7].

Srinagarind Hospital is a large 650-bed public tertiary-care referral medical center in the northeast of Thailand. The CAPD program was started here more than twenty years ago. Patients' characteristics are different from previous studies. Most of the patients are elderly and some need caregiver support to perform CAPD. Baseline characteristics and the risk of peritonitis in this patient group needs to be explored for improvement in patient care and prevention of peritonitis. Therefore, a retrospective cohort study was conducted to identify the risk factors for first peritonitis episode in the Thai population.

Material and Method

Study groups

The incidence of CAPD patients at Srinagarind Hospital from January 1995 to December 2005 was 322 cases. They were all included in the present study. A standard Tenckhoff catheter was used in most patients by both peel-away sheath bedside insertion and mini-explore technique. CAPD was started in most patients without a break-in period due to uremic conditions and inadequacy of hemodialysis back-up. The single bag connecting systems (both safe lock and manual spike) were used in 85.4% of the patients. Peritoneal dialysis solution used was a standard 1.5% dextrose with lactate buffer 1.5-2.0 liters at four exchanges per day. Patients and at least one of their caregivers were trained to perform CAPD exchange by dialysis nurses. The training process was composed of a video demonstration, simulation with a mannequin, and an evaluation of the trainee's performance. The process lasted for 3-5 days. Caregiver assisted exchange was defined as one or more CAPD exchanges per day done by a caregiver.

Diagnosis of peritonitis was based on at least two of the following criteria: abdominal pain or cloudy Peritoneal Dialysis (PD) effluent, leukocyte in peritoneal effluent more than 100 cells/mm^3, and at least 50% of the cells are polymorphonuclear leukocytes, or positive gram stain or effluent culture. Bacterial culture was performed using a BacTAlert bottle (Organon Teknika, Durham, North Carolina, USA). Peritonitis was treated with the standard antibiotic protocol of the hospital. Initial antibiotics consisted of cefazolin plus gentamicin or ceftazidime. Regimen change was based on culture and sensitivity. The decision to remove the catheter depended on the physician's opinion. Generally, culture negative peritonitis and known organisms without response and fungal peritonitis were considered as criteria for catheter removal.

Patients with severe co-morbidities such as cerebrovascular disease, malignancy, dementia and severe obstructive airway disease were not eligible for CAPD at the center. Therefore, co-morbidities other than diabetes mellitus were not considered in the analysis.

Clinical data

All identified cases were reviewed for clinical history, baseline laboratory results within one month prior to CAPD, clinical course, and follow-up. The data collection consisted of demographic information, primary renal disease, baseline and follow-up laboratory data, and performer of the CAPD, and information regarding the occurrence of peritonitis. The analyses focused on baseline characteristics and laboratory values, thus, data on dialysis adequacy were not included.

Follow-up

Patients were followed up until death, technique failure, or receiving kidney transplantation. The end of the follow-up period was December 31, 2005. Complete follow-up was defined as availability of information to the end of the study or death. The mean follow-up time was 23.9 months (range 0.2-190.8 months). The present study was approved by Khon Kaen University Ethics Committee.

Statistical analysis

Time to first peritonitis episode was examined using standard survival method, and Cox regression models for multivariate analyses. Statistical analysis was performed using STATA software. All probabilities were two-tailed and the level of significance was set at 0.05.

All data were expressed as mean $\pm$ SD for normally distributed data and median or range, for skewed data. Statistical comparison was performed

using Student's t-test and comparison of percentage between groups was made with the Chi-square test or Fisher-exact test. Actuarial survival curves were made according to the Kaplan-Meier method. Analysis was censored at death, transplantation and transfer to hemodialysis. Comparison of the survival curves of the different subgroups was made using log-rank test. The following indicator variables were tested: gender, age, baseline serum albumin, Hct, BMI, underlying disease with diabetes mellitus, type of connection (double bag vs single bag), and performed by self or caregivers. Variables that remained significant at a p value of less than 0.2 were retained in the final model of the multivariate analysis.

Results

Three hundred and twenty two incident CAPD patients were studied over a total observation period of 4,281 patient-months (mean 13.3 months, median 7.7 months). Mean age at commencement of CAPD was 56.7 $\pm$ 12.5 years (range 14-85 years). Males comprised 55% of the study group. About 70% patients lived more than 100 kilometers from the study center. Most of the patients required a caregiver to perform the CAPD exchange. Uremic status and old age were obstacles for self-performing CAPD.

Etiologies of ESRD were diabetic kidney disease (49.4%), hypertension (14.6%), chronic glomerulonephritis (9.0%), obstructive nephropathy and interstitial nephropathy (9.0%), and unknown primary renal disease (17.7%). The baseline characteristics of the study patients are presented in Table 1. Mean BMI at the start of CAPD was 22.9 $\pm$ 3.1 kg/m^2 (range 15.4-40.2); 18% of patients had BMI $\geq$ 25 kg/m^2. The single bag system was used in 275 cases, double bag system in 47 cases. Baseline concentration of serum albumin was 3.1 $\pm$ 0.7 g/dL (range 1.4-4.7). Only 2.8% had the levels of Hct less than 20%.

One hundred and twenty-four patients (38.5%) had no peritonitis episode, 198 patients (61.5%) had 1 episode, 50 patients (15.5%) had 2 episodes, and 23 patients (7.1%) had more than 2 episodes during the follow-up period. The rate of the first episode of peritonitis was 4.63 per 100 patient-months. Median time to first peritonitis was 13.7 months. Peritonitis free survival at 1, 3, 5, 7 years was 53.77%, 21.03%, 12.95% and 5.54%, respectively. Thirty eight patients (11.8%) died from peritoneal dialysis-related infection.

Causative organisms of the first episode are summarized in Table 2. Culture negative peritonitis was found quite common at 63.7%. Staphylococcus species peritonitis was found in 11.6% and Pseudomonas species in 8.6%. Among those infected with Staphylococcus species (N = 23), 10 patients (43.5%) had recurrence of peritonitis with the same organism. The incidence of gram negative peritonitis was 22.2% in CAPD patients with diabetes and 13.7% in those without diabetes. However, the incidence of gram negative or gram positive peritonitis did not differ statistically with respect to the status of diabetes.

Table 1. Baseline clinical characteristics and laboratory data of the cohort

	All patients	Peritonitis free patients	Patients with first peritonitis episode
Patients (N)	322	198	124
Age, mean $\pm$ SD (years)	56.7 $\pm$ 12.5	56.3 $\pm$ 11.2	57.3 $\pm$ 14.4
Male gender, (%male)	177 (55.0)	114 (57.6)	63 (50.8)
Cause of end stage renal disease, N (%)			
Diabetes mellitus	159 (49.4)	92 (46.5)	67 (54.0)
Glomerulonephritis	29 (9.0)	24 (12.1)	5 (4.0)
Hypertension	47 (14.6)	26 (13.1)	21 (16.9)
Polycystic kidney disease	1 (0.30	1 (0.5)	0 (0.0)
Obstructive or interstitial nephropathy	29 (9.0)	18 (9.1)	11 (8.9)
Unknown	57 (17.7)	37 (18.7)	20 (16.1)
Weight, mean $\pm$ SD (kg)	58.7 $\pm$ 10.3	58.3 $\pm$ 9.8	59.2 $\pm$ 11.1
Body mass index, mean $\pm$ SD (kg/m^2)	22.9 $\pm$ 3.1	22.8 $\pm$ 3.0	23.1 $\pm$ 3.2
Serum albumin, mean $\pm$ SD (mg/dL)	3.1 $\pm$ 0.7	3.1 $\pm$ 0.7	3.1 $\pm$ 0.7
Hematocrit, mean $\pm$ SD (g%)	29.2 $\pm$ 4.8	28.7 $\pm$ 4.7	30.0 $\pm$ 4.8
Blood urea nitrogen, mean $\pm$ SD (mg/dL)	77.6 $\pm$ 38.2	77.3 $\pm$ 40.2	78.0 $\pm$ 34.9
Creatinine, mean $\pm$ SD (mg/dL)	10.6 $\pm$ 5.4	10.7 $\pm$ 5.3	10.5 $\pm$ 5.4

Results of life table analyses of time to develop the first episode of peritonitis are shown in Table 3. The time to an initial episode of peritonitis did not vary significantly among those patients with diabetes and those without. Peritonitis-free survival was found to be statistically different with respect to the level of baseline serum albumin (p = 0.0027). Baseline Hct was also found to be hardly statistically associated with peritonitis (p = 0.046) by Cox regression model in Table 4. However, there was no statistical significance between

Table 2. Causative organisms of the first episode of peritonitis of the cohorts (N = 198)

Causative organisms	Peritonitis episodes (n)	Percentage (%)
Gram-negative organisms	17	8.59
Pseudomonas species	6	3.03
Klebsiella species	1	0.50
Acinetobacter species	2	1.01
Aeromonas species	2	1.01
Enterobacter species	6	3.03
Miscellaneous		
Gram-positive organism	2	1.01
Streptococcus species	23	11.62
Staphylococcus species	1	0.50
Methicillin Resistance *Staphylococcus aureus*	2	1.01
Miscellaneous		
Fungi	9	4.55
Mycobacterium tuberculosis	1	0.50
Peritonitis with no growth culture	126	63.64

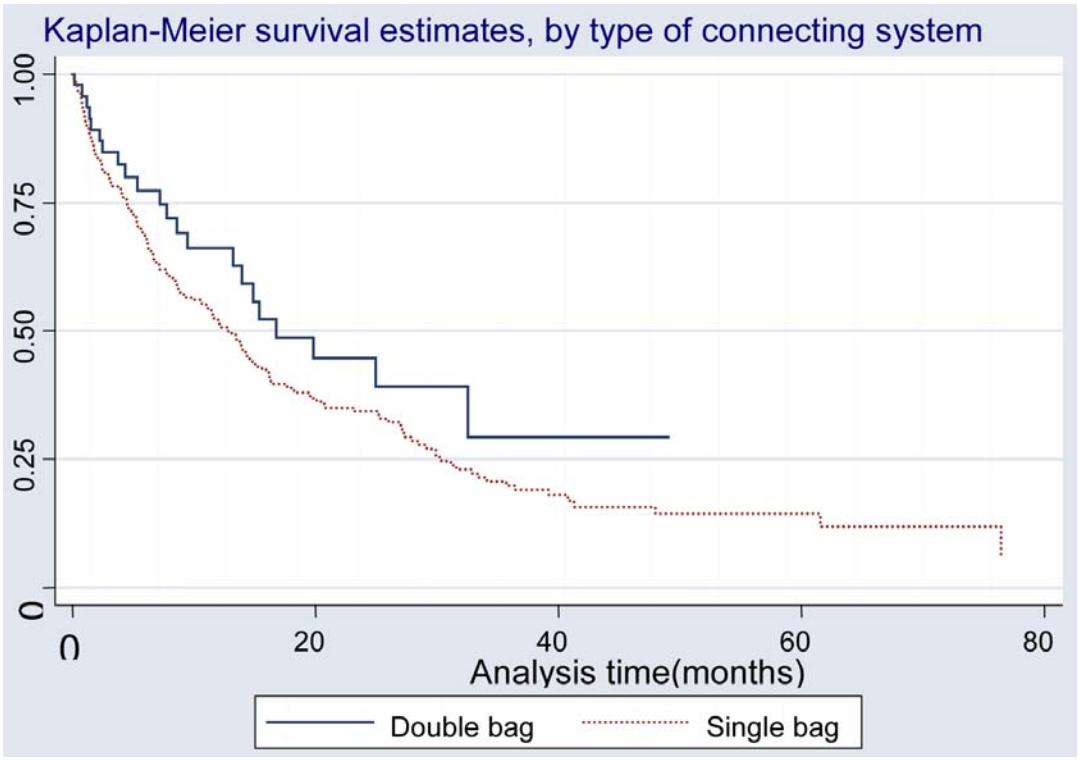
Table 3. Peritonitis free survival in subgroups: univariate analyses

	First year peritonitis free survival	
	Percent (95% CI))	p-value*
Age > 55 years	49.5 (41.12-57.32)	0.2260
Age ≤ 55 years	58.7 (49.61-66.77)	
Patient with diabetes mellitus	55.4 (46.46-63.47)	0.9220
Patient without diabetes mellitus	52.3 (43.80-60.15)	
Single bag connecting system	51.7 (45.13-57.94)	0.1322
Double bag connecting system	66.2 (49.28-78.56)	
CAPD performed by self	52.3 (45.21-58.82)	0.5380
CAPD performed by caregivers	58.7 (45.89-69.48)	
Albumin at baseline ≥ 3 g/dl	60.6 (52.63-67.59)	0.0027
Albumin at baseline < 3 g/dl	43.3 (33.82-52.43)	

* p-values based on log-rank test

Table 4. Cox regression model of time to first episode of peritonitis

Predictors	Hazard ratio	95%CI	p-value
Double bag vs Single bag	0.71	0.45-1.10	0.127
Albumin per 1 g/dL increase	0.73	0.59-0.91	0.004
Hematocrit per 1 % increase	0.97	0.94-1.00	0.046



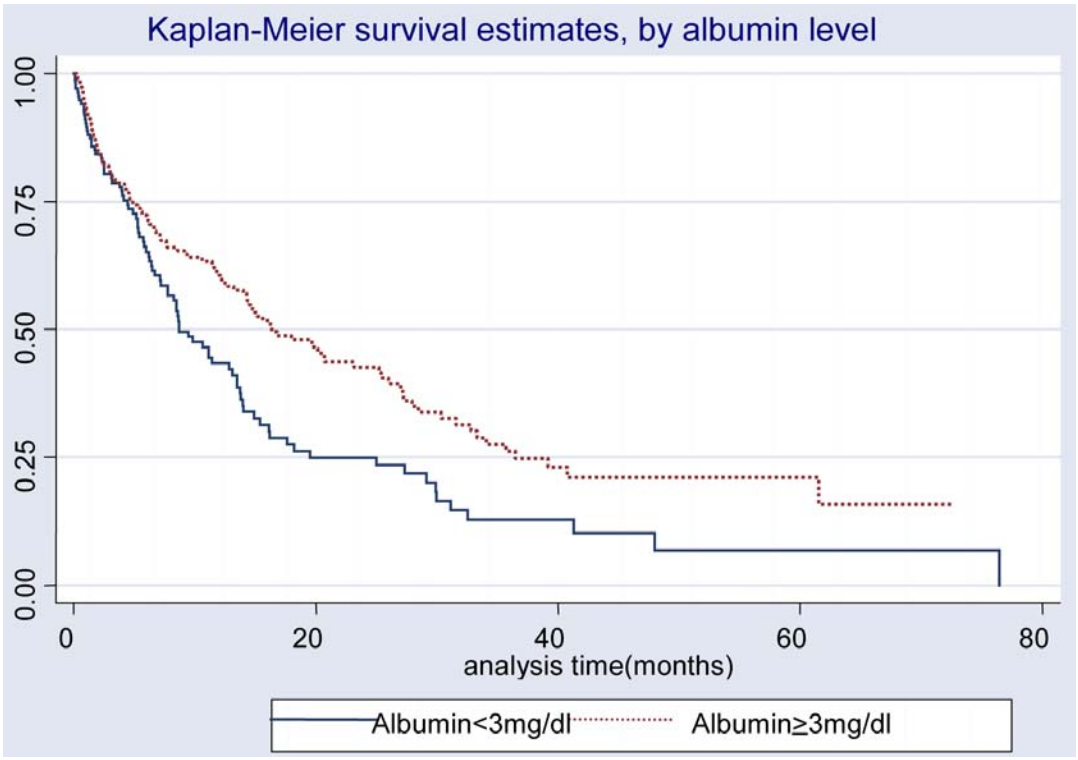


Fig. 1 Peritonitis free survival curves

age, gender, connecting system, Hct and CAPD performed by self or a caregiver, and the risk of peritonitis. Peritonitis-free survival curves compared between those with baseline albumin level less than 3 g/dL and those with the level not less than 3 g/dL, and by type of connection are shown in Fig. 1.

Cox regression models were constructed using gender, age, baseline values of albumin and Hct, BMI, underlying disease with diabetes mellitus, type of connecting system and type of performer. The final model revealed that two independent predictors of risk to develop first episode of peritonitis included baseline albumin and Hct (Table 4). If the level of baseline albumin was increased by 1 g/dL, the risk of peritonitis would decrease by 27%. A 1% increase in the level of Hct decreases the risk of developing peritonitis by 3%. The use of the double bag system was not statistically associated with a decreased risk of peritonitis

Discussion

The results show that low baseline serum albumin is a strong risk factor for first peritonitis episode in the presented patients. This represents the first large-scale risk analysis of CAPD peritonitis, especially the first episode, in a Thai population.

Studies in Western populations have shown that race, BMI, diabetic kidney disease and hypoalbuminemia are risk factors of peritonitis. The authors report no influence of patient age on the risk of peritonitis. Consistent with the report in a Chinese population[7], BMI was not the risk factor for peritonitis at the study center. The lower prevalence of obesity in the Thai CAPD population may explain the disparity from the ANZDATA study[2], in which half of their patients' BMI's were more than 25 kg/m^2. Hypoalbuminemia at baseline was a strong risk factor of peritonitis in the present study. Studies in the United States[8] and Hong Kong[9] found that every 1 g/dL decrease of serum albumin concentration increased the risk of peritonitis by 74% and 67% respectively. Our magnitude of risk was lower than these previous studies. The authors found an increased risk of 27% for every 1 g/dL decrease in serum albumin. The reason for this discrepancy is that the authors evaluated only first peritonitis event while the previous studies evaluated overall rates of peritonitis. The reason for increasing risk is not clear. Hypoalbuminemia may be the result of malnutrition and inflammatory response. Malnutrition affects host-immune response by several mechanisms such as altered immune cell populations[10,11], reduction of leukotrienes[12], and generalized increase in inflammatory mediators[13]. Interventions for improving of patients' nutritional status should be given to prevent malnutrition in CAPD patients that may lead to susceptibility to infection. Uremia itself contributes to inflammation as a result of the accumulation of pro-inflammatory compounds or products of metabolism[14]. Increased oxidative stress is also found in renal failure patients. Both factors reduce serum albumin and increase risk of death and infection.

An interesting finding is that there is no difference in peritonitis among self-performed dialysis and caregiver-performers. Most of the performers were younger family members such as patients' offspring and their siblings' children. This result may be explained by the meticulous care given to elderly family members in the Thai culture. Information on the neutral effect of caregiver performer on peritonitis has not been reported elsewhere[15]. It was formerly believed that CAPD modality is not suitable for patients who need a caregiver. The present results show that a caregiver can perform CAPD exchange without increasing the risk of peritonitis, at least in the initial phase of treatment. However, training of a caregiver is a very important step for treatment outcome. Our patient care team has had a long experience in training for both patients and caregivers. The effect of caregivers in long term should be explored by examining the impact on technique survival. Thus the inability to perform self-exchange may not be a contraindication in a Thai population, especially when cycler machines are not available countrywide.

The rate of culture negative peritonitis in the present study was quite high compared to the acceptable range (< 20%)[3], the reasons for the condition could be explained by receiving antibiotics without back-up culture results from local community hospitals prior to admission at the study center or technical problems during dialysate culture.

The relationship of diabetes and infectious organisms was not clearly defined in the present study. However, previous studies have demonstrated that diabetic patients were susceptible to gram positive peritonitis[16,17]. This could be explained by intraperitoneal insulin administration. This mode of administration was not applicable in the presented patients.

Conclusion

The present study indicates that hypoalbuminemia and anemia are the risk factors of peritonitis, with minemia being the strong factor. Awareness of the particular risk groups should be achieved to prevent

peritonitis. Caregivers can perform CAPD exchange without increasing the risk of peritonitis.

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ปัจจัยเสี่ยงของการติดเชื้อทางช่องท้องครั้งแรกในผู้ป่วยไทยที่ล้างไตทางช่องท้องแบบถาวร

ทวี ศิริวงศ์, ชลธิป พงศ์สกุล, ทัดสะลัง แก้วบุนมา, ดรุณี จันทร์เลิศฤทธิ์, กนกกร ศรีทาโส, เจฟฟ์ จอห์นส

วัตถุประสงค์: *เพื่อหาระยะเวลาปลอดการติดเชื้อทางช่องท้องและปัจจัยเสี่ยงของการติดเชื้อในผู้ป่วยไตวายเรื้อรังที่รักษาด้วยการล้างไตทางช่องท้องแบบถาวร*

วัสดุและวิธีการ: *ติดตามผู้ป่วยที่เข้ารับการรักษาด้วยการล้างไตทางช่องท้องที่โรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น ตั้งแต่เดือนมกราคม พ.ศ. 2538 – เดือนธันวาคม พ.ศ. 2548 โดยหาระยะเวลาที่ปลอดการติดเชื้อและปัจจัยเสี่ยงของการติดเชื้อทางช่องท้องครั้งแรก*

ผลการศึกษา: *ผู้ป่วยจำนวนทั้งสิ้น 322 ราย ระยะเวลาที่ติดตามการรักษาคือ 4,281 ผู้ป่วย-เดือน พบการติดเชื้อครั้งแรก 198 ครั้ง ระยะปลอดเชื้อมัธยฐานคือ 13.7 เดือน ผลการศึกษาโดยใช้ Cox regression model พบว่าการเพิ่มขึ้นของระดับอัลบูมินและระดับความเข้มข้นของเลือดที่ระดับพื้นฐานทุก 1 กรัม/ดล. และ 1% สามารถลดความเสี่ยงที่จะเกิดเยื่อบุช่องท้องอักเสบได้ 27% และ 3% ตามลำดับ (hazard ratio (95%CI): 0.73 (0.59-0.91) และ 0.97 (0.94-1.00). อย่างไรก็ตาม ไม่พบความแตกต่างของการติดเชื้อระหว่างผู้ที่ทำการเปลี่ยนถ่ายน้ำยาล้างไตเองกับกลุ่มที่ต้องพึ่งพาญาติ*

สรุป: *การศึกษานี้ยืนยันความสำคัญของระดับอัลบูมินในเลือดและระดับความเข้มข้นของเลือดในแง่ปัจจัยเสี่ยงของการติดเชื้อในผู้ป่วยไตวายที่ได้รับการล้างไตทางช่องท้องแบบถาวร แพทย์ผู้ดูแลควรให้ความสำคัญกับผู้ป่วยกลุ่มนี้เพื่อป้องกันการแทรกซ้อนดังกล่าว*