PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The analysis of risk factors and outcome in peritoneal dialysis patients with early-onset peritonitis: a multi-center, retrospective, cohort study.
AUTHORS	Ma, Xiaoyan; Shi, Yingfeng; Tao, Min; Jiang, Xiaolu; Wang, Yi; Zang, Xiujuan; Fang, Lu; Jiang, Wei; Du, Lin; Jin, Dewei; Zhuang, Shougang; Liu, Na

VERSION 1 - REVIEW

REVIEWER	Htay Htay Department of Renal Medicine, Singapore General Hospital, Singhealth, Singapore
REVIEW RETURNED	03-May-2019

GENERAL COMMENTS	Ma X et al examined risk factors and outcomes of early-onset PD related peritonitis in 357 incidents PD patients from 3 different centres. 1. Authors reported that patients who developed early-onset PD peritonitis had a high risk of technique failure compared with those with late-onset peritonitis. What are the causes of technique failure in that cohort? Are those patients with early-onset PD peritonitis had higher odds of infection-related technique failure compared with those with late-onset peritonitis? 2. Did all patients receive prophylactic IV antibiotics prior to PD catheter insertion? 3. What is the distribution of early-onset peritonitis among 3 centres? Is there any difference in term of centre practice, for example, duration of PD training, nurse to patient ratio, etc among 3 centres? 4. Types of causative organisms varied substantially between early-onset peritonitis and late-onset peritonitis group, particularly, for culture-negative peritonitis. Authors reported 89% of late-onset peritonitis were culture-negative. a. Please indicate what are the culture technique used in all the 3 centres b. Was there any difference in the incidence of culture-negative peritonitis in 3 centres? c. Is the culture technique similar for both early onset and late onset peritonitis? 5. The authors reported that ""The culture-negative proportion for the first peritonitis episode was high in the LOP patients (89.2%). This may primary attributed to early antibiotic treatment before effluent culture, especially in these patients who have received therapy at the early stage of peritonitis in local hospitals". What is

	the local practice for the management of PD peritonitis? Was there any difference in the investigations and management for early-onset and late-onset peritonitis episodes? 6. What is the median time (range) to peritonitis for both early and late- onset peritonitis group? 7. Majority of patients (55%) of early-onset peritonitis patients had ≥ 3 episodes of peritonitis during the study period. Were these episodes recurrent or repeat peritonitis? Can authors comment on it in the discussion? Is there any assisted PD in that cohort?

REVIEWER	Neil Boudville University of Western Australia
REVIEW RETURNED	09-May-2019

GENERAL COMMENTS	The topic of early onset peritonitis is important and needs further investigation, so I congratulate the authors for this study. Some comments/queries: - In abstract I would remove "...in Shanghai" in the abstract - The English requires improvement, including the last 2 sentences in the first paragraph of the introduction. - Can you confirm that this study includes all incident PD patients in these 3 PD units? It seems surprisingly small for 3 Chinese units. - "They agreed to take part in the survey and provided informed consents." How is this done retrospectively? - Additional detail of the surgical technique used in the 3 PD units would be useful - eg. was it by mini-lap? Were pre-operative antibiotics administered at the time of PD catheter insertion - How did you decide upon the definition of EOP being 6 months? This requires some justification. Additional analysis with different cut-offs would be useful as a sensitivity analysis. - With 3 months on PD as a minimum for inclusion in the study, could this lead to a change in the results? For example, could peritonitis within the first 3 months that led to technique failure but would have been excluded from this study. Can you provide some additional information about those that were excluded based upon this? - "Switching to HD...were censored" but would this have not been technique failure? - How many days on HD would be defined as permanent technique failure? - How often was mupirocin administered to the exit site? Was it recommended or is the compliance rate noted? - Rather high peritonitis rate. How does it compare with the rest of China? - Outcomes section: were these adjusted? Can EOP just be a marker of someone who does badly rather than casual? - Seems to be a rather high cure rate (17.6 and 33.8%). Is this correct? - I am confused by the numbers in the results section - If 82.4% of EOP was not cured then why did they not have technique failure? How was cure defined? - For technique failure there seems to be limited adjustment. How did you decide on adjusting for albumin and age? What about DM, smoking...?? - Were differences in outcomes seen between centres?

	- How could there be a 89.2% culture negative rate that does not seem to make sense?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. Authors reported that patients who developed early-onset PD peritonitis had a high risk of technique failure compared with those with late-onset peritonitis. What are the causes of technique failure in that cohort? Are those patients with early-onset PD peritonitis had higher odds of infection-related technique failure compared with those with late-onset peritonitis?

Technique failure was defined as the transfer to hemodialysis therapy permanently (more than 30 days).[1] The causes of technique failure in our cohort includes ultrafiltration failure, encapsulating peritoneal sclerosis and peritonitis including refractory peritonitis, fungal peritonitis and tunnel infection with peritonitis. The patients with early-onset PD peritonitis had higher odds of infection-related technique failure compared with those with late-onset peritonitis (OR=2.464, 95%CI 1.102-5.509, P=0.028).

2. Did all patients receive prophylactic IV antibiotics prior to PD catheter insertion?

Yes, all the PD patients from these three centers receive prophylactic intravenous (IV) antibiotics prior to PD catheter insertion. According to the Chinese Peritoneal Dialysis Guideline, we adopted standardized surgical catheterization technique.[2] The single dose antibiotic 30 minutes before surgery is recommended to prevent infection.[1 3] The first or second generation cephalosporin is suggested.[1 4]

3. What is the distribution of early-onset peritonitis among 3 centres? Is there any difference in term of centre practice, for example, duration of PD training, nurse to patient ratio, etc among 3 centres?

The distribution of early-onset peritonitis among 3 centers is as follows: 11 (11/61) in Shanghai East Hospital, 22 (22/142) in Shanghai Songjiang District Central Hospital, 41 (41/154) in Baoshan branch of Shanghai First People's Hospital. All the medical staffs in three centres have participated in the same standardized training in Shanghai Peritoneal Dialysis Center. The nursing care ratio in three centers was 30-50:1 according to the 2010 edition of the standard guidelines for peritoneal dialysis.[1 3 5]

4. Types of causative organisms varied substantially between early-onset peritonitis and late-onset peritonitis group, particularly, for culture-negative peritonitis. Authors reported 89% of late-onset peritonitis were culture-negative.

a. Please indicate what are the culture technique used in all the 3 centres

Before 2014, the technology of blood culture for PD effluent detection has not been widely adopted by district hospitals in Shanghai. In the district hospitals, dialysate was inoculated onto solid medium and then incubated only in aerobic environment. It accounted for about 60% of culture-negative peritonitis patients in this investigation. Since 2015, all these three units in Shanghai choose blood-culture bottle for the preferred technique to culture microorganism in PD effluent. Lacking centrifugation of PD effluent and recent antibiotic usage may the major reasons for the rest of 40% negative effluent cultures in this investigation. Considering the high culture negative rate in this study, our three PD units may take following measures to improve our culture methods. Firstly, we will centrifugate 50 ml PD effluent at 3,000 g for 15 minutes, and then resuspend the sediment in 3-5 mL supernatant and inoculate on solid culture media or standard blood-culture media. The solid media would be incubated in aerobic, microaerophilic, and anaerobic environments. Secondly, patients who have started

antibiotic treatment before culture, we will use antibiotic neutralization bottle to culture effluent. Thirdly, the specimens should arrive at the laboratory within 6 hours. Fourthly, when cultures remain negative after 3-5 days of incubation, PD effluent would be sent for repeat cell count, differential count, fungal, and mycobacterial culture. In addition, subculture on media with aerobic, anaerobic, and microaerophilic incubation conditions for a further 3-4 days may help to identify slow-growing fastidious bacteria and yeasts that are undetectable in some automated culture systems.

b. Was there any difference in the incidence of culture-negative peritonitis in 3 centres?

The incidences of culture-negative peritonitis were 37.1% (13/35) in Shanghai East Hospital, 71.7% (38/53) in Shanghai Songjiang District Central Hospital, 67.2% (84/125) in Baoshan branch of Shanghai First People's Hospital (P=0.002).

c. Is the culture technique similar for both early onset and late onset peritonitis?

Yes, the culture technique for early onset and late onset peritonitis are same. Since 2015, we choose blood-culture bottle for the preferred technique to culture bacteria and fungal in PD effluent.

5. The authors reported that “The culture-negative proportion for the first peritonitis episode was high in the LOP patients (89.2%). This may primary attributed to early antibiotic treatment before effluent culture, especially in these patients who have received therapy at the early stage of peritonitis in local hospitals”. What is the local practice for the management of PD peritonitis? Was there any difference in the investigations and management for early-onset and late-onset peritonitis episodes?

According to ISPD peritonitis recommendations: 2016 update [1] and Chinese Guidelines for the prevention and treatment of peritoneal dialysis related infections [6], treatment regimens for early-onset and late-onset peritonitis are same. Empirical antibiotic therapy be initiated as soon as possible after appropriate microbiological specimens have been obtained. And we adopted that gram-positive organisms be covered by vancomycin or a first generation cephalosporin and gram-negative organisms by a third-generation cephalosporin or an aminoglycoside. The intraperitoneal antibiotics were the preferred route of administration unless the patient has features of systemic sepsis. However, compare to late-onset peritonitis, we implement closer follow-up for early-onset peritonitis in case of recurrent or relapsing and care more about the nutritional status of patients.

6. What is the median time (range) to peritonitis for both early and late- onset peritonitis group?

The median time to first episode of peritonitis for EOP is 7 (6, 10.5) days. The median time to first episode of peritonitis for LOP is 8 (7, 9) days. There was no significantly statistical difference (P=0.579).

7. Majority of patients (55%) of early-onset peritonitis patients had ≥ 3 episodes of peritonitis during the study period. Were these episodes recurrent or repeat peritonitis? Can authors comment on it in the discussion? Is there any assisted PD in that cohort?

Among the early-onset peritonitis patients who had ≥3 episodes of peritonitis, 25 EOP patients underwent recurrent peritonitis, 16 EOP patients underwent repeat peritonitis. 43.8% repeat patients were staphylococcal peritonitis. And 75% EOP patients with≥3 episodes of peritonitis came from Baoshan Branch of Shanghai First People's Hospital. Most of these patients are fishermen living in the Chongming Island and have related poorer economic abilities and living conditions. These PD patients are easy to undergo poorer nutritional status and suffer peritonitis again.[13 14] And lacking of home visit by PD nurses makes it difficult to determine which patients require PD re-training. Lacking of technical improvement in small-scale PD units is also the important reason for high peritonitis rate.

There was no assisted PD in the cohort.

We have discussed this issue in the revised manuscript.

Reviewer: 2

1. In abstract I would remove "...in Shanghai" in the abstract.

We accepted the reviewer's suggestion and removed "...in Shanghai" in the abstract.

2. The English requires improvement, including the last 2 sentences in the first paragraph of the introduction.

We accepted the reviewer's suggestion and improved the expression of some sentences in the paper.

3. Can you confirm that this study includes all incident PD patients in these 3 PD units? It seems surprisingly small for 3 Chinese units.

The sample of this study was selected from three small-scale PD units in three districts of Shanghai (Pudong new district, Songjiang district and Baoshan district). Do not like the large-scale PD center including Ruijin hospital and Renji hospital (patients from all over the China), there are 60-100 patients in each district unit. Although the sample is limited, these three units can reflect the real status of PD patients in local district in Shanghai.

4. "They agreed to take part in the survey and provided informed consents." How is this done retrospectively?

Before PD initiation, the patients signed the informed consents for treatment strategy and agreed to share the treatment information to the hospital database in case of the late follow-up. This study was conducted according to the guidelines of the Helsinki Declaration. And we apply for the agreements from the human research ethics committees. After that we collected the information from the hospital databases. (The human research ethics committees included the Human Research Ethics Committee of Shanghai East Hospital Affiliated to Tongji University School of Medicine, Human Research Ethics Committee of Shanghai Songjiang District Central Hospital and the Human Research Ethics Committee of Baoshan Branch of Shanghai First People's Hospital).

5. Additional detail of the surgical technique used in the 3 PD units would be useful - eg. was it by mini-lap? Were pre-operative antibiotics administered at the time of PD catheter insertion.

According to the Chinese Peritoneal Dialysis Guide, we adopted standardized surgical catheterization technique.[2 3] Firstly, we chose Tenckhoff silicone tube with double polyester sleeve. Double-purse string suture or double-layer suture was adopted to fix the catheter. Fine needle and thick line were used to prevent peripheral tube leakage. The exit direction of catheter tunnel should be downward and outward, and the outer polyester sleeve should be 2 to 3 cm away from the exit. All the surgical operations are performed in the operating room. We do not use mini-lap. The single dose antibiotic 30 minutes before surgery is recommended to prevent infection.[1 3] The first or second generation cephalosporin is suggested.[1 4] We added these details in the METHODS section.

6. How did you decide upon the definition of EOP being 6 months? This requires some justification. Additional analysis with different cut-offs would be useful as a sensitivity analysis.

Currently, there is no clear definition of early onset peritonitis. A retrospective cohort study from Taiwan define the median time of the first peritonitis (20.28 months) in all subjects as the cut-off of early peritonitis.[7] A multi-center study from Australia define the peritonitis within the first year of PD therapy as EOP.[8] There is also a study which suggested that EOP is the peritonitis occurring within 3 months (90 days) after PD initiation.[9] Our study decided upon the definition of EOP being peritonitis

within the 6 months of PD initiation. This definition is consistent with other published works in other parts of China.[10 11] And we also make an additional analysis with the different cut-off (3 month). In the supplemental table 1 and table 2, after univariate and multivariate Cox analysis for technique failure and patient mortality, EOP was significantly associated with mortality compared with the LOP group, with a hazard ratio (HR) of 5.131 (Supplemental table1, P<0.001). Kaplan-Meier analysis showed that compared with LOP group, patient survival (Log rank 11.211, P=0.001, Supplemental Fig.2) was lower in the EOP group. As for technique survival, there was no significant difference between EOP and LOP group (Log rank 0.179, P=0.672, Supplemental Fig.1). We constructed the univariate and multiple logistic regression model using variables including gender, age, CCI score, diabetes, serum albumin, eGFR. We found that lower eGFR at the start of PD is an independent risk factor for EOP (Supplemental table 2).

7. With 3 months on PD as a minimum for inclusion in the study, could this lead to a change in the results? For example, could peritonitis within the first 3 months that led to technique failure but would have been excluded from this study. Can you provide some additional information about those that were excluded based upon this?

We also make an additional analysis with the different cut-off (3 month). See the answer to the question 6. There are 19 PD patients suffer the peritonitis within the first 3 months, 6 subjects died within 3 months after the initiation of PD, 3 patients transferred to hemodialysis, 0 patients underwent renal transplantation, 10 patients continued peritoneal dialysis. While these 10 PD patients lacked of the information of peritoneal equilibration test.

8. "Switching to HD...were censored" but would this have not been technique failure?

Technique failure was defined as the transfer to HD therapy permanently due to ultrafiltration failure, refractory peritonitis, exit-site infection and other operational problems. Patients who transferred to HD were censored form the patient survival analysis, and death was censored for technique failure. We have added this issue in the METHOD sections and re-analysis the data in the table 3.

9. How many days on HD would be defined as permanent technique failure?

Hemodialysis lasted for 30 days or more was defined as permanent technique failure.[1 4 12] We have added this issue in the METHOD sections.

10. How often was mupirocin administered to the exit site? Was it recommended or is the compliance rate noted?

According to the ISPD peritonitis recommendations (2010, 2016 and 2017 editions) [1 4 5] and the Chinese Peritoneal Dialysis Guide (2016) [2], we topical applicate mupirocin ointment to the catheter exit site once a day. And general measures concerning exit-site care and meticulous hand hygiene during the dialysis exchange have been emphasized during patient training.[13]

11.Rather high peritonitis rate. How does it compare with the rest of China?

By the end of the study, 509 episodes of peritonitis occurred in 213 patients, and the peritonitis rate was 0.490 episodes per patient-year. The peritonitis rates in Shanghai East Hospital, Shanghai Songjiang District Central Hospital and Baoshan Branch of Shanghai First People's Hospital were 0.41, 0.31 and 0.61 episodes per patient-year respectively. Recently, some investigations from other areas of China have indicated that the peritonitis rate was 0.196 episodes per patient-year in Taiwan,[7] 0.158 episodes per patient-year in Guangzhou,[9] 0.296 episodes per patient-year in Suzhou,[11] and 0.158 per patient-year in Hangzhou.[10] Peritonitis rate in our study is higher than the rest of China. The reason for high peritonitis rate in Baoshan Branch of Shanghai First People's Hospital may attribute to the most of PD patients who are the fishermen in the Chongming Island and have related poorer

economic abilities and living conditions. And lacking of home visit by PD nurses makes it difficult to determine which patients require PD re-training. The major reason for related high peritonitis rate in other two units owing to lack of technical improvement.

12. Outcomes section: were these adjusted? Can EOP just be a marker of someone who does badly rather than casual?

Firstly, we demonstrated the definitions of outcomes as followings: relapse was defined as an episode occurring within 4 weeks of completion of therapy of a prior episode with the same organism,[1] recurrence referred to an episode occurring within 4 weeks of completion of therapy of a prior episode but with a different organism.[1] Instead of transfering to HD therapy permanently, both relapse and recurrence were treated by antibiotics and continued PD treatment. Complete cure was defined as the resolution of peritonitis without relapse or recurrence by antibiotics alone.[9] However, some of refractory peritonitis failed to clear up effluent after 5 days of appropriate antibiotics and transferred to HD permanently. We classify this part of patients into “transfer to hemodialysis”. Other parts of HD patients were due to the serious tunnel infection with peritonitis and ultrafiltration failure induced by encapsulating peritoneal sclerosis. Secondly, we re-analyzed the outcome. The statistical results were the same as before. Thirdly, our study showed that EOP patients had a related poorer nutritional status, whose serum albumin level 30.01±7.15 g/L and had a higher rate of diabetes than LOP (73.05% vs. 56.8%, P=0.0210) and lower residual renal function (1.98 vs. 3.72, P=0.003). However, there is no significantly statistical difference in the prevalence rate of other complications, such as hypertension (P=0.258), dyslipidemia (P=0.762), cardiovascular disease (P=0.582) and cerebrovascular disease (P=0.890) between EOP and LOP. Thus, EOP might not be a marker of someone who does badly and with a serious of complications. EOP may indicated someone have the risk factors, such as hypoalbuminemia or malnutrition, to suffer peritonitis early and again.

13. Seems to be a rather high cure rate (17.6 and 33.8%). Is this correct?

Yes, LOP patients have a related higher cure rate than EOP patients in this investigation. Because we found that EOP patients were subjected to relapse or recurrence (33.8%). This is the major reason for the lower cure rate of EOP. The PD patients with poorer nutritional status are easy to suffer peritonitis again.[14 15] And our study also showed EOP patients had a lower serum albumin level than LOP (30.01±7.15 g/L vs. 33.37±4.92 g/L). The other reason for the low cure rate is that EOP patients in our study have a considerable proportion transfer to HD and death.

14. I am confused by the numbers in the results section - If 82.4% of EOP was not cured then why did they not have technique failure? How was cure defined?

We defined the outcomes as other published work.[9] Relapse was defined as an episode occurring within 4 weeks of completion of therapy of a prior episode with the same organism.[1] Recurrence referred to an episode occurring within 4 weeks of completion of therapy of a prior episode but with a different organism.[1] Instead of transfer to HD therapy permanently, both relapse and recurrence were treated by antibiotics and continued PD treatment. Complete cure was defined as the resolution of peritonitis without relapse or recurrence by antibiotics alone.[9] However, some of refractory peritonitis failed to clear up effluent after 5 days of appropriate antibiotics and transferred to HD permanently. We classify this part of patients into “transfer to hemodialysis”. Other parts of HD patients were due to the tunnel infection with peritonitis and ultrafiltration failure induced by encapsulating peritoneal sclerosis. Technique failure was defined as the transfer to HD therapy permanently.[10 11] Death was censored for the Kaplan-Meier analysis of technique failure.

15. For technique failure there seems to be limited adjustment. How did you decide on adjusting for albumin and age? What about DM, smoking...??

We accept the reviewers' suggestions and add the smoking, drinking, body mass index, hemoglobin, total cholesterol, total triglycerides, total Kt/V into Cox proportional hazards model for technique failure and patient mortality. EOP was associated with technique failure compared with the LOP group, with a hazard ratio of 1.801 (Table 3, P=0.051).

16. Were differences in outcomes seen between centres?

We analyzed the outcomes in three PD units and found that EOP have a lower cure rate compared with LOP both in Shanghai Songjiang District Central Hospital and Baoshan branch of Shanghai First People's Hospital. There was no significant difference of cure rate between EOP and LOP in Shanghai East Hospital. The proportion of patients of technique failure in Baoshan branch of Shanghai First People's Hospital is higher than other two units (Supplemental table 3).

17. How could there be a 89.2% culture negative rate that does not seem to make sense?

See the answer to the question 4 raised by the reviewer 1.

Reference

1. Li PK, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. Perit Dial Int 2016;36:481-508.

2. Chinese Expert Group on Peritoneal Dialysis Catheterization. Chinese guidelines for peritoneal dialysis catheterization. Chinese J Nephrol 2016;32:867-71.

3. Chen XM. Peritoneal dialysis standard operating procedures. People's Military Medical Press 2010.

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7. Hsieh YP, Wang SC, Chang CC, et al. The negative impact of early peritonitis on continuous ambulatory peritoneal dialysis patients. Perit Dial Int 2014;34:627-35.

8. See EJ, Johnson DW, Hawley CM, et al. Early peritonitis and its outcome in incident peritoneal dialysis patients Perit Dial Int 2017.

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14. Prasad N, Gupta A, Sharma RK, et al. Impact of nutritional status on peritonitis in CAPD patients. Perit Dial Int 2007;27:42-7.

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Supplemental table 1. Cox proportional hazards model for technique failure and patient mortality. (EOP was defined as the first episode of peritonitis occurring within 3 months)

Variable	Univariate Cox regression analysis			Multivariate Cox regression analysis		
	HR	(95%CI)	P value	HR	(95%CI)	P value
Technique failure						
Time to first peritonitis (EOP vs. LOP)	1.287	0.397-4.166	0.674			
Age (years)	1.006	0.985-1.028	0.585			
Sex (men vs. women)	1.119	0.629-1.989	0.703			
Smoking (yes vs. no)	1.078	0.578-2.010	0.814			
Drinking (yes vs. no)	0.908	0.472-1.749	0.773			
Charlson comorbidity index score	1.112	0.983-1.258	0.090			
Body mass index (kg/m2)	1.053	0.966-1.147	0.238			
Hemoglobin (g/L)	1.005	0.992-1.018	0.480			
Total cholesterol (mmol/L)	0.993	0.799-1.234	0.952			
Total triglyceride (mmol/L)	0.873	0.633-1.204	0.407			
Serum albumin (g/L)	0.981	0.935-1.030	0.439			
eGFR (ml/min/1.73 m^2)	1.015	0.948-1.086	0.676			
Diabetes (yes vs. no)	1.381	0.755-2.524	0.295			
Patient mortality						
Time to first peritonitis (EOP vs. LOP)	4.024	1.662-9.739	0.002	5.131	2.060-12.777	<0.001
Age (years)	1.012	0.989-1.037	0.308			
Sex (men vs. women)	0.830	0.451-1.526	0.548			

Smoking (yes vs. no)	0.702	0.335-1.468	0.347			
Drinking (yes vs. no)	0.611	0.280-1.337	0.217			
Charlson comorbidity index score	0.971	0.843-1.118	0.680			
Body mass index (kg/m2)	0.964	0.864-1.076	0.514			
Hemoglobin (g/L)	0.993	0.978-1.008	0.338			
Total cholesterol (mmol/L)	0.876	0.692-1.110	0.273			
Total triglyceride (mmol/L)	0.835	0.585-1.193	0.323			
Serum albumin (g/L)	0.938	0.891-0.987	0.015	0.927	0.880-0.977	0.005
eGFR (ml/min/1.73 m^2)	0.938	0.858-1.026	0.160			
Diabetes (yes vs. no)	0.936	0.503-1.740	0.833			

Variables with P value < 0.10 in univariate Cox regression analysis were chosen for further adjustment in multivariate Cox proportional hazards model.

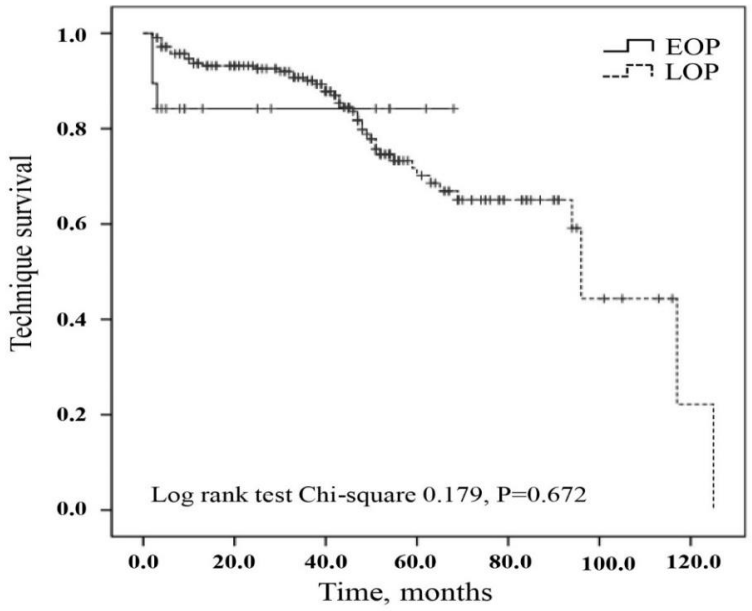
There are 19 PD patients suffer the peritonitis within the first 3 months, 6 subjects died within 3 months after the initiation of PD, 3 patients transferred to hemodialysis, 0 patients underwent renal transplantation, 10 patients continued peritoneal dialysis. While these 10 PD patients lacked of the information of peritoneal equilibration test.

Supplemental table 2. Logistic regression analysis of factors associated with early-onset peritonitis. (EOP was defined as the first episode of peritonitis occurring within 3 months)

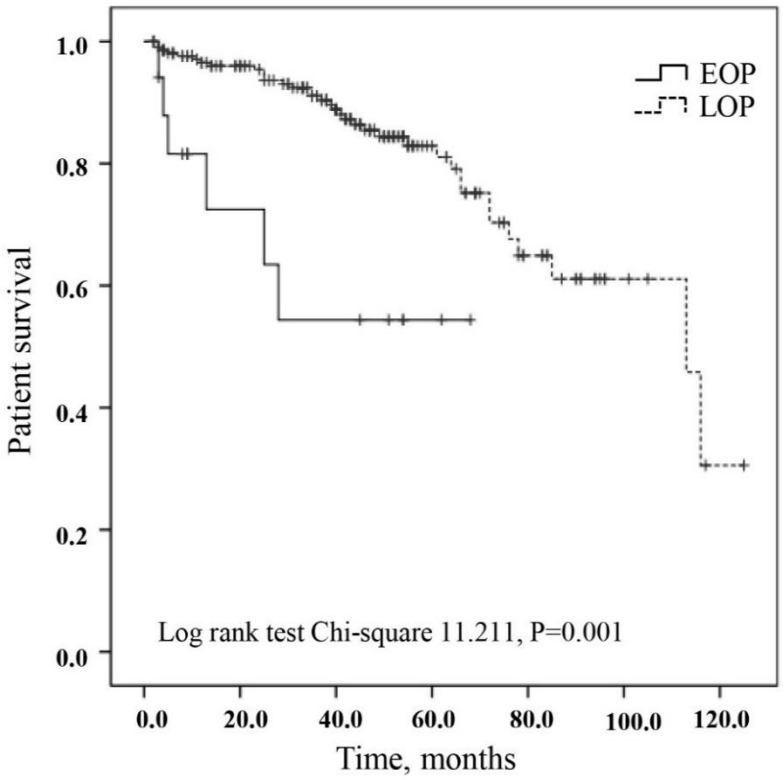
Variable	Univariate logistic regression analysis			Multivariate logistic regression analysis		
	OR	(95%CI)	P value	OR	(95%CI)	P value
Sex (men vs. women)	0.609	0.238-1.562	0.302			
Age (year)	1.036	0.997-1.078	0.074	1.029	0.988-1.071	0.165
Charlson comorbidity index score	1.004	0.803-1.255	0.973			
Diabetes	1.031	0.390-2.727	0.951			
Serum albumin (g/L)	0.982	0.906-1.064	0.660			
eGFR (ml/min/1.73 m^2)	0.723	0.584-0.894	0.003	0.724	0.580-0.903	0.004

Supplemental table 3. Outcomes of different vintages of peritonitis in three PD units

Outcomes	EOP	LOP	P value
Shanghai East Hospital			0.513
Complete cure	5 (45.5%)	10 (41.7%)	
Relapse or recurrence	3 (27.3%)	6 (25.0%)	
Transfer to hemodialysis	0 (0.0%)	4 (16.7%)	
Death	3 (27.3%)	4 (16.7%)	
Shanghai Songjiang District Central Hospital			0.108
Complete cure	6 (27.3%)	19 (61.3%)	
Relapse or recurrence	7 (31.8%)	6 (19.4%)	
Transfer to hemodialysis	3 (13.6%)	2 (6.5%)	
Death	6 (27.3%)	4 (12.9%)	
Baoshan Branch of Shanghai First People's Hospital			0.061
People's Hospital Complete cure	2 (4.9%)	18 (21.4%)	
Relapse or recurrence	15 (36.6%)	33 (39.3%)	
Transfer to hemodialysis	17 (41.5%)	21 (25.0%)	
Death	7 (17.1%)	12 (14.3%)	



Supplemental Fig.1. Technique survival according to EOP and LOP. (EOP was defined as the first episode of peritonitis occurring within 3 months)



Supplemental Fig.2. Patient survival according to EOP and LOP. (EOP was defined as the first episode of peritonitis occurring within 3 months)

VERSION 2 – REVIEW

REVIEWER	Htay Htay Singapore General Hospital, Singapore
REVIEW RETURNED	24-Jul-2019

GENERAL COMMENTS	Ma Xiaoyan and colleagues reported a multi-center study of the risk factors for early onset peritonitis (defined as peritonitis developed within 6 months of PD initiation) and risk factors associated with technique failure and all-cause mortality in incident peritoneal dialysis patients. Authors reported that higher CCI score and lower serum albumin and Kt/V at PD initiation were significantly associated with early onset peritonitis. Patients with history of early onset peritonitis were more likely developed technique failure than those who did not have it. 1. In abstract, under “results”, authors mentioned that EOP was the only predictor of technique failure though the result was not statistically significant. Authors need to revise this sentence to tone down the statement, for example, using the word “more likely”

	or “had a trend of” etc. Similarly, in the “result” section, the author indicated that “EOP was significantly associated with technique failure compared with LOP group (p=0.051)” In order to indicate the statistically significant, p value should be < 0.05. 2. In the discussion section, there is similar error, in multivariable regression, the analysis for eGFR had p value of 0.076 and authors indicated that lower eGFR was associated with EOP. 3. Author concluded that lower Kt/V as a risk factor for EOP. In EOP group, the median Kt/V was 2.1 (1.71-2.54) which was within the recommended range. In multivariable logistic regression model for EOP included both GFR and Kt/V in the final model. GFR will form part of total Kt/V with higher GFR will have higher total Kt/V, so there is possible collinearity. Can author divide total Kt/V to renal and peritoneal Kt/V and analyze using peritoneal Kt/V and GFR in the same model or using either GFR or total Kt/V in the multivariable model. 4. In “Strength and limitation of study”, authors mention that “the study did not compare the risk factors of EOP between male and female patients” It is not clear why authors indicate this as limitation here? The study aimed to identify the predictors for EOP but not the predictors of risks of EOP between male and female. So, should remove this sentence from limitation 5. Under “Methods” section, on line 113, authors indicated that “There are 19 PD patients suffer the peritonitis within the first 3months, 6 subjects died, 3 patients transferred to hemodialysis, 0 patients underwent renal transplantation, 10 patients continued peritoneal dialysis. While these 10 PD patients lacked of the information of peritoneal equilibration test” Why authors exclude patients on PD less than 90 days? With this criterion authors excluded a few patients who truly developed EOP. Can authors run sensitivity analysis with including all incident PD patients (not exclusion patients <90 days) 6. The study reported that peritonitis rate in EOP is higher than that of LOP in the abstract. However, there is no data showing this difference in the manuscript or in tables. What are the peritonitis rates between the two groups? 7. Culture negative peritonitis was substantially higher in LOP compared with EOP. Can author explain why culture negative peritonitis was higher in LOP than EOP group, despite the same study period? 8. It is a multi-centers study, so are the protocol and practice of care for PD patients (education, training, nurse to patients ratio, re-training, or home visit support, prophylactic antibiotic prior to op, daily topical anti-microbial cream at exit site) similar in the 3 participating PD units? Please indicate the practice of 3 PD units are similar or not in the methods section. As center factor can contribute to the risk and outcome of peritonitis in PD patients. Author should consider adjusting center factors in the analysis or indicate as limitation in the manuscript. Other comments - There are a few typo and grammatical error which need to be improved, for example, in “Discussion” “25 EOP patients

	underwent recurrent peritonitis" is better expressed as "25 patients from EOP group experienced/had recurrent peritonitis" - "Most of these patients are fishermen living in the Chongming Island and have related poorer economic abilities and living conditions. These PD patients are easy to undergo poorer nutritional status and suffer peritonitis again"

REVIEWER	Neil Boudville University of Western Australia Australia
REVIEW RETURNED	15-Jul-2019

GENERAL COMMENTS	Maybe I could not find it but there was no document addressing the queries from reviewers previously and guiding the second review. This makes the process rather longer unfortunately. While the alterations have addressed a number of previous issues I had raised. Ongoing issues/comments: - This seems like a small number of patients for 3 Chinese PD units. Can the authors confirm that this is the total population? - How was consent obtained in this retrospective study? - English needs to be examined more closely, for example: Line 126: According to the ISPD peritonitis recommendations,13-15 we topical applicate mupirocin ointment to the catheter exit site once a day to prevent exit site infection. Line 113: There are 19 PD patients suffer the peritonitis within the first 3 months, 6 subjects died, 3 patients transferred to hemodialysis, 0 patients underwent renal transplantation, 10 patients continued peritoneal dialysis. - This version of the paper has the peritonitis rates as much lower - going from 0.660 to 0.490 episodes per patient year. The number of peritonitis is exactly the same but the follow-up has been extended. Can the author confirm this? - I would recommend you only go to 1 or 2 decimal points. - It would be useful to have a sensitivity analysis with EOP extended to within 12 months - Can the authors confirm that the antibiotics pre-op were administered?

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

1. In abstract, under "results", authors mentioned that EOP was the only predictor of technique failure though the result was not statistically significant. Authors need to revise this sentence to tone down the statement, for example, using the word "more likely" or "had a trend of" etc. Similarly, in the "result" section, the author indicated that "EOP was significantly associated with technique failure compared with LOP group (p=0.051)" In order to indicate the statistically significant, p value should be < 0.05.

We accepted the reviewer's suggestion and tone down our statement in the manuscript. In the Cox proportional hazards model, EOP was more likely a predictor of technique failure (hazard ratio (HR) 1.801, P=0.051).

2. In the discussion section, there is similar error, in multivariable regression, the analysis for eGFR had p value of 0.076 and authors indicated that lower eGFR was associated with EOP.

We accepted the reviewer's suggestion. Considering the collinearity between eGFR and total Kt/V, we excluded the eGFR in the final multivariable logistic regression model. We found that lower total Kt/V was associated with EOP (P=0.018).

3. Author concluded that lower Kt/V as a risk factor for EOP. In EOP group, the median Kt/V was 2.1 (1.71-2.54) which was within the recommended range. In multivariable logistic regression model for EOP included both GFR and Kt/V in the final model. GFR will form part of total Kt/V with higher GFR will have higher total Kt/V, so there is possible collinearity. Can author divide total Kt/V to renal and peritoneal Kt/V and analyze using peritoneal Kt/V and GFR in the same model or using either GFR or total Kt/V in the multivariable model.

We accepted the reviewer's suggestion. We reanalyzed our data and found that the collinearity between eGFR and Kt/V. eGFR was excluded in the final multivariable logistic regression model. We found that higher CCI score (OR=1.285, 95%CI 1.058-1.561, P=0.011), lower serum albumin level (OR=0.924, 95%CI 0.867-0.985, P=0.016) and total Kt/V (OR=0.600, 95%CI 0.394-0.915, P=0.018) at the start of PD were significantly associated with EOP (Table 4).

4. In "Strength and limitation of study", authors mention that "the study did not compare the risk factors of EOP between male and female patients" It is not clear why authors indicate this as limitation here? The study aimed to identify the predictors for EOP but not the predictors of risks of EOP between male and female. So, should remove this sentence from limitation.

We accepted the reviewer's suggestion and removed the sentence that"the study did not compare the risk factors of EOP between male and female patients" in limitation section.

5. Under "Methods" section, on line 113, authors indicated that "There are 19 PD patients suffer the peritonitis within the first 3months, 6 subjects died, 3 patients transferred to hemodialysis, 0 patients underwent renal transplantation, 10 patients continued peritoneal dialysis. While these 10 PD patients lacked of the information of peritoneal equilibration test" Why authors exclude patients on PD less than 90 days? With this criterion authors excluded a few patients who truly developed EOP. Can authors run sensitivity analysis with including all incident PD patients (not exclusion patients <90 days)

We made an additional analysis with the different cut-off (3 month) including all incident PD patients (not exclusion patients <90 days). In the supplemental table 1 and table 2, after univariate and multivariate Cox analysis for technique failure and patient mortality, EOP was significantly associated with patient mortality compared with the LOP group, with a hazard ratio (HR) of 5.131 (Supplemental table1, P<0.001). Kaplan-Meier analysis showed that compared with LOP group, patient survival (Log rank 11.211, P=0.001, Supplemental Fig.2) was lower in the EOP group. As for technique survival, there was no significant difference between EOP and LOP group (Log rank 0.179, P=0.672, Supplemental Fig.1). We constructed the univariate and multiple logistic regression model using variables including gender, age, CCI score, diabetes, serum albumin, eGFR. We found that lower eGFR at the start of PD is an independent risk factor for EOP (OR=0.724, P=0.004, Supplemental table 2).

6. The study reported that peritonitis rate in EOP is higher than that of LOP in the abstract. However, there is no data showing this difference in the manuscript or in tables. What are the peritonitis rates between the two groups?

In the table1, the percentage of patients experienced more than 3 peritonitis episodes in EOP group (55.4%) is higher than LOP group (33.8%). The peritonitis rate in EOP group was 0.960 episodes per patient-year (74 patients presented 209 episodes of peritonitis during 217.75 patient-years of follow-up). The peritonitis rate in LOP group was 0.542 episodes per patient-year (139 patients presented 300 episodes of peritonitis during 553.58 patient-years of follow-up). We had added this in the revised manuscript.

7. Culture negative peritonitis was substantially higher in LOP compared with EOP. Can author explain why culture negative peritonitis was higher in LOP than EOP group, despite the same study period?

LOP patients underwent dialysis more than 6 months and have more experience in peritoneal dialysis. In the early stage of peritonitis, some of these experienced PD patients will take dialysate to wash the peritoneum to relieve abdominal pain. Diluted peritoneal fluid will result in a high negative rate of peritoneal effluent culture.

8. It is a multi-centers study, so are the protocol and practice of care for PD patients (education, training, nurse to patients ratio, re-training, or home visit support, prophylactic antibiotic prior to op, daily topical anti-microbial cream at exit site) similar in the 3 participating PD units? Please indicate the practice of 3 PD units are similar or not in the methods section. As center factor can contribute to the risk and outcome of peritonitis in PD patients. Author should consider adjusting center factors in the analysis or indicate as limitation in the manuscript.

The distribution of early-onset peritonitis among 3 centers is as follows: 11 (11/61) in Shanghai East Hospital, 22 (22/142) in Shanghai Songjiang District Central Hospital, 41 (41/154) in Baoshan branch of Shanghai First People's Hospital. All the medical staffs in three centres have participated in the same standardized training in Shanghai Peritoneal Dialysis Center. The nursing care ratio in three centers was 30-50:1 according to the 2010 edition of the standard guidelines for peritoneal dialysis [1-3]. Our study lacked of the adjustment of different center factors (education, re-training and home visit) in the multivariate analysis. We have indicated this as limitation in the manuscript.

Reviewer(s)' Comments to Author:

Reviewer: 2

1. This seems like a small number of patients for 3 Chinese PD units. Can the authors confirm that this is the total population?

We confirm that 357 is the total population of PD patients in these three small-scale PD units in Shanghai. 61 in Shanghai East Hospital, 142 in Shanghai Songjiang District Central Hospital, 154 in Baoshan branch of Shanghai First People's Hospital.

2. How was consent obtained in this retrospective study?

This study was conducted according to the guidelines of the Helsinki Declaration. The human research ethics committees approved this study and agreed to collect the information from the hospital databases. They waived the need for participant consent (The human research ethics committees included the Human Research Ethics Committee of Shanghai East Hospital Affiliated to Tongji University School of Medicine, Human Research Ethics Committee of Shanghai Songjiang District Central Hospital and the Human Research Ethics Committee of Baoshan Branch of Shanghai First People's Hospital).

3. This version of the paper has the peritonitis rates as much lower - going from 0.660 to 0.490 episodes per patient year. The number of peritonitis is exactly the same but the follow-up has been extended. Can the author confirm this?

The peritonitis rate in previous version was 0.660 episodes per patient-year (213 patients presented 509 episodes of peritonitis during 771.33 patient-years of follow-up). 771.33 patient-years of follow-up is calculated by the follow-up of PD patients who are from EOP group and LOP group.

The peritonitis rate in this version was 0.490 episodes per patient-year (213 patients presented 509 episodes of peritonitis during 1039.58 patient-years of follow-up). 1039.58 patient-years of follow-up is calculated by the follow-up of the total PD patients (EOP group, LOP group and peritonitis-free group).

4. It would be useful to have a sensitivity analysis with EOP extended to within 12 months

We also make an additional analysis with the different cut-off (EOP extended to within 12 months). In the supplemental table 3 and table 4, after univariate and multivariate Cox analysis for technique failure and patient mortality, EOP was associated with technique failure compared with the LOP group, with a hazard ratio (HR) of 2.050 (Supplemental table3, P=0.017). Kaplan-Meier analysis showed that compared with LOP group, technique survival (Log rank 6.014, P=0.014, Supplemental Fig.3) and patient survival (Log rank 7.039, P=0.008, Supplemental Fig.4) was lower in the EOP group. We constructed the univariate and multiple logistic regression model using variables including gender, age, CCI score, diabetes, serum albumin, eGFR. We found that older age, higher CCI score, lower serum albumin and eGFR at the start of PD are independent risk factors for EOP (Supplemental table 4).

5. Can the authors confirm that the antibiotics pre-op were administered?

Yes, all the PD patients from these three centers receive prophylactic intravenous (IV) antibiotics prior to PD catheter insertion. According to the Chinese Peritoneal Dialysis Guideline, we adopted standardized surgical catheterization technique.[4] The single dose antibiotic 30 minutes before surgery is used to prevent infection.[1 2] The antibiotics included first or second generation cephalosporin.[2 5]

Reference

1. Chen X. Peritoneal dialysis standard operating procedures. People's Military Medical Press 2010.

2. Li PK, Szeto CC, Piraino B, et al. ISPD Peritonitis Recommendations: 2016 Update on Prevention and Treatment. Perit Dial Int 2016;36:481-508.

3. Li PK, Szeto CC, Piraino B, et al. Peritoneal dialysis-related infections recommendations: 2010 update. Perit Dial Int 2010;30:393-423.

4. Catheterization CEGoPD. Chinese guidelines for peritoneal dialysis catheterization. Chinese J Nephrol 2016;32:867-71.

5. Szeto CC, Li PK, Johnson DW, et al. ISPD Catheter-Related Infection Recommendations: 2017 Update. Perit Dial Int 2017;37:141-54.

Supplemental table 1. Cox proportional hazards model for technique failure and patient mortality. (EOP was defined as the first episode of peritonitis occurring within 3 months)

Variable	Univariate Cox regression analysis			Multivariate Cox regression analysis		
	HR	(95%CI)	P value	HR	(95%CI)	P value
Technique failure						
Time to first peritonitis (EOP vs. LOP)	1.287	0.397-4.166	0.674			
Age (years)	1.006	0.985-1.028	0.585			
Sex (men vs. women)	1.119	0.629-1.989	0.703			
Smoking (yes vs. no)	1.078	0.578-2.010	0.814			
Drinking (yes vs. no)	0.908	0.472-1.749	0.773			
Charlson comorbidity index score	1.112	0.983-1.258	0.090			
Body mass index (kg/m2)	1.053	0.966-1.147	0.238			
Hemoglobin (g/L)	1.005	0.992-1.018	0.480			
Total cholesterol (mmol/L)	0.993	0.799-1.234	0.952			
Total triglyceride (mmol/L)	0.873	0.633-1.204	0.407			
Serum albumin (g/L)	0.981	0.935-1.030	0.439			
eGFR (ml/min/1.73 m^2)	1.015	0.948-1.086	0.676			
Diabetes (yes vs. no)	1.381	0.755-2.524	0.295			
Patient mortality						
Time to first peritonitis (EOP vs. LOP)	4.024	1.662-9.739	0.002	5.131	2.060-12.777	<0.001
Age (years)	1.012	0.989-1.037	0.308			
Sex (men vs. women)	0.830	0.451-1.526	0.548			
Smoking (yes vs. no)	0.702	0.335-1.468	0.347			
Drinking (yes vs. no)	0.611	0.280-1.337	0.217			

Charlson comorbidity index score	0.971	0.843-1.118	0.680			
Body mass index (kg/m2)	0.964	0.864-1.076	0.514			
Hemoglobin (g/L)	0.993	0.978-1.008	0.338			
Total cholesterol (mmol/L)	0.876	0.692-1.110	0.273			
Total triglyceride (mmol/L)	0.835	0.585-1.193	0.323			
Serum albumin (g/L)	0.938	0.891-0.987	0.015	0.927	0.880-0.977	0.005
eGFR (ml/min/1.73 m^2)	0.938	0.858-1.026	0.160			
Diabetes (yes vs. no)	0.936	0.503-1.740	0.833			

Variables with P value < 0.10 in univariate Cox regression analysis were chosen for further adjustment in multivariate Cox proportional hazards model.

There are 19 PD patients suffer the peritonitis within the first 3 months, 6 subjects died within 3 months after the initiation of PD, 3 patients transferred to hemodialysis, 0 patients underwent renal transplantation, 10 patients continued peritoneal dialysis. While these 10 PD patients lacked of the information of peritoneal equilibration test.

Supplemental table 2. Logistic regression analysis of factors associated with early-onset peritonitis. (EOP was defined as the first episode of peritonitis occurring within 3 months)

Variable	Univariate logistic regression analysis			Multivariate logistic regression analysis		
	OR	(95%CI)	P value	OR	(95%CI)	P value
Sex (men vs. women)	0.609	0.238-1.562	0.302			
Age (year)	1.036	0.997-1.078	0.074	1.029	0.988-1.071	0.165
Charlson comorbidity index score	1.004	0.803-1.255	0.973			
Diabetes	1.031	0.390-2.727	0.951			
Serum albumin (g/L)	0.982	0.906-1.064	0.660			
eGFR (ml/min/1.73 m^2)	0.723	0.584-0.894	0.003	0.724	0.580-0.903	0.004

Supplemental table 3. Cox proportional hazards model for technique failure and patient mortality. (EOP was defined as the first episode of peritonitis occurring within 12 months)

Variable	Univariate Cox regression analysis			Multivariate Cox regression analysis		
	HR	(95%CI)	P value	HR	(95%CI)	P value
Technique failure						
Time to first peritonitis (EOP vs. LOP)	2.050	1.138-3.692	0.017	2.050	1.138-3.692	0.017
Age (years)	1.004	0.982-1.026	0.742			
Sex (men vs. women)	1.045	0.578-1.892	0.884			
Smoking (yes vs. no)	1.112	0.583-2.120	0.747			
Drinking (yes vs. no)	0.750	0.371-1.517	0.424			
Charlson comorbidity index score	1.103	0.972-1.252	0.130			
Body mass index (kg/m2)	1.043	0.953-1.140	0.361			
Hemoglobin (g/L)	1.003	0.990-1.016	0.655			
Total cholesterol (mmol/L)	0.979	0.784-1.222	0.849			
Total triglyceride (mmol/L)	0.936	0.676-1.297	0.691			
Serum albumin (g/L)	0.990	0.941-1.040	0.686			
eGFR (ml/min/1.73 m^2)	1.016	0.947-1.090	0.664			
Diabetes (yes vs. no)	1.383	0.742-2.579	0.307			
Patient mortality						
Time to first peritonitis (EOP vs. LOP)	2.400	1.232-4.677	0.010	2.045	0.952-4.396	0.067
Age (years)	1.014	0.988-1.041	0.278			
Sex (men vs. women)	0.812	0.420-1.569	0.535			
Smoking (yes vs. no)	0.755	0.344-1.659	0.484			
Drinking (yes vs. no)	0.489	0.200-1.191	0.115			
Charlson comorbidity index score	0.946	0.811-1.103	0.476			
Body mass index (kg/m2)	0.977	0.872-1.096	0.695			
Hemoglobin (g/L)	0.996	0.981-1.011	0.591			

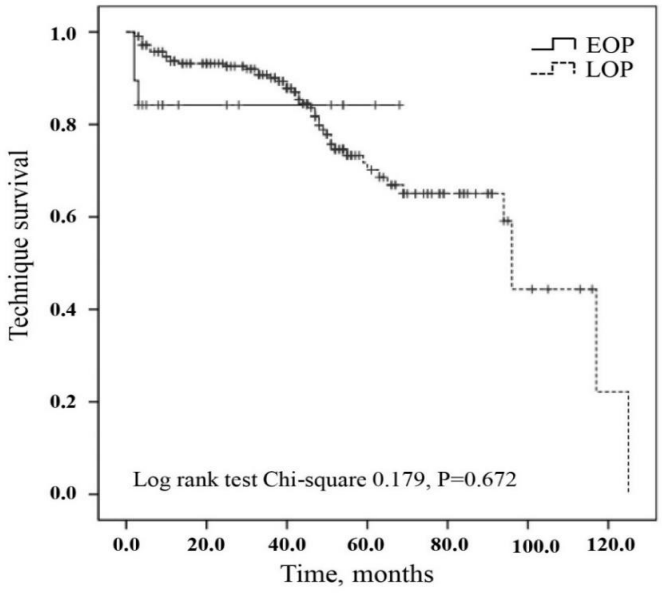
Total cholesterol (mmol/L)	0.835	0.647-1.078	0.167			
Total triglyceride (mmol/L)	0.956	0.664-1.378	0.810			
Serum albumin (g/L)	0.945	0.894-0.999	0.045	0.973	0.915-1.034	0.378
eGFR (ml/min/1.73 m^2)	0.957	0.873-1.050	0.353			
Diabetes (yes vs. no)	1.001	0.510-1.964	0.997			

Variables with P value < 0.10 in univariate Cox regression analysis were chosen for further adjustment in multivariate Cox proportional hazards model.

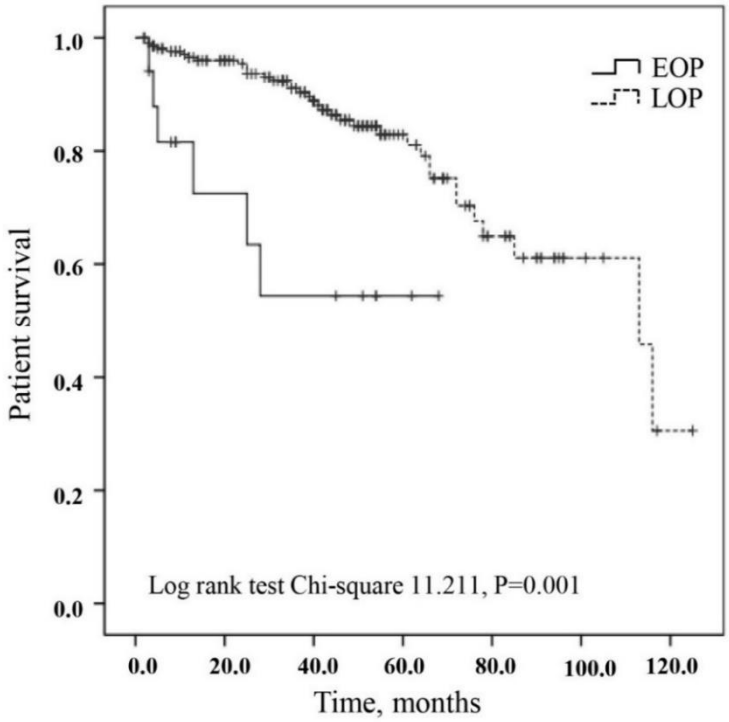
Supplemental table 4. Logistic regression analysis of factors associated with early-onset peritonitis. (EOP was defined as the first episode of peritonitis occurring within 12 months)

Variable	Univariate logistic regression analysis			Multivariate logistic regression analysis		
	OR	(95%CI)	P value	OR	(95%CI)	P value
Sex (men vs. women)	0.639	0.365-1.119	0.117			
Age (year)	1.034	1.011-1.057	0.003	1.035	1.009-1.061	0.008
Charlson comorbidity index score	1.357	1.175-1.566	<0.001	1.290	1.064-1.563	0.010
Diabetes	2.234	1.229-4.060	0.008	1.446	0.656-3.187	0.361
Serum albumin (g/L)	0.904	0.857-0.953	<0.001	0.929	0.878-0.983	0.011
eGFR (ml/min/1.73 m^2)	0.879	0.808-0.956	0.003	0.877	0.802-0.959	0.004

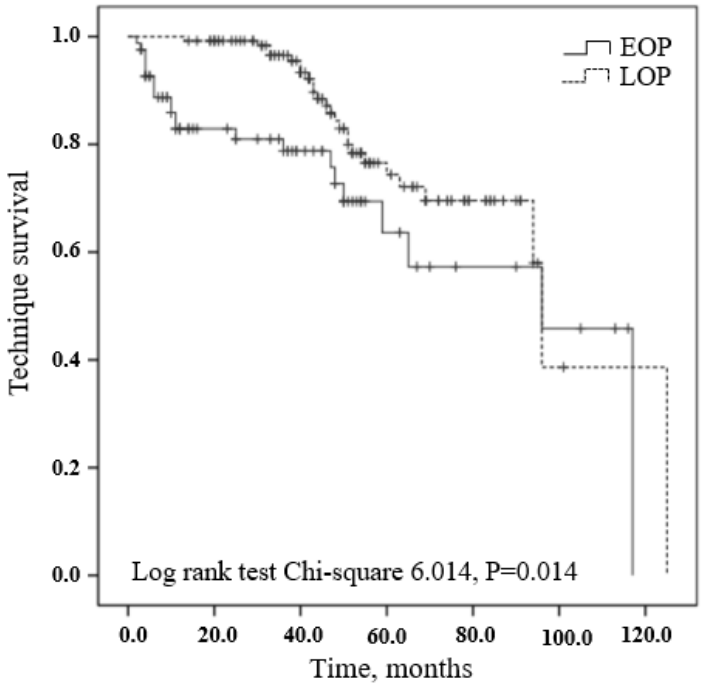
Variables with P value < 0.10 in univariate regression analysis were chosen for further adjustment in multivariate model.



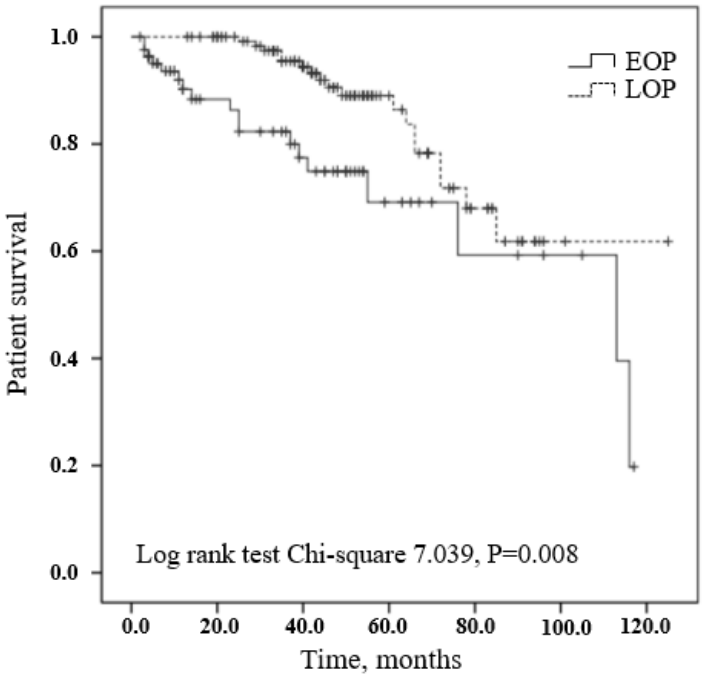
Supplemental Fig.1. Technique survival according to EOP and LOP. (EOP was defined as the first episode of peritonitis occurring within 3 months)



Supplemental Fig.2. Patient survival according to EOP and LOP. (EOP was defined as the first episode of peritonitis occurring within 3 months)



Supplemental Fig.3. Technique survival according to EOP and LOP. (EOP was defined as the first episode of peritonitis occurring within 12 months)



Supplemental Fig.4. Patient survival according to EOP and LOP. (EOP was defined as the first episode of peritonitis occurring within 12 months)

VERSION 3 – REVIEW

REVIEWER	Htay Htay Singapore General Hospital, Singapore
REVIEW RETURNED	14-Sep-2019

GENERAL COMMENTS	1. The complete cure rate in this study was extremely low for both EOP and LOP compared with those of other studies. Did all centres have an empiric antibiotic protocol (covering Gram-positive and Gram-negative organisms) for peritonitis? It is worth to explain this in the discussion section. 2. In conclusion paragraph, the second sentence “Kt/V before PD” is incorrect as Kt/V cant be performed before PD. 3. There are some grammatical errors which still need to be addressed, may need a professional editor or editing service for this.

REVIEWER	Neil Boudville University of Western Australia Perth, Australia
REVIEW RETURNED	29-Sep-2019

GENERAL COMMENTS	Thank you for allowing me to read this manuscript. It explores an area that has been under investigated. It raises the ongoing

	question of the importance of early onset peritonitis. Peritonitis has been shown to be associated with increased risk of mortality. I wonder if these findings are just related to this increased risk. Additional comments: - line 121 should read "we [applied] daily topical..." - line 165 should read "from" and not "form" - there is an extraordinarily high culture negative rate in this group - 63.4%. ISPD guidelines recommend levels should be <15% - the total peritonitis rate for the whole group (0.49) is somehow less than both EOP (0.96) and LOP (0.542) groups. This does not make sense - I note the Kaplan-Meier was significant, what about Cox model?

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1

1. The complete cure rate in this study was extremely low for both EOP and LOP compared with those of other studies. Did all centers have an empiric antibiotic protocol (covering Gram-positive and Gram-negative organisms) for peritonitis? It is worth to explain this in the discussion section.

Yes, all the PD patients from these three centers received prophylactic intravenous (IV) antibiotics prior to PD catheter insertion. According to the Chinese Peritoneal Dialysis Guideline, we adopted standardized surgical catheterization technique.[1] The single dose antibiotic 30 minutes before surgery was used to prevent infection.[2 3] Most of antibiotics used are first or second generation cephalosporin. They may not cover all the Gram-negative organisms, thereby resulting in increased rate of relapse and recurrence. To address this issue, we may have to modify our empirical antibiotic regimen by using more effective antibiotics such as third generation cephalosporin, and applying individualized treatment strategy. In addition, patients with poorer economic abilities and living conditions are easy to suffer malnutrition and peritonitis again.[4 5] Finally, the reason for the low cure rate in this study may also include a considerable number of patients with hemodialysis due to other dialysis-related complications.

2. In conclusion paragraph, the second sentence “Kt/V before PD” is incorrect as Kt/V cant be performed before PD.

We accepted the reviewer’s suggestion and used “Kt/V at PD initiation” instead of “Kt/V before PD”.

Reviewer: 2

1. Peritonitis has been shown to be associated with increased risk of mortality. I wonder if these findings are just related to this increased risk.

A higher CCI score and lower serum albumin level and Kt/V at PD initiation were significantly associated with EOP. It indicated that these risk factors will increase the risk of EOP. Moreover, EOP predicted a high peritonitis rate and poor clinical outcomes.

2. There is an extraordinarily high culture negative rate in this group - 63.4%. ISPD guidelines recommend levels should be <15%

The reasons for such high culture negative rate in small-scale PD units in Shanghai have been demonstrated in this manuscript. Considering the high culture negative rate in this study, our three PD units will take a series of measures to improve our culture methods, including centrifugation of PD effluent, incubation in aerobic, microaerophilic and anaerobic environments, using antibiotic neutralization bottle and so on.

3. The total peritonitis rate for the whole group (0.49) is somehow less than both EOP (0.96) and LOP (0.542) groups. This does not make sense.

1) The peritonitis rate (in a population included EOP group and LOP group) was 0.660 episodes per patient-year (213 patients presented 509 episodes of peritonitis during 771.33 patient-years of follow-up). 771.33 patient-years of follow-up is calculated by the follow-up of PD patients who are from EOP group and LOP group.

2) The peritonitis rate (in a population included EOP group, LOP group and peritonitis-free group) was 0.490 episodes per patient-year (213 patients presented 509 episodes of peritonitis during 1039.58 patient-years of follow-up). 1039.58 patient-years of follow-up is calculated by the follow-up of the total PD patients (EOP group, LOP group and peritonitis-free group).

3) The peritonitis rate in EOP group was 0.960 episodes per patient-year (74 patients presented 209 episodes of peritonitis during 217.75 patient-years of follow-up).

4) The peritonitis rate in LOP group was 0.542 episodes per patient-year (139 patients presented 300 episodes of peritonitis during 553.58 patient-years of follow-up).

We had added these in the revised manuscript.

The peritonitis rate in different groups

Groups	Number of patients	Episodes of peritonitis	Patient-years of follow-up	Peritonitis rate (episodes per patient-year)
EOP group	74	209	217.75	0.960
LOP group	139	300	553.58	0.542
EOP group and LOP group	213	509	771.33	0.660
EOP group, LOP group and peritonitis-free group	213	509	1039.58	0.490

4. I note the Kaplan-Meier was significant, what about Cox model?

In the univariate Cox proportional hazards model, EOP was more likely a predictor of technique failure (hazard ratio (HR) 1.801, P=0.051) and patient mortality (HR 1.968, P=0.048) (Table 3). After adjustment, there was no significant difference between the EOP and LOP groups. These results have been written in the results section.