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The analysis of risk factors and outcome in peritoneal dialysis patients with early-onset peritonitis: a multi-center, retrospective, cohort study.

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ABSTRACT

Objectives To investigate the risk factors associated with EOP and its influence on patients' technique survival and mortality in Shanghai.

Study design Retrospective, cohort study.

Setting Three peritoneal dialysis centers in Shanghai.

Participants PD patients from June 1, 2006, to May 1, 2018, were recruited and followed up until December 31, 2018. According to time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139).

Primary and secondary outcome measures Early-onset peritonitis was defined as the first episode of peritonitis occurring within 6 months after the initiation of peritoneal dialysis (PD). The outcomes were all-cause mortality and technique failure.

Results Of the 357 patients, 74 (20.7%) patients developed their first episode of peritonitis within the first 6 months. Compared with the LOP group, the EOP group had older ages, more female patients, higher Charlson comorbidity index (CCI) score and white blood cell levels, lower serum albumin levels and renal function at the time of initiation of PD and higher diabetes mellitus and peritonitis rates ($P<0.05$). Staphylococcus was the most common Gram-positive organism in both EOP and LOP groups. The multivariate logistic regression analysis showed that factors associated with EOP included older age (odds ratio (OR) 1.027, P=0.041), a higher CCI score (OR 1.298, P=0.008), low serum albumin level (OR 0.929, P=0.015) and low eGFR (OR 0.907, P=0.046) at start of PD. In the Cox proportional hazards model, EOP was a significant predictor of technique failure (hazard ratio (HR) 1.664, P=0.048). There were no differences between EOP and LOP for all-cause mortality.

Conclusion Older age, a higher CCI score and lower serum albumin level and eGFR before PD were significantly associated with EOP. EOP also predicted a high peritonitis rate and poor clinical outcomes.

KEY WORDS Peritoneal dialysis; Early-onset peritonitis; Risk factors; Outcomes.

ARTICLE SUMMARY

Article focus

- The risk factors associated with EOP and its influence on patients' technique survival and mortality in Shanghai.

Key messages

- Older age, a higher CCI score and lower serum albumin level and eGFR before PD were significantly associated with EOP.
- EOP predicted a high peritonitis rate and poor clinical outcomes.

Strengths and limitations of this study

- There is a strict exclusion criteria based on PD histories.
- We conducted a multi-center study which ensured sufficient power in obtaining the risk factors of EOP.
- This was a retrospective cohort study, lacking of some objective information such as medical level, economic development and living standard, which may cause bias.
- The study did not compare the risk factors of EOP between male and female patients.
- Although this was a multicenter study, the sample size was relatively small.

INTRODUCTION

In developing countries, the number of peritoneal dialysis (PD) patients has been increasing over time.[1 2] Peritoneal dialysis (PD)-related peritonitis is a serious complication during PD therapy and remains the major reason for technique failure.[3] Peritoneum suffered from the frequency and the timing of infection could impact peritoneum structure and change the permeability of the membrane, leading to peritoneal fibrosis.[4] Therefore, finding the risk factors for peritonitis in the early PD period is important to reduce technique failures and mortality of PD patients.

The definition of early-onset peritonitis varies widely between studies, which generally refers to peritoneal dialysis related peritonitis occurring within 3-24 months after surgical catheterization.[5 6] Previous studies showed that the first episode of peritonitis in PD patients could significantly affect the prognosis of end-stage renal disease (ESRD) patients.[7] However, few studies have specifically examined the risk factors for peritonitis in the early PD period. And most of these were observational cohort studies carried out in single centers,[5 8 9] limiting the generalizability of their observed outcomes. To determine the risk factors for early-onset peritonitis in Chinese CKD patients and its influence on patients' technique survival and mortality, we conducted this multiple-center, retrospective cohort study.

METHODS

Study Population

This was a multi-center retrospective cohort study included 357 patients with ESRD who underwent PD in Department of Nephrology in Baoshan branch of Shanghai First People's Hospital, Shanghai Songjiang District Central Hospital and Shanghai East Hospital, Tongji University School of Medicine. All incident PD patients from June 1, 2006, to May 1, 2018, were recruited and followed up until December 31, 2018. They agreed to take part in the survey and provided informed consents. The exclusion criteria were as follows: patients who had been using PD for fewer than 90 days, patients with an age younger than 18 years and patients who initiated PD in

other PD centers and previously accepted HD or kidney transplantation. Patients were followed until any of the following events: death, a change to HD, renal transplantation or until December 31, 2018. Dialysis catheters were placed through sterile surgical techniques, patients initiated PD by Dianeal with 1.5% or 2.5% dextrose (Baxter Healthcare, Guangzhou, China). Dialysate concentration was 1.5% dextrose and replaced every four hours during the day, while 2.5% at night and kept in the body. Mupirocin ointment was used in every patient to prevent exit site infection. A total of 213 patients who had at least one episode of peritonitis. According to time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (> 6 months, n=139). We collected baseline characteristics within 1-3 months from the start of PD, including demographic data (age, gender, smoking, drinking, CCI, BMI), medical history, drug-taking history, biochemical data (white blood cell, hemoglobin, serum electrolyte, fasting blood glucose, total cholesterol, total triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and serum albumin, uric acid, creatinine, blood urea nitrogen, estimated glomerular filtration rate (eGFR), the clearance rate of urea nitrogen (Kt/V), residual renal function (RRF)), cause of ESRD, peritonitis episodes. Peritoneal fluid effluent from patients with peritonitis was collected and cultured for 1 to 5 days to identify the bacterial flora in the dialysate.

Primary and secondary outcome measures

Early-onset peritonitis was defined as the first episode of peritonitis occurring within 6 months after the initiation of peritoneal dialysis (PD). The outcomes were all-cause mortality and technique failure.

Study definitions

Diagnostic criteria for peritonitis based on the 2010 International Society for

Peritoneal Dialysis (ISPD) guidelines.[6] Patients diagnosed as peritonitis should meet at least two of the following three standards: (1) Clinical symptoms or signs of peritonitis; (2) Leucocyte count (at least 100/mm^3) and polymorphonuclear neutrophilic cells proportion (at least 50%) in peritoneal fluid effluent; (3) Related pathogens in smear or culture of peritoneal fluid. Early-onset peritonitis was defined as the first episode of peritonitis occurring within 6 months after the initiation of PD. The outcomes were all-cause mortality and technique failure. Death was an end-point event in the patient survival analysis. Switching to HD or receiving renal transplantation were censored. Technique failure was defined as the transfer to HD therapy permanently due to ultrafiltration failure, peritonitis, exit-site infection and other operational problems.

Patient and public involvement

No patient was involved in the design or conduct of the study, but the results of the study will be shared to patients coming for follow-up.

Statistical analysis

All statistical analyses were performed by SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA). The normal distributed data were showed as mean±standard deviation (SD) and the skewed data were showed as median values with the 25th to 75th percentile intervals. Categorical data were expressed as frequency (n) and percentage (%). As for normally distributed data, student's t-test is using for analyzing the differences between the EOP group and LOP group, while one-way ANOVA for differences among in non-peritonitis, EOP group and LOP groups. The Wilcoxon rank sum test for skewed continuous data and the Chi-square test or Fisher's exact test for categorical data. The Kaplan-Meier survival curves were drawn for each event of interest (technique survival and patient survival) and the log-rank test was used to compare curves. Univariate Cox proportional hazards regression was

used to select significant factors associated with study outcomes. Variables whose P<0.05 were selected for inclusion in the final multivariate Cox model. Multivariate logistic regression was calculated to select significant risk factors for EOP and the inclusion standard was also P<0.05. Collinearity of variables was tested. A two-tailed P value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 357 patients with ESRD underwent CAPD in three dialysis centers in Shanghai during the study period. All patients used Dianeal with 1.5% or 2.5% dextrose. The first episode of peritonitis was experienced by 74 (20.7%) patients within 6 months after the start of PD. Median follow-up time for the 357 patients was 33.0 months (interquartile range 14.0-50.0 months). There were 211 males (59.1%) with an average age of 61.6 ± 14.0 years, and 145 females (40.9%) with an average age of 65.3 ± 12.9 years. The most common primary renal diseases were chronic glomerulonephritis (43.1%) and diabetic nephropathy (34.2%). Compared with the LOP patients, the EOP patient group had older ages, more female patients, higher Charlson comorbidity index (CCI) score and white blood cell levels, lower serum albumin levels and renal function at the time of initiation of PD and higher diabetes mellitus and peritonitis rates (P<0.05). Additional demographic and laboratory characteristics of the study population are present in Table 1.

Causative organisms

In table 2, among 213 patients with peritonitis, 47 (22.1%) were due to Gram-positive organisms, 24 (11.3%) were due to Gram-negative organisms, 6 (2.8%) were due to fungi, 1 (0.4%) were due to multiple organisms, and 135 (63.4%) were culture-negative. Staphylococcus was the most common Gram-positive organism in both groups. Compared with the EOP patient group, the LOP patient group had more

culture-negative peritonitis (89.2% vs. 14.9%, P<0.001).

Outcomes

The total peritonitis rate was 0.660 episodes per patient-year (213 patients presented 509 episodes of peritonitis during 771.33 patient-years of follow-up). Early-onset first episode of peritonitis had a lower cure rate (17.6% vs 33.8%, Table 2.), higher rate of transferring to hemodialysis (27.0% vs 19.4%, Table 2.), and higher mortality (21.6% vs 14.4%, Table 2.) compared to late-onset first episode of peritonitis.

Technique failure

After adjusting for serum albumin, age in the multivariate Cox analysis for technique failure, EOP was significantly associated with technique failure compared with the LOP group, with a hazard ratio (HR) of 1.664 (Table 3, P=0.048). Kaplan-Meier analysis showed that compared with LOP group, technique survival was lower in the EOP group (log rank 7.985, P=0.005, Fig.1).

All-cause mortality

During the study period, a total of 52 peritonitis patients died: 16 patients in the EOP group and 20 patients in the LOP group. After adjusting for age and serum albumin, there were no significant differences between the EOP and LOP groups in the multivariate Cox proportional hazards model (Table 3). Fig. 2 describes cumulative survival by EOP and LOP groups using the Kaplan-Meier analysis. Compared with LOP group, cumulative survival was lower in the EOP group (log rank 4.060, P=0.044).

Risk factors of early-onset peritonitis

Variables in Table 1 were tried in a univariate logistic regression model, and only variables with *P* value < 0.10 or traditional risk factors for peritonitis were depicted in

Table 4. Based on the simple logistic regression analysis of risk factors associated with EOP (Table 4), we constructed a 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 level and eGFR at the start of PD, were significantly associated with EOP (Table 4). Every 1 year increase in age improved the risk of EOP by 2.7% (OR 1.027, P=0.041). Every 1 score increase in the CCI improved the risk of EOP by 26.1% (OR 1.298, P=0.008). Every 1 g/L increase in the baseline serum albumin level lowered the risk of EOP by 7.4% (OR 0.929, P=0.015). Every 1 ml/min/1.73 m^2 increase in the eGFR lowered the risk of EOP by 9.8% (OR 0.907, P=0.046).

DISCUSSION

Our retrospective cohort study of 357 PD patients showed that 74 (20.7%) patients in three Shanghai dialysis centers developed the first episodes of peritonitis within the first 6 months. Older age, higher CCI score, lower serum albumin level and eGFR at the start of PD, were significantly associated with EOP. In addition, an early peritonitis onset predicted a high peritonitis rate and technique failure.

Early-onset peritonitis is a major complication of peritoneal dialysis, directly or indirectly causing the abandon of dialysis treatment. In this study, among 213 patients with peritonitis, 47 (22.1%) were due to Gram-positive organisms, 24 (11.3%) were due to Gram-negative organisms, 6 (2.8%) were due to fungi. Staphylococcus was the most common Gram-positive organism in both early-onset and late-onset peritonitis. This bacterial flora distribution and high incidence of staphylococcus were similar to previous reports.[10-12] Fungal peritonitis was rare in PD patients, but could bring out irreversible peritoneal damage.[13] Recent clinical studies confirmed that the incidence of fungal peritonitis was only 3%-6%,[13] while the relative mortality rate was up to 20%-30%.[14] 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. Several ways that pathogenic bacteria intruded into peritoneal: dialysis catheter, dialysis catheter outlet and subcutaneous tunnel, intestinal infection and hematogenous peritonitis. Thus, standardized dialysis catheter procedures and individualized antibiotics treatment are called to reduce the incidence of peritonitis.

It was well known that PD patients lost about 10 g of protein per day from abdominal cavity, especially when combined with early-onset peritonitis. Loss of protein would cause negative nitrogen balance and malnutrition, leading to a decline in immune function and increased susceptibility to pathogenic microorganisms.[15] Malnutrition was one of the most common complications in PD patients, and plasma albumin level was an important clinical predictor. Hypoalbuminemia was proved to be related with malnutrition, protein losses, and inflammation.[16 17] Wang Qin et al. discovered that patients with an initial serum albumin level less than 2.9 g/dL had a higher incidence of peritonitis. And they regarded hypoalbuminemia as an independent predictor for subsequent peritonitis at the start of PD therapy.[18] Further studies demonstrated that low serum albumin level increased all-cause, cardiovascular, and infection related mortality in both PD and HD patients.[19] In addition to peritoneal infection, hypoalbuminemia was also found to be associated with septicemia, pneumonia and other inflammatory responses.[20-24] In this study, we reaffirmed that a low baseline serum albumin level is an independent risk factors for EOP. Every 1 g/L increase in the baseline serum albumin level lowered the risk of EOP by 7.4% (OR 0.929, P=0.015).

Our study showed that older dialysis patients had a greater chance of developing early-onset peritonitis. It was reported that those patients were more likely to progress to a worse outcome, such as HD, renal transplantation or death.[25] Incidence of malnutrition in elderly PD patients was more common than young and middle-aged patients. Together with cardiovascular diseases, cerebrovascular disease, hearing and

visual impairments, all of these factors increase and aggravate the episode of peritonitis.[26-28] Malnutrition in elder not only affected the quality of dialysis patients' life, but also was an important factor in comorbidity and mortality.[29] Other elements that increased the peritonitis susceptibility in elderly patients included generalized functional deterioration, weakened immune system,[30] combined chronic diseases, bad eyesight, poor aseptic concept, lack of compliance and living alone. Their atypical clinical symptoms of peritonitis could be regarded as another essential reason. Up-regulated pain threshold, unobtrusive bellyache and mild subjective symptoms might cover up early-onset peritonitis until the occurrence of liquid turbidity, which would delay the best time for treatment.

Comparison in biochemical indicators shown that Kt/V and residual renal function decreased significantly after early-onset peritonitis. Multivariate logistic regression showed that every 1 ml/min/1.73 m^2 increase in the eGFR lowered the risk of EOP by 9.8% (OR 0.907, P=0.046). These results suggest that early infection with peritonitis might further worsen renal function, especially the scavenging capacity of solutes by residual kidney. Early inflammatory response and renal function damage might be the underlying causes of peritonitis. Many studies draw a similar conclusion that the survival rate of PD patients mainly depends on residual renal function, rather than the peritoneal cleaning capacity.[31-33] Harris et al. further put forward that residual renal function less than 4 $ml \cdot min^{-1} \cdot 1.73m^{-2}$ was associated with high mortality during peritoneal dialysis.[34] Therefore, we should pay close attention to the change of residual renal function when monitoring the adequacy of dialysis.

The relationship between peritonitis and technique failure and death have been investigated in previous Chinese single-center studies.[35 36] A study in Chinese Zhejiang province showed that, EOP was a significant predictor of all-cause mortality. As for technique failure, they found no significant differences between EOP and LOP.[35] However, a study in Chinese Guangzhou province indicated that technique failure in EOP group was lower than LOP group, but patient survival did

not differ between the two groups.[36] Our present study got the similar results with Guangzhou study. In the Cox proportional hazards model, EOP was a significant predictor of technique failure (hazard ratio (HR) 1.664, 95% CI 1.003-2.761, P=0.048). There were no differences between EOP and LOP for all-cause mortality. These conclusions might be limited by regional and demographic differences in different dialysis center. However, all three studies indicated that patients who experienced peritonitis early after the initiation of PD were likely having more episodes of peritonitis. Repeating peritonitis in EOP patients have an obvious impact on membrane permeability, increasing severe systemic inflammation, reducing ultrafiltration and leading to worse clinical outcomes.[37] Thus, we put forward several targeted opinions for each role involved in PD treatment according to the above correlation factor analysis of early-onset peritonitis, in order to reduce infection incidence, raise therapeutic effect of PD, improve patient's life quality and prognosis. (1) Patient: every PD patients should set up an aseptic concept and follow standard operation. (2) Family: family members have obligation to assist patients in completing PD operations, especially for elderly and poor eyesight patients. (3) Society: A series of policies are needed to ensure the treatment right and medical insurance benefits of PD patients. (4) Nurse: Experienced nurses should carry out professional and systematic training on normalized PD operation for patients and their families. (5) Doctor: Doctors should pay attention to the treatment of basic diseases, such as hypertension, diabetes and stroke. At the same time in preventing infection and protecting peritoneal function, doctors must grasp the opportunity of conversion from PD to HD. Studies suggested that timely transformation to HD treatment for patients with recurrent peritonitis and other PD related complications can improve survival rate.[38]

There are several limitations to this study. First, this was a retrospective cohort study, lacking of some objective information such as medical level, economic development and living standard, which may cause bias. Second, although this was a

multicenter study, the sample size was relatively small. Further larger size and prospective investigation are necessary.

CONCLUSION

In summary, this retrospective cohort study found that older age, a higher CCI score and lower serum albumin and eGFR before PD were significantly associated with EOP. In addition, an early peritonitis onset predicted a high peritonitis rate and worse clinical outcomes. Understanding the risk factors for EOP helps to develop effective measures to prevent or delay the complication of peritoneal dialysis as much as possible.

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Author Contributors

X.M., Y.S. M.T. and X.J. contributed equally to this work. X.M., Y.S. M.T. and X.J. performed the statistical analysis and wrote the manuscript; X.M., Y.S., M.T., X.J., Y.W., D.J. and X.Z. participated in the data collection; X.M., Y.S., S.Z. and N.L. contributed to discussion; X.M., S.Z. and N.L. participated in the design of the study and edited the manuscript. All authors contributed to data interpretation and revisions of the manuscript critically for important intellectual content. All authors approved the final version of the submitted manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of work are appropriately investigated and resolved.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Helsinki Declaration and was approved by 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. Written informed consent was obtained from each participant before data collection.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The data sets generated and analysed during the current study are available from the corresponding author upon reasonable request.

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Table 1.Baseline characteristic of the study population

Variable	Peritonitis-free (N=144)	EOP (N=74)	LOP (N=139)	P value between EOP and LOP	P value
Age (years)	63.18±13.91	65.87±13.20	61.40±13.53	0.022	0.075
Gender (male, n, %)	84 (58.3)	37 (50.7)	90 (64.7)	0.047	0.135
Smoking (%)	40 (27.8)	22 (29.7)	31 (22.3)	0.233	0.415
Drinking (%)	31 (21.5)	20 (27.0)	32 (23.0)	0.517	0.659
Charlson comorbidity index score	3.76±1.51	5.73±2.17	4.42±1.93	<0.001	<0.001
Body mass index (kg/m^2)	23.55±3.76	24.19±3.31	24.32±3.38	0.791	0.174
White blood cell (10^9/L)	6.42±2.21	8.33±2.67	7.13±2.53	0.001	<0.001
Hemoglobin (g/L)	83.67±17.70	89.10±22.90	88.53±19.77	0.849	0.059
Serum calcium (mmol/L)	1.98±0.29	2.14±0.41	2.11±0.33	0.514	0.001
Serum phosphorus (mmol/L)	1.77±0.55	1.91±0.61	1.83±0.78	0.457	0.349
Serum potassium (mmol/L)	4.39±0.65	4.41±0.74	4.39±0.80	0.865	0.980
Fasting blood glucose (mmol/L)	5.38±2.01	6.49±2.93	6.09±2.10	0.261	0.001
TC (mmol/L)	4.02 (3.36, 5.11)	4.59 (3.54, 6.06)	4.43 (3.57, 5.70)	0.537	0.022
TG (mmol/L)	1.28 (0.97, 1.74)	1.30 (1.00, 2.39)	1.24 (1.00, 2.17)	0.469	0.430
HDL-C (mmol/L)	1.11 (0.85, 1.33)	1.18 (0.97, 1.43)	1.19 (0.98, 1.48)	0.740	0.042
LDL-C (mmol/L)	2.44 (1.94, 3.11)	2.65 (2.01, 3.25)	2.38 (2.00, 3.09)	0.238	0.473
Serum albumin (g/L)	33.26±6.26	30.01±7.15	33.37±4.92	<0.001	<0.001
Serum uric acid (mmol/L)	516.93±142.32	495.46±183.30	536.48±185.05	0.124	0.231
Serum creatinine (μmol/L)	792.38±315.96	749.77±268.11	660.42±302.69	0.034	0.001
Blood urea nitrogen (mmol/L)	28.38±10.17	25.69±10.73	24.51±9.85	0.421	0.005
eGFR (ml/min/1.73 m^2)	6.41±3.10	6.84±3.82	8.48±4.13	0.005	<0.001
Total Kt/V	2.06 (1.69, 2.44)	2.10 (1.71, 2.54)	2.33 (1.93, 3.04)	0.008	0.001
Residual renal function	2.37 (0.43, 4.30)	1.98 (0.29, 3.82)	3.72 (1.74, 5.03)	0.003	0.002
Diabetes mellitus(%)	64 (44.4)	54 (73.0)	79 (56.8)	0.021	<0.001
Hypertension (%)	126 (87.5)	66 (89.2)	116 (83.5)	0.258	0.439
Dyslipidemia (%)	54 (37.5)	41 (55.4)	74 (53.2)	0.762	0.009
Cardiovascular disease (%)	43 (29.9)	30 (40.5)	51 (36.7)	0.582	0.241
Cerebrovascular disease (%)	21 (14.6)	30 (40.5)	55 (39.6)	0.890	<0.001
Calcium	90 (62.5)	44 (59.5)	72 (51.8)	0.285	0.179
Iron	73 (50.7)	41 (55.4)	68 (48.9)	0.367	0.664
Anti-diabetic medications (%)	54 (37.5)	38 (51.4)	46 (33.1)	0.009	0.031
Anti-hypertension medications (%)	124 (86.1)	65 (87.8)	112 (80.6)	0.178	0.284
Lipid-lowering medications (%)	38 (26.4)	36 (48.6)	61 (43.9)	0.506	0.001
Cause of ESKD				0.182	0.008
Glomerulonephritis (%)	57 (39.6)	29 (39.2)	68 (48.9)		
Diabetes (%)	42 (29.2)	34 (45.9)	46 (33.1)		
Other (%)	45 (31.3)	11 (14.9)	25 (18.0)		
Peritonitis episodes (%)				0.006	0.006
1		17 (23.0)	57 (41.0)		
2		16 (21.6)	35 (25.2)		
≥3		41 (55.4)	47 (33.8)		

EOP, early-onset peritonitis; LOP, late-onset peritonitis; TC, total cholesterol; TG total triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GFR, glomerular filtration rate; ESKD, end stage kidney disease

Table 2. Organism and outcome of different vintages of peritonitis (n, %)

Causative organisms	Early-onset peritonitis episodes (n)	Late-onset peritonitis episodes (n)	P value
Causative organisms			
Gram-positive organisms	38 (51.4)	9 (6.5)	<0.001
Staphylococcus aureus	7 (18.4)	0 (0.0)	0.163
Coagulase-negative	3 (7.9)	0 (0.0)	0.384
Staphylococcus	16 (42.1)	8 (88.9)	0.012
Streptococcus species	4 (10.5)	1 (11.1)	0.959
Enterococcus species	4 (10.5)	0 (0.0)	0.309
Other Gram-positives	4 (10.5)	0 (0.0)	0.309
Gram-negative organisms	20 (27.0)	4 (2.9)	<0.001
Escherichia coli	8 (40.0)	0 (0.0)	0.121
Klebsiella species	6 (30.0)	1 (25.0)	0.841
Acinetobacter species	4 (20.0)	1 (25.0)	0.822
Pseudomonas Aeruginosa	2 (10.0)	1 (25.0)	0.408
Other Gram-negatives	0 (0.0)	1 (25.0)	0.022
Fungi	4 (5.4)	2 (1.4)	0.096
Multiple organisms	1 (1.4)	0 (0.0)	0.170
Culture-negative peritonitis	11 (14.9)	124 (89.2)	<0.001
Outcomes			0.063
Complete cure	13 (17.6)	47 (33.8)	
Relapse or recurrence	25 (33.8)	45 (32.4)	
Transfer to hemodialysis	20 (27.0)	27 (19.4)	
Death	16 (21.6)	20 (14.4)	

Table 3. Cox proportional hazards model for technique failure and patient mortality. The analyzed variables included age, sex, time to first peritonitis (EOP vs. LOP), serum albumin，Charlson comorbidity index score，diabetes, eGFR

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)	1.872	1.201-2.919	0.006	1.664	1.003-2.761	0.048
Serum albumin	0.967	0.935-0.999	0.041	0.988	0.949-1.029	0.557
Age	1.018	1.003-1.034	0.020	1.008	0.991-1.026	0.371
Sex (men vs. women)	0.965	0.649-1.435	0.860			
Charlson comorbidity index score	1.078	0.986-1.177	0.098			
Diabetes	1.380	0.918-2.072	0.121			
eGFR	0.979	0.928-1.031	0.418			
Patient mortality						
Time to first peritonitis (EOP vs. LOP)	1.968	1.006-3.851	0.048	1.499	0.683-3.289	0.313
Serum albumin	0.949	0.907-0.993	0.025	0.961	0.902-1.023	0.214
Age	1.037	1.014-1.061	0.002	1.014	0.987-1.041	0.316
Sex (men vs. women)	0.862	0.498-1.492	0.596			
Charlson comorbidity index score	0.999	0.878-1.138	0.990			
Diabetes	1.176	0.672-2.057	0.570			
eGFR	0.935	0.860-1.016	0.111			

Table 4. Logistic regression analysis of factors associated with early-onset peritonitis

Variable	Univariate logistic regression analysis			Multivariate logistic regression analysis		
	OR	(95%CI)	P value	OR	(95%CI)	P value
Sex （men vs. women）	0.560	0.315-0.995	0.048	0.712	0.353-1.435	0.342
Age	1.026	1.004-1.049	0.023	1.027	1.001-1.054	0.041
Body mass index	0.988	0.906-1.078	0.790			
Charlson comorbidity index score	1.355	1.173-1.566	<0.001	1.298	1.069-1.574	0.008
Diabetes	2.051	1.111-3.786	0.022	1.260	0.556-2.856	0.579
Serum albumin	0.901	0.853-0.951	<0.001	0.929	0.876-0.986	0.015
eGFR	0.888	0.815-0.967	0.006	0.907	0.825-0.998	0.046

Figure legends

Fig.1. Technique survival according to EOP and LOP.

Fig.2. Patient survival according to EOP and LOP.

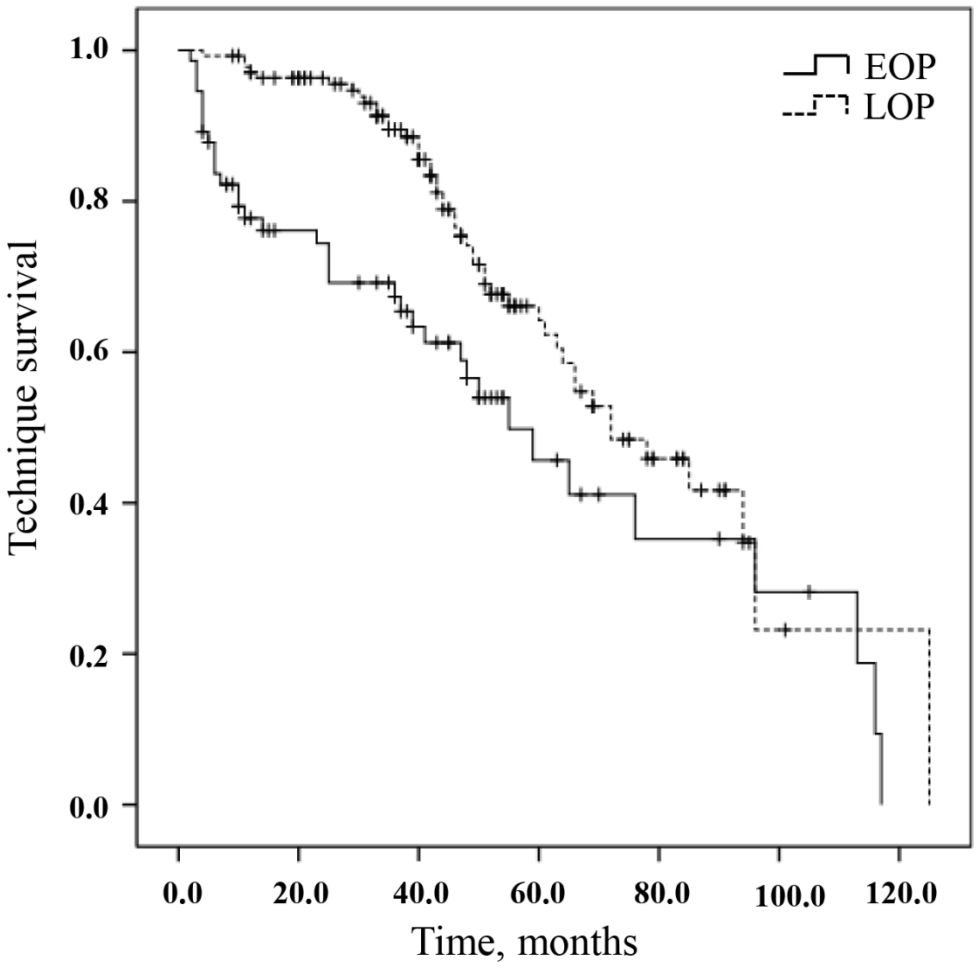

Fig.1. Technique survival according to EOP and LOP.

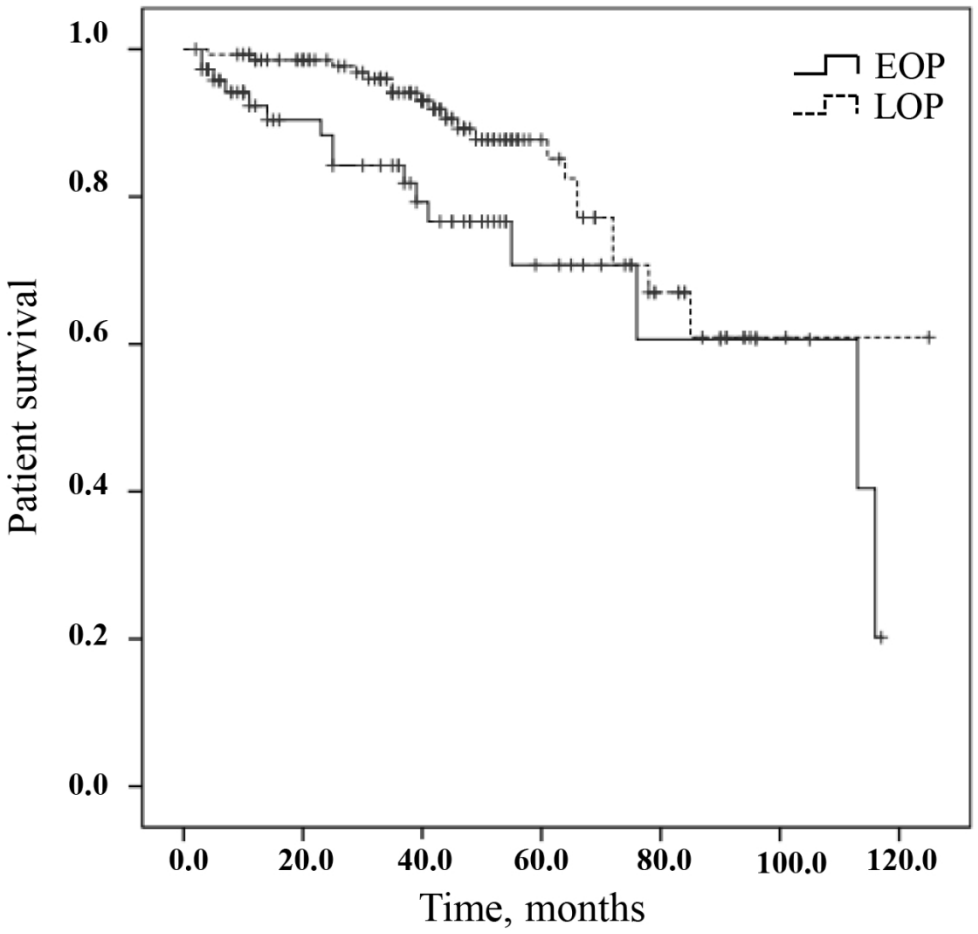

Fig.2. Patient survival according to EOP and LOP.

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The analysis of risk factors and outcome in peritoneal dialysis patients with early-onset peritonitis: a multi-center, retrospective, cohort study.

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ABSTRACT

Objectives To investigate the risk factors associated with early-onset peritonitis (EOP) and its influence on patients' technique survival and mortality.

Study design Retrospective, cohort study.

Setting Three peritoneal dialysis units in Shanghai.

Participants PD patients from June 1, 2006, to May 1, 2018, were recruited and followed up until December 31, 2018. According to time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139).

Primary and secondary outcome measures EOP was defined as the first episode of peritonitis occurring within 6 months after the initiation of peritoneal dialysis (PD). The outcomes were all-cause mortality and technique failure.

Results Of the 357 patients, 74 (20.7%) patients developed their first episode of peritonitis within the first 6 months. Compared with the LOP group, the EOP group had older ages, more female patients, higher Charlson comorbidity index (CCI) score, lower serum albumin levels and renal function at the time of initiation of PD and higher diabetes mellitus and peritonitis rates (P<0.05). Staphylococcus was the most common Gram-positive organism in both EOP and LOP groups. The multivariate logistic regression analysis showed that factors associated with EOP included a higher CCI score (odds ratio (OR) 1.318, P=0.008), lower serum albumin level (OR 0.926, P=0.021) and lower Kt/V (OR 0.631, P=0.035) at start of PD. In the Cox proportional hazards model, EOP was the only predictor of technique failure (hazard ratio (HR) 1.801, P=0.051). There was no difference between EOP and LOP for all-cause mortality.

Conclusion A higher CCI score and lower serum albumin level and Kt/V at PD initiation were significantly associated with EOP. EOP also predicted a high peritonitis rate and poor clinical outcomes.

KEY WORDS Peritoneal dialysis; Early-onset peritonitis; Risk factors; Outcomes.

ARTICLE SUMMARY

Article focus

- The risk factors associated with EOP and its influence on patients' technique survival and mortality.

Key messages

- A higher CCI score and lower serum albumin level and Kt/V at PD initiation were significantly associated with EOP.
- EOP predicted a high peritonitis rate and poor clinical outcomes.

Strengths and limitations of this study

- There is a strict exclusion criteria based on PD histories.
- We conducted a multi-center study which ensured sufficient power in obtaining the risk factors of EOP.
- This was a retrospective cohort study, lacking of some objective information such as education level, economic development and living standard, which may cause bias.
- The study did not compare the risk factors of EOP between male and female patients.
- Although this was a multicenter study, the sample size was relatively small.

INTRODUCTION

In developing countries, the number of peritoneal dialysis (PD) patients has been increasing over time.[1 2] Peritoneal dialysis (PD)-related peritonitis is a serious complication during PD therapy and remains the major reason for technique failure.[3] Severe and prolonged peritonitis leads to structural and functional alterations of the peritoneal membrane, eventually leading to peritoneal fibrosis.[4] Therefore, finding the risk factors for peritonitis in the early stage of PD would help to reduce technique failures and mortality of PD.

The definition of early-onset peritonitis varies widely between studies, which generally refers to peritoneal dialysis related peritonitis occurring within 3-24 months after surgical catheterization.[5-8] Previous studies showed that the first episode of peritonitis in PD patients could significantly affect the prognosis of end-stage renal disease (ESRD) patients.[9] However, few studies have specifically examined the risk factors for peritonitis in the early PD period. And most of these were observational cohort studies carried out in single centers,[5 10 11] limiting the generalizability of their observed outcomes. To determine the risk factors for early-onset peritonitis in Chinese CKD patients and its influence on patients' technique survival and mortality, we conducted this multiple-center, retrospective cohort study.

METHODS

Study Population

This was a multi-center retrospective cohort study included 357 patients with ESRD who underwent PD in Department of Nephrology in Baoshan branch of Shanghai First People's Hospital, Shanghai Songjiang District Central Hospital and Shanghai East Hospital, Tongji University School of Medicine. All incident PD patients from June 1, 2006, to May 1, 2018, were recruited and followed up until December 31, 2018. 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 of the three hospitals. After that we collected the information from the hospital databases. The exclusion criteria were as follows: patients who had been using PD for fewer than 90 days, patients with an age younger than 18 years and patients who initiated PD in other PD centers and previously accepted HD or kidney transplantation. 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. While these 10 PD patients lacked of the information of peritoneal equilibration test. Patients were followed until any of the following events: death, a change to HD, renal transplantation or until December 31, 2018. According to the Chinese Peritoneal Dialysis Guideline, we adopted standardized surgical catheterization technique.[12] 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 was downward and outward, and the outer polyester sleeve was 2 to 3 cm away from the exit. All the surgical operations are performed in the operating room. The single dose intravenous antibiotic 30 minutes before surgery is recommended to prevent infection.[13] The first or second generation cephalosporin is suggested.[13 14] 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. Patients initiated PD by Dianeal with 1.5% or 2.5% dextrose (Baxter Healthcare, Guangzhou, China). Dialysate concentration was 1.5% dextrose and replaced every four hours during the day, while 2.5% at night and kept in the body. A total of 213 patients who had at least one episode of peritonitis. According to time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (> 6 months, n=139). We collected baseline characteristics within 1-3 months from the start of PD, including demographic data (age, gender,

smoking, drinking, CCI, BMI), medical history, drug-taking history, biochemical data (hemoglobin, serum electrolyte, fasting blood glucose, total cholesterol, total triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and serum albumin, uric acid, creatinine, blood urea nitrogen, estimated glomerular filtration rate (eGFR), the clearance rate of urea nitrogen (Kt/V), cause of ESRD, peritonitis episodes. Peritoneal fluid effluent from patients with peritonitis was collected and cultured for 1 to 5 days to identify the bacterial flora in the dialysate.

Primary and secondary outcome measures

Early-onset peritonitis was defined as the first episode of peritonitis occurring within 6 months after the initiation of peritoneal dialysis (PD). This definition is consistent with other published article.[8 16] The outcomes were all-cause mortality and technique failure.

Study definitions

Diagnostic criteria for peritonitis based on the 2010 International Society for Peritoneal Dialysis (ISPD) guidelines.[15] Patients diagnosed as peritonitis should meet at least two of the following three standards: (1) Clinical symptoms or signs of peritonitis; (2) Leucocyte count (at least 100/mm^3) and polymorphonuclear neutrophilic cells proportion (at least 50%) in peritoneal fluid effluent; (3) Related pathogens in smear or culture of peritoneal fluid. Early-onset peritonitis was defined as the first episode of peritonitis occurring within 6 months after the initiation of PD. The outcomes were all-cause mortality and technique failure. Death was an end-point event in the patient survival analysis. Relapse was defined as an episode occurring within 4 weeks of completion of therapy of a prior episode with the same organism,[13] recurrence referred to an episode occurring within 4 weeks of completion of therapy of a prior episode but with a different organism.[13] 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.[7] 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. Patients who transferred to HD were censored form the patient survival analysis, and death was censored for technique failure. Technique failure was defined as the transfer to HD therapy permanently (lasted for 30 days or more) due to ultrafiltration failure, peritonitis, exit-site infection and other operational problems.[17]

Patient and public involvement

No patient was involved in the design or conduct of the study, but the results of the study will be shared to patients coming for follow-up.

Statistical analysis

All statistical analyses were performed by SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA). The normal distributed data were showed as mean±standard deviation (SD) and the skewed data were showed as median values with the 25th to 75th percentile intervals. Categorical data were expressed as frequency (n) and percentage (%). As for normally distributed data, student's t-test is using for analyzing the differences between the EOP group and LOP group, while one-way ANOVA for differences among in non-peritonitis, EOP group and LOP groups. The Wilcoxon rank sum test for skewed continuous data and the Chi-square test or Fisher's exact test for categorical data. The Kaplan-Meier survival curves were drawn for each event of interest (technique survival and patient survival) and the log-rank test was used to compare curves. Univariate Cox proportional hazards regression was used to select significant factors associated with study outcomes. Variables whose

P<0.10 were selected for inclusion in the final multivariate Cox model. Multivariate logistic regression was calculated to select significant risk factors for EOP and the inclusion standard was also P<0.10. Collinearity of variables was tested. A two-tailed P value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 357 patients with ESRD underwent CAPD in three dialysis centers in Shanghai during the study period. All patients used Dianeal with 1.5% or 2.5% dextrose. The first episode of peritonitis was experienced by 74 (20.7%) patients within 6 months after the start of PD. 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. Median follow-up time for the 357 patients was 33.0 months (interquartile range 14.0-50.0 months). There were 211 males (59.1%) with an average age of 61.6 ± 14.0 years, and 145 females (40.9%) with an average age of 65.3 ± 12.9 years. The most common primary renal diseases were chronic glomerulonephritis (43.1%) and diabetic nephropathy (34.2%). Compared with the LOP patients, the EOP patient group had older ages, more female patients, higher Charlson comorbidity index (CCI) score and lower serum albumin levels, renal function and Kt/V at the time of initiation of PD and higher diabetes mellitus and peritonitis rates (P<0.05). Additional demographic and laboratory characteristics of the study population are present in Table 1.

Causative organisms

In table 2, among 213 patients with peritonitis, 47 (22.1%) were due to Gram-positive organisms, 24 (11.3%) were due to Gram-negative organisms, 6 (2.8%) were due to fungi, 1 (0.4%) were due to multiple organisms, and 135 (63.4%) were culture-negative. Staphylococcus was the most common Gram-positive organism in

both groups. Compared with the EOP patient group, the LOP patient group had more culture-negative peritonitis (89.2% vs. 14.9%, $P<0.001$). 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 ($P=0.002$).

Outcomes

The total peritonitis rate was 0.490 episodes per patient-year (213 patients presented 509 episodes of peritonitis during 1039.58 patient-years of follow-up). 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. Early-onset first episode of peritonitis had a lower cure rate (17.6% vs 33.8%, Table 2.), higher rate of transferring to hemodialysis (27.0% vs 19.4%, Table 2.), and higher mortality (21.6% vs 14.4%, Table 2.) compared to late-onset first episode of peritonitis.

Technique failure

The variables including time to first peritonitis (EOP vs. LOP), age, sex, smoking, drinking, CCI, BMI, hemoglobin, total cholesterol, total triglyceride, serum albumin, eGFR, total Kt/V and diabetes, were calculated into the cox proportional hazards model for technique failure. And we found that EOP was significantly associated with technique failure compared with the LOP group, with a hazard ratio (HR) of 1.801 (Table 3, $P=0.051$). Kaplan-Meier analysis showed that compared with LOP group, technique survival was lower in the EOP group (Log rank 3.943, $P=0.047$, Fig.1).

All-cause mortality

During the study period, a total of 52 peritonitis patients died: 16 patients in the EOP group and 20 patients in the LOP group. Variables with P value < 0.10 in univariate

Cox regression analysis, including the time to first peritonitis (EOP vs. LOP), age, serum albumin and total Kt/V, were chosen for further adjustment in multivariate Cox proportional hazards model. After adjustment, there was no significant difference between the EOP and LOP groups (Table 3). Fig. 2 describes cumulative survival by EOP and LOP groups using the Kaplan-Meier analysis. Compared with LOP group, cumulative survival was lower in the EOP group (Log rank 4.060, P=0.044).

Risk factors of early-onset peritonitis

Variables in Table 1 were tried in a univariate logistic regression model, and only variables with P value < 0.10 for peritonitis were depicted in Table 4. Based on the simple logistic regression analysis of risk factors associated with EOP, we constructed a multiple logistic regression model using variables including gender, age, CCI score, diabetes, serum albumin, eGFR and Kt/V. We found that higher CCI score (OR=1.318, 95%CI 1.075-1.615, P=0.008), lower serum albumin level (OR=0.926, 95%CI 0.868-0.989, P=0.021) and Kt/V (OR=0.631, 95%CI 0.411-0.969, P=0.035) at the start of PD, were significantly associated with EOP (Table 4).

DISCUSSION

Our retrospective cohort study of 357 PD patients showed that 74 (20.7%) patients in three Shanghai dialysis centers developed the first episodes of peritonitis within the first 6 months. Higher CCI score, lower serum albumin level and Kt/V at the start of PD, were significantly associated with EOP. In addition, an early peritonitis onset predicted a high peritonitis rate and technique failure.

Early-onset peritonitis is a major complication of peritoneal dialysis, directly or indirectly causing the abandon of dialysis treatment. In this study, among 213 patients with peritonitis, 47 (22.1%) were due to Gram-positive organisms, 24 (11.3%) were due to Gram-negative organisms, 6 (2.8%) were due to fungi. Staphylococcus was the most common Gram-positive organism in both early-onset and late-onset peritonitis.

This bacterial flora distribution and high incidence of staphylococcus were similar to previous reports.[18-20] Fungal peritonitis was rare in PD patients, but could bring out irreversible peritoneal damage.[21] Recent clinical studies confirmed that the incidence of fungal peritonitis was only 3%-6%,[21] while the relative mortality rate was up to 20%-30%.[22] The culture-negative proportion for the first peritonitis episode was high in the LOP patients (89.2%). And 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). The high culture-negative proportion may primary attributed to early antibiotic treatment and limited effluent culture technique in small-scale PD units. Before 2014, the technology of blood culture for PD effluent has not been widely adopted by small-scale district hospitals in Shanghai. In the district PD units, 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 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.[13 14]

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

[5], 0.158 episodes per patient-year in Guangzhou,[7] 0.296 episodes per patient-year in Suzhou [16] and 0.158 per patient-year in Hangzhou [8]. Peritonitis rate in our study is higher than the rest of China. 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.

Our study found that lower serum albumin was one of the major risk factors for early-onset peritonitis. Loss of protein would cause negative nitrogen balance and malnutrition, leading to a decline in immune function and increased susceptibility to pathogenic microorganisms.[23] Malnutrition was one of the most common complications in PD patients, and plasma albumin level was an important clinical predictor. Hypoalbuminemia was proved to be related with malnutrition, protein losses, and inflammation.[24 25] Wang Qin et al. discovered that patients with an initial serum albumin level less than 2.9 g/dL had a higher incidence of peritonitis and regarded hypoalbuminemia as an independent predictor for subsequent peritonitis at the start of PD therapy.[26] Further studies demonstrated that low serum albumin level increased all-cause, cardiovascular, and infection related mortality in both PD and HD patients.[27] In addition to peritoneal infection, hypoalbuminemia was also found to be associated with septicemia, pneumonia and other inflammatory responses.[28-32] In this study, we reaffirmed that a low baseline serum albumin level is an independent risk factors for EOP (OR=0.926, 95%CI 0.868-0.989, P=0.021).

Although older age is not an independent risk factor for EOP, baseline data

showed that patients in EOP group older than LOP group (65.87±13.20 vs. 61.40±13.53, P=0.022). It was reported that elder patients were more likely to progress to a worse outcome, including HD, renal transplantation or death.[33] Incidence of malnutrition in elderly PD patients was more common than young and middle-aged patients. Together with cardiovascular diseases, cerebrovascular disease, hearing and visual impairments, all of these factors increase and aggravate the episode of peritonitis.[34-36] Malnutrition in elder not only affected the quality of dialysis patients' life, but also was an important factor in comorbidity and mortality.[37] Other elements that increased the peritonitis susceptibility in elderly patients included generalized functional deterioration, weakened immune system,[38] combined chronic diseases, bad eyesight, poor aseptic concept, lack of compliance and living alone. Their atypical clinical symptoms of peritonitis could be regarded as another essential reason. Up-regulated pain threshold, unobtrusive bellyache and mild subjective symptoms might cover up early-onset peritonitis until the occurrence of liquid turbidity, which would delay the best time for treatment.

Comparison in biochemical indicators shown that Kt/V and residual renal function decreased significantly after early-onset peritonitis. Multivariate logistic regression showed that lower eGFR (OR=0.916, 95%CI 0.832-1.009, P=0.076) and Kt/V (OR=0.631, 95%CI 0.411-0.969, P=0.035) at the start of PD, were associated with EOP. These results suggest that early infection with peritonitis might further worsen renal function, especially the scavenging capacity of solutes by residual kidney. Early inflammatory response and renal function damage might be the underlying causes of peritonitis. Some studies suggested that the survival rate of PD patients depends more on residual renal function than the peritoneal cleaning capacity.[39-41] Harris et al. further put forward that residual renal function less than 4 $ml \cdot min^{-1} \cdot 1.73m^{-2}$ was associated with high mortality during peritoneal dialysis.[42] Therefore, we should pay close attention to the change of residual renal function when monitoring the adequacy of dialysis.

The relationship between peritonitis and technique failure and death have been investigated in previous Chinese single-center studies.[7 8] A study in Chinese Zhejiang province showed that, EOP was a significant predictor of all-cause mortality. As for technique failure, they found no significant differences between EOP and LOP.[8] However, a study in Chinese Guangzhou province indicated that technique failure in EOP group was lower than LOP group, but patient survival did not differ between the two groups.[7] Our present study showed that EOP was the only significant predictor of technique failure (HR=1.801, 95%CI 0.996-3.257, P=0.051). There were no differences between EOP and LOP for all-cause mortality. These conclusions might be limited by regional and demographic differences in different dialysis center. However, all three studies indicated that patients who experienced peritonitis early after the initiation of PD were likely having more episodes of peritonitis. Repeating peritonitis in EOP patients have an obvious impact on membrane permeability, increasing severe systemic inflammation, reducing ultrafiltration and leading to worse clinical outcomes.[43] Thus, appropriately dealing with the risk factors of early-onset peritonitis will be good to reduce infection incidence, raise therapeutic effect of PD, improve patient's life quality and prognosis.

There are several limitations to this study. First, this was a retrospective cohort study, lacking of some objective information such as education level, economic development and living standard, which may cause bias. Second, although this was a multicenter study, the sample size was relatively small. Further larger size and prospective investigation are necessary.

CONCLUSION

In summary, this retrospective cohort study found that a higher CCI score and lower serum albumin and Kt/V before PD were significantly associated with EOP. In addition, an early peritonitis onset predicted a high peritonitis rate and worse clinical outcomes. Understanding the risk factors for EOP helps to develop effective measures

to prevent or delay the complication of peritoneal dialysis as much as possible.

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Author Contributors

X.M., Y.S. M.T. and X.J. contributed equally to this work. X.M., Y.S. M.T. and X.J. performed the statistical analysis and wrote the manuscript; X.M., Y.S., M.T., X.J., Y.W., D.J., L.F., W.J., L.D. and X.Z. participated in the data collection; X.M., Y.S., S.Z. and N.L. contributed to discussion; X.M., S.Z. and N.L. participated in the design of the study and edited the manuscript. All authors contributed to data interpretation and revisions of the manuscript critically for important intellectual content. All authors approved the final version of the submitted manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of work are appropriately investigated and resolved.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Helsinki Declaration and was approved by 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. Written informed consent was obtained from each participant before data collection.

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Table 1.Baseline characteristic of the study population

Variable	Peritonitis-free (N=144)	EOP (N=74)	LOP (N=139)	P value between EOP and LOP	P value
Age (years)	63.18±13.91	65.87±13.20	61.40±13.53	0.022	0.075
Gender (male, n, %)	84 (58.3)	37 (50.0)	90 (64.7)	0.037	0.135
Smoking (%)	40 (27.8)	22 (29.7)	31 (22.3)	0.233	0.415
Drinking (%)	31 (21.5)	20 (27.0)	32 (23.0)	0.517	0.659
Charlson comorbidity index score	3.76±1.51	5.73±2.17	4.42±1.93	<0.001	<0.001
Body mass index (kg/m²)	23.55±3.76	24.19±3.31	24.32±3.38	0.791	0.174
Hemoglobin (g/L)	83.67±17.70	89.10±22.90	88.53±19.77	0.849	0.059
Serum calcium (mmol/L)	1.98±0.29	2.14±0.41	2.11±0.33	0.514	0.001
Serum phosphorus (mmol/L)	1.77±0.55	1.91±0.61	1.83±0.78	0.457	0.349
Serum potassium (mmol/L)	4.39±0.65	4.41±0.74	4.39±0.80	0.865	0.980
Fasting blood glucose (mmol/L)	5.38±2.01	6.49±2.93	6.09±2.10	0.261	0.001
TC (mmol/L)	4.02 (3.36, 5.11)	4.59 (3.54, 6.06)	4.43 (3.57, 5.70)	0.537	0.022
TG (mmol/L)	1.28 (0.97, 1.74)	1.30 (1.00, 2.39)	1.24 (1.00, 2.17)	0.469	0.430
HDL-C (mmol/L)	1.11 (0.85, 1.33)	1.18 (0.97, 1.43)	1.19 (0.98, 1.48)	0.740	0.042
LDL-C (mmol/L)	2.44 (1.94, 3.11)	2.65 (2.01, 3.25)	2.38 (2.00, 3.09)	0.238	0.473
Serum albumin (g/L)	33.26±6.26	30.01±7.15	33.37±4.92	<0.001	<0.001
Serum uric acid (mmol/L)	516.93±142.32	495.46±183.30	536.48±185.05	0.124	0.231
Serum creatinine (μmol/L)	659.74±185.48	749.77±268.11	660.42±302.69	0.034	0.027
Blood urea nitrogen (mmol/L)	24.49±7.72	25.69±10.73	24.51±9.85	0.421	0.616
eGFR (ml/min/1.73 m²)	8.49±3.25	6.84±3.82	8.48±4.13	0.005	0.003
Total Kt/V	2.31 (1.98, 2.56)	2.10 (1.71, 2.54)	2.33 (1.93, 3.04)	0.008	0.012
Diabetes mellitus(%)	64 (44.4)	54 (73.0)	79 (56.8)	0.021	<0.001
Hypertension (%)	126 (87.5)	66 (89.2)	116 (83.5)	0.258	0.439
Dyslipidemia (%)	54 (37.5)	41 (55.4)	74 (53.2)	0.762	0.009
Cardiovascular disease (%)	43 (29.9)	30 (40.5)	51 (36.7)	0.582	0.241
Cerebrovascular disease (%)	21 (14.6)	30 (40.5)	55 (39.6)	0.890	<0.001
Calcium	90 (62.5)	44 (59.5)	72 (51.8)	0.285	0.179
Iron	73 (50.7)	41 (55.4)	68 (48.9)	0.367	0.664
Anti-diabetic medications (%)	54 (37.5)	38 (51.4)	46 (33.1)	0.009	0.031
Anti-hypertension medications (%)	124 (86.1)	65 (87.8)	112 (80.6)	0.178	0.284
Lipid-lowering medications (%)	38 (26.4)	36 (48.6)	61 (43.9)	0.506	0.001
Cause of ESKD				0.182	0.008
Glomerulonephritis (%)	57 (39.6)	29 (39.2)	68 (48.9)		
Diabetes (%)	42 (29.2)	34 (45.9)	46 (33.1)		
Other (%)	45 (31.3)	11 (14.9)	25 (18.0)		
Peritonitis episodes (%)				0.006	0.006
1		17 (23.0)	57 (41.0)		
2		16 (21.6)	35 (25.2)		
≥3		41 (55.4)	47 (33.8)		

EOP, early-onset peritonitis; LOP, late-onset peritonitis; TC, total cholesterol; TG total triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GFR, glomerular filtration rate; ESKD, end stage kidney disease

Table 2. Organism and outcome of different vintages of peritonitis (n, %)

Causative organisms	Early-onset peritonitis episodes (n)	Late-onset peritonitis episodes (n)	P value
Causative organisms			
Gram-positive organisms	38 (51.4)	9 (6.5)	<0.001
Staphylococcus aureus	7 (18.4)	0 (0.0)	0.163
Coagulase-negative	3 (7.9)	0 (0.0)	0.384
Staphylococcus	16 (42.1)	8 (88.9)	0.012
Streptococcus species	4 (10.5)	1 (11.1)	0.959
Enterococcus species	4 (10.5)	0 (0.0)	0.309
Other Gram-positives	4 (10.5)	0 (0.0)	0.309
Gram-negative organisms	20 (27.0)	4 (2.9)	<0.001
Escherichia coli	8 (40.0)	0 (0.0)	0.121
Klebsiella species	6 (30.0)	1 (25.0)	0.841
Acinetobacter species	4 (20.0)	1 (25.0)	0.822
Pseudomonas Aeruginosa	2 (10.0)	1 (25.0)	0.408
Other Gram-negatives	0 (0.0)	1 (25.0)	0.022
Fungi	4 (5.4)	2 (1.4)	0.096
Multiple organisms	1 (1.4)	0 (0.0)	0.170
Culture-negative peritonitis	11 (14.9)	124 (89.2)	<0.001
Outcomes			0.063
Complete cure	13 (17.6)	47 (33.8)	
Relapse or recurrence	25 (33.8)	45 (32.4)	
Transfer to hemodialysis	20 (27.0)	27 (19.4)	
Death	16 (21.6)	20 (14.4)	

Table 3. Cox proportional hazards model for technique failure and patient mortality.

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)	1.801	0.996-3.257	0.051	1.801	0.996-3.257	0.051
Age (year)	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			
Total Kt/V	1.008	0.737-1.379	0.959			
Diabetes (yes vs. no)	1.383	0.742-2.579	0.307			
Patient mortality						
Time to first peritonitis (EOP vs. LOP)	1.968	1.006-3.851	0.048	1.010	0.391-2.606	0.984
Age (year)	1.037	1.014-1.061	0.002	1.002	0.973-1.031	0.917
Sex (men vs. women)	0.862	0.498-1.492	0.596			
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	0.999	0.878-1.138	0.990			
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)	0.949	0.907-0.993	0.025	0.965	0.897-1.039	0.346
eGFR (ml/min/1.73 m^2)	0.935	0.860-1.016	0.111			
Total Kt/V	0.650	0.409-1.033	0.069	0.683	0.425-1.099	0.116
Diabetes (yes vs. no)	1.176	0.672-2.057	0.570			

Table 4. Logistic regression analysis of factors associated with early-onset peritonitis

Variable	Univariate logistic regression analysis			Multivariate logistic regression analysis		
	OR	(95%CI)	P value	OR	(95%CI)	P value
Sex (men vs. women)	0.544	0.307-0.966	0.038	0.784	0.369-1.665	0.526
Age (year)	1.026	1.004-1.049	0.023	1.016	0.990-1.042	0.243
Charlson comorbidity index score	1.355	1.173-1.566	<0.001	1.318	1.075-1.615	0.008
Diabetes	2.051	1.111-3.786	0.022	1.084	0.451-2.604	0.858
Serum albumin (g/L)	0.901	0.853-0.951	<0.001	0.926	0.868-0.989	0.021
eGFR (ml/min/1.73 m^2)	0.888	0.815-0.967	0.006	0.916	0.832-1.009	0.076
Kt/V	0.553	0.370-0.827	0.004	0.631	0.411-0.969	0.035

Figure legends

Fig.1. Technique survival according to EOP and LOP.

Death were censored form the technique survival analysis. Log rank test Chi-square 3.943, *P*=0.047

Fig.2. Patient survival according to EOP and LOP.

Patients who transferred to HD were censored form the patient survival analysis. Log rank test Chi-square 4.060, *P*=0.044

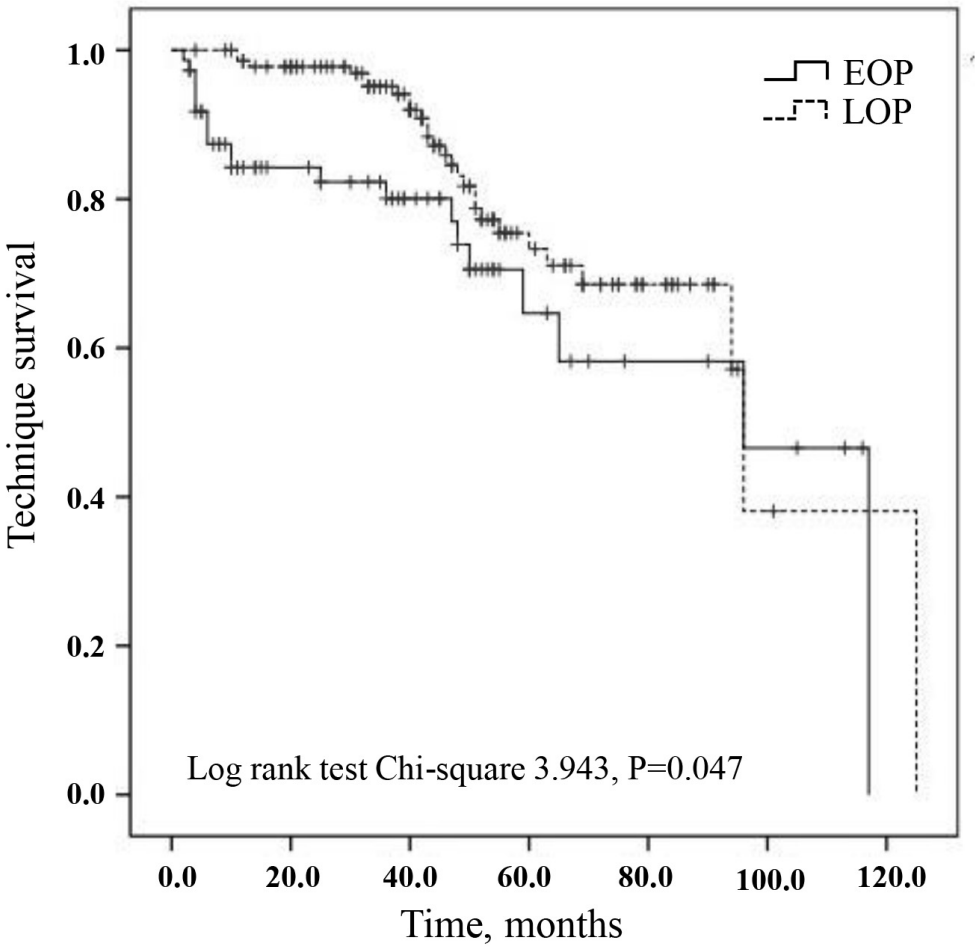

Fig.1. Technique survival according to EOP and LOP.
Death were censored form the technique survival analysis. Log rank test Chi-square 3.943, P=0.047

113x111mm (300 x 300 DPI)

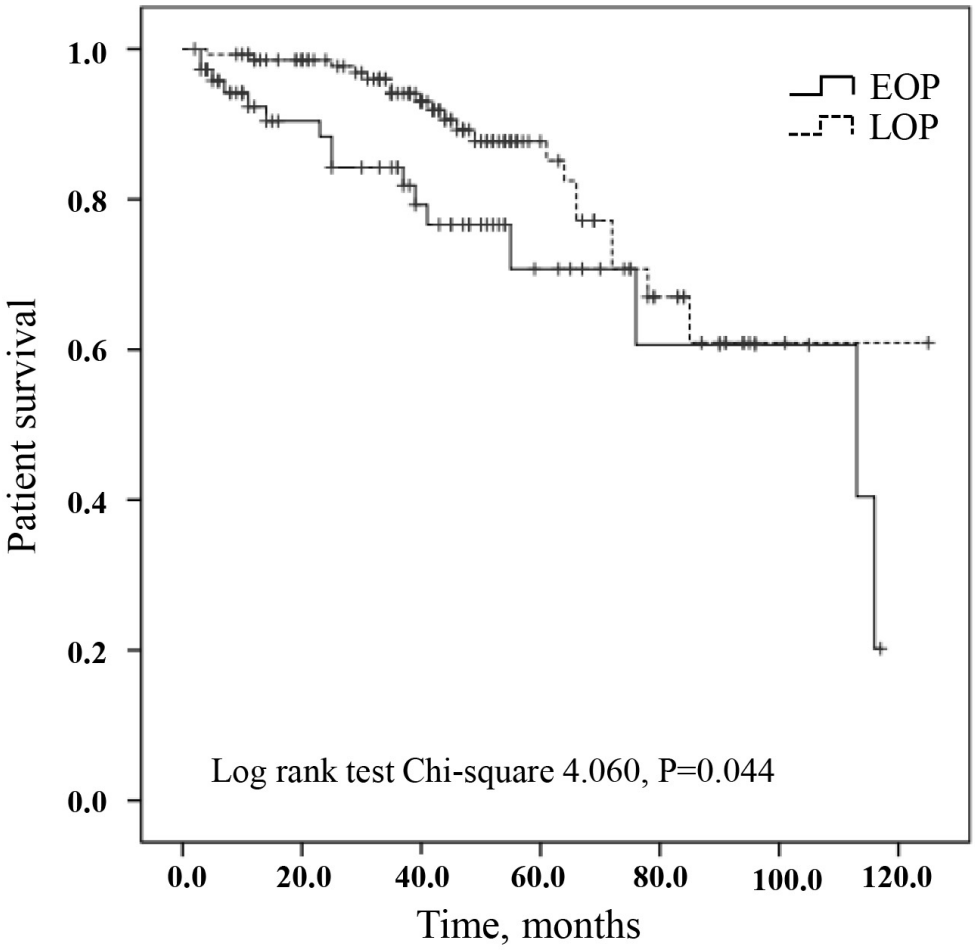

Fig.2. Patient survival according to EOP and LOP.
Patients who transferred to HD were censored form the patient survival analysis. Log rank test Chi-square 4.060, P=0.044

111x108mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	The analysis of risk factors and outcome in peritoneal dialysis patients with early-onset peritonitis: a multi-center, retrospective, cohort study.	1
		Objectives To investigate the risk factors associated with early-onset peritonitis (EOP) and its influence on patients' technique survival and mortality. **Study design** Retrospective, cohort study. **Setting** Three peritoneal dialysis units in Shanghai. **Participants** PD patients from June 1, 2006, to May 1, 2018, were recruited and followed up until December 31, 2018. According to time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139). **Primary and secondary outcome measures** EOP was defined as the first episode of peritonitis occurring within 6 months after the initiation of peritoneal dialysis (PD). The outcomes were all-cause mortality and technique failure. **Results** Of the 357 patients, 74 (20.7%) patients developed their first episode of peritonitis within the first 6 months. Compared with the LOP group, the EOP group had older ages, more female patients, higher Charlson comorbidity index (CCI) score, lower serum albumin levels and renal function at the time of initiation of PD and higher diabetes mellitus and peritonitis rates (P<0.05). Staphylococcus was the most common Gram-positive organism in both EOP and LOP groups. The multivariate logistic regression analysis showed that factors associated with EOP included a higher CCI score (odds ratio (OR) 1.318, P=0.008), lower serum albumin level (OR 0.926, P=0.021) and lower Kt/V (OR 0.631, P=0.035) at start of PD. In the Cox proportional hazards model, EOP was the only predictor of technique failure (hazard ratio (HR) 1.801, P=0.051). There was no difference between EOP and LOP for all-cause mortality. **Conclusion** A higher CCI score and lower serum albumin level and Kt/V at PD initiation were significantly associated with EOP. EOP also predicted a high peritonitis rate and poor clinical outcomes.	2
Introduction			
Background/rationale	2	The definition of early-onset peritonitis varies widely between studies, which generally refers to peritoneal dialysis related peritonitis occurring within 3-24 months after surgical catheterization.[5-8] Previous studies showed that the first episode of peritonitis in PD patients could significantly affect the prognosis of end-stage renal disease (ESRD) patients.[9] However, few studies have specifically examined the risk factors for peritonitis in the early PD period. And most of these were observational cohort studies carried out in single centers,[5 10 11] limiting the generalizability of their observed outcomes. To	4

		determine the risk factors for early-onset peritonitis in Chinese CKD patients and its influence on patients' technique survival and mortality, we conducted this multiple-center, retrospective cohort study.	
Objectives	3	PD patients from June 1, 2006, to May 1, 2018, were recruited and followed up until December 31, 2018. According to time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139).	4
Methods			
Study design	4	Retrospective, cohort study.	4
Setting	5	Three peritoneal dialysis units in Shanghai.	4
Participants	6	This was a multi-center retrospective cohort study included 357 patients with ESRD who underwent PD in Department of Nephrology in Baoshan branch of Shanghai First People's Hospital, Shanghai Songjiang District Central Hospital and Shanghai East Hospital, Tongji University School of Medicine. All incident PD patients from June 1, 2006, to May 1, 2018, were recruited and followed up until December 31, 2018. The exclusion criteria were as follows: patients who had been using PD for fewer than 90 days, patients with an age younger than 18 years and patients who initiated PD in other PD centers and previously accepted HD or kidney transplantation.	4
		According to time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139).	4
Variables	7	We collected baseline characteristics within 1-3 months from the start of PD, including demographic data (age, gender, smoking, drinking, CCI, BMI), medical history, drug-taking history, biochemical data (hemoglobin, serum electrolyte, fasting blood glucose, total cholesterol, total triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and serum albumin, uric acid, creatinine, blood urea nitrogen, estimated glomerular filtration rate (eGFR), the clearance rate of urea nitrogen (Kt/V), cause of ESRD, peritonitis episodes. Peritoneal fluid effluent from patients with peritonitis was collected and cultured for 1 to 5 days to identify the bacterial flora in the dialysate.	6
Data sources/ measurement	8*	Peritoneal fluid effluent from patients with peritonitis was collected and cultured for 1 to 5 days to identify the bacterial flora in the dialysate.	*6*
Bias	9	This was a retrospective cohort study, lacking of some objective information such as education level, economic development and living standard, which may cause bias.	3
Study size	10	357 PD patients	4
Quantitative variables	11	The normal distributed data were showed as mean±standard deviation (SD) and the skewed data were showed as median values with the 25th to 75th percentile intervals. As for normally distributed data, student's t-test is using for analyzing the differences between the EOP group and LOP group, while one-way ANOVA for differences among in non-peritonitis, EOP group and LOP groups. The Wilcoxon rank sum test for skewed continuous data.	7

Statistical methods	12	All statistical analyses were performed by SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA). The normal distributed data were showed as mean±standard deviation (SD) and the skewed data were showed as median values with the 25th to 75th percentile intervals. Categorical data were expressed as frequency (n) and percentage (%). As for normally distributed data, student's t-test is using for analyzing the differences between the EOP group and LOP group, while one-way ANOVA for differences among in non-peritonitis, EOP group and LOP groups. The Wilcoxon rank sum test for skewed continuous data and the Chi-square test or Fisher's exact test for categorical data. The Kaplan-Meier survival curves were drawn for each event of interest (technique survival and patient survival) and the log-rank test was used to compare curves. Univariate Cox proportional hazards regression was used to select significant factors associated with study outcomes. Variables whose *P*<0.10 were selected for inclusion in the final multivariate Cox model. Multivariate logistic regression was calculated to select significant risk factors for EOP and the inclusion standard was also *P*<0.10. Collinearity of variables was tested. A two-tailed *P* value <0.05 was considered statistically significant.	7
Results			
Participants	13*	The first episode of peritonitis was experienced by 74 (20.7%) patients within 6 months after the start of PD. 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. 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. While these 10 PD patients lacked of the information of peritoneal equilibration test.	8
Descriptive data	14*	Median follow-up time for the 357 patients was 33.0 months (interquartile range 14.0-50.0 months). There were 211 males (59.1%) with an average age of 61.6 ± 14.0 years, and 145 females (40.9%) with an average age of 65.3 ± 12.9 years. The most common primary renal diseases were chronic glomerulonephritis (43.1%) and diabetic nephropathy (34.2%). Compared with the LOP patients, the EOP patient group had older ages, more female patients, higher Charlson comorbidity index (CCI) score and lower serum albumin levels, renal function and Kt/V at the time of initiation of PD and higher diabetes mellitus and peritonitis rates (*P*<0.05).	8
Outcome data	15*	Of the 357 patients, 74 (20.7%) patients developed their first episode of peritonitis within the first 6 months. Compared with the LOP group, the EOP group had older ages, more female patients, higher Charlson comorbidity index (CCI) score, lower serum albumin levels and renal function at the time of initiation of PD and higher diabetes mellitus and peritonitis rates (*P*<0.05). Staphylococcus was the most common Gram-positive organism in both EOP and LOP groups.	8-9
Main results	16	The multivariate logistic regression analysis showed that factors associated with EOP included a higher CCI score (odds ratio (OR) 1.318, *P*=0.008), lower serum albumin level (OR 0.926, *P*=0.021) and lower Kt/V (OR 0.631, *P*=0.035) at start of PD. In the Cox proportional hazards model, EOP was the only predictor of technique failure (hazard ratio (HR) 1.801, *P*=0.051). There was no difference between EOP and LOP for all-cause mortality.	9-10

Other analyses	17	EOP was defined as the first episode of peritonitis occurring within 3 months. 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).	
Discussion			
Key results	18	A higher CCI score and lower serum albumin level and Kt/V at PD initiation were significantly associated with EOP. EOP also predicted a high peritonitis rate and poor clinical outcomes.	10
Limitations			
Interpretation	20	This was a retrospective cohort study, lacking of some objective information such as education level, economic development and living standard, which may cause bias. Second, although this was a multicenter study, the sample size was relatively small. Further larger size and prospective investigation are necessary.	14
Generalisability	21	There is a strict exclusion criteria based on PD histories. We conducted a multi-center study which ensured sufficient power in obtaining the risk factors of EOP.	14
Other information			
Funding	22	This study was supported by the National Nature Science Foundation of China grants (81670690, 81470991 and 81200492 to N.L., 81270778, 81470920, 81670623 and 81830021 to S.Z.), the Key Discipline Construction Project of Pudong Health Bureau of Shanghai (PWZxk2017-05 to N.L.), the Science Technology grant of Jiangxi Province Municipal Health Commision (20184077 to L.F.), the Branch grant of National key grants of Ministry of Science and Technology (2018YFA0108802 to S.Z.), the US National Institutes of Health (2R01DK08506505A1 to S.Z.), the Shanghai Scientific Committee of China (13PJ1406900 to N.L.).	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The analysis of risk factors and outcome in peritoneal dialysis patients with early-onset peritonitis: a multi-center, retrospective, cohort study.

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The analysis of risk factors and outcome in peritoneal dialysis patients with early-onset peritonitis: a multi-center, retrospective, cohort study.

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ABSTRACT

Objectives To investigate the risk factors associated with early-onset peritonitis (EOP) and its influence on patients' technique survival and mortality.

Study design Retrospective, cohort study.

Setting Three peritoneal dialysis units in Shanghai.

Participants PD patients from June 1, 2006, to May 1, 2018, were recruited and followed up until December 31, 2018. According to time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139).

Primary and secondary outcome measures EOP was defined as the first episode of peritonitis occurring within 6 months after the initiation of peritoneal dialysis (PD). The outcomes were all-cause mortality and technique failure.

Results Of the 357 patients, 74 (20.7%) patients developed their first episode of peritonitis within the first 6 months. Compared with the LOP group, the EOP group had older ages, more female patients, higher Charlson comorbidity index (CCI) score, lower serum albumin levels and renal function at the time of initiation of PD and higher diabetes mellitus and peritonitis rates (P<0.05). Staphylococcus was the most common Gram-positive organism in both EOP and LOP groups. The multivariate logistic regression analysis showed that factors associated with EOP included a higher CCI score (odds ratio (OR) 1.285, P=0.011), lower serum albumin level (OR 0.924, P=0.016) and lower Kt/V (OR 0.600, P=0.018) at start of PD. In the Cox proportional hazards model, EOP was more likely a predictor of technique failure (hazard ratio (HR) 1.801, P=0.051). There was no difference between EOP and LOP for all-cause mortality.

Conclusion A higher CCI score and lower serum albumin level and Kt/V at PD initiation were significantly associated with EOP. EOP also predicted a high peritonitis rate and poor clinical outcomes.

KEY WORDS Peritoneal dialysis; Early-onset peritonitis; Risk factors; Outcomes.

ARTICLE SUMMARY

Strengths and limitations of this study

1. There is a strict exclusion criteria based on PD histories.
2. We conducted a multi-center study which ensured sufficient power in obtaining the risk factors of EOP.
3. This was a retrospective cohort study, lacking of some objective information such as education level, economic development and living standard, which may cause bias.
4. Our study lacked of the adjustment of different center factors (education, re-training and home visit) in the multivariate analysis.
5. Although this was a multicenter study, the sample size was relatively small.

INTRODUCTION

In developing countries, the number of peritoneal dialysis (PD) patients has been increasing over time.[1] [2] Peritoneal dialysis (PD)-related peritonitis is a serious complication during PD therapy and remains the major reason for technique failure.[3] Severe and prolonged peritonitis leads to structural and functional alterations of the peritoneal membrane, eventually leading to peritoneal fibrosis.[4] Therefore, finding the risk factors for peritonitis in the early stage of PD would help to reduce technique failures and mortality of PD.

The definition of early-onset peritonitis varies widely between studies, which generally refers to peritoneal dialysis related peritonitis occurring within 3-24 months after surgical catheterization.[5-8] Previous studies showed that the first episode of

peritonitis in PD patients could significantly affect the prognosis of end-stage renal disease (ESRD) patients.[9] However, few studies have specifically examined the risk factors for peritonitis in the early PD period. And most of these were observational cohort studies carried out in single centers,[5 10 11] limiting the generalizability of their observed outcomes. To determine the risk factors for early-onset peritonitis in Chinese CKD patients and its influence on patients' technique survival and mortality, we conducted this multiple-center, retrospective cohort study.

METHODS

Study Population

This was a multi-center retrospective cohort study included 357 patients with ESRD who underwent PD in Department of Nephrology in Baoshan branch of Shanghai First People's Hospital, Shanghai Songjiang District Central Hospital and Shanghai East Hospital, Tongji University School of Medicine. All incident PD patients from June 1, 2006, to May 1, 2018, were recruited and followed up until December 31, 2018. 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). The exclusion criteria were as follows: patients who had been using PD for fewer than 90 days, patients with an age younger than 18 years and patients who initiated PD in other PD centers and previously accepted HD or kidney transplantation. 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. While these 10 PD patients lacked of the information of peritoneal equilibration test.

Patients were followed until any of the following events: death, a change to HD, renal transplantation or until December 31, 2018. According to the Chinese Peritoneal Dialysis Guideline, we adopted standardized surgical catheterization technique.[12] 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 was downward and outward, and the outer polyester sleeve was 2 to 3 cm away from the exit. All the surgical operations are performed in the operating room. The single dose intravenous antibiotic 30 minutes before surgery is recommended to prevent infection.[13] The first or second generation cephalosporin is suggested.[13 14] According to the ISPD peritonitis recommendations,[13-15] we daily topical application of mupirocin ointment to the catheter exit site to prevent exit site infection. Patients initiated PD by Dianeal with 1.5% or 2.5% dextrose (Baxter Healthcare, Guangzhou, China). Dialysate concentration was 1.5% dextrose and replaced every four hours during the day, while 2.5% at night and kept in the body. A total of 213 patients who had at least one episode of peritonitis. According to time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (> 6 months, n=139). We collected baseline characteristics within 1-3 months from the start of PD, including demographic data (age, gender, smoking, drinking, CCI, BMI), medical history, drug-taking history, biochemical data (hemoglobin, serum electrolyte, fasting blood glucose, total cholesterol, total triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and serum albumin, uric acid, creatinine, blood urea nitrogen, estimated glomerular filtration rate (eGFR), the clearance rate of urea nitrogen (Kt/V), cause of ESRD, peritonitis episodes. Peritoneal fluid effluent from patients with peritonitis was collected and cultured for 1 to 5 days to identify the bacterial flora in the dialysate.

Primary and secondary outcome measures

Early-onset peritonitis was defined as the first episode of peritonitis occurring within 6 months after the initiation of peritoneal dialysis (PD). This definition is consistent with other published article.[8 16] The outcomes were all-cause mortality and technique failure.

Study definitions

Diagnostic criteria for peritonitis based on the 2010 International Society for Peritoneal Dialysis (ISPD) guidelines.[15] Patients diagnosed as peritonitis should meet at least two of the following three standards: (1) Clinical symptoms or signs of peritonitis; (2) Leucocyte count (at least 100/mm^3) and polymorphonuclear neutrophilic cells proportion (at least 50%) in peritoneal fluid effluent; (3) Related pathogens in smear or culture of peritoneal fluid. Early-onset peritonitis was defined as the first episode of peritonitis occurring within 6 months after the initiation of PD. The outcomes were all-cause mortality and technique failure. Death was an end-point event in the patient survival analysis. Relapse was defined as an episode occurring within 4 weeks of completion of therapy of a prior episode with the same organism,[13] recurrence referred to an episode occurring within 4 weeks of completion of therapy of a prior episode but with a different organism.[13] 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.[7] However, some of refractory peritonitis failed to clear up effluent after 5 days of appropriate antibiotics and transferred to HD permanently. We classified 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. Patients who transferred to HD were censored form the patient survival analysis, and death was censored for technique failure. Technique failure was defined as the transfer to HD

therapy permanently (lasted for 30 days or more) due to ultrafiltration failure, peritonitis, exit-site infection and other operational problems.[17]

Patient and public involvement

No patient was involved in the design or conduct of the study, but the results of the study will be shared to patients coming for follow-up.

Statistical analysis

All statistical analyses were performed by SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA). The normal distributed data were showed as mean±standard deviation (SD) and the skewed data were showed as median values with the 25th to 75th percentile intervals. Categorical data were expressed as frequency (n) and percentage (%). As for normally distributed data, student's t-test is using for analyzing the differences between the EOP group and LOP group, while one-way ANOVA for differences among in non-peritonitis, EOP group and LOP groups. The Wilcoxon rank sum test for skewed continuous data and the Chi-square test or Fisher's exact test for categorical data. The Kaplan-Meier survival curves were drawn for each event of interest (technique survival and patient survival) and the log-rank test was used to compare curves. Univariate Cox proportional hazards regression was used to select significant factors associated with study outcomes. Variables whose $P<0.10$ were selected for inclusion in the final multivariate Cox model. Multivariate logistic regression was calculated to select significant risk factors for EOP and the inclusion standard was also $P<0.10$. Collinearity of variables was tested. A two-tailed P value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 357 patients with ESRD underwent CAPD in three dialysis centers in

Shanghai during the study period. All patients used Dianeal with 1.5% or 2.5% dextrose. The first episode of peritonitis was experienced by 74 (20.7%) patients within 6 months after the start of PD. 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. Median follow-up time for the 357 patients was 33.0 months (interquartile range 14.0-50.0 months). There were 211 males (59.1%) with an average age of 61.6 ± 14.0 years, and 145 females (40.9%) with an average age of 65.3 ± 12.9 years. The most common primary renal diseases were chronic glomerulonephritis (43.1%) and diabetic nephropathy (34.2%). Compared with the LOP patients, the EOP patient group had older ages, more female patients, higher Charlson comorbidity index (CCI) score and lower serum albumin levels, renal function and Kt/V at the time of initiation of PD and higher diabetes mellitus (P<0.05). The percentage of patients experienced more than 3 peritonitis episodes in EOP group (55.4%) is higher than LOP group (33.8%). Additional demographic and laboratory characteristics of the study population are present in Table 1.

Causative organisms

In table 2, among 213 patients with peritonitis, 47 (22.1%) were due to Gram-positive organisms, 24 (11.3%) were due to Gram-negative organisms, 6 (2.8%) were due to fungi, 1 (0.4%) were due to multiple organisms, and 135 (63.4%) were culture-negative. Staphylococcus was the most common Gram-positive organism in both groups. Compared with the EOP patient group, the LOP patient group had more culture-negative peritonitis (89.2% vs. 14.9%, P<0.001). 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).

Outcomes

The total peritonitis rate was 0.490 episodes per patient-year (213 patients presented 509 episodes of peritonitis during 1039.58 patient-years of follow-up). 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).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. Early-onset first episode of peritonitis had a lower cure rate (17.6% vs 33.8%, Table 2.), higher rate of transferring to hemodialysis (27.0% vs 19.4%, Table 2.), and higher mortality (21.6% vs 14.4%, Table 2.) compared to late-onset first episode of peritonitis.

Technique failure

The variables including time to first peritonitis (EOP vs. LOP), age, sex, smoking, drinking, CCI, BMI, hemoglobin, total cholesterol, total triglyceride, serum albumin, total Kt/V and diabetes were calculated into the cox proportional hazards model for technique failure. And we found that EOP was associated with technique failure compared with the LOP group, with a hazard ratio (HR) of 1.801 (Table 3, P=0.051). Kaplan-Meier analysis showed that compared with LOP group, technique survival was lower in the EOP group (Log rank 3.943, P=0.047, Fig.1).

All-cause mortality

During the study period, a total of 52 patients died: 16 patients in the EOP group and 20 patients in the LOP group. Variables with P value < 0.10 in univariate Cox regression analysis, including the time to first peritonitis (EOP vs. LOP), age, serum albumin and total Kt/V, were chosen for further adjustment in multivariate Cox

proportional hazards model. After adjustment, there was no significant difference between the EOP and LOP groups (Table 3). Fig. 2 describes cumulative survival by EOP and LOP groups using the Kaplan-Meier analysis. Compared with LOP group, cumulative survival was lower in the EOP group (Log rank 4.060, *P*=0.044).

Risk factors of early-onset peritonitis

Variables in Table 1 were tried in a univariate logistic regression model, and only variables with *P* value < 0.10 for peritonitis were depicted in Table 4. Based on the simple logistic regression analysis of risk factors associated with EOP, we constructed a multiple logistic regression model using variables including gender, age, CCI score, diabetes, serum albumin and Kt/V. 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 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).

DISCUSSION

Our retrospective cohort study of 357 PD patients showed that 74 (20.7%) patients in three Shanghai dialysis centers developed the first episodes of peritonitis within the first 6 months. Higher CCI score, lower serum albumin level and Kt/V at the start of PD, were significantly associated with EOP. In addition, an early peritonitis onset predicted a high peritonitis rate and technique failure.

Early-onset peritonitis is a major complication of peritoneal dialysis, directly or indirectly causing the abandon of dialysis treatment. In this study, among 213 patients with peritonitis, 47 (22.1%) were due to Gram-positive organisms, 24 (11.3%) were due to Gram-negative organisms, 6 (2.8%) were due to fungi. Staphylococcus was the most common Gram-positive organism in both early-onset and late-onset peritonitis. This bacterial flora distribution and high incidence of staphylococcus were similar to previous reports.[18-20] Fungal peritonitis was rare in PD patients, but could bring out

irreversible peritoneal damage.[21] Recent clinical studies confirmed that the incidence of fungal peritonitis was only 3%-6%,[21] while the relative mortality rate was up to 20%-30%.[22] The culture-negative proportion for the first peritonitis episode was high in the LOP patients (89.2%). And 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). The high culture-negative proportion may primary attributed to early antibiotic treatment and limited effluent culture technique in small-scale PD units. Before 2014, the technology of blood culture for PD effluent has not been widely adopted by small-scale district hospitals in Shanghai. In the district PD units, 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. In addition, culture negative peritonitis was higher in LOP than EOP group in the same study period. Because 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. 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.[13 14]

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 [5], 0.158 episodes per patient-year in Guangzhou,[7] 0.296 episodes per patient-year in Suzhou [16] and 0.158 per patient-year in Hangzhou [8]. Peritonitis rate in our study is higher than the rest of China. Among the early-onset peritonitis patients who had ≥3 episodes of peritonitis, 25 patients from EOP group experienced recurrent peritonitis, 16 patients from EOP group experienced 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 them are fishermen and live in the Chongming Island. Since the poorer economic abilities and living conditions, they are easy to malnutrition 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.

Our study found that lower serum albumin was one of the major risk factors for early-onset peritonitis. Loss of protein would cause negative nitrogen balance and malnutrition, leading to a decline in immune function and increased susceptibility to pathogenic microorganisms.[23] Malnutrition was one of the most common complications in PD patients, and plasma albumin level was an important clinical predictor. Hypoalbuminemia was proved to be related with malnutrition, protein losses, and inflammation.[24 25] Wang Qin et al. discovered that patients with an initial serum albumin level less than 2.9 g/dL had a higher incidence of peritonitis and regarded hypoalbuminemia as an independent predictor for subsequent peritonitis at the start of PD therapy.[26] Further studies demonstrated that low serum albumin level increased all-cause, cardiovascular, and infection related mortality in both PD and HD patients.[27] In addition to peritoneal infection, hypoalbuminemia was also found to be associated with septicemia, pneumonia and other inflammatory responses.[28-32] In this

study, we reaffirmed that a low baseline serum albumin level is an independent risk factors for EOP (OR=0.924, 95%CI 0.867-0.985, P=0.016).

Although older age is not an independent risk factor for EOP, baseline data showed that patients in EOP group older than LOP group (65.87±13.20 vs. 61.40±13.53, P=0.022). It was reported that elder patients were more likely to progress to a worse outcome, including HD, renal transplantation or death.[33] Incidence of malnutrition in elderly PD patients was more common than young and middle-aged patients. Together with cardiovascular diseases, cerebrovascular disease, hearing and visual impairments, all of these factors increase and aggravate the episode of peritonitis.[34-36] Malnutrition in elder not only affected the quality of dialysis patients' life, but also was an important factor in comorbidity and mortality.[37] Other elements that increased the peritonitis susceptibility in elderly patients included generalized functional deterioration, weakened immune system,[38] combined chronic diseases, bad eyesight, poor aseptic concept, lack of compliance and living alone. Their atypical clinical symptoms of peritonitis could be regarded as another essential reason. Up-regulated pain threshold, unobtrusive bellyache and mild subjective symptoms might cover up early-onset peritonitis until the occurrence of liquid turbidity, which would delay the best time for treatment.

Comparison in biochemical indicators shown that Kt/V and residual renal function decreased significantly after early-onset peritonitis. Multivariate logistic regression showed that lower total Kt/V (OR=0.600, 95%CI 0.394-0.915, P=0.018) at the start of PD were associated with EOP. These results suggest that early infection with peritonitis might further worsen renal function, especially the scavenging capacity of solutes by residual kidney. Early inflammatory response and renal function damage might be the underlying causes of peritonitis. Some studies suggested that the survival rate of PD patients depends more on residual renal function than the peritoneal cleaning capacity.[39-41] Harris et al. further put forward that residual renal function less than 4 $ml \cdot min^{-1} \cdot 1.73m^{-2}$ was associated with high

mortality during peritoneal dialysis.[42] Therefore, we should pay close attention to the change of residual renal function when monitoring the adequacy of dialysis.

The relationship between peritonitis and technique failure and death have been investigated in previous Chinese single-center studies.[7 8] A study in Chinese Zhejiang province showed that, EOP was a significant predictor of all-cause mortality. As for technique failure, they found no significant differences between EOP and LOP.[8] However, a study in Chinese Guangzhou province indicated that technique failure in EOP group was lower than LOP group, but patient survival did not differ between the two groups.[7] Our present study showed that EOP was more likely a predictor of technique failure (HR=1.801, 95%CI 0.996-3.257, P=0.051). There were no differences between EOP and LOP for all-cause mortality. These conclusions might be limited by regional and demographic differences in different dialysis center. However, all three studies indicated that patients who experienced peritonitis early after the initiation of PD were likely having more episodes of peritonitis. Repeating peritonitis in EOP patients have an obvious impact on membrane permeability, increasing severe systemic inflammation, reducing ultrafiltration and leading to worse clinical outcomes.[43] Thus, appropriately dealing with the risk factors of early-onset peritonitis will be good to reduce infection incidence, raise therapeutic effect of PD, improve patient's life quality and prognosis.

There are several limitations to this study. Firstly, this was a retrospective cohort study, lacking of some objective information such as education level, economic development and living standard, which may cause bias. Secondly, our study lacked of the adjustment of different center factors (education, re-training and home visit) in the multivariate analysis. Thirdly, although this was a multicenter study, the sample size was relatively small. Further larger size and prospective investigation are necessary.

CONCLUSION

In summary, this retrospective cohort study found that a higher CCI score and lower serum albumin and Kt/V before PD were significantly associated with EOP. In addition, an early peritonitis onset predicted a high peritonitis rate and worse clinical outcomes. Understanding the risk factors for EOP helps to develop effective measures to prevent or delay the complication of peritoneal dialysis as much as possible.

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Author Contributors

X.M., Y.S. M.T. and X.J. contributed equally to this work. X.M., Y.S. M.T. and X.J. performed the statistical analysis and wrote the manuscript; X.M., Y.S., M.T., X.J., Y.W., D.J., L.F., W.J., L.D. and X.Z. participated in the data collection; X.M., Y.S., S.Z. and N.L. contributed to discussion; X.M., S.Z. and N.L. participated in the design of the study and edited the manuscript. All authors contributed to data interpretation and revisions of the manuscript critically for important intellectual content. All authors approved the final version of the submitted manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of work are appropriately investigated and resolved.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Helsinki Declaration and was approved by 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. 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.

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Table 1.Baseline characteristic of the study population

Variable	Peritonitis-free (N=144)	EOP (N=74)	LOP (N=139)	P value between EOP and LOP	P value
Age (years)	63.18±13.91	65.87±13.20	61.40±13.53	0.022	0.075
Gender (male, n, %)	84 (58.3)	37 (50.0)	90 (64.7)	0.037	0.135
Smoking (%)	40 (27.8)	22 (29.7)	31 (22.3)	0.233	0.415
Drinking (%)	31 (21.5)	20 (27.0)	32 (23.0)	0.517	0.659
Charlson comorbidity index score	3.76±1.51	5.73±2.17	4.42±1.93	<0.001	<0.001
Body mass index (kg/m²)	23.55±3.76	24.19±3.31	24.32±3.38	0.791	0.174
Hemoglobin (g/L)	83.67±17.70	89.10±22.90	88.53±19.77	0.849	0.059
Serum calcium (mmol/L)	1.98±0.29	2.14±0.41	2.11±0.33	0.514	0.001
Serum phosphorus (mmol/L)	1.77±0.55	1.91±0.61	1.83±0.78	0.457	0.349
Serum potassium (mmol/L)	4.39±0.65	4.41±0.74	4.39±0.80	0.865	0.980
Fasting blood glucose (mmol/L)	5.38±2.01	6.49±2.93	6.09±2.10	0.261	0.001
TC (mmol/L)	4.02 (3.36, 5.11)	4.59 (3.54, 6.06)	4.43 (3.57, 5.70)	0.537	0.022
TG (mmol/L)	1.28 (0.97, 1.74)	1.30 (1.00, 2.39)	1.24 (1.00, 2.17)	0.469	0.430
HDL-C (mmol/L)	1.11 (0.85, 1.33)	1.18 (0.97, 1.43)	1.19 (0.98, 1.48)	0.740	0.042
LDL-C (mmol/L)	2.44 (1.94, 3.11)	2.65 (2.01, 3.25)	2.38 (2.00, 3.09)	0.238	0.473
Serum albumin (g/L)	33.26±6.26	30.01±7.15	33.37±4.92	<0.001	<0.001
Serum uric acid (mmol/L)	516.93±142.32	495.46±183.30	536.48±185.05	0.124	0.231
Serum creatinine (μmol/L)	659.74±185.48	749.77±268.11	660.42±302.69	0.034	0.027
Blood urea nitrogen (mmol/L)	24.49±7.72	25.69±10.73	24.51±9.85	0.421	0.616
eGFR (ml/min/1.73 m²)	8.49±3.25	6.84±3.82	8.48±4.13	0.005	0.003
Total Kt/V	2.31 (1.98, 2.56)	2.10 (1.71, 2.54)	2.33 (1.93, 3.04)	0.008	0.012
Diabetes mellitus(%)	64 (44.4)	54 (73.0)	79 (56.8)	0.021	<0.001
Hypertension (%)	126 (87.5)	66 (89.2)	116 (83.5)	0.258	0.439
Dyslipidemia (%)	54 (37.5)	41 (55.4)	74 (53.2)	0.762	0.009
Cardiovascular disease (%)	43 (29.9)	30 (40.5)	51 (36.7)	0.582	0.241
Cerebrovascular disease (%)	21 (14.6)	30 (40.5)	55 (39.6)	0.890	<0.001
Calcium	90 (62.5)	44 (59.5)	72 (51.8)	0.285	0.179
Iron	73 (50.7)	41 (55.4)	68 (48.9)	0.367	0.664
Anti-diabetic medications (%)	54 (37.5)	38 (51.4)	46 (33.1)	0.009	0.031
Anti-hypertension medications (%)	124 (86.1)	65 (87.8)	112 (80.6)	0.178	0.284
Lipid-lowering medications (%)	38 (26.4)	36 (48.6)	61 (43.9)	0.506	0.001
Cause of ESKD				0.182	0.008
Glomerulonephritis (%)	57 (39.6)	29 (39.2)	68 (48.9)		
Diabetes (%)	42 (29.2)	34 (45.9)	46 (33.1)		
Other (%)	45 (31.3)	11 (14.9)	25 (18.0)		
Peritonitis episodes (%)				0.006	0.006
1		17 (23.0)	57 (41.0)		
2		16 (21.6)	35 (25.2)		
≥3		41 (55.4)	47 (33.8)		

EOP, early-onset peritonitis; LOP, late-onset peritonitis; TC, total cholesterol; TG total triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GFR, glomerular filtration rate; ESKD, end stage kidney disease

Table 2. Organism and outcome of different vintages of peritonitis (n, %)

Causative organisms	Early-onset peritonitis episodes (n)	Late-onset peritonitis episodes (n)	P value
Causative organisms			
Gram-positive organisms	38 (51.4)	9 (6.5)	<0.001
Staphylococcus aureus	7 (18.4)	0 (0.0)	0.163
Coagulase-negative	3 (7.9)	0 (0.0)	0.384
Staphylococcus	16 (42.1)	8 (88.9)	0.012
Streptococcus species	4 (10.5)	1 (11.1)	0.959
Enterococcus species	4 (10.5)	0 (0.0)	0.309
Other Gram-positives	4 (10.5)	0 (0.0)	0.309
Gram-negative organisms	20 (27.0)	4 (2.9)	<0.001
Escherichia coli	8 (40.0)	0 (0.0)	0.121
Klebsiella species	6 (30.0)	1 (25.0)	0.841
Acinetobacter species	4 (20.0)	1 (25.0)	0.822
Pseudomonas Aeruginosa	2 (10.0)	1 (25.0)	0.408
Other Gram-negatives	0 (0.0)	1 (25.0)	0.022
Fungi	4 (5.4)	2 (1.4)	0.096
Multiple organisms	1 (1.4)	0 (0.0)	0.170
Culture-negative peritonitis	11 (14.9)	124 (89.2)	<0.001
Outcomes			0.063
Complete cure	13 (17.6)	47 (33.8)	
Relapse or recurrence	25 (33.8)	45 (32.4)	
Transfer to hemodialysis	20 (27.0)	27 (19.4)	
Death	16 (21.6)	20 (14.4)	

Table 3. Cox proportional hazards model for technique failure and patient mortality.

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)	1.801	0.996-3.257	0.051	1.801	0.996-3.257	0.051
Age (year)	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			
Total Kt/V	1.008	0.737-1.379	0.959			
Diabetes (yes vs. no)	1.383	0.742-2.579	0.307			
Patient mortality						
Time to first peritonitis (EOP vs. LOP)	1.968	1.006-3.851	0.048	1.010	0.391-2.606	0.984
Age (year)	1.037	1.014-1.061	0.002	1.002	0.973-1.031	0.917
Sex (men vs. women)	0.862	0.498-1.492	0.596			
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	0.999	0.878-1.138	0.990			
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)	0.949	0.907-0.993	0.025	0.965	0.897-1.039	0.346
Total Kt/V	0.650	0.409-1.033	0.069	0.683	0.425-1.099	0.116
Diabetes (yes vs. no)	1.176	0.672-2.057	0.570			

Table 4. Logistic regression analysis of factors associated with early-onset peritonitis

Variable	Univariate logistic regression analysis			Multivariate logistic regression analysis		
	OR	(95%CI)	P value	OR	(95%CI)	P value
Sex (men vs. women)	0.544	0.307-0.966	0.038	0.586	0.295-1.163	0.126
Age (year)	1.026	1.004-1.049	0.023	1.020	0.994-1.046	0.131
Charlson comorbidity index score	1.355	1.173-1.566	<0.001	1.285	1.058-1.561	0.011
Diabetes	2.051	1.111-3.786	0.022	1.084	0.457-2.571	0.854
Serum albumin (g/L)	0.901	0.853-0.951	<0.001	0.924	0.867-0.985	0.016
Total Kt/V	0.553	0.370-0.827	0.004	0.600	0.394-0.915	0.018

Figure legends

Fig.1. Technique survival according to EOP and LOP.

Death were censored form the technique survival analysis. Log rank test Chi-square 3.943, *P*=0.047

Fig.2. Patient survival according to EOP and LOP.

Patients who transferred to HD were censored form the patient survival analysis. Log rank test Chi-square 4.060, *P*=0.044

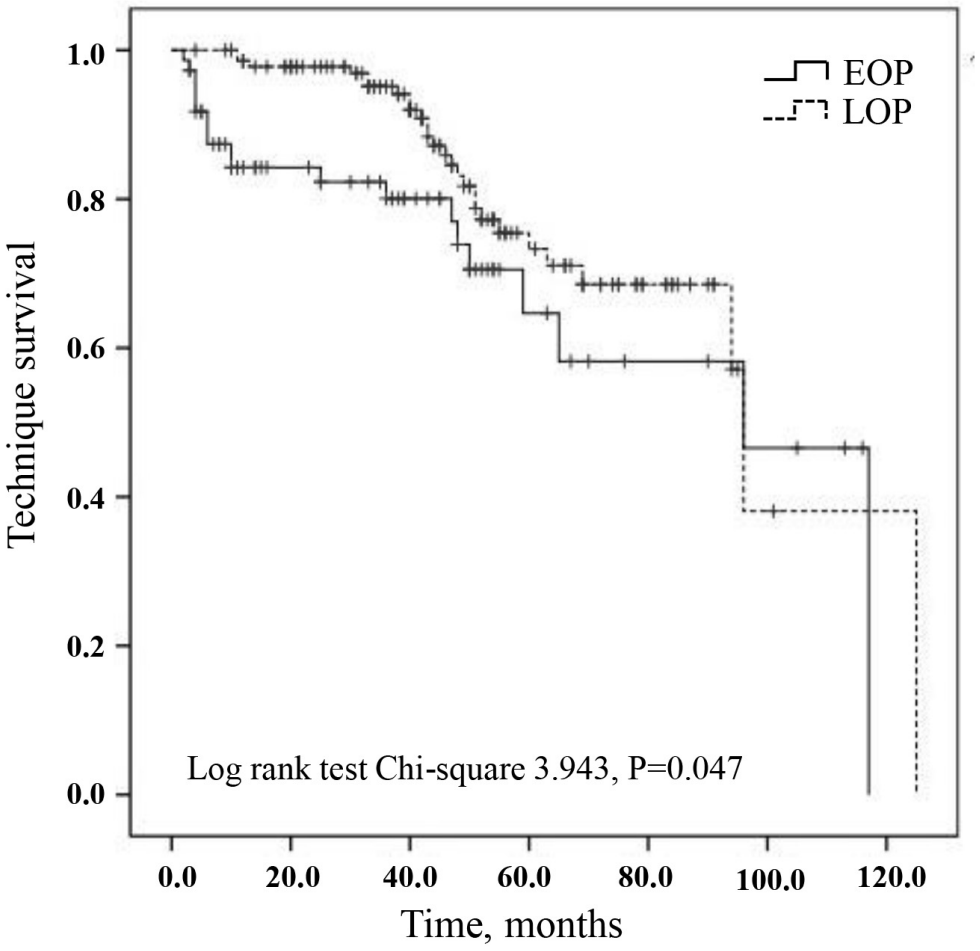

Fig.1. Technique survival according to EOP and LOP.
Death were censored form the technique survival analysis. Log rank test Chi-square 3.943, P=0.047

113x111mm (300 x 300 DPI)

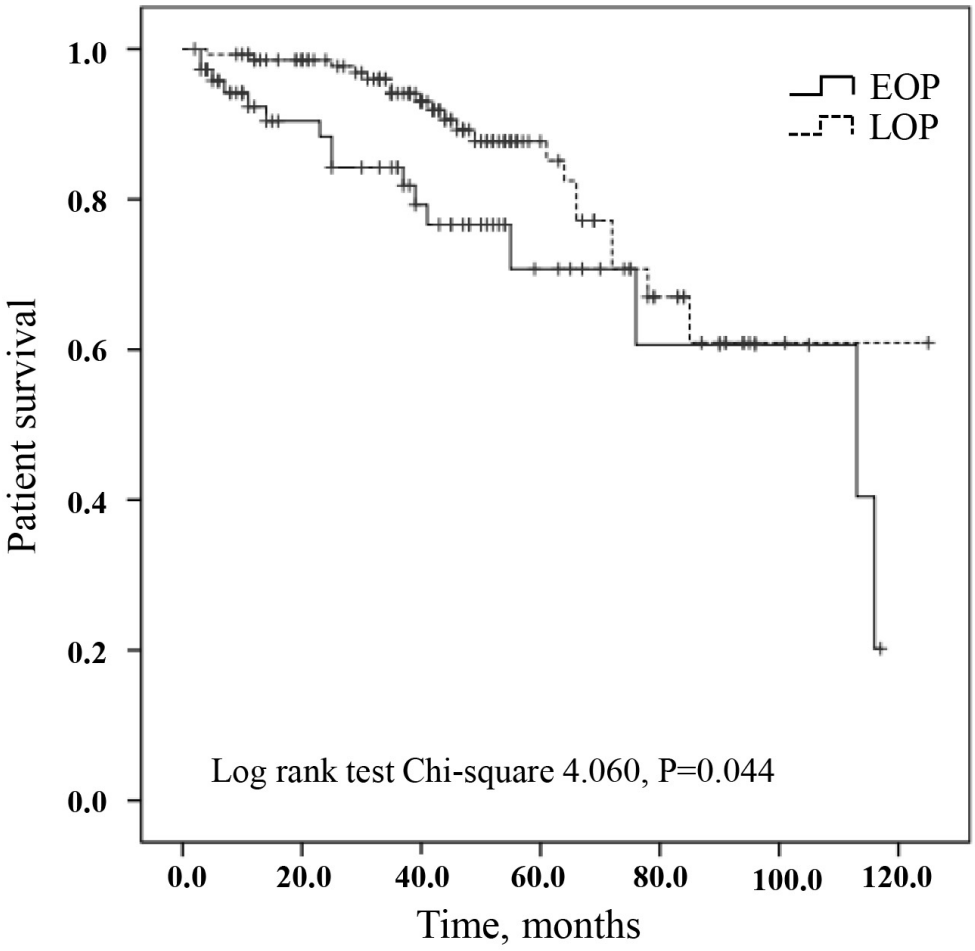

Fig.2. Patient survival according to EOP and LOP.
Patients who transferred to HD were censored form the patient survival analysis. Log rank test Chi-square 4.060, P=0.044

111x108mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	The analysis of risk factors and outcome in peritoneal dialysis patients with early-onset peritonitis: a multi-center, retrospective, cohort study.	1
		Objectives To investigate the risk factors associated with early-onset peritonitis (EOP) and its influence on patients' technique survival and mortality. **Study design** Retrospective, cohort study. **Setting** Three peritoneal dialysis units in Shanghai. **Participants** PD patients from June 1, 2006, to May 1, 2018, were recruited and followed up until December 31, 2018. According to time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139). **Primary and secondary outcome measures** EOP was defined as the first episode of peritonitis occurring within 6 months after the initiation of peritoneal dialysis (PD). The outcomes were all-cause mortality and technique failure. **Results** Of the 357 patients, 74 (20.7%) patients developed their first episode of peritonitis within the first 6 months. Compared with the LOP group, the EOP group had older ages, more female patients, higher Charlson comorbidity index (CCI) score, lower serum albumin levels and renal function at the time of initiation of PD and higher diabetes mellitus and peritonitis rates (P<0.05). Staphylococcus was the most common Gram-positive organism in both EOP and LOP groups. The multivariate logistic regression analysis showed that factors associated with EOP included a higher CCI score (odds ratio (OR) 1.285, P=0.011), lower serum albumin level (OR 0.924, P=0.016) and lower Kt/V (OR 0.600, P=0.018) at start of PD. In the Cox proportional hazards model, EOP was more likely a predictor of technique failure (hazard ratio (HR) 1.801, P=0.051). There was no difference between EOP and LOP for all-cause mortality. **Conclusion** A higher CCI score and lower serum albumin level and Kt/V at PD initiation were significantly associated with EOP. EOP also predicted a high peritonitis rate and poor clinical outcomes.	2
Introduction			
Background/rationale	2	The definition of early-onset peritonitis varies widely between studies, which generally refers to peritoneal dialysis related peritonitis occurring within 3-24 months after surgical catheterization.[5-8] Previous studies showed that the first episode of peritonitis in PD patients could significantly affect the prognosis of end-stage renal disease (ESRD) patients.[9] However, few studies have specifically examined the risk factors for peritonitis in the early PD period. And most of these were observational cohort studies carried out in single centers,[5 10 11] limiting the generalizability of their observed outcomes. To	4

		determine the risk factors for early-onset peritonitis in Chinese CKD patients and its influence on patients' technique survival and mortality, we conducted this multiple-center, retrospective cohort study.	
Objectives	3	PD patients from June 1, 2006, to May 1, 2018, were recruited and followed up until December 31, 2018. According to time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139).	4
Methods			
Study design	4	Retrospective, cohort study.	4
Setting	5	Three peritoneal dialysis units in Shanghai.	4
Participants	6	This was a multi-center retrospective cohort study included 357 patients with ESRD who underwent PD in Department of Nephrology in Baoshan branch of Shanghai First People's Hospital, Shanghai Songjiang District Central Hospital and Shanghai East Hospital, Tongji University School of Medicine. All incident PD patients from June 1, 2006, to May 1, 2018, were recruited and followed up until December 31, 2018. The exclusion criteria were as follows: patients who had been using PD for fewer than 90 days, patients with an age younger than 18 years and patients who initiated PD in other PD centers and previously accepted HD or kidney transplantation.	4
		According to time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139).	4
Variables	7	We collected baseline characteristics within 1-3 months from the start of PD, including demographic data (age, gender, smoking, drinking, CCI, BMI), medical history, drug-taking history, biochemical data (hemoglobin, serum electrolyte, fasting blood glucose, total cholesterol, total triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and serum albumin, uric acid, creatinine, blood urea nitrogen, estimated glomerular filtration rate (eGFR), the clearance rate of urea nitrogen (Kt/V), cause of ESRD, peritonitis episodes. Peritoneal fluid effluent from patients with peritonitis was collected and cultured for 1 to 5 days to identify the bacterial flora in the dialysate.	6
Data sources/ measurement	8*	Peritoneal fluid effluent from patients with peritonitis was collected and cultured for 1 to 5 days to identify the bacterial flora in the dialysate.	*6*
Bias	9	This was a retrospective cohort study, lacking of some objective information such as education level, economic development and living standard, which may cause bias.	3
Study size	10	357 PD patients	4
Quantitative variables	11	The normal distributed data were showed as mean±standard deviation (SD) and the skewed data were showed as median values with the 25th to 75th percentile intervals. As for normally distributed data, student's t-test is using for analyzing the differences between the EOP group and LOP group, while one-way ANOVA for differences among in non-peritonitis, EOP group and LOP groups. The Wilcoxon rank sum test for skewed continuous data.	7

Statistical methods	12	All statistical analyses were performed by SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA). The normal distributed data were showed as mean±standard deviation (SD) and the skewed data were showed as median values with the 25th to 75th percentile intervals. Categorical data were expressed as frequency (n) and percentage (%). As for normally distributed data, student's t-test is using for analyzing the differences between the EOP group and LOP group, while one-way ANOVA for differences among in non-peritonitis, EOP group and LOP groups. The Wilcoxon rank sum test for skewed continuous data and the Chi-square test or Fisher's exact test for categorical data. The Kaplan-Meier survival curves were drawn for each event of interest (technique survival and patient survival) and the log-rank test was used to compare curves. Univariate Cox proportional hazards regression was used to select significant factors associated with study outcomes. Variables whose *P*<0.10 were selected for inclusion in the final multivariate Cox model. Multivariate logistic regression was calculated to select significant risk factors for EOP and the inclusion standard was also *P*<0.10. Collinearity of variables was tested. A two-tailed *P* value <0.05 was considered statistically significant.	7
Results			
Participants	13*	The first episode of peritonitis was experienced by 74 (20.7%) patients within 6 months after the start of PD. 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. 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. While these 10 PD patients lacked of the information of peritoneal equilibration test.	8
Descriptive data	14*	Median follow-up time for the 357 patients was 33.0 months (interquartile range 14.0-50.0 months). There were 211 males (59.1%) with an average age of 61.6 ± 14.0 years, and 145 females (40.9%) with an average age of 65.3 ± 12.9 years. The most common primary renal diseases were chronic glomerulonephritis (43.1%) and diabetic nephropathy (34.2%). Compared with the LOP patients, the EOP patient group had older ages, more female patients, higher Charlson comorbidity index (CCI) score and lower serum albumin levels, renal function and Kt/V at the time of initiation of PD and higher diabetes mellitus and peritonitis rates (*P*<0.05).	8
Outcome data	15*	Of the 357 patients, 74 (20.7%) patients developed their first episode of peritonitis within the first 6 months. Compared with the LOP group, the EOP group had older ages, more female patients, higher Charlson comorbidity index (CCI) score, lower serum albumin levels and renal function at the time of initiation of PD and higher diabetes mellitus and peritonitis rates (*P*<0.05). Staphylococcus was the most common Gram-positive organism in both EOP and LOP groups.	8-9
Main results	16	The multivariate logistic regression analysis showed that factors associated with EOP included a higher CCI score (odds ratio (OR) 1.285, *P*=0.011), lower serum albumin level (OR 0.924, *P*=0.016) and lower Kt/V (OR 0.600, *P*=0.018) at start of PD. In the Cox proportional hazards model, EOP was more likely a predictor of technique failure (hazard ratio (HR) 1.801, *P*=0.051). There was no difference between EOP and LOP for all-cause mortality.	9-10

Other analyses	17	EOP was defined as the first episode of peritonitis occurring within 3 months. 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).	
Discussion			
Key results	18	A higher CCI score and lower serum albumin level and Kt/V at PD initiation were significantly associated with EOP. EOP also predicted a high peritonitis rate and poor clinical outcomes.	10
Limitations			
Interpretation	20	This was a retrospective cohort study, lacking of some objective information such as education level, economic development and living standard, which may cause bias. Second, although this was a multicenter study, the sample size was relatively small. Further larger size and prospective investigation are necessary.	14
Generalisability	21	There is a strict exclusion criteria based on PD histories. We conducted a multi-center study which ensured sufficient power in obtaining the risk factors of EOP.	14
Other information			
Funding	22	This study was supported by the National Nature Science Foundation of China grants (81670690, 81470991 and 81200492 to N.L., 81270778, 81470920, 81670623 and 81830021 to S.Z.), the Key Discipline Construction Project of Pudong Health Bureau of Shanghai (PWZxk2017-05 to N.L.), the Science Technology grant of Jiangxi Province Municipal Health Commision (20184077 to L.F.), the Branch grant of National key grants of Ministry of Science and Technology (2018YFA0108802 to S.Z.), the US National Institutes of Health (2R01DK08506505A1 to S.Z.), the Shanghai Scientific Committee of China (13PJ1406900 to N.L.).	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The analysis of risk factors and outcome in peritoneal dialysis patients with early-onset peritonitis: a multi-center, retrospective, cohort study.

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The analysis of risk factors and outcome in peritoneal dialysis patients with early-onset peritonitis: a multi-center, retrospective, cohort study.

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ABSTRACT

Objectives To investigate the risk factors associated with early-onset peritonitis (EOP) and its influence on patients' technique survival and mortality.

Study design Retrospective, cohort study.

Setting Three peritoneal dialysis units in Shanghai.

Participants PD patients from June 1, 2006, to May 1, 2018, were recruited and followed up until December 31, 2018. According to time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139).

Primary and secondary outcome measures EOP was defined as the first episode of peritonitis occurring within 6 months after the initiation of peritoneal dialysis (PD). The outcomes were all-cause mortality and technique failure.

Results Of the 357 patients, 74 (20.7%) patients developed their first episode of peritonitis within the first 6 months. Compared with the LOP group, the EOP group had older ages, more female patients, higher Charlson comorbidity index (CCI) score, lower serum albumin levels and renal function at the time of initiation of PD and higher diabetes mellitus and peritonitis rates (P<0.05). Staphylococcus was the most common Gram-positive organism in both EOP and LOP groups. The multivariate logistic regression analysis showed that factors associated with EOP included a higher CCI score (odds ratio (OR) 1.285, P=0.011), lower serum albumin level (OR 0.924, P=0.016) and lower Kt/V (OR 0.600, P=0.018) at start of PD. In the Cox proportional hazards model, EOP was more likely a predictor of technique failure (hazard ratio (HR) 1.801, P=0.051). There was no difference between EOP and LOP for all-cause mortality.

Conclusion A higher CCI score and lower serum albumin level and Kt/V at PD initiation were significantly associated with EOP. EOP also predicted a high peritonitis rate and poor clinical outcome.

KEY WORDS Peritoneal dialysis; Early-onset peritonitis; Risk factors; Outcomes.

ARTICLE SUMMARY

Strengths and limitations of this study

1. There is a strict exclusion criteria based on PD histories.
2. We conducted a multi-center study which ensured sufficient power in obtaining the risk factors of EOP.
3. This was a retrospective cohort study, lacking of some objective information such as education level, economic development and living standard, which may cause bias.
4. Our study was lack of the adjustment of different center factors (education, re-training and home visit) in the multivariate analysis.
5. Although this was a multicenter study, the sample size was relatively small.

INTRODUCTION

In developing countries, the number of peritoneal dialysis (PD) patients has been increasing over time.[1 2] Peritoneal dialysis (PD)-related peritonitis is a serious complication during PD therapy and remains the major reason for technique failure.[3] Severe and prolonged peritonitis leads to structural and functional alterations of the peritoneal membrane, eventually leading to peritoneal fibrosis.[4] Therefore, identification of the risk factors for peritonitis in the early stage of PD would help to reduce technique failures and mortality of PD.

The definition of early-onset peritonitis varies widely between studies, which generally refers to peritoneal dialysis related peritonitis occurring within 3-24 months after surgical catheterization.[5-8] Previous studies showed that the first episode of peritonitis in PD patients could significantly affect the prognosis of end-stage renal disease (ESRD) patients.[9] However, few studies have specifically examined the risk factors for peritonitis in the early period of PD. And most of these were observational

cohort studies carried out in single center,[5 10 11] limiting the generalizability of their observed outcomes. To determine the risk factors for early-onset peritonitis in Chinese CKD patients and its influence on patients' technique survival and mortality, we conducted this multiple-center, retrospective cohort study.

METHODS

Study Population

This was a multi-center retrospective cohort study included 357 patients with ESRD who underwent PD in the Department of Nephrology in Baoshan branch of Shanghai First People's Hospital, Shanghai Songjiang District Central Hospital and Shanghai East Hospital, Tongji University School of Medicine. All incident PD patients from June 1, 2006, to May 1, 2018, were recruited and followed up until December 31, 2018. 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). The exclusion criteria were as follows: patients who had been using PD for fewer than 90 days, patients with an age younger than 18 years and patients who initiated PD in other PD centers and previously accepted HD or kidney transplantation. There are 19 PD patients who suffered 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. While these 10 PD patients were lack of the information of peritoneal equilibration test. Patients were followed until any of the following events: death, a change to HD, renal transplantation or until December 31, 2018. According to the Chinese Peritoneal Dialysis Guideline, we adopted standardized surgical

catheterization technique.[12] 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 was downward and outward, and the outer polyester sleeve was 2 to 3 cm away from the exit. All the surgical operations are performed in the operating room. The single dose intravenous antibiotic 30 minutes before surgery is recommended to prevent infection.[13] The first or second generation cephalosporin is suggested.[13 14] According to the ISPD peritonitis recommendations,[13-15] we daily and topically applied mupirocin ointment to the catheter exit site to prevent exit site infection. Patients initiated PD by Dianeal with 1.5% or 2.5% dextrose (Baxter Healthcare, Guangzhou, China). Dialysate concentration was 1.5% dextrose and replaced every four hours during the day, while 2.5% at night and kept in the body. A total of 213 patients who had at least one episode of peritonitis. According to time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (> 6 months, n=139). We collected baseline characteristics within 1-3 months from the start of PD, including demographic data (age, gender, smoking, drinking, CCI, BMI), medical history, drug-taking history, biochemical data (hemoglobin, serum electrolyte, fasting blood glucose, total cholesterol, total triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and serum albumin, uric acid, creatinine, blood urea nitrogen, estimated glomerular filtration rate (eGFR), the clearance rate of urea nitrogen (Kt/V), causes of ESRD, peritonitis episodes. Peritoneal fluid effluent from patients with peritonitis was collected and cultured for 1 to 5 days to identify the bacterial flora in the dialysate.

Primary and secondary outcome measures

Early-onset peritonitis was defined as the first episode of peritonitis occurring within 6 months after the initiation of peritoneal dialysis. This definition is consistent with

other published article.[8] [16] The outcomes were all-cause mortality and technique failure.

Study definitions

Diagnostic criteria for peritonitis are based on the 2010 International Society for Peritoneal Dialysis (ISPD) guidelines.[15] Patients diagnosed as peritonitis should meet at least two of the following three standards: (1) Clinical symptoms or signs of peritonitis; (2) Leucocyte count (at least 100/mm^3) and polymorphonuclear neutrophilic cells proportion (at least 50%) in peritoneal fluid effluent; (3) Related pathogens in smear or culture of peritoneal fluid. Early-onset peritonitis was defined as the first episode of peritonitis occurring within 6 months after the initiation of PD. The outcomes were all-cause mortality and technique failure. Death was an end-point event in the patient survival analysis. Relapse was defined as an episode occurring within 4 weeks of completion of therapy of a prior episode with the same organism,[13] recurrence referred to an episode occurring within 4 weeks of completion of therapy of a prior episode but with a different organism.[13] Instead of transfer to HD therapy permanently, patients with 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.[7] However, some of refractory peritonitis failed to clear up effluent after 5 days of appropriate antibiotics. This population of patients was transferred to HD permanently. We classified this population of patients into “transfer to hemodialysis”. Other population of patients who were transferred to HD were due to the serious tunnel infection with peritonitis and ultrafiltration failure induced by encapsulating peritoneal sclerosis. Patients who transferred to HD were censored from the patient survival analysis, and death was censored for technique failure. Technique failure was defined as the transfer to HD therapy permanently (lasted for 30 days or more) due to ultrafiltration failure, peritonitis, exit-site infection and other operational problems.[17]

Patient and public involvement

No patient was involved in the design or conduct of the study, but the results of the study will be shared to patients coming for follow-up.

Statistical analysis

All statistical analyses were performed by using SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA). The normal distributed data were showed as mean±standard deviation (SD) and the skewed data were showed as median values with the 25th to 75th percentile intervals. Categorical data were expressed as frequency (n) and percentage (%). As for normally distributed data, student's t-test is used for analyzing the differences between the EOP group and LOP group, while one-way ANOVA for differences among in non-peritonitis, EOP group and LOP groups. The Wilcoxon rank sum test for skewed continuous data and the Chi-square test or Fisher's exact test for categorical data. The Kaplan-Meier survival curves were drawn for each event of interest (technique survival and patient survival) and the log-rank test was used to compare curves. Univariate Cox proportional hazards regression was used to select significant factors associated with study outcomes. Variables with $P<0.10$ were selected for inclusion in the final multivariate Cox model. Multivariate logistic regression was calculated to select significant risk factors for EOP and the inclusion standard was also $P<0.10$. Collinearity of variables was tested. A two-tailed P value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 357 patients with ESRD underwent CAPD in three dialysis centers in Shanghai during the study period. All patients used Dianeal with 1.5% or 2.5% dextrose. The first episode of peritonitis was experienced by 74 (20.7%) patients

within 6 months after the start of PD. 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. Median follow-up time for the 357 patients was 33.0 months (interquartile range 14.0-50.0 months). There were 211 males (59.1%) with an average age of 61.6 ± 14.0 years, and 145 females (40.9%) with an average age of 65.3 ± 12.9 years. The most common primary renal diseases were chronic glomerulonephritis (43.1%) and diabetic nephropathy (34.2%). Compared with the LOP patients, the EOP patient group had older ages, more female patients, higher Charlson comorbidity index (CCI) score and lower serum albumin levels, renal function and Kt/V at PD initiation and higher diabetes mellitus (P<0.05). The percentage of patients experienced more than 3 peritonitis episodes in EOP group (55.4%) is higher than LOP group (33.8%). Additional demographic and laboratory characteristics of the study population are presented in Table 1.

Causative organisms

In table 2, among 213 patients with peritonitis, 47 (22.1%) were due to Gram-positive organisms, 24 (11.3%) were due to Gram-negative organisms, 6 (2.8%) were due to fungi, 1 (0.4%) were due to multiple organisms, and 135 (63.4%) were culture-negative. Staphylococcus was the most common Gram-positive organism in both groups. Compared with the EOP patient group, the LOP patient group had more culture-negative peritonitis (89.2% vs. 14.9%, P<0.001). 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).

Outcomes

The total 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). 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). 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).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. Early-onset first episode of peritonitis had a lower cure rate (17.6% vs 33.8%, Table 2.), higher rate of transferring to hemodialysis (27.0% vs 19.4%, Table 2.), and higher mortality (21.6% vs 14.4%, Table 2.) compared to late-onset first episode of peritonitis.

Technique failure

The variables including time to first peritonitis (EOP vs. LOP), age, sex, smoking, drinking, CCI, BMI, hemoglobin, total cholesterol, total triglyceride, serum albumin, total Kt/V and diabetes were calculated into the cox proportional hazards model for technique failure. And we found that EOP was associated with technique failure compared with the LOP group, with a hazard ratio (HR) of 1.801 (Table 3, P=0.051). Kaplan-Meier analysis showed that compared with LOP group, technique survival was lower in the EOP group (Log rank 3.943, P=0.047, Fig.1).

All-cause mortality

During the study period, a total of 52 patients died: 16 patients in the EOP group and 20 patients in the LOP group. Variables with P value < 0.10 in univariate Cox regression analysis, including the time to first peritonitis (EOP vs. LOP), age, serum albumin and total Kt/V, were chosen for further adjustment in multivariate Cox

proportional hazards model. After adjustment, there was no significant difference between the EOP and LOP groups (Table 3). Fig. 2 describes cumulative survival by EOP and LOP groups using the Kaplan-Meier analysis. Compared with LOP group, cumulative survival was lower in the EOP group (Log rank 4.060, *P*=0.044).

Risk factors of early-onset peritonitis

Variables in Table 1 were tried in an univariate logistic regression model, and only variables with *P* value < 0.10 for peritonitis were depicted in Table 4. Based on the simple logistic regression analysis of risk factors associated with EOP, we constructed a multiple logistic regression model using variables including gender, age, CCI score, diabetes, serum albumin and Kt/V. 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 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).

DISCUSSION

Our retrospective cohort study of 357 PD patients showed that 74 (20.7%) patients in three Shanghai dialysis centers developed the first episodes of peritonitis within the first 6 months. Higher CCI score, lower serum albumin level and Kt/V at the start of PD, were significantly associated with EOP. In addition, an early peritonitis onset predicted a high peritonitis rate and technique failure.

Early-onset peritonitis is a major complication of peritoneal dialysis, directly or indirectly causing the abandon of dialysis treatment. In this study, among 213 patients with peritonitis, 47 (22.1%) were due to Gram-positive organisms, 24 (11.3%) were due to Gram-negative organisms, 6 (2.8%) were due to fungi. Staphylococcus was the most common Gram-positive organism in both early-onset and late-onset peritonitis. This bacterial flora distribution and high incidence of staphylococcus were similar to previous reports.[18-20] Fungal peritonitis was rare in PD patients, but could bring out

irreversible peritoneal damage.[21] Recent clinical studies confirmed that the incidence of fungal peritonitis was only 3%-6%,[21] while the relative mortality rate was up to 20%-30%.[22] The culture-negative proportion for the first peritonitis episode was high in the LOP patients (89.2%). And 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). The high culture-negative proportion may primarily attribute to early antibiotic treatment and limited effluent culture technique in small-scale PD units. Before 2014, the technology of blood culture for PD effluent has not been widely adopted by small-scale district hospitals in Shanghai. In the district PD units, 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 chose blood-culture bottle for the preferred technique to culture microorganism in PD effluent. Lacking centrifugation of PD effluent and recent antibiotic usage may be the major reasons for the rest of 40% negative effluent cultures in this investigation. In addition, culture negative peritonitis was higher in LOP than EOP group in the same study period, because LOP patients underwent dialysis more than 6 months and had more experience in peritoneal dialysis. In the early stage of peritonitis， some of experienced PD patients might take dialysate to wash the peritoneum to relieve abdominal pain. Diluted peritoneal fluid would result in a high negative rate of peritoneal effluent culture. 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.[13 14]

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 [5], 0.158 episodes per patient-year in Guangzhou,[7] 0.296 episodes per patient-year in Suzhou [16] and 0.158 per patient-year in Hangzhou [8]. Peritonitis rate in our study is higher than the rest of China. Among the early-onset peritonitis patients who had ≥3 episodes of peritonitis, 25 patients from EOP group experienced recurrent peritonitis, 16 patients from EOP group experienced 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 them are fishermen and live in the Chongming Island. Since the poorer economic abilities and living conditions, they are easy to get malnutrition and suffer from peritonitis again. [23] [24] 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.

The complete cure rate in our study was related low (EOP 17.6%, LOP 33.8%). All the PD patients from these three centers received prophylactic intravenous antibiotics prior to PD catheter insertion. However, 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. [23] [24] 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.

Our study indicated that lower serum albumin was one of the major risk factors for early-onset peritonitis. Loss of protein would cause negative nitrogen balance and

malnutrition, leading to a decline in immune function and increased susceptibility to pathogenic microorganisms.[25] Malnutrition was one of the most common complications in PD patients, and plasma albumin level was an important clinical predictor. Hypoalbuminemia was proved to be related with malnutrition, protein losses, and inflammation.[26 27] Wang Qin et al. discovered that patients with an initial serum albumin level less than 2.9 g/dL had a higher incidence of peritonitis and regarded hypoalbuminemia as an independent predictor for subsequent peritonitis at the start of PD therapy.[28] Further studies demonstrated that low serum albumin level increased all-cause, cardiovascular, and infection related mortality in both PD and HD patients.[29] In addition to peritoneal infection, hypoalbuminemia was also found to be associated with septicemia, pneumonia and other inflammatory responses.[30-34] In this study, we reaffirmed that a low baseline serum albumin level is an independent risk factors for EOP (OR=0.924, 95%CI 0.867-0.985, P=0.016).

Although older age is not an independent risk factor for EOP, baseline data showed that patients in EOP group older than LOP group (65.87±13.20 vs. 61.40±13.53, P=0.022). It was reported that elder patients were more likely to progress to a worse outcome, including HD, renal transplantation or death.[35] Incidence of malnutrition in elderly PD patients was more common than young and middle-aged patients. Together with cardiovascular diseases, cerebrovascular disease, hearing and visual impairments, all of these factors increase and aggravate the episode of peritonitis.[36-38] Malnutrition in elder not only affected the quality of dialysis patients' life, but also was an important factor in comorbidity and mortality.[39] Other elements that increased the peritonitis susceptibility in elderly patients included generalized functional deterioration, weakened immune system,[40] combined chronic diseases, bad eyesight, poor aseptic concept, lack of compliance and living alone. Their atypical clinical symptoms of peritonitis could be regarded as another essential reason. Up-regulated pain threshold, unobtrusive bellyache and mild subjective symptoms might cover up early-onset peritonitis until the occurrence of liquid

turbidity, which would delay the best time for treatment.

Comparison in biochemical indicators revealed that Kt/V and residual renal function decreased significantly after early-onset peritonitis. Multivariate logistic regression showed that a lower total Kt/V (OR=0.600, 95%CI 0.394-0.915, P=0.018) at the start of PD was associated with EOP. These results suggest that early infection with peritonitis might further worsen renal function, especially the scavenging capacity of solutes by residual kidney. Early inflammatory response and renal function damage might be the underlying causes of peritonitis. Some studies suggested that the survival rate of PD patients depends more on residual renal function than the peritoneal cleaning capacity.[41-43] Harris et al. further put forward that residual renal function less than 4 $ml \cdot min^{-1} \cdot 1.73m^{-2}$ was associated with high mortality during peritoneal dialysis.[44] Therefore, we should pay close attention to the change of residual renal function when monitoring the adequacy of dialysis.

The relationship between peritonitis and technique failure and death have been investigated in previous Chinese single-center studies.[7 8] A study in Chinese Zhejiang province showed that, EOP was a significant predictor of all-cause mortality. As for technique failure, they found no significant difference between EOP and LOP.[8] However, a study in Chinese Guangzhou province indicated that technique failure in EOP group was lower than LOP group, but patient survival did not differ between two groups.[7] Our present study showed that EOP was more likely a predictor of technique failure (HR=1.801, 95%CI 0.996-3.257, P=0.051). There was no difference between EOP and LOP for all-cause mortality. These conclusions might be limited by regional and demographic differences in different dialysis centers. However, all three studies indicated that patients who experienced peritonitis early after the initiation of PD tend to experience more episodes of peritonitis. Repeating peritonitis in EOP patients not only injury membrane permeability and reduce ultrafiltration, but also increase severe systemic inflammation, leading to worse clinical outcomes.[45] Thus, appropriately dealing with the risk factors of early-onset peritonitis will be good to reduce infection

incidence, raise therapeutic effect of PD and improve patient's life quality and prognosis.

There are several limitations to this study. Firstly, this was a retrospective cohort study, lacking of some objective information such as education level, economic development and living standard, which may cause bias. Secondly, our study lacked of the adjustment of different center factors (education, re-training and home visit) in the multivariate analysis. Thirdly, although this was a multicenter study, the sample size was relatively small. Further larger size and prospective investigation are necessary.

CONCLUSION

This retrospective cohort study found that a higher CCI score and lower serum albumin and Kt/V at PD initiation were significantly associated with EOP. In addition, an early peritonitis onset predicted a high peritonitis rate and worse clinical outcomes. Understanding the risk factors for EOP will help to develop effective measures to prevent or delay the complication of peritoneal dialysis as much as possible.

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Author Contributors

X.M., Y.S. M.T. and X.J. contributed equally to this work. X.M., Y.S. M.T. and X.J. performed the statistical analysis and wrote the manuscript; X.M., Y.S., M.T., X.J., Y.W., D.J., L.F., W.J., L.D. and X.Z. participated in the data collection; X.M., Y.S.,

S.Z. and N.L. contributed to discussion; X.M., S.Z. and N.L. participated in the design of the study and edited the manuscript. All authors contributed to data interpretation and revisions of the manuscript critically for important intellectual content. All authors approved the final version of the submitted manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of work are appropriately investigated and resolved.

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Competing interests None declared.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Helsinki Declaration and was approved by 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. 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.

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Table 1.Baseline characteristic of the study population

Variable	Peritonitis-free (N=144)	EOP (N=74)	LOP (N=139)	P value between EOP and LOP	P value
Age (years)	63.18±13.91	65.87±13.20	61.40±13.53	0.022	0.075
Gender (male, n, %)	84 (58.3)	37 (50.0)	90 (64.7)	0.037	0.135
Smoking (%)	40 (27.8)	22 (29.7)	31 (22.3)	0.233	0.415
Drinking (%)	31 (21.5)	20 (27.0)	32 (23.0)	0.517	0.659
Charlson comorbidity index score	3.76±1.51	5.73±2.17	4.42±1.93	<0.001	<0.001
Body mass index (kg/m^2)	23.55±3.76	24.19±3.31	24.32±3.38	0.791	0.174
Hemoglobin (g/L)	83.67±17.70	89.10±22.90	88.53±19.77	0.849	0.059
Serum calcium (mmol/L)	1.98±0.29	2.14±0.41	2.11±0.33	0.514	0.001
Serum phosphorus (mmol/L)	1.77±0.55	1.91±0.61	1.83±0.78	0.457	0.349
Serum potassium (mmol/L)	4.39±0.65	4.41±0.74	4.39±0.80	0.865	0.980
Fasting blood glucose (mmol/L)	5.38±2.01	6.49±2.93	6.09±2.10	0.261	0.001
TC (mmol/L)	4.02 (3.36, 5.11)	4.59 (3.54, 6.06)	4.43 (3.57, 5.70)	0.537	0.022
TG (mmol/L)	1.28 (0.97, 1.74)	1.30 (1.00, 2.39)	1.24 (1.00, 2.17)	0.469	0.430
HDL-C (mmol/L)	1.11 (0.85, 1.33)	1.18 (0.97, 1.43)	1.19 (0.98, 1.48)	0.740	0.042
LDL-C (mmol/L)	2.44 (1.94, 3.11)	2.65 (2.01, 3.25)	2.38 (2.00, 3.09)	0.238	0.473
Serum albumin (g/L)	33.26±6.26	30.01±7.15	33.37±4.92	<0.001	<0.001
Serum uric acid (mmol/L)	516.93±142.32	495.46±183.30	536.48±185.05	0.124	0.231
Serum creatinine (μmol/L)	659.74±185.48	749.77±268.11	660.42±302.69	0.034	0.027
Blood urea nitrogen (mmol/L)	24.49±7.72	25.69±10.73	24.51±9.85	0.421	0.616
eGFR (ml/min/1.73 m^2)	8.49±3.25	6.84±3.82	8.48±4.13	0.005	0.003
Total Kt/V	2.31 (1.98, 2.56)	2.10 (1.71, 2.54)	2.33 (1.93, 3.04)	0.008	0.012
Diabetes mellitus(%)	64 (44.4)	54 (73.0)	79 (56.8)	0.021	<0.001
Hypertension (%)	126 (87.5)	66 (89.2)	116 (83.5)	0.258	0.439
Dyslipidemia (%)	54 (37.5)	41 (55.4)	74 (53.2)	0.762	0.009
Cardiovascular disease (%)	43 (29.9)	30 (40.5)	51 (36.7)	0.582	0.241
Cerebrovascular disease (%)	21 (14.6)	30 (40.5)	55 (39.6)	0.890	<0.001
Calcium	90 (62.5)	44 (59.5)	72 (51.8)	0.285	0.179
Iron	73 (50.7)	41 (55.4)	68 (48.9)	0.367	0.664
Anti-diabetic medications (%)	54 (37.5)	38 (51.4)	46 (33.1)	0.009	0.031
Anti-hypertension medications (%)	124 (86.1)	65 (87.8)	112 (80.6)	0.178	0.284
Lipid-lowering medications (%)	38 (26.4)	36 (48.6)	61 (43.9)	0.506	0.001
Cause of ESKD				0.182	0.008
Glomerulonephritis (%)	57 (39.6)	29 (39.2)	68 (48.9)		
Diabetes (%)	42 (29.2)	34 (45.9)	46 (33.1)		

Other (%)	45 (31.3)	11 (14.9)	25 (18.0)		
Peritonitis episodes (%)				0.006	0.006
1		17 (23.0)	57 (41.0)		
2		16 (21.6)	35 (25.2)		
≥3		41 (55.4)	47 (33.8)		

EOP, early-onset peritonitis; LOP, late-onset peritonitis; TC, total cholesterol; TG total triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GFR, glomerular filtration rate; ESKD, end stage kidney disease

Table 2. Organism and outcome of different vintages of peritonitis (n, %)

Causative organisms	Early-onset peritonitis episodes (n)	Late-onset peritonitis episodes (n)	P value
Causative organisms			
Gram-positive organisms	38 (51.4)	9 (6.5)	<0.001
Staphylococcus aureus	7 (18.4)	0 (0.0)	0.163
Coagulase-negative	3 (7.9)	0 (0.0)	0.384
Staphylococcus	16 (42.1)	8 (88.9)	0.012
Streptococcus species	4 (10.5)	1 (11.1)	0.959
Enterococcus species	4 (10.5)	0 (0.0)	0.309
Other Gram-positives	4 (10.5)	0 (0.0)	0.309
Gram-negative organisms	20 (27.0)	4 (2.9)	<0.001
Escherichia coli	8 (40.0)	0 (0.0)	0.121
Klebsiella species	6 (30.0)	1 (25.0)	0.841
Acinetobacter species	4 (20.0)	1 (25.0)	0.822
Pseudomonas Aeruginosa	2 (10.0)	1 (25.0)	0.408
Other Gram-negatives	0 (0.0)	1 (25.0)	0.022
Fungi	4 (5.4)	2 (1.4)	0.096
Multiple organisms	1 (1.4)	0 (0.0)	0.170
Culture-negative peritonitis	11 (14.9)	124 (89.2)	<0.001
Outcomes			0.063
Complete cure	13 (17.6)	47 (33.8)	
Relapse or recurrence	25 (33.8)	45 (32.4)	
Transfer to hemodialysis	20 (27.0)	27 (19.4)	
Death	16 (21.6)	20 (14.4)	

Table 3. Cox proportional hazards model for technique failure and patient mortality.

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)	1.801	0.996-3.257	0.051	1.801	0.996-3.257	0.051
Age (year)	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			
Total Kt/V	1.008	0.737-1.379	0.959			
Diabetes (yes vs. no)	1.383	0.742-2.579	0.307			
Patient mortality						
Time to first peritonitis (EOP vs. LOP)	1.968	1.006-3.851	0.048	1.010	0.391-2.606	0.984
Age (year)	1.037	1.014-1.061	0.002	1.002	0.973-1.031	0.917
Sex (men vs. women)	0.862	0.498-1.492	0.596			
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	0.999	0.878-1.138	0.990			
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)	0.949	0.907-0.993	0.025	0.965	0.897-1.039	0.346
Total Kt/V	0.650	0.409-1.033	0.069	0.683	0.425-1.099	0.116
Diabetes (yes vs. no)	1.176	0.672-2.057	0.570			

Table 4. Logistic regression analysis of factors associated with early-onset peritonitis

Variable	Univariate logistic regression analysis			Multivariate logistic regression analysis		
	OR	(95%CI)	P value	OR	(95%CI)	P value
Sex (men vs. women)	0.544	0.307-0.966	0.038	0.586	0.295-1.163	0.126
Age (year)	1.026	1.004-1.049	0.023	1.020	0.994-1.046	0.131
Charlson comorbidity index score	1.355	1.173-1.566	<0.001	1.285	1.058-1.561	0.011
Diabetes	2.051	1.111-3.786	0.022	1.084	0.457-2.571	0.854
Serum albumin (g/L)	0.901	0.853-0.951	<0.001	0.924	0.867-0.985	0.016
Total Kt/V	0.553	0.370-0.827	0.004	0.600	0.394-0.915	0.018

Figure legends

Fig.1. Technique survival according to EOP and LOP.

Death were censored form the technique survival analysis. Log rank test Chi-square 3.943, *P*=0.047

Fig.2. Patient survival according to EOP and LOP.

Patients who transferred to HD were censored form the patient survival analysis. Log rank test Chi-square 4.060, *P*=0.044

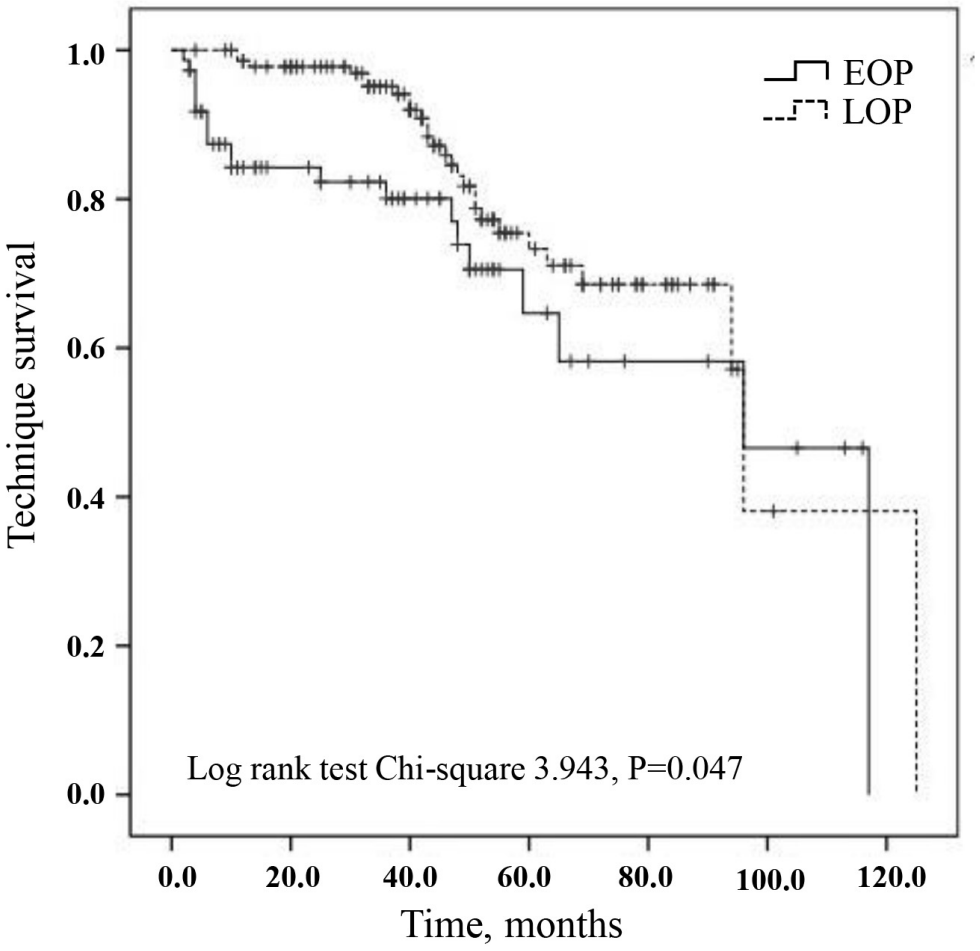

Fig.1. Technique survival according to EOP and LOP.
Death were censored form the technique survival analysis. Log rank test Chi-square 3.943, P=0.047

113x111mm (300 x 300 DPI)

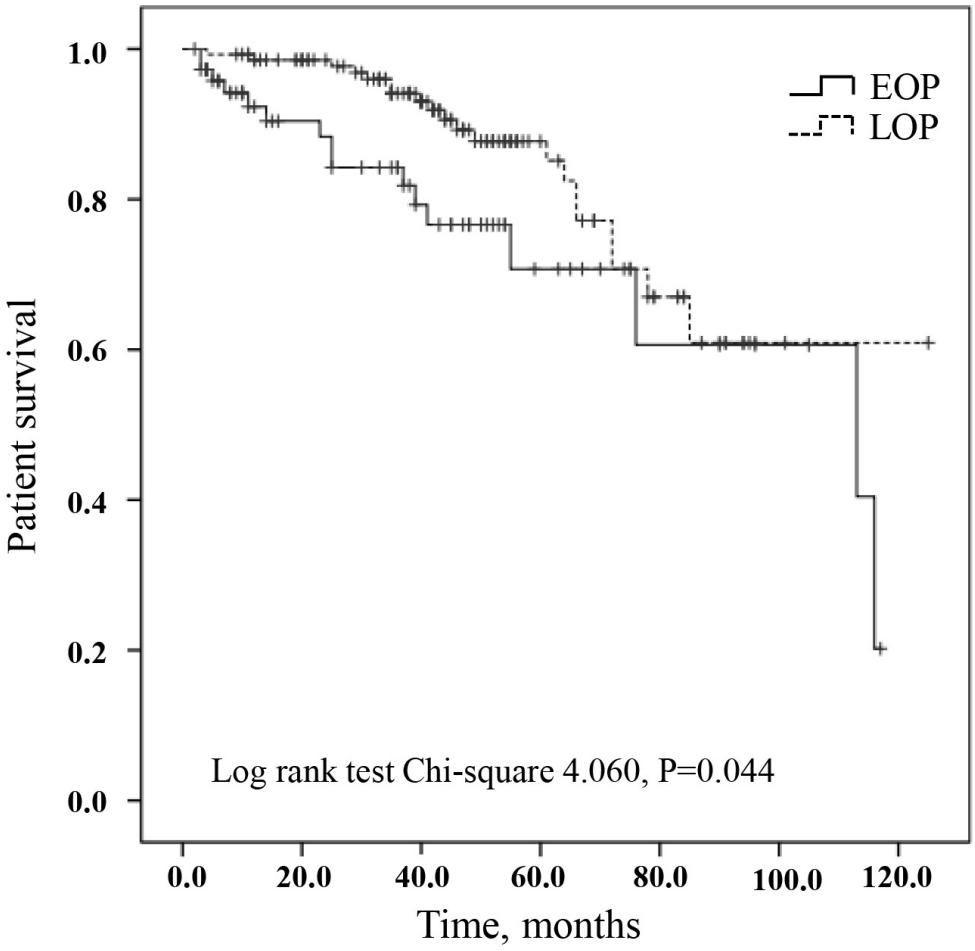

Fig.2. Patient survival according to EOP and LOP.
Patients who transferred to HD were censored form the patient survival analysis. Log rank test Chi-square 4.060, P=0.044

111x108mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	The analysis of risk factors and outcome in peritoneal dialysis patients with early-onset peritonitis: a multi-center, retrospective, cohort study.	1
		Objectives To investigate the risk factors associated with early-onset peritonitis (EOP) and its influence on patients' technique survival and mortality. **Study design** Retrospective, cohort study. **Setting** Three peritoneal dialysis units in Shanghai. **Participants** PD patients from June 1, 2006, to May 1, 2018, were recruited and followed up until December 31, 2018. According to time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139). **Primary and secondary outcome measures** EOP was defined as the first episode of peritonitis occurring within 6 months after the initiation of peritoneal dialysis (PD). The outcomes were all-cause mortality and technique failure. **Results** Of the 357 patients, 74 (20.7%) patients developed their first episode of peritonitis within the first 6 months. Compared with the LOP group, the EOP group had older ages, more female patients, higher Charlson comorbidity index (CCI) score, lower serum albumin levels and renal function at the time of initiation of PD and higher diabetes mellitus and peritonitis rates (P<0.05). Staphylococcus was the most common Gram-positive organism in both EOP and LOP groups. The multivariate logistic regression analysis showed that factors associated with EOP included a higher CCI score (odds ratio (OR) 1.285, P=0.011), lower serum albumin level (OR 0.924, P=0.016) and lower Kt/V (OR 0.600, P=0.018) at start of PD. In the Cox proportional hazards model, EOP was more likely a predictor of technique failure (hazard ratio (HR) 1.801, P=0.051). There was no difference between EOP and LOP for all-cause mortality. **Conclusion** A higher CCI score and lower serum albumin level and Kt/V at PD initiation were significantly associated with EOP. EOP also predicted a high peritonitis rate and poor clinical outcomes.	2
Introduction			
Background/rationale	2	The definition of early-onset peritonitis varies widely between studies, which generally refers to peritoneal dialysis related peritonitis occurring within 3-24 months after surgical catheterization.[5-8] Previous studies showed that the first episode of peritonitis in PD patients could significantly affect the prognosis of end-stage renal disease (ESRD) patients.[9] However, few studies have specifically examined the risk factors for peritonitis in the early PD period. And most of these were observational cohort studies carried out in single centers,[5 10 11] limiting the generalizability of their observed outcomes. To	4

		determine the risk factors for early-onset peritonitis in Chinese CKD patients and its influence on patients' technique survival and mortality, we conducted this multiple-center, retrospective cohort study.	
Objectives	3	PD patients from June 1, 2006, to May 1, 2018, were recruited and followed up until December 31, 2018. According to time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139).	4
Methods			
Study design	4	Retrospective, cohort study.	4
Setting	5	Three peritoneal dialysis units in Shanghai.	4
Participants	6	This was a multi-center retrospective cohort study included 357 patients with ESRD who underwent PD in Department of Nephrology in Baoshan branch of Shanghai First People's Hospital, Shanghai Songjiang District Central Hospital and Shanghai East Hospital, Tongji University School of Medicine. All incident PD patients from June 1, 2006, to May 1, 2018, were recruited and followed up until December 31, 2018. The exclusion criteria were as follows: patients who had been using PD for fewer than 90 days, patients with an age younger than 18 years and patients who initiated PD in other PD centers and previously accepted HD or kidney transplantation.	4
		According to time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139).	4
Variables	7	We collected baseline characteristics within 1-3 months from the start of PD, including demographic data (age, gender, smoking, drinking, CCI, BMI), medical history, drug-taking history, biochemical data (hemoglobin, serum electrolyte, fasting blood glucose, total cholesterol, total triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and serum albumin, uric acid, creatinine, blood urea nitrogen, estimated glomerular filtration rate (eGFR), the clearance rate of urea nitrogen (Kt/V), cause of ESRD, peritonitis episodes. Peritoneal fluid effluent from patients with peritonitis was collected and cultured for 1 to 5 days to identify the bacterial flora in the dialysate.	6
Data sources/ measurement	8*	Peritoneal fluid effluent from patients with peritonitis was collected and cultured for 1 to 5 days to identify the bacterial flora in the dialysate.	*6*
Bias	9	This was a retrospective cohort study, lacking of some objective information such as education level, economic development and living standard, which may cause bias.	3
Study size	10	357 PD patients	4
Quantitative variables	11	The normal distributed data were showed as mean±standard deviation (SD) and the skewed data were showed as median values with the 25th to 75th percentile intervals. As for normally distributed data, student's t-test is using for analyzing the differences between the EOP group and LOP group, while one-way ANOVA for differences among in non-peritonitis, EOP group and LOP groups. The Wilcoxon rank sum test for skewed continuous data.	7

Statistical methods	12	All statistical analyses were performed by SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA). The normal distributed data were showed as mean±standard deviation (SD) and the skewed data were showed as median values with the 25th to 75th percentile intervals. Categorical data were expressed as frequency (n) and percentage (%). As for normally distributed data, student's t-test is using for analyzing the differences between the EOP group and LOP group, while one-way ANOVA for differences among in non-peritonitis, EOP group and LOP groups. The Wilcoxon rank sum test for skewed continuous data and the Chi-square test or Fisher's exact test for categorical data. The Kaplan-Meier survival curves were drawn for each event of interest (technique survival and patient survival) and the log-rank test was used to compare curves. Univariate Cox proportional hazards regression was used to select significant factors associated with study outcomes. Variables whose *P*<0.10 were selected for inclusion in the final multivariate Cox model. Multivariate logistic regression was calculated to select significant risk factors for EOP and the inclusion standard was also *P*<0.10. Collinearity of variables was tested. A two-tailed *P* value <0.05 was considered statistically significant.	7
Results			
Participants	13*	The first episode of peritonitis was experienced by 74 (20.7%) patients within 6 months after the start of PD. 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. 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. While these 10 PD patients lacked of the information of peritoneal equilibration test.	8
Descriptive data	14*	Median follow-up time for the 357 patients was 33.0 months (interquartile range 14.0-50.0 months). There were 211 males (59.1%) with an average age of 61.6 ± 14.0 years, and 145 females (40.9%) with an average age of 65.3 ± 12.9 years. The most common primary renal diseases were chronic glomerulonephritis (43.1%) and diabetic nephropathy (34.2%). Compared with the LOP patients, the EOP patient group had older ages, more female patients, higher Charlson comorbidity index (CCI) score and lower serum albumin levels, renal function and Kt/V at the time of initiation of PD and higher diabetes mellitus and peritonitis rates (*P*<0.05).	8
Outcome data	15*	Of the 357 patients, 74 (20.7%) patients developed their first episode of peritonitis within the first 6 months. Compared with the LOP group, the EOP group had older ages, more female patients, higher Charlson comorbidity index (CCI) score, lower serum albumin levels and renal function at the time of initiation of PD and higher diabetes mellitus and peritonitis rates (*P*<0.05). Staphylococcus was the most common Gram-positive organism in both EOP and LOP groups.	8-9
Main results	16	The multivariate logistic regression analysis showed that factors associated with EOP included a higher CCI score (odds ratio (OR) 1.285, *P*=0.011), lower serum albumin level (OR 0.924, *P*=0.016) and lower Kt/V (OR 0.600, *P*=0.018) at start of PD. In the Cox proportional hazards model, EOP was more likely a predictor of technique failure (hazard ratio (HR) 1.801, *P*=0.051). There was no difference between EOP and LOP for all-cause mortality.	9-10

Other analyses	17	EOP was defined as the first episode of peritonitis occurring within 3 months. 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).	
Discussion			
Key results	18	A higher CCI score and lower serum albumin level and Kt/V at PD initiation were significantly associated with EOP. EOP also predicted a high peritonitis rate and poor clinical outcomes.	10
Limitations			
Interpretation	20	This was a retrospective cohort study, lacking of some objective information such as education level, economic development and living standard, which may cause bias. Second, although this was a multicenter study, the sample size was relatively small. Further larger size and prospective investigation are necessary.	14
Generalisability	21	There is a strict exclusion criteria based on PD histories. We conducted a multi-center study which ensured sufficient power in obtaining the risk factors of EOP.	14
Other information			
Funding	22	This study was supported by the National Nature Science Foundation of China grants (81670690, 81470991 and 81200492 to N.L., 81270778, 81470920, 81670623 and 81830021 to S.Z.), the Key Discipline Construction Project of Pudong Health Bureau of Shanghai (PWZxk2017-05 to N.L.), the Science Technology grant of Jiangxi Province Municipal Health Commision (20184077 to L.F.), the Branch grant of National key grants of Ministry of Science and Technology (2018YFA0108802 to S.Z.), the US National Institutes of Health (2R01DK08506505A1 to S.Z.), the Shanghai Scientific Committee of China (13PJ1406900 to N.L.).	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.