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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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4 1 **The analysis of risk factors and outcome in peritoneal dialysis patients with**
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6 2 **early-onset peritonitis: a multi-center, retrospective, cohort study.**

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4 29 **ABSTRACT**

5 30 **Objectives** To investigate the risk factors associated with EOP and its influence on
6
7 31 patients' technique survival and mortality in Shanghai.

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9 32 **Study design** Retrospective, cohort study.

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11 33 **Setting** Three peritoneal dialysis centers in Shanghai.

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13 34 **Participants** PD patients from June 1, 2006, to May 1, 2018, were recruited and
14
15 35 followed up until December 31, 2018. According to time-to-first episode of
16
17 36 peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis
18
19 37 (≤ 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139).

20
21 38 **Primary and secondary outcome measures** Early-onset peritonitis was defined as
22
23 39 the first episode of peritonitis occurring within 6 months after the initiation of
24
25 40 peritoneal dialysis (PD). The outcomes were all-cause mortality and technique failure.

26
27 41 **Results** Of the 357 patients, 74 (20.7%) patients developed their first episode of
28
29 42 peritonitis within the first 6 months. Compared with the LOP group, the EOP group
30
31 43 had older ages, more female patients, higher Charlson comorbidity index (CCI) score
32
33 44 and white blood cell levels, lower serum albumin levels and renal function at the time
34
35 45 of initiation of PD and higher diabetes mellitus and peritonitis rates ($P<0.05$).
36
37 46 Staphylococcus was the most common Gram-positive organism in both EOP and LOP
38
39 47 groups. The multivariate logistic regression analysis showed that factors associated
40
41 48 with EOP included older age (odds ratio (OR) 1.027, $P=0.041$), a higher CCI score
42
43 49 (OR 1.298, $P=0.008$), low serum albumin level (OR 0.929, $P=0.015$) and low eGFR
44
45 50 (OR 0.907, $P=0.046$) at start of PD. In the Cox proportional hazards model, EOP was
46
47 51 a significant predictor of technique failure (hazard ratio (HR) 1.664, $P=0.048$). There
48
49 52 were no differences between EOP and LOP for all-cause mortality.

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51 53 **Conclusion** Older age, a higher CCI score and lower serum albumin level and eGFR
52
53 54 before PD were significantly associated with EOP. EOP also predicted a high
54
55 55 peritonitis rate and poor clinical outcomes.

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4 57 **KEY WORDS** Peritoneal dialysis; Early-onset peritonitis; Risk factors; Outcomes.
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11 59 **ARTICLE SUMMARY**

12 60 **Article focus**

- 13 61 ● The risk factors associated with EOP and its influence on patients' technique
14
15 62 survival and mortality in Shanghai.

16 63 **Key messages**

- 17
18 64 ● Older age, a higher CCI score and lower serum albumin level and eGFR before
19
20 65 PD were significantly associated with EOP.
21
22 66 ● EOP predicted a high peritonitis rate and poor clinical outcomes.
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29 67 **Strengths and limitations of this study**

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31 68 ● There is a strict exclusion criteria based on PD histories.
32
33 69 ● We conducted a multi-center study which ensured sufficient power in obtaining
34
35 70 the risk factors of EOP.
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37 71 ● This was a retrospective cohort study, lacking of some objective information such
38
39 72 as medical level, economic development and living standard, which may cause
40
41 73 bias.
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43 74 ● The study did not compare the risk factors of EOP between male and female
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45 75 patients.
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47 76 ● Although this was a multicenter study, the sample size was relatively small.
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79 INTRODUCTION

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

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

98 METHODS

99 Study Population

100 This was a multi-center retrospective cohort study included 357 patients with ESRD
101 who underwent PD in Department of Nephrology in Baoshan branch of Shanghai
102 First People's Hospital, Shanghai Songjiang District Central Hospital and Shanghai
103 East Hospital, Tongji University School of Medicine. All incident PD patients from
104 June 1, 2006, to May 1, 2018, were recruited and followed up until December 31,
105 2018. They agreed to take part in the survey and provided informed consents. The
106 exclusion criteria were as follows: patients who had been using PD for fewer than 90
107 days, patients with an age younger than 18 years and patients who initiated PD in

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4 108 other PD centers and previously accepted HD or kidney transplantation. Patients were
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6 109 followed until any of the following events: death, a change to HD, renal
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8 110 transplantation or until December 31, 2018. Dialysis catheters were placed through
9
10 111 sterile surgical techniques, patients initiated PD by Dianeal with 1.5% or 2.5%
11
12 112 dextrose (Baxter Healthcare, Guangzhou, China). Dialysate concentration was 1.5%
13
14 113 dextrose and replaced every four hours during the day, while 2.5% at night and kept
15
16 114 in the body. Mupirocin ointment was used in every patient to prevent exit site
17
18 115 infection. A total of 213 patients who had at least one episode of peritonitis.
19
20 116 According to time-to-first episode of peritonitis, patients were divided into
21
22 117 non-peritonitis (n=144), early-onset peritonitis (≤ 6 months, n=74) and late-onset
23
24 118 peritonitis (> 6 months, n=139). We collected baseline characteristics within 1-3
25
26 119 months from the start of PD, including demographic data (age, gender, smoking,
27
28 120 drinking, CCI, BMI), medical history, drug-taking history, biochemical data (white
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30 121 blood cell, hemoglobin, serum electrolyte, fasting blood glucose, total cholesterol,
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32 122 total triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein
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34 123 cholesterol, and serum albumin, uric acid, creatinine, blood urea nitrogen, estimated
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36 124 glomerular filtration rate (eGFR), the clearance rate of urea nitrogen (Kt/V), residual
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38 125 renal function (RRF)), cause of ESRD, peritonitis episodes. Peritoneal fluid effluent
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40 126 from patients with peritonitis was collected and cultured for 1 to 5 days to identify the
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42 127 bacterial flora in the dialysate.
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129 **Primary and secondary outcome measures**

48 130 Early-onset peritonitis was defined as the first episode of peritonitis occurring within
49
50 131 6 months after the initiation of peritoneal dialysis (PD). The outcomes were all-cause
51
52 132 mortality and technique failure.
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56 134 **Study definitions**

58 135 Diagnostic criteria for peritonitis based on the 2010 International Society for
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4 136 Peritoneal Dialysis (ISPD) guidelines.⁶ Patients diagnosed as peritonitis should meet
5
6 137 at least two of the following three standards: (1) Clinical symptoms or signs of
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8 138 peritonitis; (2) Leucocyte count (at least 100/mm³) and polymorphonuclear
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10 139 neutrophilic cells proportion (at least 50%) in peritoneal fluid effluent; (3) Related
11
12 140 pathogens in smear or culture of peritoneal fluid. Early-onset peritonitis was defined
13
14 141 as the first episode of peritonitis occurring within 6 months after the initiation of PD.
15
16 142 The outcomes were all-cause mortality and technique failure. Death was an end-point
17
18 143 event in the patient survival analysis. Switching to HD or receiving renal
19
20 144 transplantation were censored. Technique failure was defined as the transfer to HD
21
22 145 therapy permanently due to ultrafiltration failure, peritonitis, exit-site infection and
23
24 146 other operational problems.
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28 148 **Patient and public involvement**

29
30 149 No patient was involved in the design or conduct of the study, but the results of the
31
32 150 study will be shared to patients coming for follow-up.
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36 152 **Statistical analysis**

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38 153 All statistical analyses were performed by SPSS 20.0 for Windows (IBM Corp.,
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40 154 Armonk, NY, USA). The normal distributed data were showed as mean±standard
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42 155 deviation (SD) and the skewed data were showed as median values with the 25th to
43
44 156 75th percentile intervals. Categorical data were expressed as frequency (n) and
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46 157 percentage (%). As for normally distributed data, student's t-test is using for
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48 158 analyzing the differences between the EOP group and LOP group, while one-way
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50 159 ANOVA for differences among in non-peritonitis, EOP group and LOP groups. The
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52 160 Wilcoxon rank sum test for skewed continuous data and the Chi-square test or
53
54 161 Fisher's exact test for categorical data. The Kaplan-Meier survival curves were drawn
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56 162 for each event of interest (technique survival and patient survival) and the log-rank
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58 163 test was used to compare curves. Univariate Cox proportional hazards regression was
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4 164 used to select significant factors associated with study outcomes. Variables whose
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6 165 $P < 0.05$ were selected for inclusion in the final multivariate Cox model. Multivariate
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8 166 logistic regression was calculated to select significant risk factors for EOP and the
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10 167 inclusion standard was also $P < 0.05$. Collinearity of variables was tested. A two-tailed
11
12 168 P value < 0.05 was considered statistically significant.

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15 16 170 **RESULTS**

17 18 171 **Patient Characteristics**

19
20 172 A total of 357 patients with ESRD underwent CAPD in three dialysis centers in
21
22 173 Shanghai during the study period. All patients used Dianeal with 1.5% or 2.5%
23
24 174 dextrose. The first episode of peritonitis was experienced by 74 (20.7%) patients
25
26 175 within 6 months after the start of PD. Median follow-up time for the 357 patients was
27
28 176 33.0 months (interquartile range 14.0-50.0 months). There were 211 males (59.1%)
29
30 177 with an average age of 61.6 ± 14.0 years, and 145 females (40.9%) with an average
31
32 178 age of 65.3 ± 12.9 years. The most common primary renal diseases were chronic
33
34 179 glomerulonephritis (43.1%) and diabetic nephropathy (34.2%). Compared with the
35
36 180 LOP patients, the EOP patient group had older ages, more female patients, higher
37
38 181 Charlson comorbidity index (CCI) score and white blood cell levels, lower serum
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40 182 albumin levels and renal function at the time of initiation of PD and higher diabetes
41
42 183 mellitus and peritonitis rates ($P < 0.05$). Additional demographic and laboratory
43
44 184 characteristics of the study population are present in Table 1.

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47 48 186 **Causative organisms**

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50 187 In table 2, among 213 patients with peritonitis, 47 (22.1%) were due to Gram-positive
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52 188 organisms, 24 (11.3%) were due to Gram-negative organisms, 6 (2.8%) were due to
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54 189 fungi, 1 (0.4%) were due to multiple organisms, and 135 (63.4%) were
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56 190 culture-negative. Staphylococcus was the most common Gram-positive organism in
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58 191 both groups. Compared with the EOP patient group, the LOP patient group had more

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4 192 culture-negative peritonitis (89.2% vs. 14.9%, $P < 0.001$).

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8 194 **Outcomes**

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10 195 The total peritonitis rate was 0.660 episodes per patient-year (213 patients presented
11 196 509 episodes of peritonitis during 771.33 patient-years of follow-up). Early-onset first
12 197 episode of peritonitis had a lower cure rate (17.6% vs 33.8%, Table 2.), higher rate of
13 198 transferring to hemodialysis (27.0% vs 19.4%, Table 2.), and higher mortality (21.6%
14 199 vs 14.4%, Table 2.) compared to late-onset first episode of peritonitis.

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18 201 **Technique failure**

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20 202 After adjusting for serum albumin, age in the multivariate Cox analysis for technique
21 203 failure, EOP was significantly associated with technique failure compared with the
22 204 LOP group, with a hazard ratio (HR) of 1.664 (Table 3, $P = 0.048$). Kaplan-Meier
23 205 analysis showed that compared with LOP group, technique survival was lower in the
24 206 EOP group (log rank 7.985, $P = 0.005$, Fig.1).

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28 208 **All-cause mortality**

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30 209 During the study period, a total of 52 peritonitis patients died: 16 patients in the EOP
31 210 group and 20 patients in the LOP group. After adjusting for age and serum albumin,
32 211 there were no significant differences between the EOP and LOP groups in the
33 212 multivariate Cox proportional hazards model (Table 3). Fig. 2 describes cumulative
34 213 survival by EOP and LOP groups using the Kaplan-Meier analysis. Compared with
35 214 LOP group, cumulative survival was lower in the EOP group (log rank 4.060,
36 215 $P = 0.044$).

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40 217 **Risk factors of early-onset peritonitis**

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42 218 Variables in Table 1 were tried in a univariate logistic regression model, and only
43 219 variables with P value < 0.10 or traditional risk factors for peritonitis were depicted in
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4 220 Table 4. Based on the simple logistic regression analysis of risk factors associated
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6 221 with EOP (Table 4), we constructed a multiple logistic regression model using
7
8 222 variables including gender, age, CCI score, diabetes, serum albumin, eGFR. We
9
10 223 found that older age, higher CCI score, lower serum albumin level and eGFR at the
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12 224 start of PD, were significantly associated with EOP (Table 4). Every 1 year increase
13
14 225 in age improved the risk of EOP by 2.7% (OR 1.027, P=0.041). Every 1 score
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16 226 increase in the CCI improved the risk of EOP by 26.1% (OR 1.298, P=0.008). Every
17
18 227 1 g/L increase in the baseline serum albumin level lowered the risk of EOP by 7.4%
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20 228 (OR 0.929, P=0.015). Every 1 ml/min/1.73 m² increase in the eGFR lowered the risk
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22 229 of EOP by 9.8% (OR 0.907, P=0.046).

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25 26 231 **DISCUSSION**

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29 232 Our retrospective cohort study of 357 PD patients showed that 74 (20.7%) patients in
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31 233 three Shanghai dialysis centers developed the first episodes of peritonitis within the
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33 234 first 6 months. Older age, higher CCI score, lower serum albumin level and eGFR at
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35 235 the start of PD, were significantly associated with EOP. In addition, an early
36
37 236 peritonitis onset predicted a high peritonitis rate and technique failure.

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39 237 Early-onset peritonitis is a major complication of peritoneal dialysis, directly or
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41 238 indirectly causing the abandon of dialysis treatment. In this study, among 213 patients
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43 239 with peritonitis, 47 (22.1%) were due to Gram-positive organisms, 24 (11.3%) were
44
45 240 due to Gram-negative organisms, 6 (2.8%) were due to fungi. Staphylococcus was the
46
47 241 most common Gram-positive organism in both early-onset and late-onset peritonitis.
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49 242 This bacterial flora distribution and high incidence of staphylococcus were similar to
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51 243 previous reports.¹⁰⁻¹² Fungal peritonitis was rare in PD patients, but could bring out
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53 244 irreversible peritoneal damage.¹³ Recent clinical studies confirmed that the incidence
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55 245 of fungal peritonitis was only 3%-6%,¹³ while the relative mortality rate was up to
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57 246 20%-30%.¹⁴ The culture-negative proportion for the first peritonitis episode was high
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59 247 in the LOP patients (89.2%). This may primary attributed to early antibiotic treatment
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4 248 before effluent culture, especially in these patients who have received therapy at the
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6 249 early stage of peritonitis in local hospitals. Several ways that pathogenic bacteria
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8 250 intruded into peritoneal: dialysis catheter, dialysis catheter outlet and subcutaneous
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10 251 tunnel, intestinal infection and hematogenous peritonitis. Thus, standardized dialysis
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12 252 catheter procedures and individualized antibiotics treatment are called to reduce the
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14 253 incidence of peritonitis.

15
16 254 It was well known that PD patients lost about 10 g of protein per day from
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18 255 abdominal cavity, especially when combined with early-onset peritonitis. Loss of
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20 256 protein would cause negative nitrogen balance and malnutrition, leading to a decline
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22 257 in immune function and increased susceptibility to pathogenic microorganisms.¹⁵
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24 258 Malnutrition was one of the most common complications in PD patients, and plasma
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26 259 albumin level was an important clinical predictor. Hypoalbuminemia was proved to
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28 260 be related with malnutrition, protein losses, and inflammation.^{16 17} Wang Qin et al.
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30 261 discovered that patients with an initial serum albumin level less than 2.9 g/dL had a
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32 262 higher incidence of peritonitis. And they regarded hypoalbuminemia as an
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34 263 independent predictor for subsequent peritonitis at the start of PD therapy.¹⁸ Further
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36 264 studies demonstrated that low serum albumin level increased all-cause,
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38 265 cardiovascular, and infection related mortality in both PD and HD patients.¹⁹ In
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40 266 addition to peritoneal infection, hypoalbuminemia was also found to be associated
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42 267 with septicemia, pneumonia and other inflammatory responses.²⁰⁻²⁴ In this study, we
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44 268 reaffirmed that a low baseline serum albumin level is an independent risk factors for
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46 269 EOP. Every 1 g/L increase in the baseline serum albumin level lowered the risk of
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48 270 EOP by 7.4% (OR 0.929, P=0.015).

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50 271 Our study showed that older dialysis patients had a greater chance of developing
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52 272 early-onset peritonitis. It was reported that those patients were more likely to progress
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54 273 to a worse outcome, such as HD, renal transplantation or death.²⁵ Incidence of
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56 274 malnutrition in elderly PD patients was more common than young and middle-aged
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58 275 patients. Together with cardiovascular diseases, cerebrovascular disease, hearing and
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4 276 visual impairments, all of these factors increase and aggravate the episode of
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6 277 peritonitis.²⁶⁻²⁸ Malnutrition in elder not only affected the quality of dialysis patients'
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8 278 life, but also was an important factor in comorbidity and mortality.²⁹ Other elements
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10 279 that increased the peritonitis susceptibility in elderly patients included generalized
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12 280 functional deterioration, weakened immune system,³⁰ combined chronic diseases, bad
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14 281 eyesight, poor aseptic concept, lack of compliance and living alone. Their atypical
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16 282 clinical symptoms of peritonitis could be regarded as another essential reason.
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18 283 Up-regulated pain threshold, unobtrusive bellyache and mild subjective symptoms
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20 284 might cover up early-onset peritonitis until the occurrence of liquid turbidity, which
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22 285 would delay the best time for treatment.

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24 286 Comparison in biochemical indicators shown that Kt/V and residual renal
25
26 287 function decreased significantly after early-onset peritonitis. Multivariate logistic
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28 288 regression showed that every 1 ml/min/1.73 m² increase in the eGFR lowered the risk
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30 289 of EOP by 9.8% (OR 0.907, P=0.046). These results suggest that early infection with
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32 290 peritonitis might further worsen renal function, especially the scavenging capacity of
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34 291 solutes by residual kidney. Early inflammatory response and renal function damage
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36 292 might be the underlying causes of peritonitis. Many studies draw a similar conclusion
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38 293 that the survival rate of PD patients mainly depends on residual renal function, rather
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40 294 than the peritoneal cleaning capacity.³¹⁻³³ Harris et al. further put forward that residual
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42 295 renal function less than 4 ml·min⁻¹·1.73m⁻² was associated with high mortality during
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44 296 peritoneal dialysis.³⁴ Therefore, we should pay close attention to the change of
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46 297 residual renal function when monitoring the adequacy of dialysis.

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48 298 The relationship between peritonitis and technique failure and death have been
49
50 299 investigated in previous Chinese single-center studies.^{35 36} A study in Chinese
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52 300 Zhejiang province showed that, EOP was a significant predictor of all-cause
53
54 301 mortality. As for technique failure, they found no significant differences between
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56 302 EOP and LOP.³⁵ However, a study in Chinese Guangzhou province indicated that
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58 303 technique failure in EOP group was lower than LOP group, but patient survival did
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4 304 not differ between the two groups.³⁶ Our present study got the similar results with
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6 305 Guangzhou study. In the Cox proportional hazards model, EOP was a significant
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8 306 predictor of technique failure (hazard ratio (HR) 1.664, 95% CI 1.003-2.761,
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10 307 P=0.048). There were no differences between EOP and LOP for all-cause mortality.
11
12 308 These conclusions might be limited by regional and demographic differences in
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14 309 different dialysis center. However, all three studies indicated that patients who
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16 310 experienced peritonitis early after the initiation of PD were likely having more
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18 311 episodes of peritonitis. Repeating peritonitis in EOP patients have an obvious impact
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20 312 on membrane permeability, increasing severe systemic inflammation, reducing
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22 313 ultrafiltration and leading to worse clinical outcomes.³⁷ Thus, we put forward several
23
24 314 targeted opinions for each role involved in PD treatment according to the above
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26 315 correlation factor analysis of early-onset peritonitis, in order to reduce infection
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28 316 incidence, raise therapeutic effect of PD, improve patient's life quality and prognosis.
29
30 317 (1) Patient: every PD patients should set up an aseptic concept and follow standard
31
32 318 operation. (2) Family: family members have obligation to assist patients in
33
34 319 completing PD operations, especially for elderly and poor eyesight patients. (3)
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36 320 Society: A series of policies are needed to ensure the treatment right and medical
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38 321 insurance benefits of PD patients. (4) Nurse: Experienced nurses should carry out
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40 322 professional and systematic training on normalized PD operation for patients and their
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42 323 families. (5) Doctor: Doctors should pay attention to the treatment of basic diseases,
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44 324 such as hypertension, diabetes and stroke. At the same time in preventing infection
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46 325 and protecting peritoneal function, doctors must grasp the opportunity of conversion
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48 326 from PD to HD. Studies suggested that timely transformation to HD treatment for
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50 327 patients with recurrent peritonitis and other PD related complications can improve
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52 328 survival rate.³⁸

53
54 329 There are several limitations to this study. First, this was a retrospective cohort
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56 330 study, lacking of some objective information such as medical level, economic
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58 331 development and living standard, which may cause bias. Second, although this was a
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4 332 multicenter study, the sample size was relatively small. Further larger size and
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6 333 prospective investigation are necessary.
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9
10 335 **CONCLUSION**

11 336 In summary, this retrospective cohort study found that older age, a higher CCI score
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13 337 and lower serum albumin and eGFR before PD were significantly associated with
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15 338 EOP. In addition, an early peritonitis onset predicted a high peritonitis rate and worse
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17 339 clinical outcomes. Understanding the risk factors for EOP helps to develop effective
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19 340 measures to prevent or delay the complication of peritoneal dialysis as much as
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21 341 possible.
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38 349 **Author Contributors**

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17 391 **REFERENCES**

18
19 392 1. Li PK, Chow KM, Van de Luitgaarden MW, et al. Changes in the worldwide
20
21 393 epidemiology of peritoneal dialysis. *Nat Rev Nephrol* 2017;13:90-103.

22
23 394 2. Jain AK, Blake P, Cordy P, et al. Global trends in rates of peritoneal dialysis. *J Am*
24
25 395 *Soc Nephrol* 2012;23:533-44.

26
27 396 3. Cho Y, Johnson DW. Peritoneal dialysis-related peritonitis: towards improving
28
29 397 evidence, practices, and outcomes. *Am J Kidney Dis* 2014;64:278-89.

30
31 398 4. Thirugnanasambathan T, Hawley CM, Badve SV, et al. Repeated peritoneal
32
33 399 dialysis-associated peritonitis: a multicenter registry study. *Am J Kidney Dis*
34
35 400 2012;59:84-91.

36
37 401 5. Feng S, Wang Y, Qiu B, et al. Impact of early-onset peritonitis on mortality and
38
39 402 technique survival in peritoneal dialysis patients. *Springerplus* 2016;5:1676.

40
41 403 6. Li P, Szeto C, Piraino B, et al. Peritoneal dialysis-related infections
42
43 404 recommendations: 2010 update. *Perit Dial Int* 2010;30:393-423.

44
45 405 7. Béchade C, Guittet L, Evans D, et al. Early failure in patients starting peritoneal
46
47 406 dialysis: a competing risks approach. *Nephrol Dial Transplant* 2014;29:2127-35.

48
49 407 8. Hsieh YP, Wang SC, Chang CC, et al. The negative impact of early peritonitis on
50
51 408 continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 2014;34:627-35.

52
53 409 9. Fourtounas C, Savidaki E, Dousdabanis P, et al. Peritonitis during the first year
54
55 410 after commencement of peritoneal dialysis has an impact on technique survival and
56
57 411 patient morbidity. *Adv Perit Dial* 2006;22:50-4.

58
59 412 10. Hsieh Y, Wang S, Chang C, et al. The negative impact of early peritonitis on
60

- 1
2
3
4 413 continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 2014;34:627-35.
- 5
6 414 11. Barretti P, Doles J, Pinotti D, et al. Efficacy of antibiotic therapy for peritoneal
7
8 415 dialysis-associated peritonitis: a proportional meta-analysis. *BMC Infect Dis*
9
10 416 2014;14:445.
- 11
12 417 12. Govindarajulu S, Hawley C, McDonald S, et al. Staphylococcus aureus peritonitis
13
14 418 in Australian peritoneal dialysis patients: predictors, treatment, and outcomes in
15
16 419 503 cases. *Perit Dial Int* 2010;30:311-9.
- 17
18 420 13. Matuszkiewicz-Rowinska J. Update on fungal peritonitis and its treatment. *Perit*
19
20 421 *Dial Int* 2009;29 Suppl 2:S161-5.
- 21
22 422 14. Szeto C, Chow K. Gram-negative peritonitis--the Achilles heel of peritoneal
23
24 423 dialysis? *Perit Dial Int* 2007;27 Suppl 2:S267-71.
- 25
26 424 15. Li Z, An X, Mao H, et al. Association between depression and
27
28 425 malnutrition-inflammation complex syndrome in patients with continuous
29
30 426 ambulatory peritoneal dialysis. *Int Urol Nephrol* 2011;43:875-82.
- 31
32 427 16. Fanali G, di Masi A, Trezza V, et al. Human serum albumin: from bench to
33
34 428 bedside. *Mol Aspects Med* 2012;33:209-90.
- 35
36 429 17. Yu Z, Tan B, Dainty S, et al. Hypoalbuminaemia, systemic albumin leak and
37
38 430 endothelial dysfunction in peritoneal dialysis patients. *Nephrol Dial Transplant*
39
40 431 2012;27:4437-45.
- 41
42 432 18. Wang Q, Bernardini J, Piraino B, et al. Albumin at the start of peritoneal dialysis
43
44 433 predicts the development of peritonitis. *Am J Kidney Dis* 2003;41:664-9.
- 45
46 434 19. Mehrotra R, Duong U, Jiwakanon S, et al. Serum albumin as a predictor of
47
48 435 mortality in peritoneal dialysis: comparisons with hemodialysis. *Am J Kidney Dis*
49
50 436 2011;58:418-28.
- 51
52 437 20. Seo M, Choa M, You J, et al. Hypoalbuminemia, Low Base Excess Values, and
53
54 438 Tachypnea Predict 28-Day Mortality in Severe Sepsis and Septic Shock Patients
55
56 439 in the Emergency Department. *Yonsei Med J* 2016;57:1361-9.
- 57
58 440 21. Mizuno T, Mizokami F, Fukami K, et al. The influence of severe
59
60

- 1
2
3
4 441 hypoalbuminemia on the half-life of vancomycin in elderly patients with
5
6 442 methicillin-resistant *Staphylococcus aureus* hospital-acquired pneumonia. *Clin*
7
8 443 *Interv Aging* 2013;8:1323-8.
- 9
10 444 22. Juneja M, Baidoo L, Schwartz M, et al. Geriatric inflammatory bowel disease:
11
12 445 phenotypic presentation, treatment patterns, nutritional status, outcomes, and
13
14 446 comorbidity. *Dig Dis Sci* 2012;57:2408-15.
- 15
16 447 23. Don B, Kaysen G. Serum albumin: relationship to inflammation and nutrition.
17
18 448 *Semin Dial* 2004;17:432-7.
- 19
20 449 24. Magnussen B, Oren Gradel K, Gorm Jensen T, et al. Association between
21
22 450 Hypoalbuminaemia and Mortality in Patients with Community-Acquired
23
24 451 Bacteraemia Is Primarily Related to Acute Disorders. *PLoS ONE*
25
26 452 2016;11:e0160466.
- 27
28 453 25. Maitra S, Burkart J, Fine A, et al. Patients on chronic peritoneal dialysis for ten
29
30 454 years or more in North America. *Peritoneal Dialysis International Journal of the*
31
32 455 *International Society for Peritoneal Dialysis* 2000;20 Suppl 2:S127.
- 33
34 456 26. Sakaci T, Ahabap E, Koc Y, et al. Clinical outcomes and mortality in elderly
35
36 457 peritoneal dialysis patients. *Clinics (Sao Paulo)* 2015;70:363-8.
- 37
38 458 27. Valderrabano F, Jofre R, Lopez-Gomez JM. Quality of life in end-stage renal
39
40 459 disease patients. *Am J Kidney Dis* 2001;38:443-64.
- 41
42 460 28. Joly D, Anglicheau D, Alberti C, et al. Octogenarians reaching end-stage renal
43
44 461 disease: cohort study of decision-making and clinical outcomes. *J Am Soc*
45
46 462 *Nephrol* 2003;14:1012-21.
- 47
48 463 29. Tennankore KK, Bargman JM. Nutrition and the kidney: recommendations for
49
50 464 peritoneal dialysis. *Advances in Chronic Kidney Disease* 2013;20:190-201.
- 51
52 465 30. Hsieh YP, Chang CC, Wen YK, et al. Predictors of Peritonitis and the Impact of
53
54 466 Peritonitis on Clinical Outcomes of Continuous Ambulatory Peritoneal Dialysis
55
56 467 Patients in Taiwan—10 Years' Experience in a Single Center. *Peritoneal Dialysis*
57
58 468 *International Journal of the International Society for Peritoneal Dialysis*
59
60

- 1
2
3
4 469 2014;34:85.
- 5
6 470 31. Szeto C, Kwan B, Chow K, et al. Predictors of residual renal function decline in
7
8 471 patients undergoing continuous ambulatory peritoneal dialysis. *Perit Dial Int*
9
10 472 2015;35:180-8.
- 11
12 473 32. Vilar E, Farrington K. Emerging importance of residual renal function in
13
14 474 end-stage renal failure. *Semin Dial* 2011;24:487-94.
- 15
16 475 33. Raimann J, Kitzler T, Levin N. Factors affecting loss of residual renal function(s)
17
18 476 in dialysis. *Contrib Nephrol* 2012;178:150-6.
- 19
20 477 34. Harris S, Lamping D, Brown E, et al. Clinical outcomes and quality of life in
21
22 478 elderly patients on peritoneal dialysis versus hemodialysis. *Perit Dial Int*
23
24 479 2002;22:463-70.
- 25
26 480 35. Tian Y, Xie X, Xiang S, et al. Risk Factors and Outcomes of Early-Onset
27
28 481 Peritonitis in Chinese Peritoneal Dialysis Patients. *Kidney Blood Press Res*
29
30 482 2017;42:1266-76.
- 31
32 483 36. Wu H, Huang R, Yi C, et al. Risk Factors for Early-Onset Peritonitis in Southern
33
34 484 Chinese Peritoneal Dialysis Patients. *Perit Dial Int* 2016;36:640-46.
- 35
36 485 37. van Diepen AT, van Esch S, Struijk DG, et al. The first peritonitis episode alters
37
38 486 the natural course of peritoneal membrane characteristics in peritoneal dialysis
39
40 487 patients. *Perit Dial Int* 2015;35:324-32.
- 41
42 488 38. Panagoutsos S, Kantartzi K, Passadakis P, et al. Timely transfer of peritoneal
43
44 489 dialysis patients to hemodialysis improves survival rates. *Clin Nephrol*
45
46 490 2006;65:43-7.
- 47
48
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52 492
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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

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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)	

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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			

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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

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7 579 **Figure legends**

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9 581 Fig.1. Technique survival according to EOP and LOP.

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11 583 Fig.2. Patient survival according to EOP and LOP.

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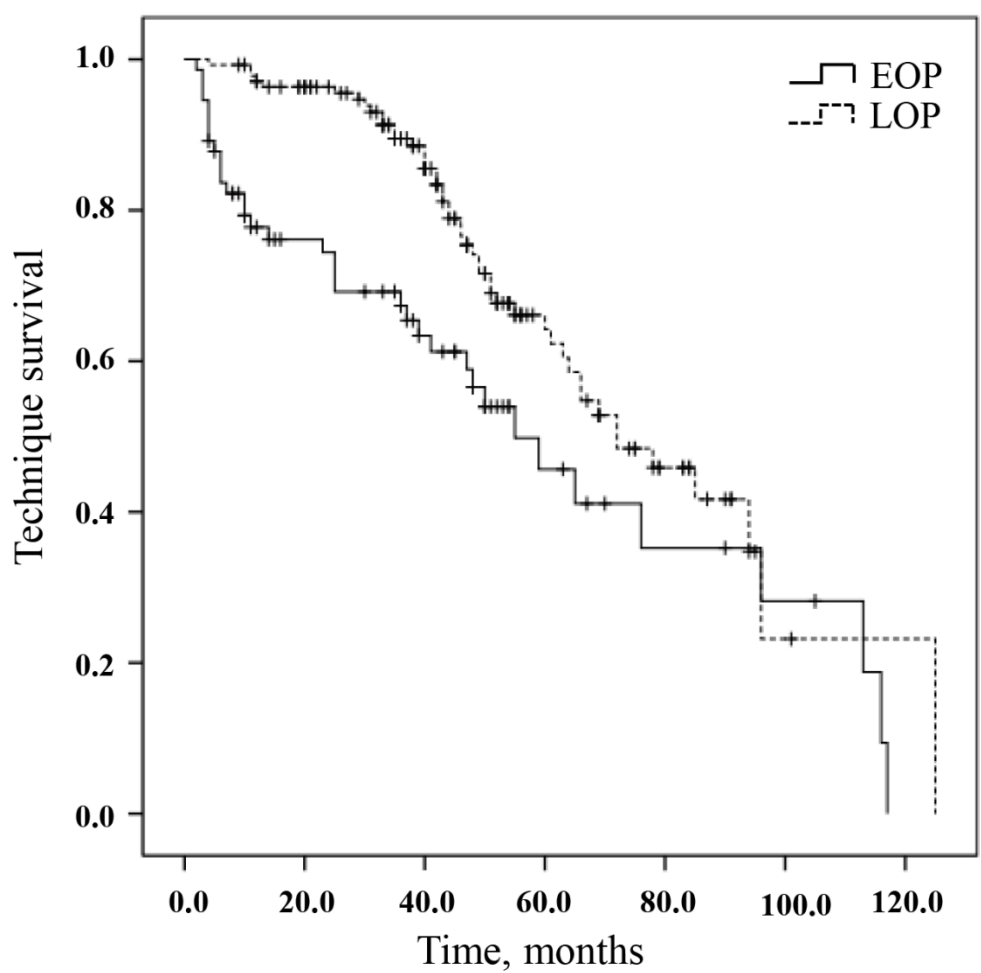


Fig.1. Technique survival according to EOP and LOP.

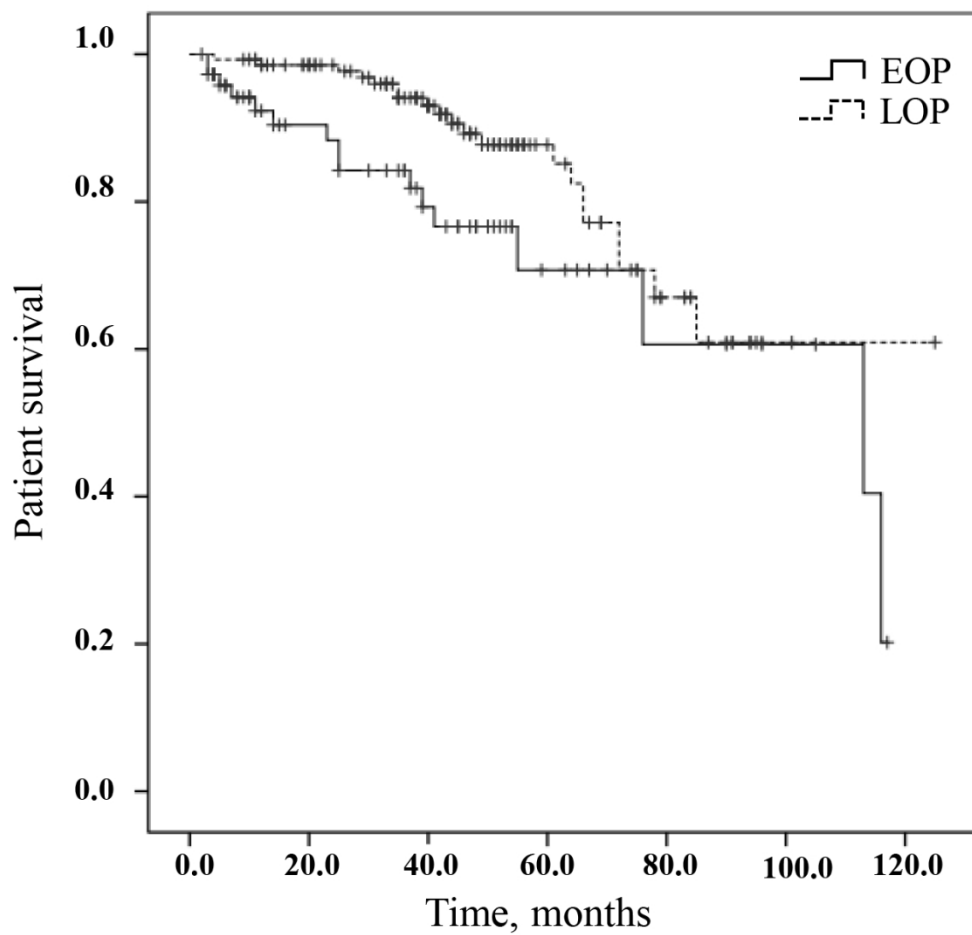


Fig.2. Patient survival according to EOP and LOP.

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4 1 **The analysis of risk factors and outcome in peritoneal dialysis patients with**
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6 2 **early-onset peritonitis: a multi-center, retrospective, cohort study.**

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26 12 *These authors make an equal contribution to this study.

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4 29 **ABSTRACT**

5 30 **Objectives** To investigate the risk factors associated with early-onset peritonitis
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8 31 (EOP) and its influence on patients' technique survival and mortality.

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10 32 **Study design** Retrospective, cohort study.

11
12 33 **Setting** Three peritoneal dialysis units in Shanghai.

13
14 34 **Participants** PD patients from June 1, 2006, to May 1, 2018, were recruited and
15
16 35 followed up until December 31, 2018. According to time-to-first episode of
17
18 36 peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis
19
20 37 (≤ 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139).

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22 38 **Primary and secondary outcome measures** EOP was defined as the first episode of
23
24 39 peritonitis occurring within 6 months after the initiation of peritoneal dialysis (PD).
25
26 40 The outcomes were all-cause mortality and technique failure.

27
28 41 **Results** Of the 357 patients, 74 (20.7%) patients developed their first episode of
29
30 42 peritonitis within the first 6 months. Compared with the LOP group, the EOP group
31
32 43 had older ages, more female patients, higher Charlson comorbidity index (CCI) score,
33
34 44 lower serum albumin levels and renal function at the time of initiation of PD and
35
36 45 higher diabetes mellitus and peritonitis rates ($P<0.05$). Staphylococcus was the most
37
38 46 common Gram-positive organism in both EOP and LOP groups. The multivariate
39
40 47 logistic regression analysis showed that factors associated with EOP included a higher
41
42 48 CCI score (odds ratio (OR) 1.318, $P=0.008$), lower serum albumin level (OR 0.926,
43
44 49 $P=0.021$) and lower Kt/V (OR 0.631, $P=0.035$) at start of PD. In the Cox proportional
45
46 50 hazards model, EOP was the only predictor of technique failure (hazard ratio (HR)
47
48 51 1.801, $P=0.051$). There was no difference between EOP and LOP for all-cause
49
50 52 mortality.

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52 53 **Conclusion** A higher CCI score and lower serum albumin level and Kt/V at PD
53
54 54 initiation were significantly associated with EOP. EOP also predicted a high
55
56 55 peritonitis rate and poor clinical outcomes.

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4 57 **KEY WORDS** Peritoneal dialysis; Early-onset peritonitis; Risk factors; Outcomes.
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11 59 **ARTICLE SUMMARY**

12 60 **Article focus**

- 13 61 ● The risk factors associated with EOP and its influence on patients' technique
14
15 62 survival and mortality.

16 63 **Key messages**

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18 64 ● A higher CCI score and lower serum albumin level and Kt/V at PD initiation
19
20 65 were significantly associated with EOP.
21
22 66 ● EOP predicted a high peritonitis rate and poor clinical outcomes.
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29 67 **Strengths and limitations of this study**

- 30
31 68 ● There is a strict exclusion criteria based on PD histories.
32
33 69 ● We conducted a multi-center study which ensured sufficient power in obtaining
34
35 70 the risk factors of EOP.
36
37 71 ● This was a retrospective cohort study, lacking of some objective information such
38
39 72 as education level, economic development and living standard, which may cause
40
41 73 bias.
42
43 74 ● The study did not compare the risk factors of EOP between male and female
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45 75 patients.
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47 76 ● Although this was a multicenter study, the sample size was relatively small.
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79 INTRODUCTION

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

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

98 METHODS

99 Study Population

100 This was a multi-center retrospective cohort study included 357 patients with ESRD
101 who underwent PD in Department of Nephrology in Baoshan branch of Shanghai
102 First People's Hospital, Shanghai Songjiang District Central Hospital and Shanghai
103 East Hospital, Tongji University School of Medicine. All incident PD patients from
104 June 1, 2006, to May 1, 2018, were recruited and followed up until December 31,
105 2018. Before PD initiation, the patients signed the informed consents for treatment
106 strategy and agreed to share the treatment information to the hospital database in case
107 of the late follow-up. This study was conducted according to the guidelines of the

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4 108 Helsinki Declaration. And we apply for the agreements from the human research
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6 109 ethics committees of the three hospitals. After that we collected the information from
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8 110 the hospital databases. The exclusion criteria were as follows: patients who had been
9
10 111 using PD for fewer than 90 days, patients with an age younger than 18 years and
11
12 112 patients who initiated PD in other PD centers and previously accepted HD or kidney
13
14 113 transplantation. There are 19 PD patients suffer the peritonitis within the first 3
15
16 114 months, 6 subjects died, 3 patients transferred to hemodialysis, 0 patients underwent
17
18 115 renal transplantation, 10 patients continued peritoneal dialysis. While these 10 PD
19
20 116 patients lacked of the information of peritoneal equilibration test. Patients were
21
22 117 followed until any of the following events: death, a change to HD, renal
23
24 118 transplantation or until December 31, 2018. According to the Chinese Peritoneal
25
26 119 Dialysis Guideline, we adopted standardized surgical catheterization technique.¹² We
27
28 120 chose Tenckhoff silicone tube with double polyester sleeve. Double-purse string
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30 121 suture or double-layer suture was adopted to fix the catheter. Fine needle and thick
31
32 122 line were used to prevent peripheral tube leakage. The exit direction of catheter tunnel
33
34 123 was downward and outward, and the outer polyester sleeve was 2 to 3 cm away from
35
36 124 the exit. All the surgical operations are performed in the operating room. The single
37
38 125 dose intravenous antibiotic 30 minutes before surgery is recommended to prevent
39
40 126 infection.¹³ The first or second generation cephalosporin is suggested.^{13 14} According
41
42 127 to the ISPD peritonitis recommendations,¹³⁻¹⁵ we topical apply mupirocin ointment
43
44 128 to the catheter exit site once a day to prevent exit site infection. Patients initiated PD
45
46 129 by Dianeal with 1.5% or 2.5% dextrose (Baxter Healthcare, Guangzhou, China).
47
48 130 Dialysate concentration was 1.5% dextrose and replaced every four hours during the
49
50 131 day, while 2.5% at night and kept in the body. A total of 213 patients who had at least
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52 132 one episode of peritonitis. According to time-to-first episode of peritonitis, patients
53
54 133 were divided into non-peritonitis (n=144), early-onset peritonitis (\leq 6 months, n=74)
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56 134 and late-onset peritonitis ($>$ 6 months, n=139). We collected baseline characteristics
57
58 135 within 1-3 months from the start of PD, including demographic data (age, gender,
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4 136 smoking, drinking, CCI, BMI), medical history, drug-taking history, biochemical data
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6 137 (hemoglobin, serum electrolyte, fasting blood glucose, total cholesterol, total
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8 138 triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol,
9
10 139 and serum albumin, uric acid, creatinine, blood urea nitrogen, estimated glomerular
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12 140 filtration rate (eGFR), the clearance rate of urea nitrogen (Kt/V), cause of ESRD,
13
14 141 peritonitis episodes. Peritoneal fluid effluent from patients with peritonitis was
15
16 142 collected and cultured for 1 to 5 days to identify the bacterial flora in the dialysate.
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19 20 144 **Primary and secondary outcome measures**

21
22 145 Early-onset peritonitis was defined as the first episode of peritonitis occurring within
23
24 146 6 months after the initiation of peritoneal dialysis (PD). This definition is consistent
25
26 147 with other published article.^{8 16} The outcomes were all-cause mortality and technique
27
28 148 failure.
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31 32 150 **Study definitions**

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34 151 Diagnostic criteria for peritonitis based on the 2010 International Society for
35
36 152 Peritoneal Dialysis (ISPD) guidelines.¹⁵ Patients diagnosed as peritonitis should meet
37
38 153 at least two of the following three standards: (1) Clinical symptoms or signs of
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40 154 peritonitis; (2) Leucocyte count (at least 100/mm³) and polymorphonuclear
41
42 155 neutrophilic cells proportion (at least 50%) in peritoneal fluid effluent; (3) Related
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44 156 pathogens in smear or culture of peritoneal fluid. Early-onset peritonitis was defined
45
46 157 as the first episode of peritonitis occurring within 6 months after the initiation of PD.
47
48 158 The outcomes were all-cause mortality and technique failure. Death was an end-point
49
50 159 event in the patient survival analysis. Relapse was defined as an episode occurring
51
52 160 within 4 weeks of completion of therapy of a prior episode with the same organism,¹³
53
54 161 recurrence referred to an episode occurring within 4 weeks of completion of therapy
55
56 162 of a prior episode but with a different organism.¹³ Instead of transfer to HD therapy
57
58 163 permanently, both relapse and recurrence were treated by antibiotics and continued
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4 164 PD treatment. Complete cure was defined as the resolution of peritonitis without
5
6 165 relapse or recurrence by antibiotics alone.⁷ However, some of refractory peritonitis
7
8 166 failed to clear up effluent after 5 days of appropriate antibiotics and transferred to HD
9
10 167 permanently. We classify this part of patients into “transfer to hemodialysis”. Other
11
12 168 parts of HD patients were due to the serious tunnel infection with peritonitis and
13
14 169 ultrafiltration failure induced by encapsulating peritoneal sclerosis. Patients who
15
16 170 transferred to HD were censored from the patient survival analysis, and death was
17
18 171 censored for technique failure. Technique failure was defined as the transfer to HD
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20 172 therapy permanently (lasted for 30 days or more) due to ultrafiltration failure,
21
22 173 peritonitis, exit-site infection and other operational problems.¹⁷
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26 175 **Patient and public involvement**

27
28 176 No patient was involved in the design or conduct of the study, but the results of the
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30 177 study will be shared to patients coming for follow-up.
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34 179 **Statistical analysis**

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36 180 All statistical analyses were performed by SPSS 20.0 for Windows (IBM Corp.,
37
38 181 Armonk, NY, USA). The normal distributed data were showed as mean±standard
39
40 182 deviation (SD) and the skewed data were showed as median values with the 25th to
41
42 183 75th percentile intervals. Categorical data were expressed as frequency (n) and
43
44 184 percentage (%). As for normally distributed data, student's t-test is using for
45
46 185 analyzing the differences between the EOP group and LOP group, while one-way
47
48 186 ANOVA for differences among in non-peritonitis, EOP group and LOP groups. The
49
50 187 Wilcoxon rank sum test for skewed continuous data and the Chi-square test or
51
52 188 Fisher's exact test for categorical data. The Kaplan-Meier survival curves were drawn
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54 189 for each event of interest (technique survival and patient survival) and the log-rank
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56 190 test was used to compare curves. Univariate Cox proportional hazards regression was
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58 191 used to select significant factors associated with study outcomes. Variables whose
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4 192 $P < 0.10$ were selected for inclusion in the final multivariate Cox model. Multivariate
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6 193 logistic regression was calculated to select significant risk factors for EOP and the
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8 194 inclusion standard was also $P < 0.10$. Collinearity of variables was tested. A two-tailed
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10 195 P value < 0.05 was considered statistically significant.

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13 14 197 **RESULTS**

15 16 198 **Patient Characteristics**

17
18 199 A total of 357 patients with ESRD underwent CAPD in three dialysis centers in
19
20 200 Shanghai during the study period. All patients used Dianeal with 1.5% or 2.5%
21
22 201 dextrose. The first episode of peritonitis was experienced by 74 (20.7%) patients
23
24 202 within 6 months after the start of PD. 11 (11/61) in Shanghai East Hospital, 22
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26 203 (22/142) in Shanghai Songjiang District Central Hospital, 41 (41/154) in Baoshan
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28 204 branch of Shanghai First People's Hospital. Median follow-up time for the 357
29
30 205 patients was 33.0 months (interquartile range 14.0-50.0 months). There were 211
31
32 206 males (59.1%) with an average age of 61.6 ± 14.0 years, and 145 females (40.9%)
33
34 207 with an average age of 65.3 ± 12.9 years. The most common primary renal diseases
35
36 208 were chronic glomerulonephritis (43.1%) and diabetic nephropathy (34.2%).
37
38 209 Compared with the LOP patients, the EOP patient group had older ages, more female
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40 210 patients, higher Charlson comorbidity index (CCI) score and lower serum albumin
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42 211 levels, renal function and Kt/V at the time of initiation of PD and higher diabetes
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44 212 mellitus and peritonitis rates ($P < 0.05$). Additional demographic and laboratory
45
46 213 characteristics of the study population are present in Table 1.

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48 214

49 50 215 **Causative organisms**

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52 216 In table 2, among 213 patients with peritonitis, 47 (22.1%) were due to Gram-positive
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54 217 organisms, 24 (11.3%) were due to Gram-negative organisms, 6 (2.8%) were due to
55
56 218 fungi, 1 (0.4%) were due to multiple organisms, and 135 (63.4%) were
57
58 219 culture-negative. Staphylococcus was the most common Gram-positive organism in
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60

220 both groups. Compared with the EOP patient group, the LOP patient group had more
221 culture-negative peritonitis (89.2% vs. 14.9%, $P<0.001$). The incidences of
222 culture-negative peritonitis were 37.1% (13/35) in Shanghai East Hospital, 71.7%
223 (38/53) in Shanghai Songjiang District Central Hospital, 67.2% (84/125) in Baoshan
224 branch of Shanghai First People's Hospital ($P=0.002$).

225

226 **Outcomes**

227 The total peritonitis rate was 0.490 episodes per patient-year (213 patients presented
228 509 episodes of peritonitis during 1039.58 patient-years of follow-up). The peritonitis
229 rates in Shanghai East Hospital, Shanghai Songjiang District Central Hospital and
230 Baoshan Branch of Shanghai First People's Hospital were 0.41, 0.31 and 0.61
231 episodes per patient-year respectively. Early-onset first episode of peritonitis had a
232 lower cure rate (17.6% vs 33.8%, Table 2.), higher rate of transferring to
233 hemodialysis (27.0% vs 19.4%, Table 2.), and higher mortality (21.6% vs 14.4%,
234 Table 2.) compared to late-onset first episode of peritonitis.

235

236 **Technique failure**

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

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245 **All-cause mortality**

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

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4 248 Cox regression analysis, including the time to first peritonitis (EOP vs. LOP), age,
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6 249 serum albumin and total Kt/V, were chosen for further adjustment in multivariate Cox
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8 250 proportional hazards model. After adjustment, there was no significant difference
9
10 251 between the EOP and LOP groups (Table 3). Fig. 2 describes cumulative survival by
11
12 252 EOP and LOP groups using the Kaplan-Meier analysis. Compared with LOP group,
13
14 253 cumulative survival was lower in the EOP group (Log rank 4.060, $P=0.044$).
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16 254

17 18 255 **Risk factors of early-onset peritonitis**

19
20 256 Variables in Table 1 were tried in a univariate logistic regression model, and only
21
22 257 variables with P value < 0.10 for peritonitis were depicted in Table 4. Based on the
23
24 258 simple logistic regression analysis of risk factors associated with EOP, we constructed
25
26 259 a multiple logistic regression model using variables including gender, age, CCI score,
27
28 260 diabetes, serum albumin, eGFR and Kt/V. We found that higher CCI score
29
30 261 (OR=1.318, 95%CI 1.075-1.615, $P=0.008$), lower serum albumin level (OR=0.926,
31
32 262 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
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34 263 the start of PD, were significantly associated with EOP (Table 4).
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37 38 265 **DISCUSSION**

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41 266 Our retrospective cohort study of 357 PD patients showed that 74 (20.7%) patients in
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43 267 three Shanghai dialysis centers developed the first episodes of peritonitis within the
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45 268 first 6 months. Higher CCI score, lower serum albumin level and Kt/V at the start of
46
47 269 PD, were significantly associated with EOP. In addition, an early peritonitis onset
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49 270 predicted a high peritonitis rate and technique failure.

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51 271 Early-onset peritonitis is a major complication of peritoneal dialysis, directly or
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53 272 indirectly causing the abandon of dialysis treatment. In this study, among 213 patients
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55 273 with peritonitis, 47 (22.1%) were due to Gram-positive organisms, 24 (11.3%) were
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57 274 due to Gram-negative organisms, 6 (2.8%) were due to fungi. Staphylococcus was the
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59 275 most common Gram-positive organism in both early-onset and late-onset peritonitis.
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4 276 This bacterial flora distribution and high incidence of staphylococcus were similar to
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6 277 previous reports.¹⁸⁻²⁰ Fungal peritonitis was rare in PD patients, but could bring out
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8 278 irreversible peritoneal damage.²¹ Recent clinical studies confirmed that the incidence
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10 279 of fungal peritonitis was only 3%-6%,²¹ while the relative mortality rate was up to
11
12 280 20%-30%.²² The culture-negative proportion for the first peritonitis episode was high
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14 281 in the LOP patients (89.2%). And the incidences of culture-negative peritonitis were
15
16 282 37.1% (13/35) in Shanghai East Hospital, 71.7% (38/53) in Shanghai Songjiang
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18 283 District Central Hospital, 67.2% (84/125) in Baoshan branch of Shanghai First
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20 284 People's Hospital ($P=0.002$). The high culture-negative proportion may primary
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22 285 attributed to early antibiotic treatment and limited effluent culture technique in
23
24 286 small-scale PD units. Before 2014, the technology of blood culture for PD effluent
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26 287 has not been widely adopted by small-scale district hospitals in Shanghai. In the
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28 288 district PD units, dialysate was inoculated onto solid medium and then incubated only
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30 289 in aerobic environment. It accounted for about 60% of culture-negative peritonitis
31
32 290 patients in this investigation. Since 2015, all these three units in Shanghai choose
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34 291 blood-culture bottle for the preferred technique to culture microorganism in PD
35
36 292 effluent. Lacking centrifugation of PD effluent and recent antibiotic usage may the
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38 293 major reasons for the rest of 40% negative effluent cultures in this investigation.
39
40 294 Considering the high culture negative rate in this study, our three PD units will take a
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42 295 series of measures to improve our culture methods, including centrifugation of PD
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44 296 effluent, incubation in aerobic, microaerophilic and anaerobic environments, using
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46 297 antibiotic neutralization bottle and so on.^{13 14}

48 298 By the end of the study, 509 episodes of peritonitis occurred in 213 patients, and
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50 299 the peritonitis rate was 0.490 episodes per patient-year. The peritonitis rates in
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52 300 Shanghai East Hospital, Shanghai Songjiang District Central Hospital and Baoshan
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54 301 Branch of Shanghai First People's Hospital were 0.41, 0.31 and 0.61 episodes per
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56 302 patient-year respectively. Recently, some investigations from other areas of China
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58 303 have indicated that the peritonitis rate was 0.196 episodes per patient-year in Taiwan
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4 304 ⁵, 0.158 episodes per patient-year in Guangzhou,⁷ 0.296 episodes per patient-year in
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6 305 Suzhou ¹⁶ and 0.158 per patient-year in Hangzhou ⁸. Peritonitis rate in our study is
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8 306 higher than the rest of China. Among the early-onset peritonitis patients who had ≥ 3
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10 307 episodes of peritonitis, 25 EOP patients underwent recurrent peritonitis, 16 EOP
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12 308 patients underwent repeat peritonitis. 43.8% repeat patients were staphylococcal
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14 309 peritonitis. And 75% EOP patients with ≥ 3 episodes of peritonitis came from Baoshan
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16 310 Branch of Shanghai First People's Hospital. Most of these patients are fishermen
17
18 311 living in the Chongming Island and have related poorer economic abilities and living
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20 312 conditions. These PD patients are easy to undergo poorer nutritional status and suffer
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22 313 peritonitis again [13, 14]. And lacking of home visit by PD nurses makes it difficult to
23
24 314 determine which patients require PD re-training. Lacking of technical improvement in
25
26 315 small-scale PD units is also the important reason for high peritonitis rate.

27
28 316 Our study found that lower serum albumin was one of the major risk factors for
29
30 317 early-onset peritonitis. Loss of protein would cause negative nitrogen balance and
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32 318 malnutrition, leading to a decline in immune function and increased susceptibility to
33
34 319 pathogenic microorganisms.²³ Malnutrition was one of the most common
35
36 320 complications in PD patients, and plasma albumin level was an important clinical
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38 321 predictor. Hypoalbuminemia was proved to be related with malnutrition, protein
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40 322 losses, and inflammation.^{24 25} Wang Qin et al. discovered that patients with an initial
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42 323 serum albumin level less than 2.9 g/dL had a higher incidence of peritonitis and
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44 324 regarded hypoalbuminemia as an independent predictor for subsequent peritonitis at
45
46 325 the start of PD therapy.²⁶ Further studies demonstrated that low serum albumin level
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48 326 increased all-cause, cardiovascular, and infection related mortality in both PD and HD
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50 327 patients.²⁷ In addition to peritoneal infection, hypoalbuminemia was also found to be
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52 328 associated with septicemia, pneumonia and other inflammatory responses.²⁸⁻³² In this
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54 329 study, we reaffirmed that a low baseline serum albumin level is an independent risk
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56 330 factors for EOP (OR=0.926, 95%CI 0.868-0.989, P=0.021).

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58 331 Although older age is not an independent risk factor for EOP, baseline data
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4 332 showed that patients in EOP group older than LOP group (65.87 ± 13.20 vs.
5 333 61.40 ± 13.53 , $P=0.022$). It was reported that elder patients were more likely to
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7 334 progress to a worse outcome, including HD, renal transplantation or death.³³
8
9 335 Incidence of malnutrition in elderly PD patients was more common than young and
10
11 336 middle-aged patients. Together with cardiovascular diseases, cerebrovascular disease,
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13 337 hearing and visual impairments, all of these factors increase and aggravate the episode
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15 338 of peritonitis.³⁴⁻³⁶ Malnutrition in elder not only affected the quality of dialysis
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17 339 patients' life, but also was an important factor in comorbidity and mortality.³⁷ Other
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19 340 elements that increased the peritonitis susceptibility in elderly patients included
20
21 341 generalized functional deterioration, weakened immune system,³⁸ combined chronic
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23 342 diseases, bad eyesight, poor aseptic concept, lack of compliance and living alone.
24
25 343 Their atypical clinical symptoms of peritonitis could be regarded as another essential
26
27 344 reason. Up-regulated pain threshold, unobtrusive bellyache and mild subjective
28
29 345 symptoms might cover up early-onset peritonitis until the occurrence of liquid
30
31 346 turbidity, which would delay the best time for treatment.

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34 347 Comparison in biochemical indicators shown that Kt/V and residual renal
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36 348 function decreased significantly after early-onset peritonitis. Multivariate logistic
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38 349 regression showed that lower eGFR (OR=0.916, 95%CI 0.832-1.009, $P=0.076$) and
39
40 350 Kt/V (OR=0.631, 95%CI 0.411-0.969, $P=0.035$) at the start of PD, were associated
41
42 351 with EOP. These results suggest that early infection with peritonitis might further
43
44 352 worsen renal function, especially the scavenging capacity of solutes by residual
45
46 353 kidney. Early inflammatory response and renal function damage might be the
47
48 354 underlying causes of peritonitis. Some studies suggested that the survival rate of PD
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50 355 patients depends more on residual renal function than the peritoneal cleaning
51
52 356 capacity.³⁹⁻⁴¹ Harris et al. further put forward that residual renal function less than 4
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54 357 $\text{ml} \cdot \text{min}^{-1} \cdot 1.73\text{m}^{-2}$ was associated with high mortality during peritoneal dialysis.⁴²
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56 358 Therefore, we should pay close attention to the change of residual renal function
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58 359 when monitoring the adequacy of dialysis.
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4 360 The relationship between peritonitis and technique failure and death have been
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6 361 investigated in previous Chinese single-center studies.^{7,8} A study in Chinese Zhejiang
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8 362 province showed that, EOP was a significant predictor of all-cause mortality. As for
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10 363 technique failure, they found no significant differences between EOP and LOP.⁸
11
12 364 However, a study in Chinese Guangzhou province indicated that technique failure in
13
14 365 EOP group was lower than LOP group, but patient survival did not differ between the
15
16 366 two groups.⁷ Our present study showed that EOP was the only significant predictor of
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18 367 technique failure (HR=1.801, 95%CI 0.996-3.257, P=0.051). There were no
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20 368 differences between EOP and LOP for all-cause mortality. These conclusions might
21
22 369 be limited by regional and demographic differences in different dialysis center.
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24 370 However, all three studies indicated that patients who experienced peritonitis early
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26 371 after the initiation of PD were likely having more episodes of peritonitis. Repeating
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28 372 peritonitis in EOP patients have an obvious impact on membrane permeability,
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30 373 increasing severe systemic inflammation, reducing ultrafiltration and leading to worse
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32 374 clinical outcomes.⁴³ Thus, appropriately dealing with the risk factors of early-onset
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34 375 peritonitis will be good to reduce infection incidence, raise therapeutic effect of PD,
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36 376 improve patient's life quality and prognosis.

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38 377 There are several limitations to this study. First, this was a retrospective cohort
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40 378 study, lacking of some objective information such as education level, economic
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42 379 development and living standard, which may cause bias. Second, although this was a
43
44 380 multicenter study, the sample size was relatively small. Further larger size and
45
46 381 prospective investigation are necessary.

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49 383 **CONCLUSION**

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51 384 In summary, this retrospective cohort study found that a higher CCI score and lower
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53 385 serum albumin and Kt/V before PD were significantly associated with EOP. In
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55 386 addition, an early peritonitis onset predicted a high peritonitis rate and worse clinical
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57 387 outcomes. Understanding the risk factors for EOP helps to develop effective measures
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388 to prevent or delay the complication of peritoneal dialysis as much as possible.

389

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395

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397 X.M., Y.S. M.T. and X.J. contributed equally to this work. X.M., Y.S. M.T. and X.J.

398 performed the statistical analysis and wrote the manuscript; X.M., Y.S., M.T., X.J.,

399 Y.W., D.J., L.F., W.J., L.D. and X.Z. participated in the data collection; X.M., Y.S.,

400 S.Z. and N.L. contributed to discussion; X.M., S.Z. and N.L. participated in the

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7
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11
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28
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441 **REFERENCES**

- 442 1. Li PK, Chow KM, Van de Luijngaarden MW, et al. Changes in the worldwide
443 epidemiology of peritoneal dialysis. *Nat Rev Nephrol* 2017;13:90-103.
- 444 2. Jain AK, Blake P, Cordy P, et al. Global trends in rates of peritoneal dialysis. *J Am*
445 *Soc Nephrol* 2012;23:533-44.
- 446 3. Cho Y, Johnson DW. Peritoneal dialysis-related peritonitis: towards improving
447 evidence, practices, and outcomes. *Am J Kidney Dis* 2014;64:278-89.
- 448 4. Thirugnanasambathan T, Hawley CM, Badve SV, et al. Repeated peritoneal
449 dialysis-associated peritonitis: a multicenter registry study. *Am J Kidney Dis*
450 2012;59:84-91.
- 451 5. Hsieh YP, Wang SC, Chang CC, et al. The negative impact of early peritonitis on
452 continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 2014;34:627-35.
- 453 6. See EJ, Johnson DW, Hawley CM, et al. Early peritonitis and its outcome in
454 incident peritoneal dialysis patients *Perit Dial Int* 2017.
- 455 7. Wu H, Huang R, Yi C, et al. Risk factors for early-onset peritonitis in southern
456 Chinese peritoneal dialysis patients. *Perit Dial Int* 2016;36:640-46.
- 457 8. Tian Y, Xie X, Xiang S, et al. Risk factors and outcomes of early-onset peritonitis
458 in Chinese peritoneal dialysis patients. *Kidney Blood Press Res* 2017;42:1266-76.
- 459 9. Béchade C, Guittet L, Evans D, et al. Early failure in patients starting peritoneal
460 dialysis: a competing risks approach. *Nephrol Dial Transplant* 2014;29:2127-35.
- 461 10. Feng S, Wang Y, Qiu B, et al. Impact of early-onset peritonitis on mortality and
462 technique survival in peritoneal dialysis patients. *Springerplus* 2016;5:1676.
- 463 11. Fourtounas C, Savidaki E, Dousdabanis P, et al. Peritonitis during the first year
464 after commencement of peritoneal dialysis has an impact on technique survival
465 and patient morbidity. *Adv Perit Dial* 2006;22:50-4.
- 466 12. Chinese Expert Group on Peritoneal Dialysis Catheterization. Chinese guidelines
467 for peritoneal dialysis catheterization. *Chinese J Nephrol* 2016;32:867-71.
- 468 13. Li PK, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update
469 on prevention and treatment. *Perit Dial Int* 2016;36:481-508.

- 1
2
3
4 470 14. Szeto CC, Li PK, Johnson DW, et al. ISPD catheter-related infection
5
6 471 recommendations: 2017 Update. *Perit Dial Int* 2017;37:141-54.
7
8 472 15. Li PK, Szeto CC, Piraino B, et al. Peritoneal dialysis-related infections
9
10 473 recommendations: 2010 update. *Perit Dial Int* 2010;30:393-423.
11
12 474 16. Wang Z, Jiang L, Feng S, et al. Early peritonitis is an independent risk factor for
13
14 475 mortality in elderly peritoneal dialysis patients. *Kidney Blood Press Res*
15
16 476 2015;40:298-305.
17
18 477 17. Shen JI, Mitani AA, Saxena AB, et al. Determinants of peritoneal dialysis
19
20 478 technique failure in incident US patients. *Perit Dial Int* 2013;33:155-66.
21
22 479 18. Hsieh Y, Wang S, Chang C, et al. The negative impact of early peritonitis on
23
24 480 continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 2014;34:627-35.
25
26 481 19. Barretti P, Doles J, Pinotti D, et al. Efficacy of antibiotic therapy for peritoneal
27
28 482 dialysis-associated peritonitis: a proportional meta-analysis. *BMC Infect Dis*
29
30 483 2014;14:445.
31
32 484 20. Govindarajulu S, Hawley C, McDonald S, et al. Staphylococcus aureus peritonitis
33
34 485 in Australian peritoneal dialysis patients: predictors, treatment, and outcomes in
35
36 486 503 cases. *Perit Dial Int* 2010;30:311-9.
37
38 487 21. Matuszkiewicz-Rowinska J. Update on fungal peritonitis and its treatment. *Perit*
39
40 488 *Dial Int* 2009;29 Suppl 2:S161-5.
41
42 489 22. Szeto C, Chow K. Gram-negative peritonitis--the Achilles heel of peritoneal
43
44 490 dialysis? *Perit Dial Int* 2007;27 Suppl 2:S267-71.
45
46 491 23. Li Z, An X, Mao H, et al. Association between depression and
47
48 492 malnutrition-inflammation complex syndrome in patients with continuous
49
50 493 ambulatory peritoneal dialysis. *Int Urol Nephrol* 2011;43:875-82.
51
52 494 24. Fanali G, di Masi A, Trezza V, et al. Human serum albumin: from bench to
53
54 495 bedside. *Mol Aspects Med* 2012;33:209-90.
55
56 496 25. Yu Z, Tan B, Dainty S, et al. Hypoalbuminaemia, systemic albumin leak and
57
58 497 endothelial dysfunction in peritoneal dialysis patients. *Nephrol Dial Transplant*
59
60

- 1
2
3
4 498 2012;27:4437-45.
- 5
6 499 26. Wang Q, Bernardini J, Piraino B, et al. Albumin at the start of peritoneal dialysis
7
8 500 predicts the development of peritonitis. *Am J Kidney Dis* 2003;41:664-9.
- 9
10 501 27. Mehrotra R, Duong U, Jiwakanon S, et al. Serum albumin as a predictor of
11
12 502 mortality in peritoneal dialysis: comparisons with hemodialysis. *Am J Kidney Dis*
13
14 503 2011;58:418-28.
- 15
16 504 28. Seo M, Choa M, You J, et al. Hypoalbuminemia, low base excess values, and
17
18 505 tachypnea predict 28-day mortality in severe sepsis and septic shock patients in
19
20 506 the emergency department. *Yonsei Med J* 2016;57:1361-9.
- 21
22 507 29. Mizuno T, Mizokami F, Fukami K, et al. The influence of severe
23
24 508 hypoalbuminemia on the half-life of vancomycin in elderly patients with
25
26 509 methicillin-resistant *Staphylococcus aureus* hospital-acquired pneumonia. *Clin*
27
28 510 *Interv Aging* 2013;8:1323-8.
- 29
30 511 30. Juneja M, Baidoo L, Schwartz M, et al. Geriatric inflammatory bowel disease:
31
32 512 phenotypic presentation, treatment patterns, nutritional status, outcomes, and
33
34 513 comorbidity. *Dig Dis Sci* 2012;57:2408-15.
- 35
36 514 31. Don B, Kaysen G. Serum albumin: relationship to inflammation and nutrition.
37
38 515 *Semin Dial* 2004;17:432-7.
- 39
40 516 32. Magnussen B, Oren Gradel K, Gorm Jensen T, et al. Association between
41
42 517 hypoalbuminaemia and mortality in patients with community-acquired
43
44 518 bacteraemia is primarily related to acute disorders. *PLoS ONE* 2016;11:e0160466.
- 45
46 519 33. Maitra S, Burkart J, Fine A, et al. Patients on chronic peritoneal dialysis for ten
47
48 520 years or more in North America. *Perit Dial Int* 2000;20 Suppl 2:S127.
- 49
50 521 34. Sakaci T, Ahabap E, Koc Y, et al. Clinical outcomes and mortality in elderly
51
52 522 peritoneal dialysis patients. *Clinics (Sao Paulo)* 2015;70:363-8.
- 53
54 523 35. Valderrabano F, Jofre R, Lopez-Gomez JM. Quality of life in end-stage renal
55
56 524 disease patients. *Am J Kidney Dis* 2001;38:443-64.
- 57
58 525 36. Joly D, Anglicheau D, Alberti C, et al. Octogenarians reaching end-stage renal
59
60

- 1
2
3
4 526 disease: cohort study of decision-making and clinical outcomes. *J Am Soc*
5
6 527 *Nephrol* 2003;14:1012-21.
- 7
8 528 37. Tennankore KK, Bargman JM. Nutrition and the kidney: recommendations for
9
10 529 peritoneal dialysis. *Adv Chronic Kidney Dis* 2013;20:190-201.
- 11
12 530 38. Hsieh YP, Chang CC, Wen YK, et al. Predictors of peritonitis and the impact of
13
14 531 peritonitis on clinical outcomes of continuous ambulatory peritoneal dialysis
15
16 532 patients in Taiwan—10 years' experience in a single center. *Perit Dial Int*
17
18 533 2014;34:85.
- 19
20 534 39. Szeto C, Kwan B, Chow K, et al. Predictors of residual renal function decline in
21
22 535 patients undergoing continuous ambulatory peritoneal dialysis. *Perit Dial Int*
23
24 536 2015;35:180-8.
- 25
26 537 40. Vilar E, Farrington K. Emerging importance of residual renal function in
27
28 538 end-stage renal failure. *Semin Dial* 2011;24:487-94.
- 29
30 539 41. Raimann J, Kitzler T, Levin N. Factors affecting loss of residual renal function(s)
31
32 540 in dialysis. *Contrib Nephrol* 2012;178:150-6.
- 33
34 541 42. Harris S, Lamping D, Brown E, et al. Clinical outcomes and quality of life in
35
36 542 elderly patients on peritoneal dialysis versus hemodialysis. *Perit Dial Int*
37
38 543 2002;22:463-70.
- 39
40 544 43. van Diepen AT, van Esch S, Struijk DG, et al. The first peritonitis episode alters
41
42 545 the natural course of peritoneal membrane characteristics in peritoneal dialysis
43
44 546 patients. *Perit Dial Int* 2015;35:324-32.

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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

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

Causative organisms	Early-onset peritonitis		Late-onset peritonitis		P value
	episodes	(n)	episodes	(n)	
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					
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)	

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576 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/m ²)	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/m ²)	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			

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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

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4 619 **Figure legends**

5
6 620 **Fig.1. Technique survival according to EOP and LOP.**

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8 621 Death were censored form the technique survival analysis. Log rank test Chi-square

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10 622 3.943, $P=0.047$

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16 625 **Fig.2. Patient survival according to EOP and LOP.**

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18 626 Patients who transferred to HD were censored form the patient survival analysis. Log

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20 627 rank test Chi-square 4.060, $P=0.044$

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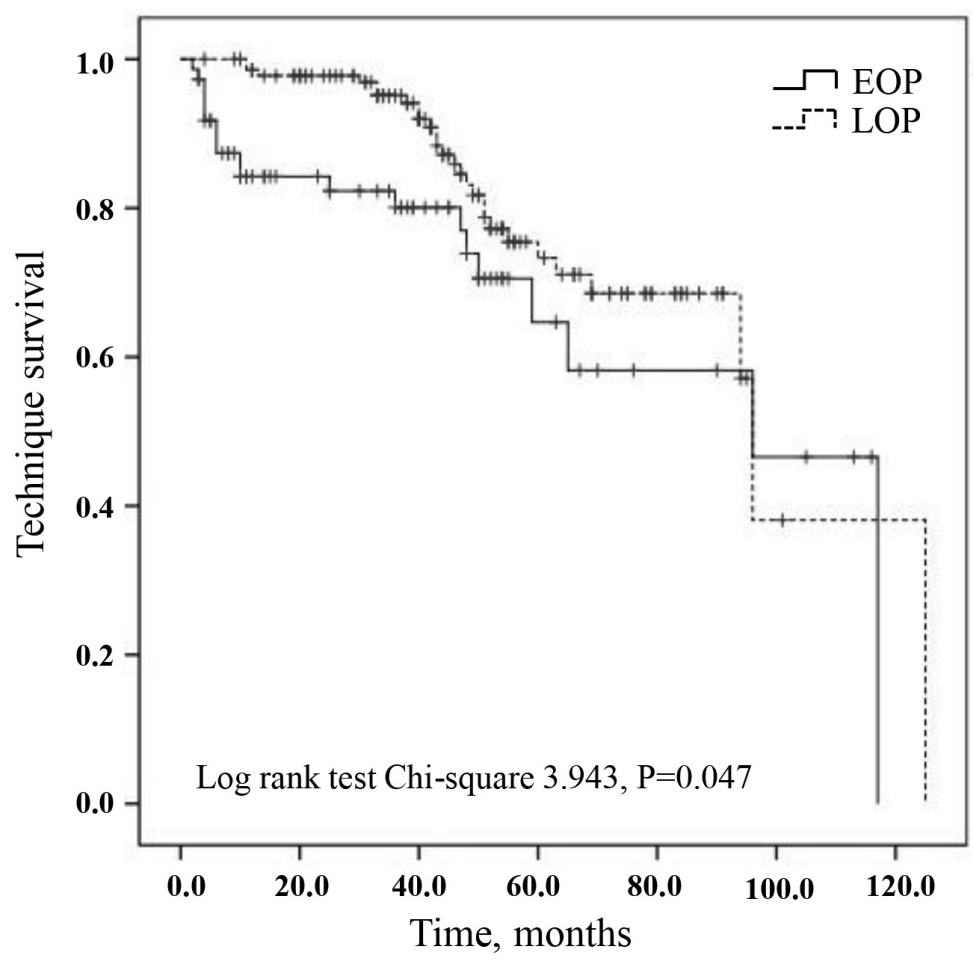


Fig.1. Technique survival according to EOP and LOP. Death were censored form the technique survival analysis. Log rank test Chi-square 3.943, P=0.047

113x111mm (300 x 300 DPI)

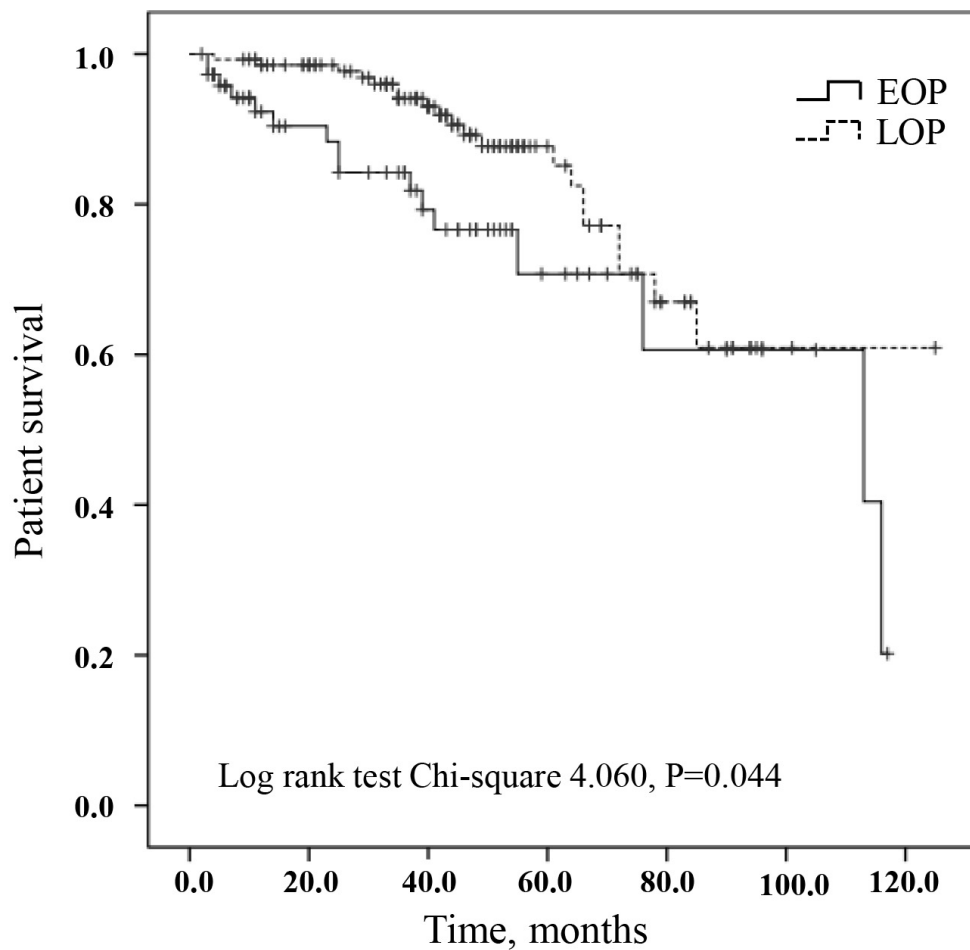


Fig.2. Patient survival according to EOP and LOP. Patients who transferred to HD were censored from the patient survival analysis. Log rank test Chi-square 4.060, P=0.044

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
		<p>Objectives To investigate the risk factors associated with early-onset peritonitis (EOP) and its influence on patients' technique survival and mortality.</p> <p>Study design Retrospective, cohort study.</p> <p>Setting Three peritoneal dialysis units in Shanghai.</p> <p>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).</p> <p>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.</p> <p>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.</p> <p>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.</p>	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 \pm 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 Commission (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.

BMJ Open

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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Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Patient-centred medicine
Keywords:	Peritoneal dialysis, Early-onset peritonitis, Risk factors, Outcomes

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4 1 **The analysis of risk factors and outcome in peritoneal dialysis patients with**
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6 2 **early-onset peritonitis: a multi-center, retrospective, cohort study.**

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8 3 Xiaoyan Ma^{1*}, Yingfeng Shi^{1*}, Min Tao^{1*}, Xiaolu Jiang^{1*}, Yi Wang¹, Xiujuan Zang²,
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10 4 Lu Fang¹, Wei Jiang¹, Lin Du¹, Dewei Jin¹, Shougang Zhuang^{1,3}, Na Liu¹

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26 12 *These authors make an equal contribution to this study.

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34 16 district, Shanghai 200120, China. **E-mail:** naliubrown@163.com.

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4 29 **ABSTRACT**

5 30 **Objectives** To investigate the risk factors associated with early-onset peritonitis
6
7 31 (EOP) and its influence on patients' technique survival and mortality.

8
9 32 **Study design** Retrospective, cohort study.

10
11 33 **Setting** Three peritoneal dialysis units in Shanghai.

12
13 34 **Participants** PD patients from June 1, 2006, to May 1, 2018, were recruited and
14
15 35 followed up until December 31, 2018. According to time-to-first episode of
16
17 36 peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis
18
19 37 (≤ 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139).

20
21 38 **Primary and secondary outcome measures** EOP was defined as the first episode of
22
23 39 peritonitis occurring within 6 months after the initiation of peritoneal dialysis (PD).
24
25 40 The outcomes were all-cause mortality and technique failure.

26
27 41 **Results** Of the 357 patients, 74 (20.7%) patients developed their first episode of
28
29 42 peritonitis within the first 6 months. Compared with the LOP group, the EOP group
30
31 43 had older ages, more female patients, higher Charlson comorbidity index (CCI) score,
32
33 44 lower serum albumin levels and renal function at the time of initiation of PD and
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35 45 higher diabetes mellitus and peritonitis rates ($P<0.05$). Staphylococcus was the most
36
37 46 common Gram-positive organism in both EOP and LOP groups. The multivariate
38
39 47 logistic regression analysis showed that factors associated with EOP included a higher
40
41 48 CCI score (odds ratio (OR) 1.285, $P=0.011$), lower serum albumin level (OR 0.924,
42
43 49 $P=0.016$) and lower Kt/V (OR 0.600, $P=0.018$) at start of PD. In the Cox proportional
44
45 50 hazards model, EOP was more likely a predictor of technique failure (hazard ratio
46
47 51 (HR) 1.801, $P=0.051$). There was no difference between EOP and LOP for all-cause
48
49 52 mortality.

50
51 53 **Conclusion** A higher CCI score and lower serum albumin level and Kt/V at PD
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53 54 initiation were significantly associated with EOP. EOP also predicted a high
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55 55 peritonitis rate and poor clinical outcomes.

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4 57 **KEY WORDS** Peritoneal dialysis; Early-onset peritonitis; Risk factors; Outcomes.
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11 59 **ARTICLE SUMMARY**

12 60 **Strengths and limitations of this study**

- 13 61 1. There is a strict exclusion criteria based on PD histories.
- 14
15 62 2. We conducted a multi-center study which ensured sufficient power in obtaining
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17
18 63 the risk factors of EOP.
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21 64 3. This was a retrospective cohort study, lacking of some objective information such
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23
24 65 as education level, economic development and living standard, which may cause
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27 66 bias.
- 28
29 67 4. Our study lacked of the adjustment of different center factors (education,
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31
32 68 re-training and home visit) in the multivariate analysis.
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35 69 5. Although this was a multicenter study, the sample size was relatively small.
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38 39 71 **INTRODUCTION**

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41 72 In developing countries, the number of peritoneal dialysis (PD) patients has been
42
43 73 increasing over time.^{1 2} Peritoneal dialysis (PD)-related peritonitis is a serious
44
45 74 complication during PD therapy and remains the major reason for technique failure.³
46
47 75 Severe and prolonged peritonitis leads to structural and functional alterations of the
48
49 76 peritoneal membrane, eventually leading to peritoneal fibrosis.⁴ Therefore, finding the
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51 77 risk factors for peritonitis in the early stage of PD would help to reduce technique
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53 78 failures and mortality of PD.

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55 79 The definition of early-onset peritonitis varies widely between studies, which
56
57 80 generally refers to peritoneal dialysis related peritonitis occurring within 3-24 months
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59 81 after surgical catheterization.⁵⁻⁸ Previous studies showed that the first episode of

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4 82 peritonitis in PD patients could significantly affect the prognosis of end-stage renal
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6 83 disease (ESRD) patients.⁹ However, few studies have specifically examined the risk
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8 84 factors for peritonitis in the early PD period. And most of these were observational
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10 85 cohort studies carried out in single centers,^{5 10 11} limiting the generalizability of their
11
12 86 observed outcomes. To determine the risk factors for early-onset peritonitis in
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14 87 Chinese CKD patients and its influence on patients' technique survival and mortality,
15
16 88 we conducted this multiple-center, retrospective cohort study.

17 89

19 90 **METHODS**

21 91 **Study Population**

22
23 92 This was a multi-center retrospective cohort study included 357 patients with ESRD
24
25 93 who underwent PD in Department of Nephrology in Baoshan branch of Shanghai
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27 94 First People's Hospital, Shanghai Songjiang District Central Hospital and Shanghai
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29 95 East Hospital, Tongji University School of Medicine. All incident PD patients from
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31 96 June 1, 2006, to May 1, 2018, were recruited and followed up until December 31,
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33 97 2018. This study was conducted according to the guidelines of the Helsinki
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35 98 Declaration. The human research ethics committees approved this study and agreed to
36
37 99 collect the information from the hospital databases. They waived the need for
38
39 100 participant consent (The human research ethics committees included the Human
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41 101 Research Ethics Committee of Shanghai East Hospital Affiliated to Tongji University
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43 102 School of Medicine, Human Research Ethics Committee of Shanghai Songjiang
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45 103 District Central Hospital and the Human Research Ethics Committee of Baoshan
46
47 104 Branch of Shanghai First People's Hospital). The exclusion criteria were as follows:
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49 105 patients who had been using PD for fewer than 90 days, patients with an age younger
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51 106 than 18 years and patients who initiated PD in other PD centers and previously
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53 107 accepted HD or kidney transplantation. There are 19 PD patients suffer the peritonitis
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55 108 within the first 3 months, 6 subjects died, 3 patients transferred to hemodialysis, 0
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57 109 patients underwent renal transplantation, 10 patients continued peritoneal dialysis.
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59 110 While these 10 PD patients lacked of the information of peritoneal equilibration test.

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4 111 Patients were followed until any of the following events: death, a change to HD, renal
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6 112 transplantation or until December 31, 2018. According to the Chinese Peritoneal
7
8 113 Dialysis Guideline, we adopted standardized surgical catheterization technique.¹² We
9
10 114 chose Tenckhoff silicone tube with double polyester sleeve. Double-purse string
11
12 115 suture or double-layer suture was adopted to fix the catheter. Fine needle and thick
13
14 116 line were used to prevent peripheral tube leakage. The exit direction of catheter tunnel
15
16 117 was downward and outward, and the outer polyester sleeve was 2 to 3 cm away from
17
18 118 the exit. All the surgical operations are performed in the operating room. The single
19
20 119 dose intravenous antibiotic 30 minutes before surgery is recommended to prevent
21
22 120 infection.¹³ The first or second generation cephalosporin is suggested.^{13 14} According
23
24 121 to the ISPD peritonitis recommendations,¹³⁻¹⁵ we daily topical application of
25
26 122 mupirocin ointment to the catheter exit site to prevent exit site infection. Patients
27
28 123 initiated PD by Dianeal with 1.5% or 2.5% dextrose (Baxter Healthcare, Guangzhou,
29
30 124 China). Dialysate concentration was 1.5% dextrose and replaced every four hours
31
32 125 during the day, while 2.5% at night and kept in the body. A total of 213 patients who
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34 126 had at least one episode of peritonitis. According to time-to-first episode of
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36 127 peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis
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38 128 (≤ 6 months, n=74) and late-onset peritonitis (> 6 months, n=139). We collected
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40 129 baseline characteristics within 1-3 months from the start of PD, including
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42 130 demographic data (age, gender, smoking, drinking, CCI, BMI), medical history,
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44 131 drug-taking history, biochemical data (hemoglobin, serum electrolyte, fasting blood
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46 132 glucose, total cholesterol, total triglyceride, high-density lipoprotein cholesterol,
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48 133 low-density lipoprotein cholesterol, and serum albumin, uric acid, creatinine, blood
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50 134 urea nitrogen, estimated glomerular filtration rate (eGFR), the clearance rate of urea
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52 135 nitrogen (Kt/V), cause of ESRD, peritonitis episodes. Peritoneal fluid effluent from
53
54 136 patients with peritonitis was collected and cultured for 1 to 5 days to identify the
55
56 137 bacterial flora in the dialysate.
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139 **Primary and secondary outcome measures**

140 Early-onset peritonitis was defined as the first episode of peritonitis occurring within
141 6 months after the initiation of peritoneal dialysis (PD). This definition is consistent
142 with other published article.^{8 16} The outcomes were all-cause mortality and technique
143 failure.

145 **Study definitions**

146 Diagnostic criteria for peritonitis based on the 2010 International Society for
147 Peritoneal Dialysis (ISPD) guidelines.¹⁵ Patients diagnosed as peritonitis should meet
148 at least two of the following three standards: (1) Clinical symptoms or signs of
149 peritonitis; (2) Leucocyte count (at least 100/mm³) and polymorphonuclear
150 neutrophilic cells proportion (at least 50%) in peritoneal fluid effluent; (3) Related
151 pathogens in smear or culture of peritoneal fluid. Early-onset peritonitis was defined
152 as the first episode of peritonitis occurring within 6 months after the initiation of PD.
153 The outcomes were all-cause mortality and technique failure. Death was an end-point
154 event in the patient survival analysis. Relapse was defined as an episode occurring
155 within 4 weeks of completion of therapy of a prior episode with the same organism,¹³
156 recurrence referred to an episode occurring within 4 weeks of completion of therapy
157 of a prior episode but with a different organism.¹³ Instead of transfer to HD therapy
158 permanently, both relapse and recurrence were treated by antibiotics and continued
159 PD treatment. Complete cure was defined as the resolution of peritonitis without
160 relapse or recurrence by antibiotics alone.⁷ However, some of refractory peritonitis
161 failed to clear up effluent after 5 days of appropriate antibiotics and transferred to HD
162 permanently. We classified this part of patients into “transfer to hemodialysis”. Other
163 parts of HD patients were due to the serious tunnel infection with peritonitis and
164 ultrafiltration failure induced by encapsulating peritoneal sclerosis. Patients who
165 transferred to HD were censored form the patient survival analysis, and death was
166 censored for technique failure. Technique failure was defined as the transfer to HD

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4 167 therapy permanently (lasted for 30 days or more) due to ultrafiltration failure,
5 168 peritonitis, exit-site infection and other operational problems.¹⁷
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9 170 **Patient and public involvement**

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11 171 No patient was involved in the design or conduct of the study, but the results of the
12
13 172 study will be shared to patients coming for follow-up.
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17 174 **Statistical analysis**

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19
20 175 All statistical analyses were performed by SPSS 20.0 for Windows (IBM Corp.,
21
22 176 Armonk, NY, USA). The normal distributed data were showed as mean±standard
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24 177 deviation (SD) and the skewed data were showed as median values with the 25th to
25
26 178 75th percentile intervals. Categorical data were expressed as frequency (n) and
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28 179 percentage (%). As for normally distributed data, student's t-test is using for
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30 180 analyzing the differences between the EOP group and LOP group, while one-way
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36 183 Fisher's exact test for categorical data. The Kaplan-Meier survival curves were drawn
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38 184 for each event of interest (technique survival and patient survival) and the log-rank
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40 185 test was used to compare curves. Univariate Cox proportional hazards regression was
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42 186 used to select significant factors associated with study outcomes. Variables whose
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44 187 $P < 0.10$ were selected for inclusion in the final multivariate Cox model. Multivariate
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46 188 logistic regression was calculated to select significant risk factors for EOP and the
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48 189 inclusion standard was also $P < 0.10$. Collinearity of variables was tested. A two-tailed
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50 190 P value < 0.05 was considered statistically significant.
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53 192 **RESULTS**

54 193 **Patient Characteristics**

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58 194 A total of 357 patients with ESRD underwent CAPD in three dialysis centers in
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4 195 Shanghai during the study period. All patients used Dianeal with 1.5% or 2.5%
5
6 196 dextrose. The first episode of peritonitis was experienced by 74 (20.7%) patients
7
8 197 within 6 months after the start of PD. 11 (11/61) in Shanghai East Hospital, 22
9
10 198 (22/142) in Shanghai Songjiang District Central Hospital, 41 (41/154) in Baoshan
11
12 199 branch of Shanghai First People's Hospital. Median follow-up time for the 357
13
14 200 patients was 33.0 months (interquartile range 14.0-50.0 months). There were 211
15
16 201 males (59.1%) with an average age of 61.6 ± 14.0 years, and 145 females (40.9%)
17
18 202 with an average age of 65.3 ± 12.9 years. The most common primary renal diseases
19
20 203 were chronic glomerulonephritis (43.1%) and diabetic nephropathy (34.2%).
21
22 204 Compared with the LOP patients, the EOP patient group had older ages, more female
23
24 205 patients, higher Charlson comorbidity index (CCI) score and lower serum albumin
25
26 206 levels, renal function and Kt/V at the time of initiation of PD and higher diabetes
27
28 207 mellitus ($P < 0.05$). The percentage of patients experienced more than 3 peritonitis
29
30 208 episodes in EOP group (55.4%) is higher than LOP group (33.8%). Additional
31
32 209 demographic and laboratory characteristics of the study population are present in
33
34 210 Table 1.

211

212 **Causative organisms**

213 In table 2, among 213 patients with peritonitis, 47 (22.1%) were due to Gram-positive
214 organisms, 24 (11.3%) were due to Gram-negative organisms, 6 (2.8%) were due to
215 fungi, 1 (0.4%) were due to multiple organisms, and 135 (63.4%) were
216 culture-negative. Staphylococcus was the most common Gram-positive organism in
217 both groups. Compared with the EOP patient group, the LOP patient group had more
218 culture-negative peritonitis (89.2% vs. 14.9%, $P < 0.001$). The incidences of
219 culture-negative peritonitis were 37.1% (13/35) in Shanghai East Hospital, 71.7%
220 (38/53) in Shanghai Songjiang District Central Hospital, 67.2% (84/125) in Baoshan
221 branch of Shanghai First People's Hospital ($P = 0.002$).

222

223 **Outcomes**

224 The total peritonitis rate was 0.490 episodes per patient-year (213 patients presented
225 509 episodes of peritonitis during 1039.58 patient-years of follow-up). The peritonitis
226 rate in EOP group was 0.960 episodes per patient-year (74 patients presented 209
227 episodes of peritonitis during 217.75 patient-years of follow-up). The peritonitis rate
228 in LOP group was 0.542 episodes per patient-year (139 patients presented 300
229 episodes of peritonitis during 553.58 patient-years of follow-up). The peritonitis rates
230 in Shanghai East Hospital , Shanghai Songjiang District Central Hospital and
231 Baoshan Branch of Shanghai First People's Hospital were 0.41, 0.31 and 0.61
232 episodes per patient-year respectively. Early-onset first episode of peritonitis had a
233 lower cure rate (17.6% vs 33.8%, Table 2.), higher rate of transferring to
234 hemodialysis (27.0% vs 19.4%, Table 2.), and higher mortality (21.6% vs 14.4%,
235 Table 2.) compared to late-onset first episode of peritonitis.

237 **Technique failure**

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

246 **All-cause mortality**

247 During the study period, a total of 52 patients died: 16 patients in the EOP group and
248 20 patients in the LOP group. Variables with P value < 0.10 in univariate Cox
249 regression analysis, including the time to first peritonitis (EOP vs. LOP), age, serum
250 albumin and total Kt/V, were chosen for further adjustment in multivariate Cox

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4 251 proportional hazards model. After adjustment, there was no significant difference
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6 252 between the EOP and LOP groups (Table 3). Fig. 2 describes cumulative survival by
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8 253 EOP and LOP groups using the Kaplan-Meier analysis. Compared with LOP group,
9
10 254 cumulative survival was lower in the EOP group (Log rank 4.060, $P=0.044$).

11 255

12 256 **Risk factors of early-onset peritonitis**

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16 257 Variables in Table 1 were tried in a univariate logistic regression model, and only
17
18 258 variables with P value < 0.10 for peritonitis were depicted in Table 4. Based on the
19
20 259 simple logistic regression analysis of risk factors associated with EOP, we constructed
21
22 260 a multiple logistic regression model using variables including gender, age, CCI score,
23
24 261 diabetes, serum albumin and Kt/V. We found that higher CCI score (OR=1.285,
25
26 262 95%CI 1.058-1.561, $P=0.011$), lower serum albumin level (OR=0.924, 95%CI
27
28 263 0.867-0.985, $P=0.016$) and Kt/V (OR=0.600, 95%CI 0.394-0.915, $P=0.018$) at the
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30 264 start of PD, were significantly associated with EOP (Table 4).

31 265

32 266 **DISCUSSION**

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37 267 Our retrospective cohort study of 357 PD patients showed that 74 (20.7%) patients in
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39 268 three Shanghai dialysis centers developed the first episodes of peritonitis within the
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41 269 first 6 months. Higher CCI score, lower serum albumin level and Kt/V at the start of
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43 270 PD, were significantly associated with EOP. In addition, an early peritonitis onset
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45 271 predicted a high peritonitis rate and technique failure.

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47 272 Early-onset peritonitis is a major complication of peritoneal dialysis, directly or
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49 273 indirectly causing the abandon of dialysis treatment. In this study, among 213 patients
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51 274 with peritonitis, 47 (22.1%) were due to Gram-positive organisms, 24 (11.3%) were
52
53 275 due to Gram-negative organisms, 6 (2.8%) were due to fungi. Staphylococcus was the
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55 276 most common Gram-positive organism in both early-onset and late-onset peritonitis.
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57 277 This bacterial flora distribution and high incidence of staphylococcus were similar to
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59 278 previous reports.¹⁸⁻²⁰ Fungal peritonitis was rare in PD patients, but could bring out
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4 279 irreversible peritoneal damage.²¹ Recent clinical studies confirmed that the incidence
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6 280 of fungal peritonitis was only 3%-6%,²¹ while the relative mortality rate was up to
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8 281 20%-30%.²² The culture-negative proportion for the first peritonitis episode was high
9
10 282 in the LOP patients (89.2%). And the incidences of culture-negative peritonitis were
11
12 283 37.1% (13/35) in Shanghai East Hospital, 71.7% (38/53) in Shanghai Songjiang
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14 284 District Central Hospital, 67.2% (84/125) in Baoshan branch of Shanghai First
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16 285 People's Hospital ($P=0.002$). The high culture-negative proportion may primary
17
18 286 attributed to early antibiotic treatment and limited effluent culture technique in
19
20 287 small-scale PD units. Before 2014, the technology of blood culture for PD effluent
21
22 288 has not been widely adopted by small-scale district hospitals in Shanghai. In the
23
24 289 district PD units, dialysate was inoculated onto solid medium and then incubated only
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26 290 in aerobic environment. It accounted for about 60% of culture-negative peritonitis
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28 291 patients in this investigation. Since 2015, all these three units in Shanghai choose
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30 292 blood-culture bottle for the preferred technique to culture microorganism in PD
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32 293 effluent. Lacking centrifugation of PD effluent and recent antibiotic usage may the
33
34 294 major reasons for the rest of 40% negative effluent cultures in this investigation. In
35
36 295 addition, culture negative peritonitis was higher in LOP than EOP group in the same
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38 296 study period. Because LOP patients underwent dialysis more than 6 months and have
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40 297 more experience in peritoneal dialysis. In the early stage of peritonitis, some of these
41
42 298 experienced PD patients will take dialysate to wash the peritoneum to relieve
43
44 299 abdominal pain. Diluted peritoneal fluid will result in a high negative rate of
45
46 300 peritoneal effluent culture. Considering the high culture negative rate in this study,
47
48 301 our three PD units will take a series of measures to improve our culture methods,
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50 302 including centrifugation of PD effluent, incubation in aerobic, microaerophilic and
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52 303 anaerobic environments, using antibiotic neutralization bottle and so on.^{13 14}

54 304 By the end of the study, 509 episodes of peritonitis occurred in 213 patients, and
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56 305 the peritonitis rate was 0.490 episodes per patient-year. The peritonitis rates in
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58 306 Shanghai East Hospital, Shanghai Songjiang District Central Hospital and Baoshan
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4 307 Branch of Shanghai First People's Hospital were 0.41, 0.31 and 0.61 episodes per
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6 308 patient-year respectively. Recently, some investigations from other areas of China
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8 309 have indicated that the peritonitis rate was 0.196 episodes per patient-year in Taiwan
9
10 310 ⁵, 0.158 episodes per patient-year in Guangzhou,⁷ 0.296 episodes per patient-year in
11
12 311 Suzhou ¹⁶ and 0.158 per patient-year in Hangzhou ⁸. Peritonitis rate in our study is
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14 312 higher than the rest of China. Among the early-onset peritonitis patients who had ≥ 3
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16 313 episodes of peritonitis, 25 patients from EOP group experienced recurrent peritonitis,
17
18 314 16 patients from EOP group experienced repeat peritonitis. 43.8% repeat patients
19
20 315 were staphylococcal peritonitis. And 75% EOP patients with ≥ 3 episodes of peritonitis
21
22 316 came from Baoshan Branch of Shanghai First People's Hospital. Most of them are
23
24 317 fishermen and live in the Chongming Island. Since the poorer economic abilities and
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26 318 living conditions, they are easy to malnutrition and suffer peritonitis again [13, 14].
27
28 319 And lacking of home visit by PD nurses makes it difficult to determine which patients
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30 320 require PD re-training. Lacking of technical improvement in small-scale PD units is
31
32 321 also the important reason for high peritonitis rate.

322 Our study found that lower serum albumin was one of the major risk factors for
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324 early-onset peritonitis. Loss of protein would cause negative nitrogen balance and
325
326 malnutrition, leading to a decline in immune function and increased susceptibility to
327
328 pathogenic microorganisms.²³ Malnutrition was one of the most common
329
330 complications in PD patients, and plasma albumin level was an important clinical
331
332 predictor. Hypoalbuminemia was proved to be related with malnutrition, protein
333
334 losses, and inflammation.^{24 25} Wang Qin et al. discovered that patients with an initial
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336 serum albumin level less than 2.9 g/dL had a higher incidence of peritonitis and
337
338 regarded hypoalbuminemia as an independent predictor for subsequent peritonitis at
339
340 the start of PD therapy.²⁶ Further studies demonstrated that low serum albumin level
341
342 increased all-cause, cardiovascular, and infection related mortality in both PD and HD
343
344 patients.²⁷ In addition to peritoneal infection, hypoalbuminemia was also found to be
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346 associated with septicemia, pneumonia and other inflammatory responses.²⁸⁻³² In this

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4 335 study, we reaffirmed that a low baseline serum albumin level is an independent risk
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6 336 factors for EOP (OR=0.924, 95%CI 0.867-0.985, P=0.016).

7
8 337 Although older age is not an independent risk factor for EOP, baseline data
9
10 338 showed that patients in EOP group older than LOP group (65.87±13.20 vs.
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12 339 61.40±13.53, P=0.022). It was reported that elder patients were more likely to
13
14 340 progress to a worse outcome, including HD, renal transplantation or death.³³
15
16 341 Incidence of malnutrition in elderly PD patients was more common than young and
17
18 342 middle-aged patients. Together with cardiovascular diseases, cerebrovascular disease,
19
20 343 hearing and visual impairments, all of these factors increase and aggravate the episode
21
22 344 of peritonitis.³⁴⁻³⁶ Malnutrition in elder not only affected the quality of dialysis
23
24 345 patients' life, but also was an important factor in comorbidity and mortality.³⁷ Other
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26 346 elements that increased the peritonitis susceptibility in elderly patients included
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28 347 generalized functional deterioration, weakened immune system,³⁸ combined chronic
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30 348 diseases, bad eyesight, poor aseptic concept, lack of compliance and living alone.
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32 349 Their atypical clinical symptoms of peritonitis could be regarded as another essential
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34 350 reason. Up-regulated pain threshold, unobtrusive bellyache and mild subjective
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36 351 symptoms might cover up early-onset peritonitis until the occurrence of liquid
37
38 352 turbidity, which would delay the best time for treatment.

39
40 353 Comparison in biochemical indicators shown that Kt/V and residual renal
41
42 354 function decreased significantly after early-onset peritonitis. Multivariate logistic
43
44 355 regression showed that lower total Kt/V (OR=0.600, 95%CI 0.394-0.915, P=0.018) at
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46 356 the start of PD were associated with EOP. These results suggest that early infection
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48 357 with peritonitis might further worsen renal function, especially the scavenging
49
50 358 capacity of solutes by residual kidney. Early inflammatory response and renal
51
52 359 function damage might be the underlying causes of peritonitis. Some studies
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54 360 suggested that the survival rate of PD patients depends more on residual renal
55
56 361 function than the peritoneal cleaning capacity.³⁹⁻⁴¹ Harris et al. further put forward
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58 362 that residual renal function less than $4 \text{ ml}\cdot\text{min}^{-1}\cdot 1.73\text{m}^{-2}$ was associated with high
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4 363 mortality during peritoneal dialysis.⁴² Therefore, we should pay close attention to the
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6 364 change of residual renal function when monitoring the adequacy of dialysis.

7
8 365 The relationship between peritonitis and technique failure and death have been
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10 366 investigated in previous Chinese single-center studies.^{7 8} A study in Chinese Zhejiang
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12 367 province showed that, EOP was a significant predictor of all-cause mortality. As for
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14 368 technique failure, they found no significant differences between EOP and LOP.⁸
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16 369 However, a study in Chinese Guangzhou province indicated that technique failure in
17
18 370 EOP group was lower than LOP group, but patient survival did not differ between the
19
20 371 two groups.⁷ Our present study showed that EOP was more likely a predictor of
21
22 372 technique failure (HR=1.801, 95%CI 0.996-3.257, P=0.051). There were no
23
24 373 differences between EOP and LOP for all-cause mortality. These conclusions might
25
26 374 be limited by regional and demographic differences in different dialysis center.
27
28 375 However, all three studies indicated that patients who experienced peritonitis early
29
30 376 after the initiation of PD were likely having more episodes of peritonitis. Repeating
31
32 377 peritonitis in EOP patients have an obvious impact on membrane permeability,
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34 378 increasing severe systemic inflammation, reducing ultrafiltration and leading to worse
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36 379 clinical outcomes.⁴³ Thus, appropriately dealing with the risk factors of early-onset
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38 380 peritonitis will be good to reduce infection incidence, raise therapeutic effect of PD,
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40 381 improve patient's life quality and prognosis.

41
42 382 There are several limitations to this study. Firstly, this was a retrospective cohort
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44 383 study, lacking of some objective information such as education level, economic
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46 384 development and living standard, which may cause bias. Secondly, our study lacked
47
48 385 of the adjustment of different center factors (education, re-training and home visit) in
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50 386 the multivariate analysis. Thirdly, although this was a multicenter study, the sample
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52 387 size was relatively small. Further larger size and prospective investigation are
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54 388 necessary.

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57
58 390 **CONCLUSION**

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4 391 In summary, this retrospective cohort study found that a higher CCI score and lower
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6 392 serum albumin and Kt/V before PD were significantly associated with EOP. In
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8 393 addition, an early peritonitis onset predicted a high peritonitis rate and worse clinical
9
10 394 outcomes. Understanding the risk factors for EOP helps to develop effective measures
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12 395 to prevent or delay the complication of peritoneal dialysis as much as possible.
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25
26 402

27 28 403 **Author Contributors**

29
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31
32 405 performed the statistical analysis and wrote the manuscript; X.M., Y.S., M.T., X.J.,
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35
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37
38 408 design of the study and edited the manuscript. All authors contributed to data
39
40 409 interpretation and revisions of the manuscript critically for important intellectual
41
42 410 content. All authors approved the final version of the submitted manuscript and
43
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13
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15
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17
18 426 **Ethics approval and consent to participate**

19
20 427 The study was conducted according to the guidelines of the Helsinki Declaration and
21
22 428 was approved by the Human Research Ethics Committee of Shanghai East Hospital
23
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25
26 430 Committee of Shanghai Songjiang District Central Hospital and the Human Research
27
28 431 Ethics Committee of Baoshan Branch of Shanghai First People's Hospital. The human
29
30 432 research ethics committees approved this study and agreed to collect the information
31
32 433 from the hospital databases. They waived the need for participant consent.

33
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37 435 **Data availability statement** The data sets generated and analyzed during the
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39
40 436 current study are available from the corresponding author upon reasonable request.

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10
11 447 **REFERENCES**

- 12
13 448 1. Li PK, Chow KM, Van de Luitgaarden MW, et al. Changes in the worldwide
14
15 449 epidemiology of peritoneal dialysis. *Nat Rev Nephrol* 2017;13:90-103.
16
17 450 2. Jain AK, Blake P, Cordy P, et al. Global trends in rates of peritoneal dialysis. *J Am*
18
19 451 *Soc Nephrol* 2012;23:533-44.
20
21 452 3. Cho Y, Johnson DW. Peritoneal dialysis-related peritonitis: towards improving
22
23 453 evidence, practices, and outcomes. *Am J Kidney Dis* 2014;64:278-89.
24
25 454 4. Thirugnanasambathan T, Hawley CM, Badve SV, et al. Repeated peritoneal
26
27 455 dialysis-associated peritonitis: a multicenter registry study. *Am J Kidney Dis*
28
29 456 2012;59:84-91.
30
31 457 5. Hsieh YP, Wang SC, Chang CC, et al. The negative impact of early peritonitis on
32
33 458 continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 2014;34:627-35.
34
35 459 6. See EJ, Johnson DW, Hawley CM, et al. Early peritonitis and its outcome in
36
37 460 incident peritoneal dialysis patients *Perit Dial Int* 2017.
38
39 461 7. Wu H, Huang R, Yi C, et al. Risk factors for early-onset peritonitis in southern
40
41 462 Chinese peritoneal dialysis patients. *Perit Dial Int* 2016;36:640-46.
42
43 463 8. Tian Y, Xie X, Xiang S, et al. Risk factors and outcomes of early-onset peritonitis
44
45 464 in Chinese peritoneal dialysis patients. *Kidney Blood Press Res* 2017;42:1266-76.
46
47 465 9. Béchade C, Guittet L, Evans D, et al. Early failure in patients starting peritoneal
48
49 466 dialysis: a competing risks approach. *Nephrol Dial Transplant* 2014;29:2127-35.
50
51 467 10. Feng S, Wang Y, Qiu B, et al. Impact of early-onset peritonitis on mortality and
52
53 468 technique survival in peritoneal dialysis patients. *Springerplus* 2016;5:1676.
54
55 469 11. Fourtounas C, Savidaki E, Dousdabanis P, et al. Peritonitis during the first year
56
57 470 after commencement of peritoneal dialysis has an impact on technique survival
58
59 471 and patient morbidity. *Adv Perit Dial* 2006;22:50-4.

- 1
2
3
4 472 12. Chinese Expert Group on Peritoneal Dialysis Catheterization. Chinese guidelines
5 for peritoneal dialysis catheterization. *Chinese J Nephrol* 2016;32:867-71.
6 473
7
8 474 13. Li PK, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update
9 on prevention and treatment. *Perit Dial Int* 2016;36:481-508.
10 475
11
12 476 14. Szeto CC, Li PK, Johnson DW, et al. ISPD catheter-related infection
13 recommendations: 2017 Update. *Perit Dial Int* 2017;37:141-54.
14 477
15
16 478 15. Li PK, Szeto CC, Piraino B, et al. Peritoneal dialysis-related infections
17 recommendations: 2010 update. *Perit Dial Int* 2010;30:393-423.
18 479
19
20 480 16. Wang Z, Jiang L, Feng S, et al. Early peritonitis is an independent risk factor for
21 mortality in elderly peritoneal dialysis patients. *Kidney Blood Press Res*
22 481 2015;40:298-305.
23 482
24
25
26 483 17. Shen JI, Mitani AA, Saxena AB, et al. Determinants of peritoneal dialysis
27 technique failure in incident US patients. *Perit Dial Int* 2013;33:155-66.
28 484
29
30 485 18. Hsieh Y, Wang S, Chang C, et al. The negative impact of early peritonitis on
31 continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 2014;34:627-35.
32 486
33
34 487 19. Barretti P, Doles J, Pinotti D, et al. Efficacy of antibiotic therapy for peritoneal
35 dialysis-associated peritonitis: a proportional meta-analysis. *BMC Infect Dis*
36 488 2014;14:445.
37 489
38
39
40 490 20. Govindarajulu S, Hawley C, McDonald S, et al. Staphylococcus aureus peritonitis
41 in Australian peritoneal dialysis patients: predictors, treatment, and outcomes in
42 491 503 cases. *Perit Dial Int* 2010;30:311-9.
43 492
44
45
46 493 21. Matuszkiewicz-Rowinska J. Update on fungal peritonitis and its treatment. *Perit*
47 494 *Dial Int* 2009;29 Suppl 2:S161-5.
48
49
50 495 22. Szeto C, Chow K. Gram-negative peritonitis--the Achilles heel of peritoneal
51 dialysis? *Perit Dial Int* 2007;27 Suppl 2:S267-71.
52 496
53
54 497 23. Li Z, An X, Mao H, et al. Association between depression and
55 malnutrition-inflammation complex syndrome in patients with continuous
56 498 ambulatory peritoneal dialysis. *Int Urol Nephrol* 2011;43:875-82.
57 499
58
59
60

- 1
2
3
4 500 24. Fanali G, di Masi A, Trezza V, et al. Human serum albumin: from bench to
5
6 501 bedside. *Mol Aspects Med* 2012;33:209-90.
- 7
8 502 25. Yu Z, Tan B, Dainty S, et al. Hypoalbuminaemia, systemic albumin leak and
9
10 503 endothelial dysfunction in peritoneal dialysis patients. *Nephrol Dial Transplant*
11
12 504 2012;27:4437-45.
- 13
14 505 26. Wang Q, Bernardini J, Piraino B, et al. Albumin at the start of peritoneal dialysis
15
16 506 predicts the development of peritonitis. *Am J Kidney Dis* 2003;41:664-9.
- 17
18 507 27. Mehrotra R, Duong U, Jiwakanon S, et al. Serum albumin as a predictor of
19
20 508 mortality in peritoneal dialysis: comparisons with hemodialysis. *Am J Kidney Dis*
21
22 509 2011;58:418-28.
- 23
24 510 28. Seo M, Choa M, You J, et al. Hypoalbuminemia, low base excess values, and
25
26 511 tachypnea predict 28-day mortality in severe sepsis and septic shock patients in
27
28 512 the emergency department. *Yonsei Med J* 2016;57:1361-9.
- 29
30 513 29. Mizuno T, Mizokami F, Fukami K, et al. The influence of severe
31
32 514 hypoalbuminemia on the half-life of vancomycin in elderly patients with
33
34 515 methicillin-resistant *Staphylococcus aureus* hospital-acquired pneumonia. *Clin*
35
36 516 *Interv Aging* 2013;8:1323-8.
- 37
38 517 30. Juneja M, Baidoo L, Schwartz M, et al. Geriatric inflammatory bowel disease:
39
40 518 phenotypic presentation, treatment patterns, nutritional status, outcomes, and
41
42 519 comorbidity. *Dig Dis Sci* 2012;57:2408-15.
- 43
44 520 31. Don B, Kaysen G. Serum albumin: relationship to inflammation and nutrition.
45
46 521 *Semin Dial* 2004;17:432-7.
- 47
48 522 32. Magnussen B, Oren Gradel K, Gorm Jensen T, et al. Association between
49
50 523 hypoalbuminaemia and mortality in patients with community-acquired
51
52 524 bacteraemia is primarily related to acute disorders. *PLoS ONE* 2016;11:e0160466.
- 53
54 525 33. Maitra S, Burkart J, Fine A, et al. Patients on chronic peritoneal dialysis for ten
55
56 526 years or more in North America. *Perit Dial Int* 2000;20 Suppl 2:S127.
- 57
58 527 34. Sakaci T, Ahbap E, Koc Y, et al. Clinical outcomes and mortality in elderly
59
60

- 1
2
3
4 528 peritoneal dialysis patients. *Clinics (Sao Paulo)* 2015;70:363-8.
- 5
6 529 35. Valderrabano F, Jofre R, Lopez-Gomez JM. Quality of life in end-stage renal
7
8 530 disease patients. *Am J Kidney Dis* 2001;38:443-64.
- 9
10 531 36. Joly D, Anglicheau D, Alberti C, et al. Octogenarians reaching end-stage renal
11
12 532 disease: cohort study of decision-making and clinical outcomes. *J Am Soc*
13
14 533 *Nephrol* 2003;14:1012-21.
- 15
16 534 37. Tennankore KK, Bargman JM. Nutrition and the kidney: recommendations for
17
18 535 peritoneal dialysis. *Adv Chronic Kidney Dis* 2013;20:190-201.
- 19
20 536 38. Hsieh YP, Chang CC, Wen YK, et al. Predictors of peritonitis and the impact of
21
22 537 peritonitis on clinical outcomes of continuous ambulatory peritoneal dialysis
23
24 538 patients in Taiwan—10 years' experience in a single center. *Perit Dial Int*
25
26 539 2014;34:85.
- 27
28 540 39. Szeto C, Kwan B, Chow K, et al. Predictors of residual renal function decline in
29
30 541 patients undergoing continuous ambulatory peritoneal dialysis. *Perit Dial Int*
31
32 542 2015;35:180-8.
- 33
34 543 40. Vilar E, Farrington K. Emerging importance of residual renal function in
35
36 544 end-stage renal failure. *Semin Dial* 2011;24:487-94.
- 37
38 545 41. Raimann J, Kitzler T, Levin N. Factors affecting loss of residual renal function(s)
39
40 546 in dialysis. *Contrib Nephrol* 2012;178:150-6.
- 41
42 547 42. Harris S, Lamping D, Brown E, et al. Clinical outcomes and quality of life in
43
44 548 elderly patients on peritoneal dialysis versus hemodialysis. *Perit Dial Int*
45
46 549 2002;22:463-70.
- 47
48 550 43. van Diepen AT, van Esch S, Struijk DG, et al. The first peritonitis episode alters
49
50 551 the natural course of peritoneal membrane characteristics in peritoneal dialysis
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52 552 patients. *Perit Dial Int* 2015;35:324-32.
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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

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

Causative organisms	Early-onset peritonitis		Late-onset peritonitis		P value
	episodes	(n)	episodes	(n)	
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					
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)	

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579 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/m ²)	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/m ²)	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			

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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

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4 625 **Figure legends**

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6 626 **Fig.1. Technique survival according to EOP and LOP.**

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8 627 Death were censored form the technique survival analysis. Log rank test Chi-square

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10 628 3.943, $P=0.047$

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16 631 **Fig.2. Patient survival according to EOP and LOP.**

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18 632 Patients who transferred to HD were censored form the patient survival analysis. Log

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20 633 rank test Chi-square 4.060, $P=0.044$

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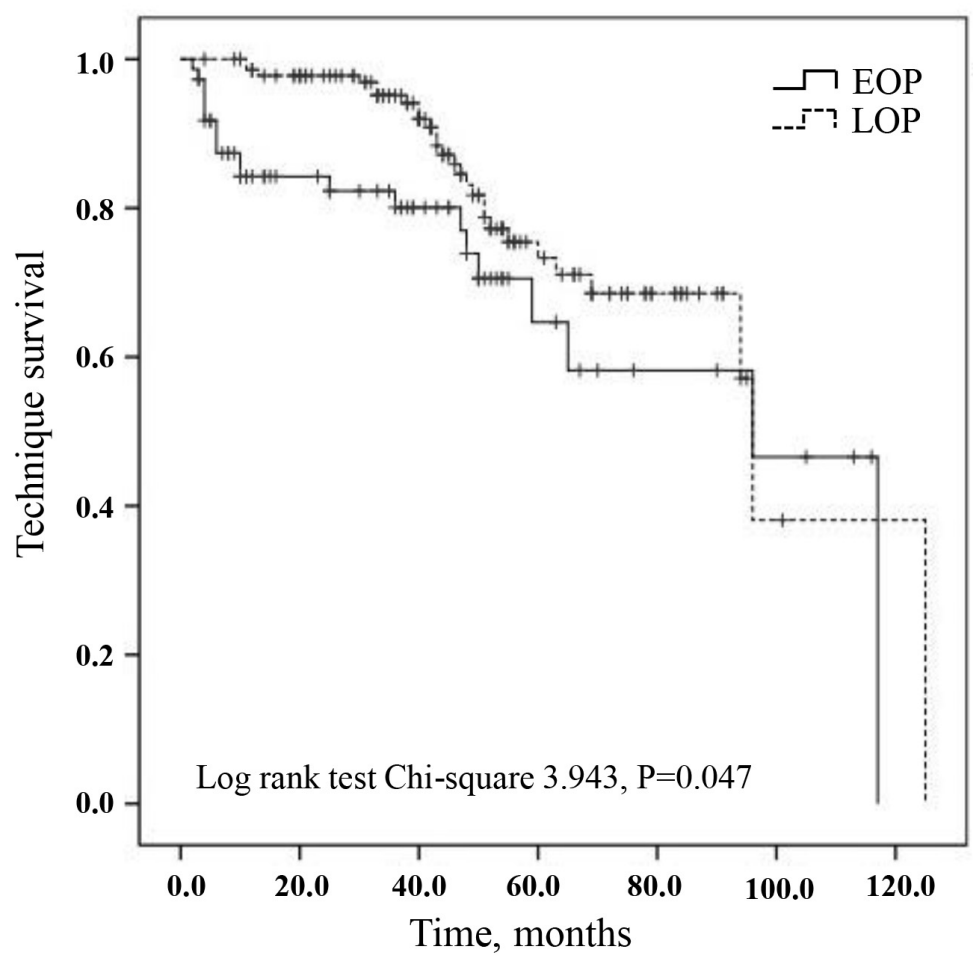


Fig.1. Technique survival according to EOP and LOP. Death were censored form the technique survival analysis. Log rank test Chi-square 3.943, P=0.047

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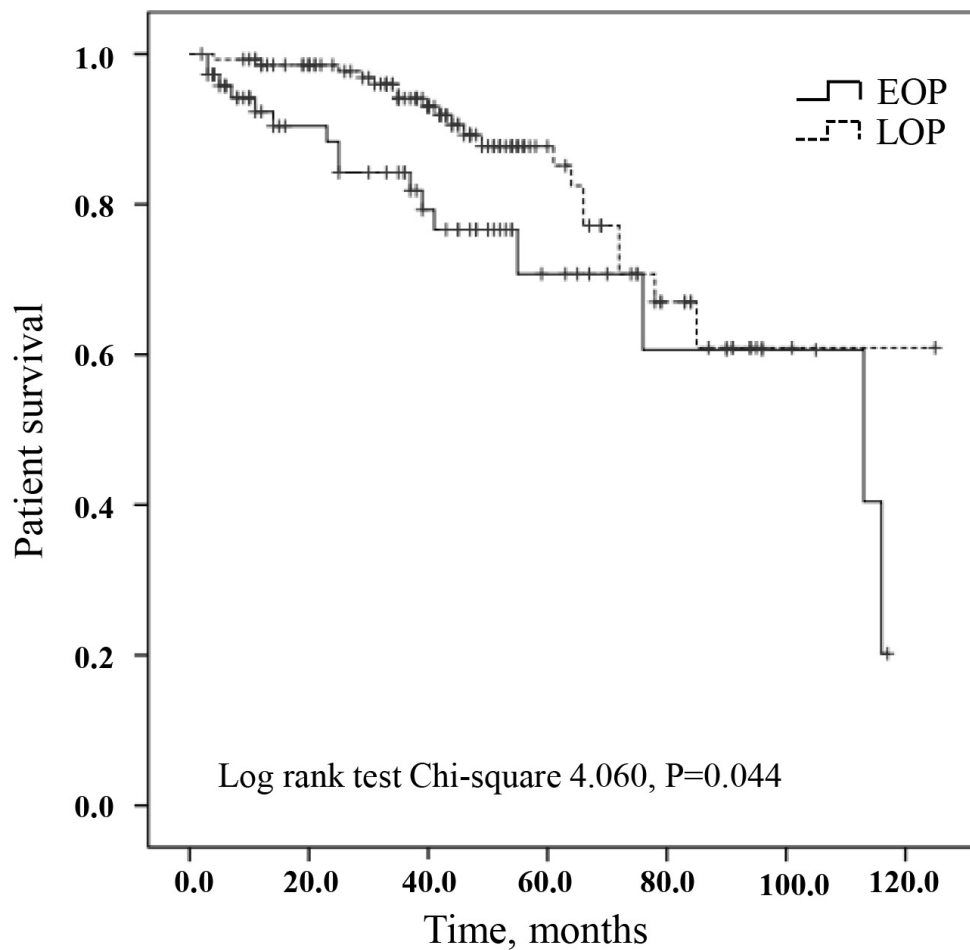


Fig.2. Patient survival according to EOP and LOP. Patients who transferred to HD were censored from the patient survival analysis. Log rank test Chi-square 4.060, P=0.044

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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
		<p>Objectives To investigate the risk factors associated with early-onset peritonitis (EOP) and its influence on patients' technique survival and mortality.</p> <p>Study design Retrospective, cohort study.</p> <p>Setting Three peritoneal dialysis units in Shanghai.</p> <p>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).</p> <p>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.</p> <p>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.</p> <p>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.</p>	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 \pm 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

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15	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
16	Results			
17 18 19 20 21 22 23	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
24 25 26 27 28 29 30	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
31 32 33 34 35	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
36 37 38 39 40 41 42 43 44 45 46	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 Commission (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.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-029949.R3
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4 1 **The analysis of risk factors and outcome in peritoneal dialysis patients with**
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6 2 **early-onset peritonitis: a multi-center, retrospective, cohort study.**

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4 29 **ABSTRACT**

5 30 **Objectives** To investigate the risk factors associated with early-onset peritonitis
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8 31 (EOP) and its influence on patients' technique survival and mortality.

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10 32 **Study design** Retrospective, cohort study.

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12 33 **Setting** Three peritoneal dialysis units in Shanghai.

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14 34 **Participants** PD patients from June 1, 2006, to May 1, 2018, were recruited and
15
16 35 followed up until December 31, 2018. According to time-to-first episode of
17
18 36 peritonitis, patients were divided into non-peritonitis (n=144), early-onset peritonitis
19
20 37 (≤ 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139).

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22 38 **Primary and secondary outcome measures** EOP was defined as the first episode of
23
24 39 peritonitis occurring within 6 months after the initiation of peritoneal dialysis (PD).
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26 40 The outcomes were all-cause mortality and technique failure.

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28 41 **Results** Of the 357 patients, 74 (20.7%) patients developed their first episode of
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30 42 peritonitis within the first 6 months. Compared with the LOP group, the EOP group
31
32 43 had older ages, more female patients, higher Charlson comorbidity index (CCI) score,
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34 44 lower serum albumin levels and renal function at the time of initiation of PD and
35
36 45 higher diabetes mellitus and peritonitis rates ($P<0.05$). Staphylococcus was the most
37
38 46 common Gram-positive organism in both EOP and LOP groups. The multivariate
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40 47 logistic regression analysis showed that factors associated with EOP included a higher
41
42 48 CCI score (odds ratio (OR) 1.285, $P=0.011$), lower serum albumin level (OR 0.924,
43
44 49 $P=0.016$) and lower Kt/V (OR 0.600, $P=0.018$) at start of PD. In the Cox proportional
45
46 50 hazards model, EOP was more likely a predictor of technique failure (hazard ratio
47
48 51 (HR) 1.801, $P=0.051$). There was no difference between EOP and LOP for all-cause
49
50 52 mortality.

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52 53 **Conclusion** A higher CCI score and lower serum albumin level and Kt/V at PD
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54 54 initiation were significantly associated with EOP. EOP also predicted a high
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56 55 peritonitis rate and poor clinical outcome.

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4 57 **KEY WORDS** Peritoneal dialysis; Early-onset peritonitis; Risk factors; Outcomes.
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10 59 **ARTICLE SUMMARY**

11 60 **Strengths and limitations of this study**

- 12 61 1. There is a strict exclusion criteria based on PD histories.
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14 62 2. We conducted a multi-center study which ensured sufficient power in obtaining
15
16 63 the risk factors of EOP.
17
18 64 3. This was a retrospective cohort study, lacking of some objective information such
19
20 65 as education level, economic development and living standard, which may cause
21
22 66 bias.
23
24 67 4. Our study was lack of the adjustment of different center factors (education,
25
26 68 re-training and home visit) in the multivariate analysis.
27
28 69 5. Although this was a multicenter study, the sample size was relatively small.
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32 71 **INTRODUCTION**

33
34 72 In developing countries, the number of peritoneal dialysis (PD) patients has been
35
36 73 increasing over time.^{1 2} Peritoneal dialysis (PD)-related peritonitis is a serious
37
38 74 complication during PD therapy and remains the major reason for technique failure.³
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40 75 Severe and prolonged peritonitis leads to structural and functional alterations of the
41
42 76 peritoneal membrane, eventually leading to peritoneal fibrosis.⁴ Therefore,
43
44 77 identification of the risk factors for peritonitis in the early stage of PD would help to
45
46 78 reduce technique failures and mortality of PD.

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48 79 The definition of early-onset peritonitis varies widely between studies, which
49
50 80 generally refers to peritoneal dialysis related peritonitis occurring within 3-24 months
51
52 81 after surgical catheterization.⁵⁻⁸ Previous studies showed that the first episode of
53
54 82 peritonitis in PD patients could significantly affect the prognosis of end-stage renal
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56 83 disease (ESRD) patients.⁹ However, few studies have specifically examined the risk
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58 84 factors for peritonitis in the early period of PD. And most of these were observational
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4 85 cohort studies carried out in single center,^{5 10 11} limiting the generalizability of their
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6 86 observed outcomes. To determine the risk factors for early-onset peritonitis in
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8 87 Chinese CKD patients and its influence on patients' technique survival and mortality,
9
10 88 we conducted this multiple-center, retrospective cohort study.

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13 90 **METHODS**

15 91 **Study Population**

17 92 This was a multi-center retrospective cohort study included 357 patients with ESRD
18
19 93 who underwent PD in the Department of Nephrology in Baoshan branch of Shanghai
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21 94 First People's Hospital, Shanghai Songjiang District Central Hospital and Shanghai
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23 95 East Hospital, Tongji University School of Medicine. All incident PD patients from
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25 96 June 1, 2006, to May 1, 2018, were recruited and followed up until December 31,
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27 97 2018. This study was conducted according to the guidelines of the Helsinki
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29 98 Declaration. The human research ethics committees approved this study and agreed to
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31 99 collect the information from the hospital databases. They waived the need for
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34 100 participant consent (The human research ethics committees included the Human
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36 101 Research Ethics Committee of Shanghai East Hospital Affiliated to Tongji University
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38 102 School of Medicine, Human Research Ethics Committee of Shanghai Songjiang
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40 103 District Central Hospital and the Human Research Ethics Committee of Baoshan
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42 104 Branch of Shanghai First People's Hospital). The exclusion criteria were as follows:
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44 105 patients who had been using PD for fewer than 90 days, patients with an age younger
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46 106 than 18 years and patients who initiated PD in other PD centers and previously
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48 107 accepted HD or kidney transplantation. There are 19 PD patients who suffered the
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50 108 peritonitis within the first 3 months, 6 subjects died, 3 patients transferred to
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52 109 hemodialysis, 0 patients underwent renal transplantation, 10 patients continued
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54 110 peritoneal dialysis. While these 10 PD patients were lack of the information of
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56 111 peritoneal equilibration test. Patients were followed until any of the following events:
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58 112 death, a change to HD, renal transplantation or until December 31, 2018. According
59
60 113 to the Chinese Peritoneal Dialysis Guideline, we adopted standardized surgical

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4 114 catheterization technique.¹² We chose Tenckhoff silicone tube with double polyester
5
6 115 sleeve. Double-purse string suture or double-layer suture was adopted to fix the
7
8 116 catheter. Fine needle and thick line were used to prevent peripheral tube leakage. The
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10 117 exit direction of catheter tunnel was downward and outward, and the outer polyester
11
12 118 sleeve was 2 to 3 cm away from the exit. All the surgical operations are performed in
13
14 119 the operating room. The single dose intravenous antibiotic 30 minutes before surgery
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16 120 is recommended to prevent infection.¹³ The first or second generation cephalosporin
17
18 121 is suggested.^{13 14} According to the ISPD peritonitis recommendations,¹³⁻¹⁵ we daily
19
20 122 and topically applied mupirocin ointment to the catheter exit site to prevent exit site
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22 123 infection. Patients initiated PD by Dianeal with 1.5% or 2.5% dextrose (Baxter
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24 124 Healthcare, Guangzhou, China). Dialysate concentration was 1.5% dextrose and
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26 125 replaced every four hours during the day, while 2.5% at night and kept in the body. A
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28 126 total of 213 patients who had at least one episode of peritonitis. According to
29
30 127 time-to-first episode of peritonitis, patients were divided into non-peritonitis (n=144),
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32 128 early-onset peritonitis (≤ 6 months, n=74) and late-onset peritonitis (> 6 months,
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34 129 n=139). We collected baseline characteristics within 1-3 months from the start of PD,
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36 130 including demographic data (age, gender, smoking, drinking, CCI, BMI), medical
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38 131 history, drug-taking history, biochemical data (hemoglobin, serum electrolyte, fasting
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40 132 blood glucose, total cholesterol, total triglyceride, high-density lipoprotein
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42 133 cholesterol, low-density lipoprotein cholesterol, and serum albumin, uric acid,
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44 134 creatinine, blood urea nitrogen, estimated glomerular filtration rate (eGFR), the
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46 135 clearance rate of urea nitrogen (Kt/V), causes of ESRD, peritonitis episodes.
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48 136 Peritoneal fluid effluent from patients with peritonitis was collected and cultured for 1
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50 137 to 5 days to identify the bacterial flora in the dialysate.

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53 54 139 **Primary and secondary outcome measures**

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56 140 Early-onset peritonitis was defined as the first episode of peritonitis occurring within
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58 141 6 months after the initiation of peritoneal dialysis. This definition is consistent with
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4 142 other published article.^{8 16} The outcomes were all-cause mortality and technique
5 143 failure.

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10 145 **Study definitions**

11 146 Diagnostic criteria for peritonitis are based on the 2010 International Society for
12 Peritoneal Dialysis (ISPD) guidelines.¹⁵ Patients diagnosed as peritonitis should meet
13 147 at least two of the following three standards: (1) Clinical symptoms or signs of
14 148 peritonitis; (2) Leucocyte count (at least 100/mm³) and polymorphonuclear
15 149 neutrophilic cells proportion (at least 50%) in peritoneal fluid effluent; (3) Related
16 150 pathogens in smear or culture of peritoneal fluid. Early-onset peritonitis was defined
17 151 as the first episode of peritonitis occurring within 6 months after the initiation of PD.

18 152 The outcomes were all-cause mortality and technique failure. Death was an end-point
19 153 event in the patient survival analysis. Relapse was defined as an episode occurring
20 154 within 4 weeks of completion of therapy of a prior episode with the same organism,¹³
21 155 recurrence referred to an episode occurring within 4 weeks of completion of therapy
22 156 of a prior episode but with a different organism.¹³ Instead of transfer to HD therapy
23 157 permanently, patients with both relapse and recurrence were treated by antibiotics and
24 158 continued PD treatment. Complete cure was defined as the resolution of peritonitis
25 159 without relapse or recurrence by antibiotics alone.⁷ However, some of refractory
26 160 peritonitis failed to clear up effluent after 5 days of appropriate antibiotics. This
27 161 population of patients was transferred to HD permanently. We classified this
28 162 population of patients into “transfer to hemodialysis”. Other population of patients
29 163 who were transferred to HD were due to the serious tunnel infection with peritonitis
30 164 and ultrafiltration failure induced by encapsulating peritoneal sclerosis. Patients who
31 165 transferred to HD were censored from the patient survival analysis, and death was
32 166 censored for technique failure. Technique failure was defined as the transfer to HD
33 167 therapy permanently (lasted for 30 days or more) due to ultrafiltration failure,
34 168 peritonitis, exit-site infection and other operational problems.¹⁷
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6 171 **Patient and public involvement**

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8 172 No patient was involved in the design or conduct of the study, but the results of the
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10 173 study will be shared to patients coming for follow-up.

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14 175 **Statistical analysis**

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16 176 All statistical analyses were performed by using SPSS 20.0 for Windows (IBM Corp.,
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18 177 Armonk, NY, USA). The normal distributed data were showed as mean±standard
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20 178 deviation (SD) and the skewed data were showed as median values with the 25th to
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22 179 75th percentile intervals. Categorical data were expressed as frequency (n) and
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24 180 percentage (%). As for normally distributed data, student's t-test is used for analyzing
25
26 181 the differences between the EOP group and LOP group, while one-way ANOVA for
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28 182 differences among in non-peritonitis, EOP group and LOP groups. The Wilcoxon
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30 183 rank sum test for skewed continuous data and the Chi-square test or Fisher's exact test
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32 184 for categorical data. The Kaplan-Meier survival curves were drawn for each event of
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34 185 interest (technique survival and patient survival) and the log-rank test was used to
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36 186 compare curves. Univariate Cox proportional hazards regression was used to select
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38 187 significant factors associated with study outcomes. Variables with $P<0.10$ were
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40 188 selected for inclusion in the final multivariate Cox model. Multivariate logistic
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42 189 regression was calculated to select significant risk factors for EOP and the inclusion
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44 190 standard was also $P<0.10$. Collinearity of variables was tested. A two-tailed P value
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46 191 <0.05 was considered statistically significant.

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50 193 **RESULTS**

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52 194 **Patient characteristics**

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54 195 A total of 357 patients with ESRD underwent CAPD in three dialysis centers in
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56 196 Shanghai during the study period. All patients used Dianeal with 1.5% or 2.5%
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58 197 dextrose. The first episode of peritonitis was experienced by 74 (20.7%) patients
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4 198 within 6 months after the start of PD. 11 (11/61) in Shanghai East Hospital, 22
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6 199 (22/142) in Shanghai Songjiang District Central Hospital, 41 (41/154) in Baoshan
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8 200 branch of Shanghai First People's Hospital. Median follow-up time for the 357
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10 201 patients was 33.0 months (interquartile range 14.0-50.0 months). There were 211
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12 202 males (59.1%) with an average age of 61.6 ± 14.0 years, and 145 females (40.9%)
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14 203 with an average age of 65.3 ± 12.9 years. The most common primary renal diseases
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16 204 were chronic glomerulonephritis (43.1%) and diabetic nephropathy (34.2%).
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18 205 Compared with the LOP patients, the EOP patient group had older ages, more female
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20 206 patients, higher Charlson comorbidity index (CCI) score and lower serum albumin
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22 207 levels, renal function and Kt/V at PD initiation and higher diabetes mellitus ($P<0.05$).
23
24 208 The percentage of patients experienced more than 3 peritonitis episodes in EOP group
25
26 209 (55.4%) is higher than LOP group (33.8%). Additional demographic and laboratory
27
28 210 characteristics of the study population are presented in Table 1.

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31 32 212 **Causative organisms**

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34 213 In table 2, among 213 patients with peritonitis, 47 (22.1%) were due to Gram-positive
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36 214 organisms, 24 (11.3%) were due to Gram-negative organisms, 6 (2.8%) were due to
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38 215 fungi, 1 (0.4%) were due to multiple organisms, and 135 (63.4%) were
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40 216 culture-negative. Staphylococcus was the most common Gram-positive organism in
41
42 217 both groups. Compared with the EOP patient group, the LOP patient group had more
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44 218 culture-negative peritonitis (89.2% vs. 14.9%, $P<0.001$). The incidences of
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46 219 culture-negative peritonitis were 37.1% (13/35) in Shanghai East Hospital, 71.7%
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48 220 (38/53) in Shanghai Songjiang District Central Hospital, 67.2% (84/125) in Baoshan
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50 221 branch of Shanghai First People's Hospital ($P=0.002$).

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53 54 223 **Outcomes**

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56 224 The total peritonitis rate (in a population included EOP group, LOP group and
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58 225 peritonitis-free group) was 0.490 episodes per patient-year (213 patients presented
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4 226 509 episodes of peritonitis during 1039.58 patient-years of follow-up). The peritonitis
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6 227 rate (in a population included EOP group and LOP group) was 0.660 episodes per
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8 228 patient-year (213 patients presented 509 episodes of peritonitis during 771.33
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10 229 patient-years of follow-up). The peritonitis rate in EOP group was 0.960 episodes per
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12 230 patient-year (74 patients presented 209 episodes of peritonitis during 217.75
13
14 231 patient-years of follow-up). The peritonitis rate in LOP group was 0.542 episodes per
15
16 232 patient-year (139 patients presented 300 episodes of peritonitis during 553.58
17
18 233 patient-years of follow-up). The peritonitis rates in Shanghai East Hospital, Shanghai
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20 234 Songjiang District Central Hospital and Baoshan Branch of Shanghai First People's
21
22 235 Hospital were 0.41, 0.31 and 0.61 episodes per patient-year respectively. Early-onset
23
24 236 first episode of peritonitis had a lower cure rate (17.6% vs 33.8%, Table 2.), higher
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26 237 rate of transferring to hemodialysis (27.0% vs 19.4%, Table 2.), and higher mortality
27
28 238 (21.6% vs 14.4%, Table 2.) compared to late-onset first episode of peritonitis.

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31 32 240 **Technique failure**

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34 241 The variables including time to first peritonitis (EOP vs. LOP), age, sex, smoking,
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36 242 drinking, CCI, BMI, hemoglobin, total cholesterol, total triglyceride, serum albumin,
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38 243 total Kt/V and diabetes were calculated into the cox proportional hazards model for
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40 244 technique failure. And we found that EOP was associated with technique failure
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42 245 compared with the LOP group, with a hazard ratio (HR) of 1.801 (Table 3, $P=0.051$).
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44 246 Kaplan-Meier analysis showed that compared with LOP group, technique survival
45
46 247 was lower in the EOP group (Log rank 3.943, $P=0.047$, Fig.1).

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49 50 249 **All-cause mortality**

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52 250 During the study period, a total of 52 patients died: 16 patients in the EOP group and
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54 251 20 patients in the LOP group. Variables with P value < 0.10 in univariate Cox
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56 252 regression analysis, including the time to first peritonitis (EOP vs. LOP), age, serum
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58 253 albumin and total Kt/V, were chosen for further adjustment in multivariate Cox
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4 254 proportional hazards model. After adjustment, there was no significant difference
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6 255 between the EOP and LOP groups (Table 3). Fig. 2 describes cumulative survival by
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8 256 EOP and LOP groups using the Kaplan-Meier analysis. Compared with LOP group,
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10 257 cumulative survival was lower in the EOP group (Log rank 4.060, $P=0.044$).

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13 14 259 **Risk factors of early-onset peritonitis**

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16 260 Variables in Table 1 were tried in an univariate logistic regression model, and only
17
18 261 variables with P value < 0.10 for peritonitis were depicted in Table 4. Based on the
19
20 262 simple logistic regression analysis of risk factors associated with EOP, we constructed
21
22 263 a multiple logistic regression model using variables including gender, age, CCI score,
23
24 264 diabetes, serum albumin and Kt/V. We found that higher CCI score (OR=1.285,
25
26 265 95%CI 1.058-1.561, $P=0.011$), lower serum albumin level (OR=0.924, 95%CI
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28 266 0.867-0.985, $P=0.016$) and Kt/V (OR=0.600, 95%CI 0.394-0.915, $P=0.018$) at the
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30 267 start of PD, were significantly associated with EOP (Table 4).

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33 34 269 **DISCUSSION**

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37 270 Our retrospective cohort study of 357 PD patients showed that 74 (20.7%) patients in
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39 271 three Shanghai dialysis centers developed the first episodes of peritonitis within the
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41 272 first 6 months. Higher CCI score, lower serum albumin level and Kt/V at the start of
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43 273 PD, were significantly associated with EOP. In addition, an early peritonitis onset
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45 274 predicted a high peritonitis rate and technique failure.

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47 275 Early-onset peritonitis is a major complication of peritoneal dialysis, directly or
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49 276 indirectly causing the abandon of dialysis treatment. In this study, among 213 patients
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51 277 with peritonitis, 47 (22.1%) were due to Gram-positive organisms, 24 (11.3%) were
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53 278 due to Gram-negative organisms, 6 (2.8%) were due to fungi. Staphylococcus was the
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55 279 most common Gram-positive organism in both early-onset and late-onset peritonitis.
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57 280 This bacterial flora distribution and high incidence of staphylococcus were similar to
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59 281 previous reports.¹⁸⁻²⁰ Fungal peritonitis was rare in PD patients, but could bring out
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4 282 irreversible peritoneal damage.²¹ Recent clinical studies confirmed that the incidence
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6 283 of fungal peritonitis was only 3%-6%,²¹ while the relative mortality rate was up to
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8 284 20%-30%.²² The culture-negative proportion for the first peritonitis episode was high
9
10 285 in the LOP patients (89.2%). And the incidences of culture-negative peritonitis were
11
12 286 37.1% (13/35) in Shanghai East Hospital, 71.7% (38/53) in Shanghai Songjiang
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14 287 District Central Hospital, 67.2% (84/125) in Baoshan branch of Shanghai First
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16 288 People's Hospital ($P=0.002$). The high culture-negative proportion may primarily
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18 289 attribute to early antibiotic treatment and limited effluent culture technique in
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20 290 small-scale PD units. Before 2014, the technology of blood culture for PD effluent
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22 291 has not been widely adopted by small-scale district hospitals in Shanghai. In the
23
24 292 district PD units, dialysate was inoculated onto solid medium and then incubated only
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26 293 in aerobic environment. It accounted for about 60% of culture-negative peritonitis
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28 294 patients in this investigation. Since 2015, all these three units in Shanghai chose
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30 295 blood-culture bottle for the preferred technique to culture microorganism in PD
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32 296 effluent. Lacking centrifugation of PD effluent and recent antibiotic usage may be the
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34 297 major reasons for the rest of 40% negative effluent cultures in this investigation. In
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36 298 addition, culture negative peritonitis was higher in LOP than EOP group in the same
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38 299 study period, because LOP patients underwent dialysis more than 6 months and had
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40 300 more experience in peritoneal dialysis. In the early stage of peritonitis, some of
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42 301 experienced PD patients might take dialysate to wash the peritoneum to relieve
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44 302 abdominal pain. Diluted peritoneal fluid would result in a high negative rate of
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46 303 peritoneal effluent culture. Considering the high culture negative rate in this study,
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48 304 our three PD units will take a series of measures to improve our culture methods,
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50 305 including centrifugation of PD effluent, incubation in aerobic, microaerophilic and
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52 306 anaerobic environments, using antibiotic neutralization bottle and so on.^{13 14}

54 307 By the end of the study, 509 episodes of peritonitis occurred in 213 patients, and
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56 308 the peritonitis rate was 0.490 episodes per patient-year. The peritonitis rates in
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58 309 Shanghai East Hospital, Shanghai Songjiang District Central Hospital and Baoshan
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4 310 Branch of Shanghai First People's Hospital were 0.41, 0.31 and 0.61 episodes per
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6 311 patient-year respectively. Recently, some investigations from other areas of China
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8 312 have indicated that the peritonitis rate was 0.196 episodes per patient-year in Taiwan
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10 313 ⁵, 0.158 episodes per patient-year in Guangzhou,⁷ 0.296 episodes per patient-year in
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12 314 Suzhou ¹⁶ and 0.158 per patient-year in Hangzhou ⁸. Peritonitis rate in our study is
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14 315 higher than the rest of China. Among the early-onset peritonitis patients who had ≥ 3
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16 316 episodes of peritonitis, 25 patients from EOP group experienced recurrent peritonitis,
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18 317 16 patients from EOP group experienced repeat peritonitis. 43.8% repeat patients
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20 318 were staphylococcal peritonitis. And 75% EOP patients with ≥ 3 episodes of peritonitis
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22 319 came from Baoshan Branch of Shanghai First People's Hospital. Most of them are
23
24 320 fishermen and live in the Chongming Island. Since the poorer economic abilities and
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26 321 living conditions, they are easy to get malnutrition and suffer from peritonitis again. ²³
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28 322 ²⁴ And lacking of home visit by PD nurses makes it difficult to determine which
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30 323 patients require PD re-training. Lacking of technical improvement in small-scale PD
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32 324 units is also the important reason for high peritonitis rate.

34 325 The complete cure rate in our study was related low (EOP 17.6%, LOP 33.8%).
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36 326 All the PD patients from these three centers received prophylactic intravenous
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38 327 antibiotics prior to PD catheter insertion. However, most of antibiotics used are first
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40 328 or second generation cephalosporin. They may not cover all the Gram-negative
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42 329 organisms, thereby resulting in increased rate of relapse and recurrence. To address
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44 330 this issue, we may have to modify our empirical antibiotic regimen by using more
45
46 331 effective antibiotics such as third generation cephalosporin, and applying
47
48 332 individualized treatment strategy. In addition, patients with poorer economic abilities
49
50 333 and living conditions are easy to suffer malnutrition and peritonitis again. ^{23 24} Finally,
51
52 334 the reason for the low cure rate in this study may also include a considerable number
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54 335 of patients with hemodialysis due to other dialysis-related complications.

56 336 Our study indicated that lower serum albumin was one of the major risk factors
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58 337 for early-onset peritonitis. Loss of protein would cause negative nitrogen balance and
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4 338 malnutrition, leading to a decline in immune function and increased susceptibility to
5
6 339 pathogenic microorganisms.²⁵ Malnutrition was one of the most common
7
8 340 complications in PD patients, and plasma albumin level was an important clinical
9
10 341 predictor. Hypoalbuminemia was proved to be related with malnutrition, protein
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12 342 losses, and inflammation.^{26 27} Wang Qin et al. discovered that patients with an initial
13
14 343 serum albumin level less than 2.9 g/dL had a higher incidence of peritonitis and
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16 344 regarded hypoalbuminemia as an independent predictor for subsequent peritonitis at
17
18 345 the start of PD therapy.²⁸ Further studies demonstrated that low serum albumin level
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20 346 increased all-cause, cardiovascular, and infection related mortality in both PD and HD
21
22 347 patients.²⁹ In addition to peritoneal infection, hypoalbuminemia was also found to be
23
24 348 associated with septicemia, pneumonia and other inflammatory responses.³⁰⁻³⁴ In this
25
26 349 study, we reaffirmed that a low baseline serum albumin level is an independent risk
27
28 350 factors for EOP (OR=0.924, 95%CI 0.867-0.985, P=0.016).

30 351 Although older age is not an independent risk factor for EOP, baseline data
31
32 352 showed that patients in EOP group older than LOP group (65.87±13.20 vs.
33
34 353 61.40±13.53, P=0.022). It was reported that elder patients were more likely to
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36 354 progress to a worse outcome, including HD, renal transplantation or death.³⁵
37
38 355 Incidence of malnutrition in elderly PD patients was more common than young and
39
40 356 middle-aged patients. Together with cardiovascular diseases, cerebrovascular disease,
41
42 357 hearing and visual impairments, all of these factors increase and aggravate the episode
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44 358 of peritonitis.³⁶⁻³⁸ Malnutrition in elder not only affected the quality of dialysis
45
46 359 patients' life, but also was an important factor in comorbidity and mortality.³⁹ Other
47
48 360 elements that increased the peritonitis susceptibility in elderly patients included
49
50 361 generalized functional deterioration, weakened immune system,⁴⁰ combined chronic
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52 362 diseases, bad eyesight, poor aseptic concept, lack of compliance and living alone.
53
54 363 Their atypical clinical symptoms of peritonitis could be regarded as another essential
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56 364 reason. Up-regulated pain threshold, unobtrusive bellyache and mild subjective
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58 365 symptoms might cover up early-onset peritonitis until the occurrence of liquid
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4 366 turbidity, which would delay the best time for treatment.

5 367 Comparison in biochemical indicators revealed that Kt/V and residual renal
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7 368 function decreased significantly after early-onset peritonitis. Multivariate logistic
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9 369 regression showed that a lower total Kt/V (OR=0.600, 95%CI 0.394-0.915, P=0.018)
10
11 370 at the start of PD was associated with EOP. These results suggest that early infection
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13 371 with peritonitis might further worsen renal function, especially the scavenging
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15 372 capacity of solutes by residual kidney. Early inflammatory response and renal
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17 373 function damage might be the underlying causes of peritonitis. Some studies
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19 374 suggested that the survival rate of PD patients depends more on residual renal
20
21 375 function than the peritoneal cleaning capacity.⁴¹⁻⁴³ Harris et al. further put forward
22
23 376 that residual renal function less than $4 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73\text{m}^{-2}$ was associated with high
24
25 377 mortality during peritoneal dialysis.⁴⁴ Therefore, we should pay close attention to the
26
27 378 change of residual renal function when monitoring the adequacy of dialysis.

28
29 379 The relationship between peritonitis and technique failure and death have been
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31 380 investigated in previous Chinese single-center studies.^{7 8} A study in Chinese Zhejiang
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33 381 province showed that, EOP was a significant predictor of all-cause mortality. As for
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35 382 technique failure, they found no significant difference between EOP and LOP.⁸
36
37 383 However, a study in Chinese Guangzhou province indicated that technique failure in
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39 384 EOP group was lower than LOP group, but patient survival did not differ between two
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41 385 groups.⁷ Our present study showed that EOP was more likely a predictor of technique
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43 386 failure (HR=1.801, 95%CI 0.996-3.257, P=0.051). There was no difference between
44
45 387 EOP and LOP for all-cause mortality. These conclusions might be limited by regional
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47 388 and demographic differences in different dialysis centers. However, all three studies
48
49 389 indicated that patients who experienced peritonitis early after the initiation of PD tend
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51 390 to experience more episodes of peritonitis. Repeating peritonitis in EOP patients not
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53 391 only injury membrane permeability and reduce ultrafiltration, but also increase severe
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55 392 systemic inflammation, leading to worse clinical outcomes.⁴⁵ Thus, appropriately
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57 393 dealing with the risk factors of early-onset peritonitis will be good to reduce infection
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4 394 incidence, raise therapeutic effect of PD and improve patient's life quality and
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6 395 prognosis.

7
8 396 There are several limitations to this study. Firstly, this was a retrospective cohort
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10 397 study, lacking of some objective information such as education level, economic
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12 398 development and living standard, which may cause bias. Secondly, our study lacked
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14 399 of the adjustment of different center factors (education, re-training and home visit) in
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16 400 the multivariate analysis. Thirdly, although this was a multicenter study, the sample
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18 401 size was relatively small. Further larger size and prospective investigation are
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20 402 necessary.

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23 24 404 **CONCLUSION**

25
26 405 This retrospective cohort study found that a higher CCI score and lower serum
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28 406 albumin and Kt/V at PD initiation were significantly associated with EOP. In
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30 407 addition, an early peritonitis onset predicted a high peritonitis rate and worse clinical
31
32 408 outcomes. Understanding the risk factors for EOP will help to develop effective
33
34 409 measures to prevent or delay the complication of peritoneal dialysis as much as
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36 410 possible.

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50 417

51 52 418 **Author Contributors**

53
54 419 X.M., Y.S. M.T. and X.J. contributed equally to this work. X.M., Y.S. M.T. and X.J.
55
56 420 performed the statistical analysis and wrote the manuscript; X.M., Y.S., M.T., X.J.,
57
58 421 Y.W., D.J., L.F., W.J., L.D. and X.Z. participated in the data collection; X.M., Y.S.,
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4 422 S.Z. and N.L. contributed to discussion; X.M., S.Z. and N.L. participated in the
5
6 423 design of the study and edited the manuscript. All authors contributed to data
7
8 424 interpretation and revisions of the manuscript critically for important intellectual
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11
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37
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40 440

42 441 **Ethics approval and consent to participate**

43
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53
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55
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4 450 **Data availability statement** The data sets generated and analyzed during the
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6 451 current study are available from the corresponding author upon reasonable request.

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27 28 462 **REFERENCES**

- 29
30 463 1. Li PK, Chow KM, Van de Luitgaarden MW, et al. Changes in the worldwide
31
32 464 epidemiology of peritoneal dialysis. *Nat Rev Nephrol* 2017;13:90-103.
- 33
34 465 2. Jain AK, Blake P, Cordy P, et al. Global trends in rates of peritoneal dialysis. *J Am*
35
36 466 *Soc Nephrol* 2012;23:533-44.
- 37
38 467 3. Cho Y, Johnson DW. Peritoneal dialysis-related peritonitis: towards improving
39
40 468 evidence, practices, and outcomes. *Am J Kidney Dis* 2014;64:278-89.
- 41
42 469 4. Thirugnanasambathan T, Hawley CM, Badve SV, et al. Repeated peritoneal
43
44 470 dialysis-associated peritonitis: a multicenter registry study. *Am J Kidney Dis*
45
46 471 2012;59:84-91.
- 47
48 472 5. Hsieh YP, Wang SC, Chang CC, et al. The negative impact of early peritonitis on
49
50 473 continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 2014;34:627-35.
- 51
52 474 6. See EJ, Johnson DW, Hawley CM, et al. Early peritonitis and its outcome in
53
54 475 incident peritoneal dialysis patients. *Perit Dial Int* 2017.
- 55
56 476 7. Wu H, Huang R, Yi C, et al. Risk factors for early-onset peritonitis in Southern
57
58 477 Chinese peritoneal dialysis patients. *Perit Dial Int* 2016;36:640-46.
- 59
60

- 1
2
3
4 478 8. Tian Y, Xie X, Xiang S, et al. Risk factors and outcomes of early-onset peritonitis
5
6 479 in Chinese peritoneal dialysis patients. *Kidney Blood Press Res* 2017;42:1266-76.
- 7
8 480 9. Béchade C, Guittet L, Evans D, et al. Early failure in patients starting peritoneal
9
10 481 dialysis: a competing risks approach. *Nephrol Dial Transplant* 2014;29:2127-35.
- 11
12 482 10. Feng S, Wang Y, Qiu B, et al. Impact of early-onset peritonitis on mortality and
13
14 483 technique survival in peritoneal dialysis patients. *Springerplus* 2016;5:1676.
- 15
16 484 11. Fourtounas C, Savidaki E, Dousdabanis P, et al. Peritonitis during the first year
17
18 485 after commencement of peritoneal dialysis has an impact on technique survival
19
20 486 and patient morbidity. *Adv Perit Dial* 2006;22:50-4.
- 21
22 487 12. Catheterization CEGoPD. Chinese guidelines for peritoneal dialysis
23
24 488 catheterization. *Chinese J Nephrol* 2016;32:867-71.
- 25
26 489 13. Li PK, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update
27
28 490 on prevention and treatment. *Perit Dial Int* 2016;36:481-508.
- 29
30 491 14. Szeto CC, Li PK, Johnson DW, et al. ISPD catheter-related infection
31
32 492 recommendations: 2017 Update. *Perit Dial Int* 2017;37:141-54.
- 33
34 493 15. Li PK, Szeto CC, Piraino B, et al. Peritoneal dialysis-related infections
35
36 494 recommendations: 2010 update. *Perit Dial Int* 2010;30:393-423.
- 37
38 495 16. Wang Z, Jiang L, Feng S, et al. Early peritonitis is an independent risk factor for
39
40 496 mortality in elderly peritoneal dialysis patients. *Kidney Blood Press Res*
41
42 497 2015;40:298-305.
- 43
44 498 17. Shen JI, Mitani AA, Saxena AB, et al. Determinants of peritoneal dialysis
45
46 499 technique failure in incident US patients. *Perit Dial Int* 2013;33:155-66.
- 47
48 500 18. Hsieh Y, Wang S, Chang C, et al. The negative impact of early peritonitis on
49
50 501 continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 2014;34:627-35.
- 51
52 502 19. Barretti P, Doles J, Pinotti D, et al. Efficacy of antibiotic therapy for peritoneal
53
54 503 dialysis-associated peritonitis: a proportional meta-analysis. *BMC Infect Dis*
55
56 504 2014;14:445.
- 57
58 505 20. Govindarajulu S, Hawley C, McDonald S, et al. Staphylococcus aureus peritonitis
59
60

- 1
2
3
4 506 in Australian peritoneal dialysis patients: predictors, treatment, and outcomes in
5
6 507 503 cases. *Perit Dial Int* 2010;30:311-9.
7
8 508 21. Matuszkiewicz-Rowinska J. Update on fungal peritonitis and its treatment. *Perit*
9
10 509 *Dial Int* 2009;29 Suppl 2:S161-5.
11
12 510 22. Szeto C, Chow K. Gram-negative peritonitis--the Achilles heel of peritoneal
13
14 511 dialysis? *Perit Dial Int* 2007;27 Suppl 2:S267-71.
15
16 512 23. Prasad N, Gupta A, Sharma RK, et al. Impact of nutritional status on peritonitis in
17
18 513 CAPD patients. *Perit Dial Int* 2007;27:42-7.
19
20 514 24. Wang Q, Bernardini J, Piraino B, et al. Albumin at the start of peritoneal dialysis
21
22 515 predicts the development of peritonitis. *Am J Kidney Dis* 2003;41:664-9.
23
24 516 25. Li Z, An X, Mao H, et al. Association between depression and
25
26 517 malnutrition-inflammation complex syndrome in patients with continuous
27
28 518 ambulatory peritoneal dialysis. *Int Urol Nephrol* 2011;43:875-82.
29
30 519 26. Fanali G, di Masi A, Trezza V, et al. Human serum albumin: from bench to
31
32 520 bedside. *Mol Aspects Med* 2012;33:209-90.
33
34 521 27. Yu Z, Tan B, Dainty S, et al. Hypoalbuminaemia, systemic albumin leak and
35
36 522 endothelial dysfunction in peritoneal dialysis patients. *Nephrol Dial Transplant*
37
38 523 2012;27:4437-45.
39
40 524 28. Wang Q, Bernardini J, Piraino B, et al. Albumin at the start of peritoneal dialysis
41
42 525 predicts the development of peritonitis. *Am J Kidney Dis* 2003;41:664-9.
43
44 526 29. Mehrotra R, Duong U, Jiwakanon S, et al. Serum albumin as a predictor of
45
46 527 mortality in peritoneal dialysis: comparisons with hemodialysis. *Am J Kidney Dis*
47
48 528 2011;58:418-28.
49
50 529 30. Seo M, Choa M, You J, et al. Hypoalbuminemia, low base excess values, and
51
52 530 tachypnea predict 28-day mortality in severe sepsis and septic shock patients in
53
54 531 the emergency department. *Yonsei Med J* 2016;57:1361-9.
55
56 532 31. Mizuno T, Mizokami F, Fukami K, et al. The influence of severe
57
58 533 hypoalbuminemia on the half-life of vancomycin in elderly patients with
59
60

- 1
2
3
4 534 methicillin-resistant staphylococcus aureus hospital-acquired pneumonia. *Clin*
5
6 535 *Interv Aging* 2013;8:1323-8.
- 7
8 536 32. Juneja M, Baidoo L, Schwartz M, et al. Geriatric inflammatory bowel disease:
9
10 537 phenotypic presentation, treatment patterns, nutritional status, outcomes, and
11
12 538 comorbidity. *Dig Dis Sci* 2012;57:2408-15.
- 13
14 539 33. Don B, Kaysen G. Serum albumin: relationship to inflammation and nutrition.
15
16 540 *Semin Dial* 2004;17:432-7.
- 17
18 541 34. Magnussen B, Oren Gradel K, Gorm Jensen T, et al. Association between
19
20 542 hypoalbuminaemia and mortality in patients with community-acquired
21
22 543 bacteraemia is primarily related to acute disorders. *PLoS ONE* 2016;11:e0160466.
- 23
24 544 35. Maitra S, Burkart J, Fine A, et al. Patients on chronic peritoneal dialysis for ten
25
26 545 years or more in North America. *Perit Dial Int* 2000;20 Suppl 2:S127.
- 27
28 546 36. Sakaci T, Ahbap E, Koc Y, et al. Clinical outcomes and mortality in elderly
29
30 547 peritoneal dialysis patients. *Clinics (Sao Paulo)* 2015;70:363-8.
- 31
32 548 37. Valderrabano F, Jofre R, Lopez-Gomez JM. Quality of life in end-stage renal
33
34 549 disease patients. *Am J Kidney Dis* 2001;38:443-64.
- 35
36 550 38. Joly D, Anglicheau D, Alberti C, et al. Octogenarians reaching end-stage renal
37
38 551 disease: cohort study of decision-making and clinical outcomes. *J Am Soc*
39
40 552 *Nephrol* 2003;14:1012-21.
- 41
42 553 39. Tennankore KK, Bargman JM. Nutrition and the kidney: recommendations for
43
44 554 peritoneal dialysis. *Adv Chronic Kidney Dis* 2013;20:190-201.
- 45
46 555 40. Hsieh YP, Chang CC, Wen YK, et al. Predictors of Peritonitis and the Impact of
47
48 556 Peritonitis on Clinical Outcomes of Continuous Ambulatory Peritoneal Dialysis
49
50 557 Patients in Taiwan—10 Years' Experience in a Single Center. *Perit Dial Int*
51
52 558 2014;34:85.
- 53
54 559 41. Szeto C, Kwan B, Chow K, et al. Predictors of residual renal function decline in
55
56 560 patients undergoing continuous ambulatory peritoneal dialysis. *Perit Dial Int*
57
58 561 2015;35:180-8.
- 59
60

- 1
2
3
4 562 42. Vilar E, Farrington K. Emerging importance of residual renal function in
5
6 563 end-stage renal failure. *Semin Dial* 2011;24:487-94.
7
8 564 43. Raimann J, Kitzler T, Levin N. Factors affecting loss of residual renal function(s)
9
10 565 in dialysis. *Contrib Nephrol* 2012;178:150-6.
11
12 566 44. Harris S, Lamping D, Brown E, et al. Clinical outcomes and quality of life in
13
14 567 elderly patients on peritoneal dialysis versus hemodialysis. *Perit Dial Int*
15
16 568 2002;22:463-70.
17
18 569 45. van Diepen AT, van Esch S, Struijk DG, et al. The first peritonitis episode alters
19
20 570 the natural course of peritoneal membrane characteristics in peritoneal dialysis
21
22 571 patients. *Perit Dial Int* 2015;35:324-32.
23
24
25 572
26
27
28 573
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30 574
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32 575
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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

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

Causative organisms	Early-onset peritonitis		Late-onset peritonitis		P value
	episodes	(n)	episodes	(n)	
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					
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)	

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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/m ²)	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/m ²)	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			

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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

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60 662 **Fig.1. Technique survival according to EOP and LOP.**

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14 668 Patients who transferred to HD were censored form the patient survival analysis. Log
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16 669 rank test Chi-square 4.060, $P=0.044$

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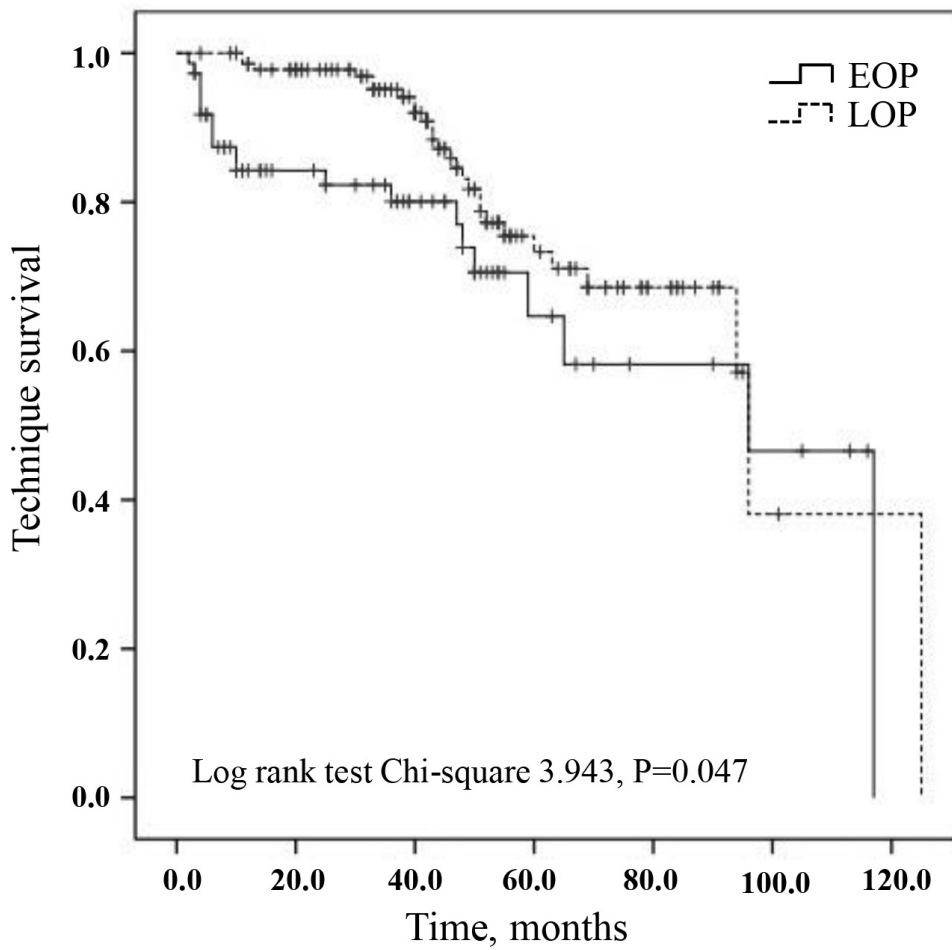


Fig.1. Technique survival according to EOP and LOP. Death were censored form the technique survival analysis. Log rank test Chi-square 3.943, P=0.047

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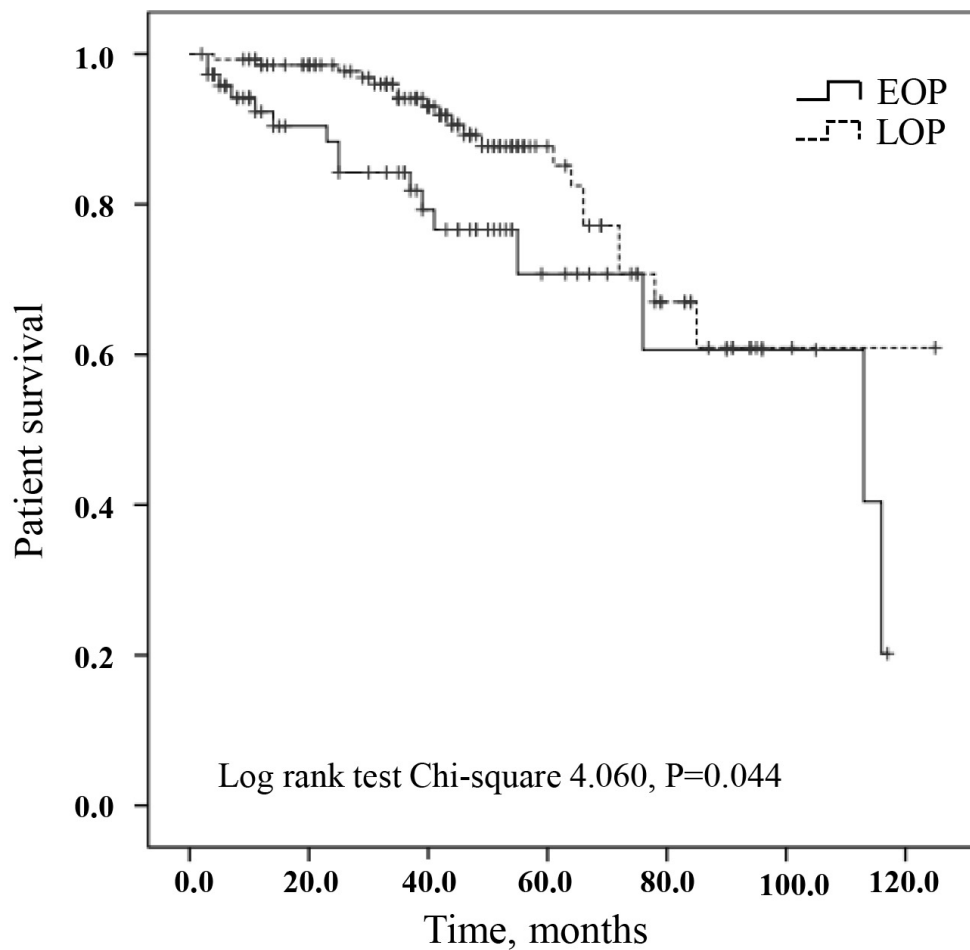


Fig.2. Patient survival according to EOP and LOP. Patients who transferred to HD were censored from the patient survival analysis. Log rank test Chi-square 4.060, P=0.044

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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
		<p>Objectives To investigate the risk factors associated with early-onset peritonitis (EOP) and its influence on patients' technique survival and mortality.</p> <p>Study design Retrospective, cohort study.</p> <p>Setting Three peritoneal dialysis units in Shanghai.</p> <p>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 (\leq 6 months, n=74) and late-onset peritonitis (LOP) (> 6 months, n=139).</p> <p>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.</p> <p>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.</p> <p>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.</p>	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 \pm 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

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15	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
16	Results			
17 18 19 20 21 22 23	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
24 25 26 27 28 29 30	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
31 32 33 34 35	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
36 37 38 39 40 41 42 43 44 45 46	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 Commission (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.