The Significance of Follow-Up Serum Uric Acid Levels in Predicting All-Cause Mortality and Cardiovascular Mortality in Peritoneal Dialysis Patients

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Research

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Abstract

Background: Studies on the correlation between serum uric acid (SUA) and all-cause mortality in peritoneal dialysis (PD) patients were mainly based on the results of baseline SUA. We aimed to analyze the change of SUA level post PD, and the correlation between follow-up SUA and prognosis in PD patients.

Methods: All patients who received PD catheterization and maintaining PD in our center from March 2, 2001 to March 8, 2017 were screened. Kaplan-Meier and Cox proportional-hazards regression models were used to analyze the effect of SUA levels on the risks of death. We graded SUA levels at baseline, 6 months, 12 months, 18 months and 24 months post PD by mean of SUA plus or minus a standard deviation as cut-off values, and compared all-cause and cardiovascular mortality among patients with different SUA grades.

Results: A total of 1402 patients were included, 763 males (54.42%) and 639 females (45.58%). Their average age at PD start was 49.50±14.20 years. The SUA levels were 7.97±1.79mg/dl at baseline, 7.12±1.48mg/dl at 6 months, 7.05±1.33mg/dl at 12 months, 7.01±1.30mg/dl at 18 months, and 6.93±1.26mg/dl at 24 months. During median follow-up time of 31 (18, 49) months, 173 (12.34%) all-cause deaths occurred, including 68 (4.85%) cardiovascular deaths. There were no significant differences on all-cause mortality among groups with graded SUA levels at baseline, 12 months, 18 months and 24 months during follow-up or on cardiovascular mortality among groups with graded SUA levels at baseline, 6 months, 12 months, 18 months and 24 months during follow-up. At 6 months post PD，Kaplan Meier analysis showed there was significant difference on all-cause mortality among graded SUA levels (c^2=11.315, P=0.010), and the all-cause mortality was lowest in grade of 5.65mg/dl≤SUA<7.13mg/dl.

Conclusion: SUA level decreased during follow up post PD. At 6 months post PD, a grade of 5.65mg/dl≤SUA<7.13mg/dl was appropriate for better patients' survival.

Background

Uric acid (UA) is the final product of purine nucleotides metabolism. Purine metabolism disorder or the abnormal renal UA excretion can affect serum UA (SUA) level. Hyperuricemia is common in patients with renal failure, which is caused by impaired SUA excretion in the kidney [1, 2]. In addition, hyperuricemia has been reported to be closely correlated with cardiovascular events and mortality in patients with chronic renal failure [3–5]. Peritoneal dialysis (PD) is one of the main renal replacement therapies, which was increasingly used in patients of end stage renal disease (ESRD) in China [6]. The mortality of PD patients is still high, which is affected by many risk factors [7]. A retrospective study of 156 PD patients showed that elevated SUA level was an independent risk factor for all-cause mortality[8]. Another cohort in Chinese population showed that elevated SUA level was an independent risk factor for all-cause and cardiovascular mortalities in male PD patients [9, 10]. However, the results of 2264 PD patients from seven centers in China showed that the predictive value of SUA as a continuous categorized variable decreased or disappeared after adjusting for traditional cardiovascular risk factors related to uremia among PD patients[11].

The above studies on the correlation between SUA level and all-cause mortality and cardiovascular mortality in PD patients were mainly based on the results of baseline SUA level [8–11]. This study analyzed the change of SUA level post PD, and the correlation between follow-up SUA levels and prognosis of PD patients in our center. We studied the effects of SUA on all-cause mortality and cardiovascular mortality, and explored the appropriate SUA level in different periods of PD therapy to improve the patients' survival.

Subjects And Methods

All the patients who received PD catheterization and maintaining PD therapy in the Kidney Disease Center, the First Affiliated Hospital, Zhejiang University School of Medicine from March 2, 2001 to March 8, 2017 were screened. The exclusion criteria were as follows: 1) the duration of PD treatment was less than 6 months; 2) lack of any one of the information including outcome, follow-up time, or SUA at 6 months of PD; 3) lack of more than 5 values of key indicators during follow up; 4) conversion to hemodialysis; 5) younger than 18 years old at the start of PD.

We collected the data at the start of PD including gender, age, body mass index (BMI), SUA, C-reactive protein(CRP), hemoglobin, intact parathyroid hormone(iPTH), systolic blood pressure(SBP), diastolic blood pressure (DBP), Charlson comorbidity index (CCI), creatinine clearance rate (Ccr), and serum creatinine, potassium, calcium, phosphorus, albumin, triglyceride, total cholesterol(TC), high density lipoprotein cholesterol(HDL-C), low density lipoprotein cholesterol(LDL-C), alkaline phosphatase(AKP) and serum glucose. We also collected SUA levels at 6, 12, 18, and 24 months after PD, PD duration and patients' outcomes. The sample mean standard deviation method was used to grade SUA during the follow-up period.

Statistical analysis

Statistical analysis was performed using Graphpad Prism 8.0 and SPSS 23.0 software package. The results were expressed as means ± standard deviation for normally distributed continuous variables, median values (interquartile ranges, IQR) for non-normally distributed continuous variables, or proportions for categorical variables. Student's t-test was used for comparisons of normally distributed continuous variables. Comparisons of non-normally distributed continuous variables were performed using Mann-Whitney U-test. Chi-square test was used for comparisons of categorical variables. The difference of SUA levels at different time points during the PD follow-up period was compared by repeated measurement variance analysis. The mean standard deviation method was used to grade SUA during the follow-up period. SUA levels and the risks of death were analyzed by Kaplan-Meier and Cox proportional-hazards regression models. We reported the multivariable adjusted hazards ratios (HR) with 95% CIs. All probabilities were two-tailed, and the level of significance was set at 0.05.

Results

In this retrospective study, 2320 PD patients were screened while 918 patients were excluded. Among the patients excluded, 269 patients were followed up for less than 6 months, 263 patients were converted to hemodialysis treatment, 97 patients had no key clinical information, 264 patients had no complete data of research indicators, and 25 patients were under 18 years old. A total of 1402 patients were included. There were 763 males (54.42%) and 639 females (45.58%). Their average age at the start of PD was 49.50 ± 14.20 years old. There were 317 (22.61%) patients received renal transplantation and 22 (1.57%) patients lost follow-up.

The trend of SUA level during PD follow up was shown in Fig. 1. The SUA levels were 7.97 ± 1.79 mg/dl at baseline, 7.12 ± 1.48 mg/dl at 6 months, 7.05 ± 1.33 mg/dl at 12 months, 7.01 ± 1.30 mg/dl at 18 months, and 6.93 ± 1.26 mg/dl at 24 months. There were significant differences in SUA between baseline and each follow up time (6, 12, 18 or 24 months of PD) ($P < 0.01$),and there was statistical difference between 6 months and 24 months ($P < 0.01$).

During median follow-up time of 31 (18, 49) months, 173 (12.34%) all-cause deaths occurred, including 68 (4.85%) cardiovascular deaths. The characteristics of the patients with all-cause deaths and cardiovascular deaths were shown in Table 1. The values of age, SUA at 6 months, serum glucose and CCI were higher in patients with all-cause deaths than the other patients; while the values of follow-up time, baseline SUA, DBP, and serum levels of creatinine, phosphorus and albumin were lower in patients with all-cause deaths than the other patients. The values of age, SBP, CCI, and serum levels of triglyceride and glucose were higher in patients with cardiovascular deaths than the other patients; while the values of follow-up time, baseline SUA, serum levels of creatinine and albumin were lower in patients with cardiovascular deaths than the other patients.

Table 1
Clinical characteristics according to groups by prognosis.

Variants	Total	Grouped by all-cause death			Grouped by cardiovascular death	
	(n = 1402)	All-cause death(173)	Other(1229)	*P* value	Cardiovascular death(68)	Other(1334)
Follow-up duration (m)	36.11 ± 23.26	30.82 ± 18.04	36.85 ± 23.81	0.001	30.35 ± 19.47	36.40 ± 23.40
Male (N, %)	763(54.42)	90(52.0)	673(54.76)	0.499	42(61.76)	721(54.05)
Age (y)	49.50 ± 14.20	61.27 ± 13.24	47.84 ± 13.53	< 0.001	58.57 ± 13.36	49.04 ± 14.09
SUA (baseline)（mg/dl）	7.97 ± 1.79	7.65 ± 1.91	8.01 ± 1.77	0.014	7.52 ± 1.66	7.99 ± 1.79
SUA(PD 6m)（mg/dl）	7.12 ± 1.48	7.38 ± 1.81	7.08 ± 1.43	0.015	7.30 ± 1.91	7.11 ± 1.46
SUA(PD 12m)（mg/dl）	7.05 ± 1.33	7.11 ± 1.43	7.04 ± 1.32	0.569	6.98 ± 1.18	7.06 ± 1.34
SUA(PD 18m)（mg/dl）	7.01 ± 1.30	7.15 ± 1.33	6.99 ± 1.30	0.186	7.03 ± 1.23	7.01 ± 1.31
SUA(PD 24m)（mg/dl）	6.93 ± 1.26	6.96 ± 1.47	6.93 ± 1.24	0.792	7.10 ± 1.43	6.93 ± 1.26
BMI (kg/m^2)	21.52 ± 3.26	21.63 ± 3.51	21.50 ± 3.22	0.633	22.27 ± 3.16	21.48 ± 3.26
Serum creatinine(mg/dl)	8.54 ± 3.16	7.66 ± 3.02	8.67 ± 3.16	< 0.001	7.62 ± 2.54	8.59 ± 3.18
Potassium (mmol/L)	4.54 ± 0.70	4.51 ± 0.71	4.54 ± 0.70	0.590	4.50 ± 0.70	4.54 ± 0.70
Calcium (mmol/L)	2.08 ± 0.25	2.10 ± 0.23	2.08 ± 0.26	0.504	2.11 ± 0.22	2.08 ± 0.25
Phosphorus (mmol/L)	1.82 ± 0.49	1.72 ± 0.54	1.83 ± 0.26	0.007	1.74 ± 0.48	1.82 ± 0.49
Albumin (g/L)	36.92 ± 5.32	35.29 ± 5.23	37.15 ± 5.30	< 0.001	35.36 ± 5.51	37.00 ± 5.30
Triglyceride(mmol/L)	1.54 ± 0.97	1.65 ± 1.02	1.53 ± 0.97	0.139	1.80 ± 1.24	1.53 ± 0.96
TC(mmol/L)	4.31 ± 1.19	4.42 ± 1.34	4.29 ± 1.17	0.172	4.11 ± 1.36	4.30 ± 1.18
HDL-C(mmol/L)	1.11 ± 0.35	1.09 ± 0.37	1.11 ± 0.35	0.42	1.05 ± 0.33	1.11 ± 0.35
LDL-C(mmol/L)	2.38 ± 0.87	2.44 ± 0.98	2.37 ± 0.85	0.307	2.45 ± 1.00	2.37 ± 0.86
AKP(U/L)	78.52 ± 52.85	82.74 ± 58.11	77.92 ± 52.07	0.262	79.49 ± 29.89	78.48 ± 53.77
Glucose(mmol/L)	4.82 ± 1.20	5.33 ± 2.00	4.74 ± 1.03	< 0.001	5.60 ± 2.60	4.77 ± 1.07
CRP(mg/L)	9.75(2.5,9.75)	2.30(1.50,7.53)	2.90(1.50,7.70)	0.588	2.80(1.80,9.20)	9.75(2.5,9.75)
Hemoglobin (g/L)	83.49 ± 16.74	82.19 ± 17.59	83.67 ± 16.62	0.274	83.36 ± 19.35	83.50 ± 16.61
iPTH (pg/mL)	285.00(151.75,454.00)	224.00(128.98,365.75)	288.50(155.00,467.50)	0.089	203.00(108.00,330.50)	290.00(154.00,45
SBP(mmHg)	146.57 ± 20.59	148.43 ± 25.54	146.31 ± 19.80	0.203	151.40 ± 25.48	146.32 ± 20.29
DBP(mmHg)	88.76 ± 14.09	85.23 ± 15.43	89.26 ± 13.82	< 0.001	87.18 ± 15.86	88.85 ± 14.00
Ccr (ml×week/min/ /1.73 m^2)	52.24 ± 36.31	50.57 ± 36.15	52.48 ± 34.68	0.502	55.03 ± 38.81	52.11 ± 34.65
CCI	2.51 ± 0.94	2.97 ± 1.24	2.44 ± 0.87	< 0.001	3.06 ± 1.13	2.48 ± 0.92

We graded SUA levels at baseline, 6 months, 12 months, 18 months and 24 months during follow-up by mean of SUA plus or minus a standard deviation as cut-off values. Kaplan-Meier survival analysis and Cox regression analysis showed that there were no significant differences on all-cause mortality among groups with graded SUA levels at baseline, 12 months, 18 months and 24 months during follow-up (Fig. 2, ACDE; Table 2),or on cardiovascular mortality among groups with graded SUA levels at baseline, 6 months, 12 months, 18 months and 24 months during follow-up (data not shown).

Table 2
Multivariate Cox regression analysis of follow-up SUA levels and all-cause mortality.

	Baseline		6 months		12 months		18 months		24 months	
	HR(95%CI)	P	HR(95%CI)	P	HR(95%CI)	P	HR(95%CI)	P	HR(95%CI)	P
Grade1	0.972(0.649–1.454)	0.889	1.428(0.886–2.302)	0.143	0.932(0.545–1.595)	0.798	0.500(0.235–1.064)	0.072	0.678(0.367–1.251)	0.214
Grade2	reference		reference		reference		reference		reference	
Grade3	0.784(0.536–1.145)	0.207	1.524(1.046–2.219)	0.028	1.000(0.684–1.461)	0.999	0.907(0.597–1.376)	0.646	0.543(0.337–0.875)	0.012
Grade4	0.806(0.484–1.340)	0.406	1.824(1.181–2.817)	0.007	1.287(0.793–2.089)	0.307	0.903(0.531–1.535)	0.705	0.979(0.566–1.694)	0.939

Note: Reference group is Grade2 group. Multivariate Cox regression analysis was performed at baseline, 6 months, 12 months, 18 months and 24 months. The factors adjusted included age, serum creatinine, serum phosphorus, serum albumin, serum glucose, DBP and CCI.

For SUA at 6 months of PD, we graded the PD patients into Grade 1 (SUA < 5.65 mg/dl), Grade 2 (5.65 mg/dl ≤ SUA < 7.13 mg/dl), Grade3 (7.13 mg/dl ≤ SUA ≤ 8.61 mg/dl) and Grade4 (SUA > 8.61 mg/dl) according to mean of SUA plus or minus a standard deviation as cut-off values. Kaplan Meier analysis showed that there was significant difference on all-cause mortality among the above Grades (χ^2 = 11.315, *P* = 0.010) (Fig. 2B). The all-cause mortality tended to be lowest in Grade 2, and significantly lower in Grade 2 than those in Grade 3 and Grade 4 (HR = 2.219, *P* = 0.028; HR = 2.817, *P* = 0.007, respectively) (Table 2).

For SUA at 24 months of PD, we graded the PD patients into Grade 1 (SUA < 5.68 mg/dl), Grade 2 (5.68 mg/dl ≤ SUA < 6.94 mg/dl), Grade 3 (6.94 mg/dl ≤ SUA ≤ 8.20) and Grade 4 (SUA > 8.20 mg/dl) according to mean of SUA plus or minus a standard deviation as cut-off values. Kaplan Meier analysis showed that there was no significant difference in all-cause survival rates among the above groups (χ^2 = 6.145, *P* = 0.105) (Fig. 2E). However, the all-cause mortality tended to be lowest in grade 3, and significantly lower in Grade 3 than that in Grade 2 (HR = 0.543, *P* = 0.012) (Table 2).

Discussion

This study showed that the SUA levels post PD were decreasing, with significant differences between baseline and follow up periods. The reason may be that PD can discharge UA and improve hyperuricemia [12], and the aggravated nutritional status with long-term PD treatment. For most studies on the correlation between SUA and mortality in PD patients, the SUA values were taken from baseline SUA values at the beginning of PD. According to the trend of SUA during the follow-up periods, we believe that the baseline SUA may not be able to represent the SUA level during PD, which may be the main reason for inconsistent conclusions based on baseline SUA. Therefore, we used SUA levels at different follow-up periods (baseline, 6, 12, 18, and 24months) to analyze the correlation between SUA and the long-term prognosis of PD patients.

Cox regression analysis shows that high SUA at 6 months post PD is an independent risk factor for all-cause death in PD patients. It was reported that elevated SUA level may play a role in endothelial dysfunction[12], and it showed that there was independent correlation between SUA level and the degree of endothelial dysfunction in long-term PD patients[13]. Furthermore, a study of 134 PD patients from Korea found that hyperuricemia was significantly correlated with the decline rate of residual renal function(RRF) after adjusting demographic data [14]. And RRF, inflammation and left ventricular hypertrophy were interrelated, which would increase the risk for mortality in PD patients[15]. The preservation of RRF and proper management of the comorbidities may help to improve the survival of maintaining PD patients[16]. However, at 24 months after PD, this study showed that slightly higher SUA level was a protective factor for all-cause death in PD patients. Studies showed that low SUA levels might increase the risk for all-cause death in hemodialysis patients [17, 18]. It also showed that SUA level was positively correlated with albumin levels and negatively correlated with comorbidity index[17]. And a large retrospective study on PD patients showed that low SUA was independently associated with low serum albumin, low BMI and low serum phosphorus level, indicating malnutritional status[19]. It also showed that low serum albumin level in PD patients was associated with all-cause mortality[20–22]. The aggravation of nutritional status was shown to be the relative risk factor for death in PD patients [23], and malnutrition was the main factor leading to the increase of mortality in patients with low SUA [24]. Thus, decreased SUA in long-term PD patients may be correlated with aggravated malnutrition, hypoalbuminemia and/or more severe comorbidities, which would increase the mortality.

There were some limitations in our study. First, the patients were from a single center. Second, this was a retrospective study with a relatively large time span of the enrolled patients, which may cause bias in the treatments. Third, some traditional risk factors, like smoking and some co-morbidities were not available. It is necessary to do a prospective multicenter trial to find the appropriate SUA level to improve the long-term survival in maintaining PD patients.

Conclusion

In summary, our study showed that the SUA level decreased during the follow up period of PD. At 6 months post PD, higher SUA level was an independent risk factor of all-cause mortality, while slightly high SUA level at 24 months post PD might be a protective factor. Further studies are needed to clarify the underlying mechanisms.

Abbreviations

UA: Uric acid; SUA: serum uric acid; PD: Peritoneal dialysis; ESRD: end stage renal disease; BMI: body mass index; CRP: C-reactive protein, iPTH: intact parathyroid hormone; SBP: systolic blood pressure; DBP: diastolic blood pressure; CCI: Charlson comorbidity index; Ccr: creatinine clearance rate; TC: total

cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; AKP: alkaline phosphatase; RRF: residual renal function

Declarations

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Authors' contributions

PR and QZ contributed equally to this manuscript. PR and FH designed the study. PR collected and analyzed the data with QZ and YP. YL, CL, ZF and XZ were involved in data interpretation. XX and SX contributed to reviewing the manuscript. JC and HF supervised and sponcerd the study. All the authors read and approved the final submitted manuscript.

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Availability of data and materials

All data used and/or analyzed during the this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Zhejiang University(NO.2018761). All participants gave written informed consent before inclusion in the study.

Consent for publication

All authors have seen and approved the manuscript being submitted.

Competing interests

The authors declare that they have no competing interests.

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Figures

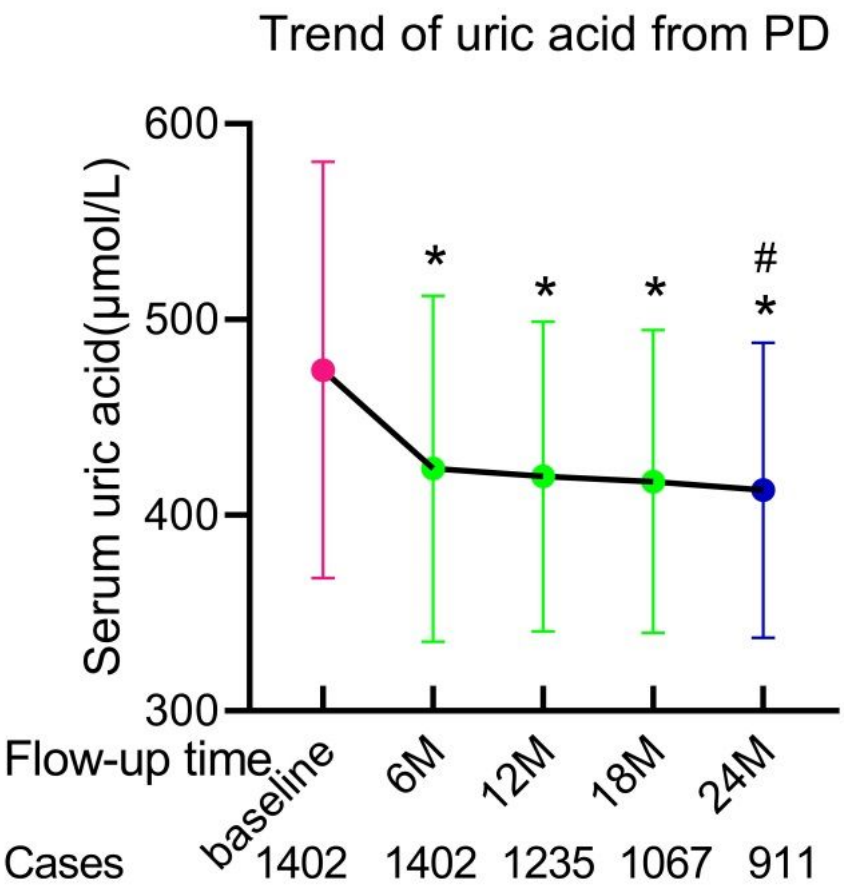

Figure 1

Trend chart of serum uric acid levels at baseline and follow-up PD periods. * P <0.05 compared with baseline. # P <0.05 compared with PD 6 months.

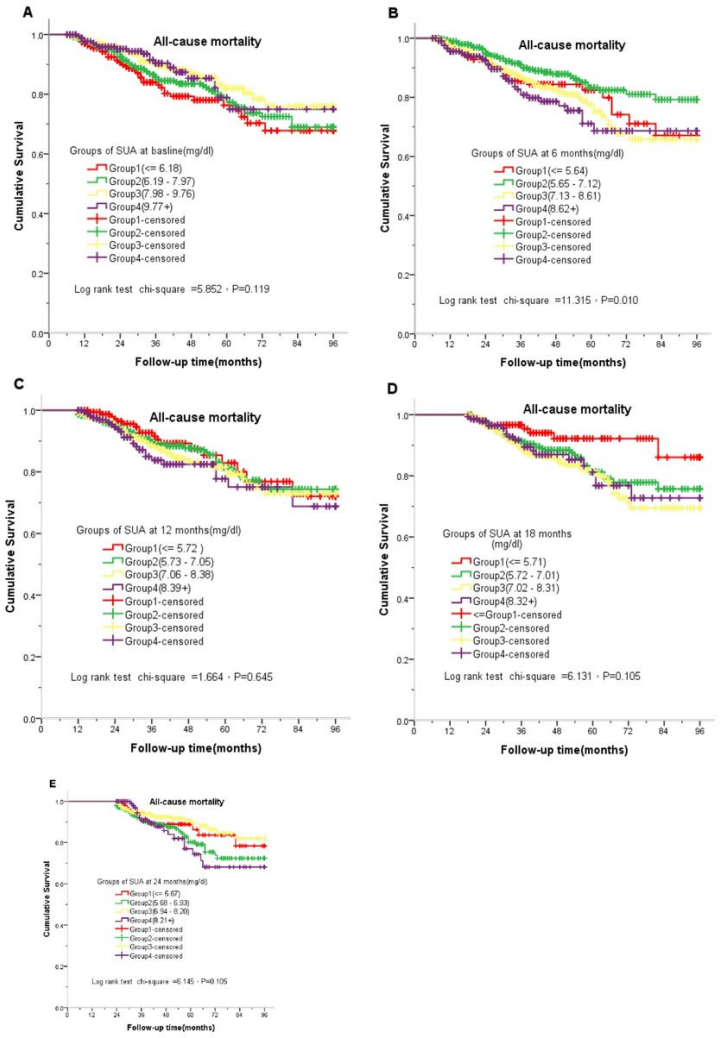

Figure 2

PD patients' all-cause survival curves in patients grouped by the serum uric acid levels at baseline(A) and follow-up periods (B, 6months; C, 12 months; D, 18months; E, 24months) post PD. * P<0.05 among groups.