ANNALS OF MEDICINE
2021, VOL. 53, NO. 1, 2132–2141
https://doi.org/10.1080/07853890.2021.1999489

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ORIGINAL ARTICLE

Serum potassium, albumin and vitamin B_{12} as potential oxidative stress markers of fungal peritonitis

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ABSTRACT

Background: Biomarkers of oxidative stress (OS) have been poorly explored in fungal peritonitis (FP). Potassium is a regulator of pro-oxidants and antioxidants. Albumin and vitamin B_{12} (B_{12}) are vital antioxidant agents in the circulatory system. This study aimed to investigate the antioxidative role of serum potassium, albumin and B_{12} in FP.

Methods: Serum levels of potassium, albumin and B_{12} were retrospectively analyzed in 21 patients with a confirmed diagnosis of FP, 105 bacterial peritonitis (BP) patients and 210 patients receiving peritoneal dialysis without peritonitis.

Results: Serum levels of potassium, albumin and B_{12} were lower in FP patients than in BP patients. Serum potassium concentration was statistically related to albumin concentration in peritonitis patients. Univariate and multivariate binary logistic regression analysis suggested that serum level of potassium and albumin were independent risk factors of FP when compared with BP. Lower potassium and B_{12} levels were independently associated with higher rates of technique failure in peritonitis.

Conclusion: These findings suggest lower serum potassium, albumin and B_{12} as potential oxidative stress markers of FP and raise the hypothesis that an increased level of OS could contribute to FP.

KEY MESSAGES

- FP remains a serious complication of peritoneal dialysis (PD), with higher morbidity (1–23.8%) and mortality (2–25%), and oxidative stress plays a role in it.
- Our study suggested serum potassium, albumin and vitamin B_{12} as potential oxidative stress markers of fungal peritonitis.

ARTICLE HISTORY
Received 14 July 2021
Revised 20 October 2021
Accepted 22 October 2021

KEYWORDS
Potassium; albumin; vitamin B_{12}; oxidative stress; fungal peritonitis

1. Introduction

Fungal peritonitis (FP) remains a serious complication of peritoneal dialysis (PD), with higher morbidity (1–23.8%) and mortality (2–25%) than bacterial PD-related peritonitis (PDRP). Updated guidelines recommend effective antifungal therapy and expeditious catheter removal once the diagnosis is established. However, early diagnosis and treatment are often difficult since the clinical manifestations are not specific and microbiological results are belated [1]. Therefore, it is urgent to identify inexpensive, accessible, and sensitive laboratory markers for predicting the disease.

Elevated level of oxidative stress (OS) status in the PD population contributes to peritonitis [2]. On the other hand, inflammation such as peritonitis induces OS which often leads to reduced antioxidant levels and elevated production of oxidants [3]. Unfortunately, literatures comparing levels of OS between bacterial peritonitis (BP) and FP are scarce, and there have been no accessible laboratory markers to suggest the OS of FP. Previous studies suggested that the transition of potassium was associated with OS [4–6]. Albumin, a non-enzymatic antioxidant, is the main component of total antioxidants [7,8]. Vitamin B_{12} (B_{12}) possesses the most antioxidant capacity via scavenging free radical reactive oxygen species (ROS) and modulating cytokine and growth factors [9,10]. It suggested that the OS process in peritonitis may

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Supplemental data for this article is available online at https://doi.org/10.1080/07853890.2021.1999489.

involve alterations of K^+ channel and antioxidants including albumin and B_{12} [5,10,6].

Hypokalaemia has been tightly associated with peritonitis [11]. Although hypokalaemia is common in FP [12], few studies have been designed to investigate the difference in serum potassium between FP and BP. It was reported that lower serum albumin was strongly correlated to the risk of peritonitis in PD patients [13,14]. FP patients showed a lower level of serum albumin than BP patients in several studies [12,15,16]. To our knowledge, it is the first study on the comparison of serum B_{12} between FP and BP. Overall, the role of serum potassium, albumin and B_{12} as markers of antioxidant status in FP is not well established.

The aim of this study was to explore that serum potassium together with albumin and B_{12} is the accessible biomarkers of the OS process in FP patients when compared with BP.

2. Materials and methods

This is a single-center and retrospective analysis of all patients suffering FP in the Fifth Affiliated Hospital of Sun Yat-Sen University, Zhuhai, China between April 2015 and April 2020. All FP episodes (FP group) were matched in a 1:5 ratio with bacterial peritonitis patients (BP group) diagnosed and hospitalized in the same period. PD patients without peritonitis (control group) were matched with FP patients in a 1:10 ratio.

2.1. Inclusion and exclusion criteria

PDRP was defined based on the current guidelines [17], and confirmed when meeting at least 2 of the following criteria: (1) clinical manifestations of peritonitis; (2) dialysis effluent leukocyte $>100/\mu L$; (3) a positive effluent culture. FP and BP were demonstrated by the isolation of microorganisms from effluent culture. Serial 3 dialysate cultures were taken after admission. If no microbial growth occurred the media were incubated for 7 days before being regarded as negative. The exclusion criteria were as follows: (1) <14 years old; (2) severe hepatic impairment and/or thyroid disease; (3) other ongoing infection; (4) pre-existing terminal illness, for instance, haemato-oncological diseases; (5) routine B_{12} supplementation.

2.2. Data collection and measurements

All medical records and data were collected including demographic data, cause for end-stage renal disease (ESRD), comorbidities, clinical features, lab parameters, antifungal therapy, and outcomes.

Serum levels of biochemical parameters including potassium, albumin and vitamin B_{12} (B_{12}) were measured using a Cobas c702 or 801 automatic biochemical analyzers (Roche, Basel, Switzerland). Haemocytes were measured using a Sysmex XN-10 (B1) automatic haematology analyzer (Sysmex Corporation, Kobe, Japan).

Hypokalaemia was generally defined as a low serum potassium level of <3.5 mmol/L and severe hypokalaemia as a serum potassium level of <3.0 mmol/L.

2.3. Microorganism identification

In the laboratory, BAC-T/ALERT®3D Blood Culture Instrument and BACT/Alert FA (BioMérieux, Durham, NC, USA) were used for inoculation and anaerobic cultures were obtained using blood agar, MacConkey agar, chocolate agar, and Schindler's agar. Sabouraud agar was used for fungal cultures.

Potassium, albumin, B_{12} and microbial culture were measured on the day of admission.

2.4. Treatment

Empirical antibiotic regimen (voriconazole as the first choice) would eventually be adjusted according to results of culture and susceptibilities. Catheter removal was the main treatment of fungal peritonitis except when patients strongly disagreed or died. All the management was based on clinical features, guidelines of ISPD [17], and our experience.

2.5. Clinical outcome of the study

The outcome was technique failure defined as transfer to haemodialysis for ≥ 30 days or death (including death within 30 days of transferring to haemodialysis) [18]. Resolved in this study was defined as recovery from peritonitis without ever transferring to haemodialysis or death.

2.6. Statistical analysis

Data were reported as mean ± standard variation, median (interquartile range, IQR), or count with percent determined by continuity and distribution. Kolmogorov-Smirnov was conducted to test continuous variables for normality and the one-way ANOVA was performed to test homoscedasticity. Differences between groups (FP group and BP group) were

evaluated by Student's *t*-test for parametric data and Mann–Whitney *U* test for nonparametric data. Fisher's exact test or Chi-squared test for comparisons of percentages between groups. Pearson or Spearman correlations were used to determine the correlation between two parameters. The associations of parameters with risk factors of peritonitis were examined using univariate and multivariate logistics regression models. Univariate and stepwise multivariate binary logistic regression models were performed using the type of peritonitis as the dependent variable to determine significant predictors for FP. Among peritonitis patients, univariate and stepwise multivariate binary logistic regression models were performed using the clinical outcome as the dependent variable to determine significant predictors for technique failure. We used IBM© SPSS® Statistics Version 25 for statistical analyses. A *p*-value $< .05$ was considered statistically significant.

3. Results

A total of 291 episodes of peritonitis were observed between April 2015 and April 2020, including 21 cases of FP. The peritonitis incidence was 0.249 episode/patient-year.

3.1. Clinical characteristics

Patients' demographic and clinical characteristics between FP and BP groups were similar (Table 1). There was no significant difference in sex and age between FP and BP groups. The aetiologies of ESRD between the two groups were similar, for instance, chronic glomerulonephritis, diabetic mellitus, hypertension (all $p > .05$). And FP patients were more likely to have cerebrovascular diseases as comorbidity than BP patients ($p < .05$). High incidence of anuric (>50%) and lack of urine output were observed in FP and BP (all $p > .05$). FP patients had higher rates of previous antibiotic use than BP patients ($p < .05$).

FP patients were older than the control group and showed a higher incidence of ischaemic heart disease and cerebrovascular disease (all $p < .01$). Peritonitis patients (FP and BP group) had less urine output than the control group ($p < .05$). Patients in the FP group showed higher rates of previous antibiotic use and immunosuppressive therapy than those in the control group (both $p < .05$).

3.2. Causative fungi

Of the patients with fungal peritonitis, *Candida* species accounted for 13 of 21 (61.90%) (Figure 1(a)). The remaining episodes were caused by *Aspergillus* species, *Trichosporon* species, *Trichosporon asahii*, *Rhodotorula* species and unclassified species. Of the FP patients, 5 of 13 (38.46%) of *Candida* isolates were *Candida albicans*; 4 (30.77%) were *Candida parapsilosis*; 4 (30.77%), *Candida tropicalis*. Antifungal susceptibility tests indicated that most of the isolates were susceptible to the antifungal drugs itraconazole, voriconazole, fluconazole, amphotericin B and 5-fluorocytosine. Only 1 isolate (*Candida tropicalis*) showed an intermediate range for itraconazole. Regarding the death cases, *Candida parapsilosis* (1 episode), *Candida tropicalis* (3 episode), *Candida albicans* (2 episodes) and unclassified species (1 episode) were identified in FP patients. Pathogenic bacteria in the BP group are shown in Figure 1(b).

3.3. Treatment and outcome

Anti-fungal treatment was immediately initiated after the PD effluent culture was reported. None of these patients had received antifungal prophylaxis. IP (intraperitoneal injection) or IV (intravenous injection)

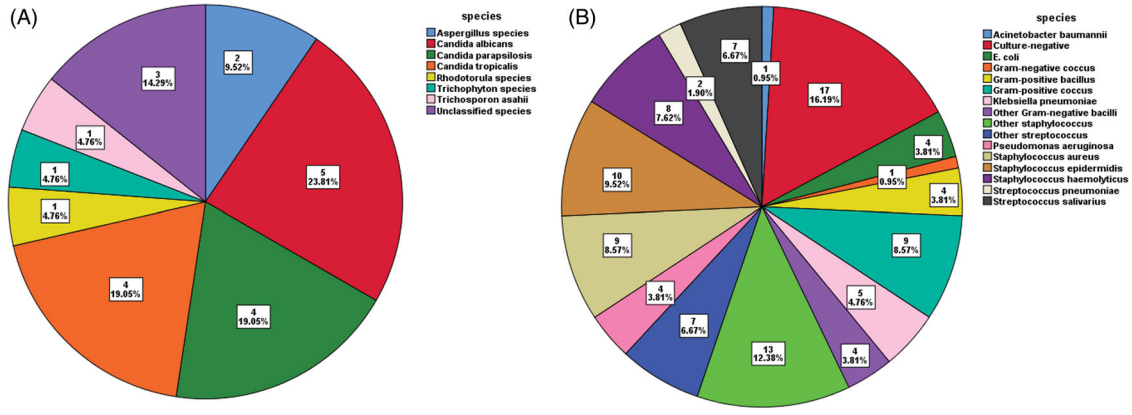

Figure 1. (a, b) Microbiological findings in the FP and BP.

Table 1. Characteristics of patients with fungal and bacterial peritonitis (1:5 ratio matching).

Characteristics	Fungal peritonitis $n = 21$ Median [IQR] or n (%)	Bacterial peritonitis $n = 105$ Median [IQR] or n (%)	Control group $n = 210$ Median [IQR] or n (%)	p^1-Value[a]	p^2-Value[b]	p^3-Value[c]
Median age (years)	61.00 [46.00–71.50]	50.00 [43.00–60.50]	51.00 [42.75–61.00]	.053	.024*	.921
Female	11/21 (52.38)	54/105 (51.43)	109/210 (51.90)	.936	.967	.936
PD duration (months)	43.00 [19.00–65.50]	42.00 [12.00–72.00]	18.00 [5.00–64.25]	.874	.076	.023*
Diabetes mellitus	5/21 (23.81)	14/105 (13.33)	74/210 (35.24)	.312	.293	.000***
Ischaemic heart disease	7/21 (33.33)	26/105 (24.76)	16/210 (7.62)	.424	.002**	.000***
Chronic lung disease	1/21 (4.76)	4/105 (3.81)	1/210 (0.48)	1.000	.174	.044*
Cerebrovascular disease	8/21 (38.10)	16/105 (15.24)	16/210 (7.62)	.029	.000***	.035*
Previous failed kidney transplant	0/21 (0.00)	3/105 (2.86)	0/210 (0.00)	1.000		.036*
Hypertension	17/21 (80.95)	90/105 (85.71)	157/210 (74.76)	.522	.530	.026*
Hepatopathy	3/21 (14.29)	14/105 (13.33)	23/210 (10.95)	1.000	.714	.536
Anuric	13/21 (61.90)	54/105 (51.43)	68/210 (32.38)	.475	.007**	.001**
Urine output (mL/day)	0 [0–250.00]	87.50 [0–650.00]	500.00 [0–1000.00]	.072	.000***	.000***
Exchange volume (L/day)	8.00 [8.00–8.00]	8.00 [7.00–8.00]	8.00[6.00–10.00]	.803	.975	.674
1.5% DS exchange volume	5.00 [2.50–6.00]	6.00 [4.00–8.00]	6.00 [4.00–8.00]	.424	.053	.083
2.5% DS exchange volume	4.00 [0–6.00]	2.00 [0–4.00]	0 [0–4.00]	.297	.053	.186
4.25% DS	0/21 (0.00)	1/105 (0.95)	4/210 (1.90)	1.000	1.000	.668
Previous peritonitis episodes	10/21 (47.62)	26/105 (24.76)		.061		
Poor appetite	15/21 (71.43)	64/105 (60.95)	30/210 (18.10)	.462	.000***	.000***
Vomiting	5/21 (23.81)	22/105 (20.95)	7/210 (3.33)	.774	.002**	.000***
Diarrhoea	6/21 (28.57)	27/105 (25.71)	13/210 (6.19)	.789	.003**	.000***
Time between culture positivity and onset of symptoms (days)	7.00 [7.00–15.50]	4.00 [3.75–6.00]		.000***		
Hospital stay (days)	22.00 [13.50–32.00]	14.00 [13.00–19.00]	–	.013*		
Aetiology ESRD						
Chronic glomerulonephritis	11/21 (52.38)	68/105 (64.76)	108/210 (51.43)	.327	.934	.025*
Diabetic mellitus	2/21 (9.52)	9/105 (8.57)	42/210 (20.00)	1.000	.382	.009**
Hypertension	3/21 (14.29)	5/105 (4.76)	19/210 (9.05)	.128	.432	.177
Polycystic kidney disease	0/21 (0.00)	7/105 (6.67)	2/210 (0.95)	.600	1.000	.007**
Systemic lupus erythematosus	1/21 (4.76)	1/105 (0.95)	4/210 (1.90)	.307	.382	.668
ANCA-relate glomerulonephritis	2/21 (9.52)	3/105 (2.86)	0/210 (0.00)	.194	.008**	.036*
Other[a]	2/21 (9.52)	12/105 (11.43)	35/210 (16.67)	1.000	.542	.219
Accompanying medication						
Diuretics or K+-binding resins	0/21 (0.00)	3/105 (2.86)	7/210 (3.33)	1.000	1.000	1.000
RAAS inhibitors	9/21 (42.86)	46/105 (43.81)	80/210 (38.10)	.936	.669	.329
Under immunosuppressive therapy	3/21 (14.29)	6/105 (5.71)	4/210 (1.90)	.172	.018*	.089
Previous antibiotic use[b]	7/21 (33.33)	11/105 (10.48)	10/210 (4.76)	.013*	.000***	.055
Duration of antibiotic treatment (days)	14.00 [12.00–14.00]	14.00 [13.00–14.00]	3.00 [3.00–5.00]	.954	.002**	.002**
Outcome						
Resolved (%)	3/21 (14.29)	88/105 (83.91)		.000***		
Catheter removal (%)	12/21 (57.14)	8/105 (7.62)		.000***		
Technique failure (%)	18/21 (85.14)	17/105 (16.19)		.000***		
Time to occurrence (days)	8 [6–19]	5 [1.5–17]		.229		
Death	7/21 (33.33)	5/105 (4.76)[c]		.001***		
Time to occurrence (days)	17 [5.5–24.75]	1 [1–1]		.400		
ICU-admission	3/21 (14.29)	1/105 (0.95)		.015*		

Abbreviations. PD: peritoneal dialysis; ESRD: end stage renal disease; DS: dialysis solution; RAAS: renin-angiotensin-aldosterone system.
[a]Includes gouty nephropathy, renal calculi disease.
[b]Within the preceding 3 months.
[c]Includes 4 patients giving up treatment and without exact death date.
p^1: FP vs. BP patients; p^2: FP patients vs. control group; p^3: BP patients vs. control group. The differences were considered significant if p-value $< .05$. ***p-value $< .001$; **p-value $< .01$; *p-value $< .05$.

fluconazole was initially administrated in most FP patients except oral itraconazole was used in two of them. IP cefazolin combined with ceftazidime was used as empiric therapy in all BP patients, and therapeutic regimens were adjusted according to results of culture and susceptibilities when peritonitis was not resolved. Details of the 21 fungal peritonitis are shown in Table 2.

Regarding the clinical outcome (Table 1), patients with FP had a longer duration of hospitalization and a higher rate of ICU admission than BP ($p < .05$). FP peritonitis was associated with a significantly higher rate of technique failure and death (85.14% vs 16.19%, 33.33% vs 4.76%, respectively) ($p < .05$) (Table 1).

3.4. Comparison between FP, BP, and control group

Summarised clinical features and laboratory parameters associated with different types of peritonitis are illustrated in Supplementary data, Table S1. When

Table 2. Clinical and laboratory details of the 21 fungal peritonitis.

	n (%)	Remarks
Aged $\geq$ 65 years	9 (42.86)	
PD duration $\geq$ 3 years	13 (61.90)	
Cloudy effluent	20 (95.24)	
Abdominal pain	21 (100)	
Gastrointestinal symptom[a]	19 (90.48)	
Fever	13 (61.90)	
Hypotension[b]	8 (38.10)	
Peripheral WBC elevated	7 (33.33%)	
Hypoalbuminemia	21 (100)	Serum albumin reached severe low level ($<$ 25 g/L) in 11 patients
Anaemia	15 (71.43)	Serum haemoglobin $\leq$ 90g/L in 7 patients
With intestinal obstruction	3 (14.29)	
Early antifungal administration[c]	9 (42.86)	
Initial treatment with IP fluconazole	11 (52.38)	
Fluconazole as IV choice	9 (42.86)	
Had oral antifungal administration	14 (66.67)	
Had 2 antifungal drugs	6 (28.57)	

Abbreviations. IP: intraperitoneal injection; IV: intravenous injection.
[a]Includes nausea, vomiting, diarrhoea, or abnormal findings from stool examination.
[b]SBP $\leq$ 90 mmHg and (or) DBP $\leq$ 60 mmHg.
[c]Antifungal administration within 5 days after admission.

compared with the BP group, the FP group showed significantly lower systolic blood pressure (SBP), diastolic blood pressure (DBP), serum levels of creatine (Cr), potassium, total protein, albumin and B_{12} (all $p <$ .05) (Figure 2).

In this study, 76.19% of the patients were complicated with hypokalaemia in the FP group and 53.33% in the BP group ($p = .058$). Potassium concentrations lower than 3 mmol/L were found in more patients in FP than in the BP group, 61.90% and 24.76%, respectively ($p = .001$). Although hypokalaemia was also prevalent in FP patients in the study of Hu et al., statistical difference of serum potassium levels between FP and BP patients has not been observed [12].

In peritonitis patients, SBP, DBP, Cr, potassium and albumin were positively related to the risk of FP using the univariable binary logistic regression model (all $p < .05$) (Table 3). After including these variables in the same model, only serum potassium and albumin level were still independently associated with the risk of FP (both $p < .05$), while SBP, DBP and Cr were no longer related (Table 3).

After including those significant variables found in the univariable logistic regression model, multivariate logistic regression analysis was performed using the control group as a reference group (Supplementary data, Table S2). The results indicated that serum potassium, albumin, total protein, percentage of neutrophil, C-reactive protein, chlorine levels, and temperature were independently associated with risk of peritonitis (all $p < .05$).

Three groups were stratified for urine output. Among patients with urine output $\leq$100 mL/day, serum potassium and albumin levels were lowest in FP and highest in the control group (Supplementary data, Table S3).

3.5. Comparison of peritonitis patients with different clinical outcomes

When compared to resolved patients, patients with technique failure showed significantly lower urine output, SBP, DBP, serum levels of potassium, albumin, direct bilirubin (DBIL) and B_{12} (all $p < .05$) (Figure 1). Summarized clinical features and laboratory parameters of peritonitis associated with different clinical outcomes are illustrated in Supplementary data, Table S4.

Urine output, SBP, DBP, potassium, albumin and B_{12} were positively related to the risk of technique failure using the univariable logistic regression model (all $p <$ .05) (Supplementary data, Table S5). After including these variables in the same model, only urine output, serum potassium and B_{12} level were still statistically significant (all $p < .05$).

Bivariate correlation analysis (Spearman's rho) in all the peritonitis patients between potassium and BMI, SBP, DBP, albumin, Cr, DBIL and B_{12} were calculated (Supplementary data, Table S6). Serum potassium level was correlated with SBP, DBP, albumin and Cr levels in peritonitis patients (all $p < .05$).

3.6. ROC analyses

To explore the predictive ability of albumin, potassium and B_{12} level in FP, ROC curve analyses were performed (Figure 3(a)). The AUC for albumin, potassium and B_{12} was 0.766 (0.666–0.866), 0.758 (0.642–0874) and 0.641 (0.506–0.777), respectively (all $p < .05$). The cut-off value of albumin, potassium and B_{12} was 29.5 g/L, 3.05 mmol/L and 558 pg/mL with a sensitivity of 85.71%, 71.43% and 71.43%, and specificity of 59.62%, 69.52% and 59.62% (Figure 3(a)).

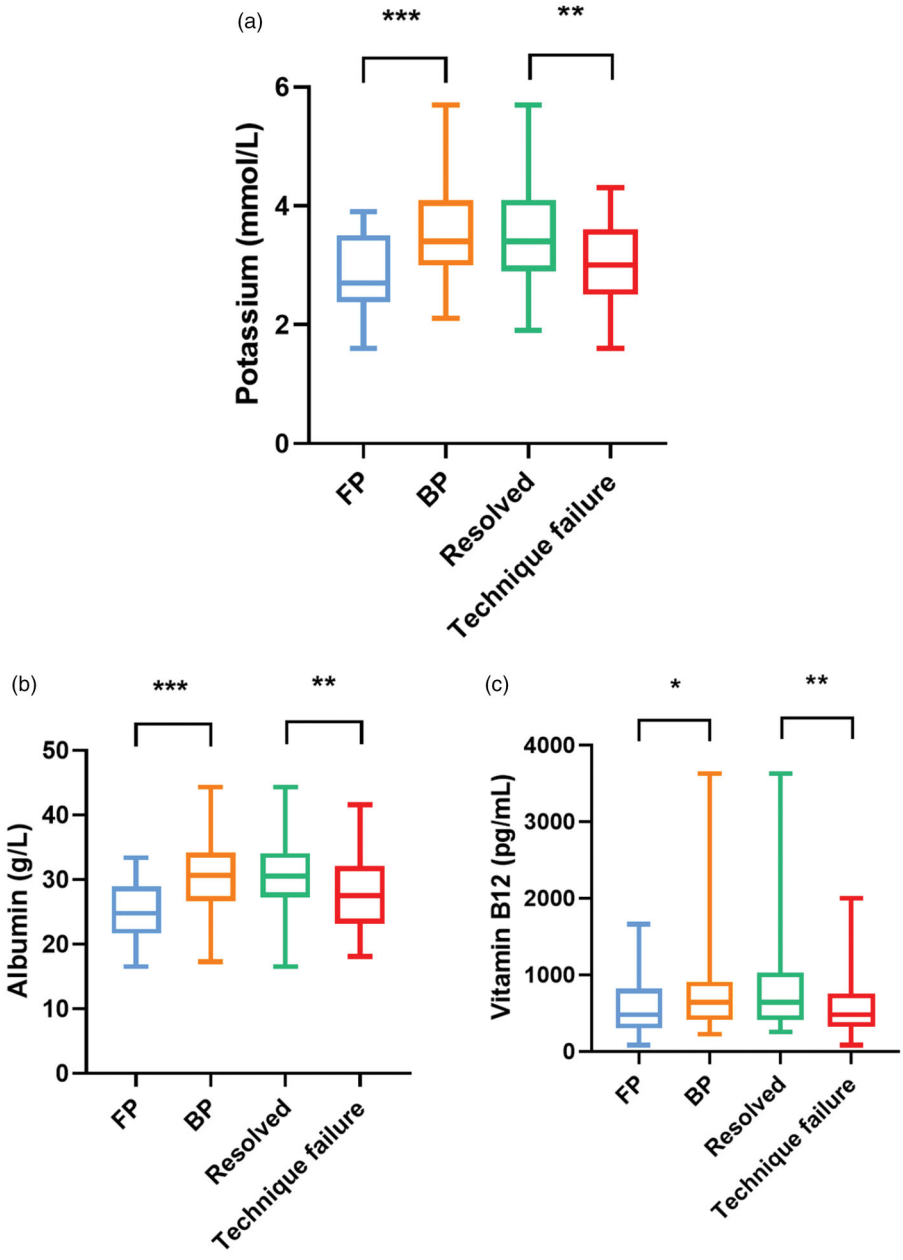

Figure 2. Comparison of serum levels of potassium, albumin and vitamin B_{12} in patients with fungal peritonitis, bacterial peritonitis, resolved outcome and technique failure. (a) Serum potassium (b) Serum albumin (c) Vitamin B_{12}. ***p-value $<$ .001; **p-value $<$ .01; *p-value $<$ .05.

To identify technique failure, the AUC for albumin, potassium and B_{12} was 0.659 (0.546–0.773), 0.681 (0.583–0.779) and 0.651 (0.543–0.759), respectively (all $p < .01$). The cut-off value of albumin, potassium and vitamin B_{12} was 28.85 g/L, 3.72 mmol/L and 558 pg/mL with a sensitivity of 62.86%, 88.57% and 65.71%, and specificity of 68.89%, 41.11% and 62.22% (Figure 3(b)).

4. Discussion

Interestingly, we documented lower serum potassium, albumin, B_{12} in fungal peritonitis. Lower levels of potassium and albumin B_{12} were associated higher risk of fungal peritonitis, and decreased potassium and B_{12} concentrations were independently associated with technique failure of peritonitis.

Previous studies revealed that OS might play a vital role in the pathogenesis and prognosis of peritonitis in humans [15], however, the role of the serological parameter as a biomarker of OS in FP is not well established. Taken together, lower potassium, albumin and B_{12} concentrations were considered as biomarkers of the higher level of OS in FP patients for the first time. In addition, an increased level of OS of

decreased potassium, albumin and B_{12} concentrations may be a marker associated with a bleak prognosis in peritonitis.

4.1. Low serum potassium and FP

Our study suggested that lower serum potassium was associated with an increased risk factor of fungal peritonitis. Hypokalaemia was common in PD patients accounting for 10–60% [19–21]. Losses of potassium in dialysate, urinary and gastrointestinal tract were contributing factors to hypokalaemia in PD patients in some studies [22–24]. However, we found no statistical difference in the gastrointestinal tract (percentage of poor appetite, vomiting and diarrhoea, Fisher's exact or Chi-squared test) and urinary tract (percentage of anuric and urine output) (all $p > .05$). And there were no significant differences in the use of accompanying medication (such as diuretic, K+-binding resins and RAAS inhibitors) and acid-base statuses (carbon dioxide combining power) (all $p > .05$). It is reasonable to speculate that peritoneum is most likely associated with loss of potassium in FP patients in this study.

In PD patients, peritoneal clearance of potassium depends on the characteristics of the peritoneum, the dialysis solution, and importantly inflammatory states of the peritoneum oftentimes increase the clearance of potassium to the dialysate. In this study, serum potassium concentration was not correlated with peritoneal daily exchange volume and use of dialysis solution of different concentrations (Spearman's rho, all $p > .05$). Studies confirm impaired free water transport is present during peritonitis [25], which is usually associated with the peritoneal handling of K+ [26]. K + deficiency could induce OS [5,27] through regulating the pathophysiologic equilibrium between pro-oxidants and antioxidants [6], and OS conversely affected potassium activities [4,28]. Therefore, a higher level of OS associated with hypokalaemia is the most likely mechanism.

Interestingly, a study showed that PD patients with hypokalaemia had a higher prevalence of abnormal breath hydrogen test, which suggested intestinal bacterial overgrowth [29]. Na, K-ATPase was found a vital regulator of bacterial penetration through the intestinal epithelial barrier [30]. In this study, gastrointestinal infection (5 episodes) accounted for 23.81% of the FP. Thus, we hypothesize that FP may be one of the frequent consequences of fungal transition in the gastrointestinal tract via OS and potassium.

Table 3. Predictors of FP: univariate and multivariate binary logistic regression analysis.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
SBP (mmHg)	1.032	1.011–1.052	**.002****	1.017	0.991–1.045	.207
DBP (mmHg)	1.063	1.023–1.105	**.002****	1.027	0.978–1.078	.281
Cr (μmol/L)	1.003	1.001–1.005	**.014***	1.000	0.997–1.003	.904
Potassium (mmol/L)	4.921	2.021–11.982	**.000*****	2.828	1.014–7.888	**.047***
Albumin (g/L)	1.203	1.087–1.333	**.000*****	1.17	1.022–1.340	**.023***
B_{12} (pg/mL)	1.001	1.000–1.002	.141	1.001	1.000–1.003	.080

ORs indicate the relative increased risk of FP with each change in SD (for SBP, DBP, Cr, potassium and albumin) when compared with BP. In multivariable regression analysis, these five variables were included in the same model.
Abbreviations. OR: odds ratio; CI: confidence interval.
The differences were considered significant if *p*-value < .05. ***p*-value < .001; **p*-value < .01; *p*-value < .05.

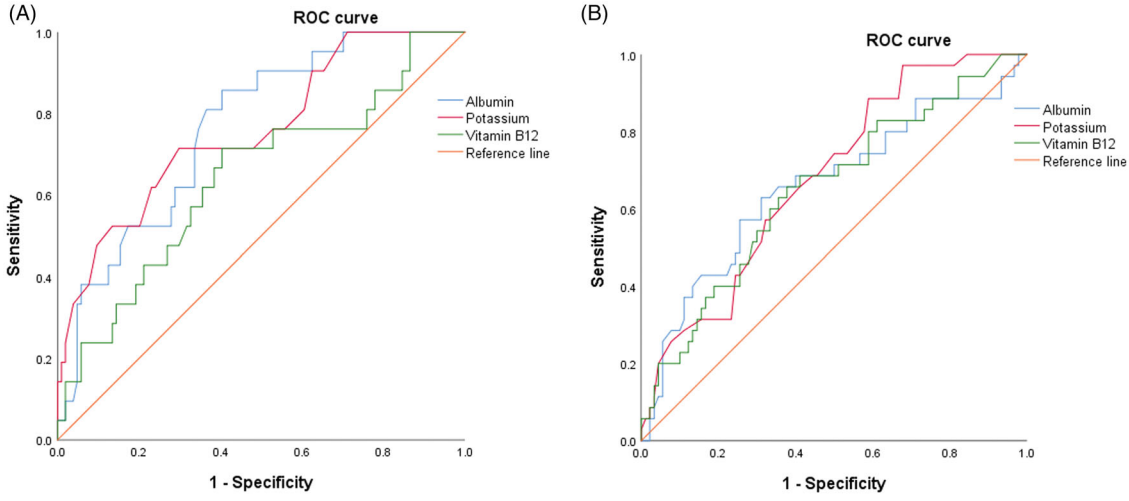

Figure 3. ROC curves comparing the potential of different variables to predict FP and technique failure in peritonitis (a) The prediction of FP variables (b) Predictive ability of different variables of technique failure in peritonitis patients. Blue, albumin; red, potassium; green, vitamin B_{12}; orange, reference line.

4.2. Low serum albumin and FP

Some published studies showed lower albumin in fungal peritonitis patients when compared to bacterial peritonitis [12]. In this study, lower serum concentration of albumin was associated with FP and technique failure, and statistically related to potassium concentration in peritonitis patients. Generally, serum albumin levels depend on the general state of health, nutrition [16,31], liver function, urinary losses and inflammatory states. In PD patients, peritoneal losses are clinically most relevant and those losses are potentiated during PD-associated peritonitis. However, this study noted no difference in other nutritive indicators (weight, BMI and serum lipid), digestive symptoms (poor appetite, nausea, vomiting and diarrhoea) and liver function (cholinesterase and bilirubin) between the FP group and BP group (all $p > .05$). Moreover, albumin concentrations were significantly lower in BP and FP group than in the control group. Thus, we attribute hypoproteinemia mainly to peritoneal loss.

Albumin represents the most abundant protein with a potent antioxidant capacity in the circulation, associated with the properties to bind metal ions and scavenge free radicals [7,8]. Hypoalbuminemia was observed to increase blood ROS levels in PAN nephrotic rats, and sphingosine 1 phosphate (S1P) may be a possible connection between hypoalbuminemia and peritoneal oxidative stress [32], which further causes peritonitis. Observational studies have suggested that inflammation reduced protein levels by inhibiting synthesis, increasing catabolism and vascular permeability [33]. Thus, one can hypothesize that albumin reduction is the vital explanation for OS in FP and hypoproteinemia is one of the biomarkers of the OS in FP patients.

4.3. Low serum vitamin B_{12} and FP

To our knowledge, no literature is available to investigate the relationship between serum vitamin B_{12} concentration and fungal peritonitis. In the current study, serum levels of vitamin B_{12} in the FP group were significantly lower than in the BP group and lower B_{12} was associated with technique failure. However, none of the patients in our study accepted vitamin B_{12} supplementation. And there was no significant difference in haemoglobin concentration between FP and BP patients ($p > .05$). It is well known that long-term B_{12} deficiencies are linked with anaemia [34]. Thus, our results suggest lower B_{12} level was related to the instantaneous reaction in FP patients.

It was observed that the growth of fungi requires B_{12} [35,36], and patients with chronic exposures to fungi had persistent vitamin B_{12} deficiencies [37]. Moreover, evidence suggests that B_{12} has potential antioxidant properties: (1) a direct scavenger of ROS [10,38]; (2) an indirect stimulation of ROS scavenging by the preservation of glutathione [9,39]; (3) modulates cytokine and growth factor production to protect against immune response-induced OS [40]; (4) induces reduction of OS caused by homocysteine [41] and advanced glycation end products (AGE) [42,43]. Although clearance of vitamin B_{12} by peritoneal dialysis is generally minimal [44], lower serum B_{12} levels may be associated with activated OS in FP in our study.

Our study has some limitations. First, this is a cross-sectional retrospective study, thus it remains uncertain if the associations between FP and serum potassium, albumin and B_{12} are causal. Second, although we excluded many confounders, levels of potassium or vitamin B_{12} in the dialysate were not measured in patients. More multicenter, prospective, clinical studies and confirmatory studies are warranted in the future, to investigate whether the higher level of OS participates in FP, or that the elevated OS status represents a marker of FP.

5. Conclusion

Our study reported for the first time that serum levels of potassium, albumin and B_{12} are lower in FP patients than in BP patients. Moreover, decreased potassium and albumin were independently associated with FP, and lower potassium and B_{12} levels were associated with technique failure. These findings suggest lower serum potassium, albumin and B_{12} as potential oxidative stress markers of FP and raise the hypothesis that a high level of OS could contribute to FP, which requires replication in confirmatory studies.

Ethical approval

This is an observational study. The Ethics Committee of Fifth Affiliated Hospital of Sun Yat-Sen University has confirmed that no ethical approval is required.

Acknowledgements

We would like to appreciate all participants and staff in the cohort.

Author contributions

Conceptualization: Lingling Liu, Kehang Xie; Methodology: Mengmeng Yin, Xiaoqiu Chen, Binhuan Chen, Jianting Ke; Writing-original draft preparation: Lingling Liu; Writing-review and editing: Kehang Xie; Supervision: Cheng Wang.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

[1] Posteraro B, Efremov L, Leoncini E, et al. Are the conventional commercial yeast identification methods still helpful in the era of new clinical microbiology diagnostics? A Meta-Analysis of their accuracy. J Clin Microbiol. 2015;53(8):2439–2450.

[2] Roumeliotis S, Eleftheriadis T, Liakopoulos V. Is oxidative stress an issue in peritoneal dialysis? Semin Dial. 2019;32(5):463–466.

[3] Federico A, Morgillo F, Tuccillo C, et al. Chronic inflammation and oxidative stress in human carcinogenesis. Int J Cancer. 2007;121(11):2381–2386.

[4] Koong AC, Giaccia AJ, Hahn GM, et al. Activation of potassium channels by hypoxia and reoxygenation in the human lung adenocarcinoma cell line A549. J Cell Physiol. 1993;156(2):341–347.

[5] Robinson AD, Ramanathan KB, McGee JE, et al. Oxidative stress and cardiomyocyte necrosis with elevated serum troponins: pathophysiologic mechanisms. Am J Med Sci. 2011;342(2):129–134.

[6] Kapincharanon C, Thongboonkerd V. K+ deficiency caused defects in renal tubular cell proliferation, oxidative stress response, tissue repair and tight junction integrity, but enhanced energy production, proteasome function and cellular K+ uptake. Cell Adh Migr. 2018;12(3):247–258.

[7] Faure P, Troncy L, Lecomte M, et al. Albumin antioxidant capacity is modified by methylglyoxal. Diabetes Metab. 2005;31(2):169–177.

[8] Rondeau P, Armenta S, Caillens H, et al. Assessment of temperature effects on beta-aggregation of native and glycated albumin by FTIR spectroscopy and PAGE: relations between structural changes and antioxidant properties. Arch Biochem Biophys. 2007;460(1):141–150.

[9] Karamshetty V, Acharya JD, Ghaskadbi S, et al. Mathematical modeling of glutathione status in type 2 diabetics with vitamin B12 deficiency. Front Cell Dev Biol. 2016;4:16.

[10] Chan W, Almasieh M, Catrinescu MM, et al. Cobalamin-associated superoxide scavenging in neuronal cells is a potential mechanism for vitamin B12-deprivation optic neuropathy. Am J Pathol. 2018;188(1):160–172.

[11] Liu D, Lin Y, Gong N, et al. Degree and duration of hypokalemia associated with peritonitis in patients undergoing peritoneal dialysis. Int J Clin Pract. 2021;75(8):e14188.

[12] Hu S, Tong R, Bo Y, et al. Fungal peritonitis in peritoneal dialysis: 5-year review from a North China center. Infection. 2019;47(1):35–43.

[13] Tian Y, Xie X, Xiang S, et al. Risk factors and outcomes of high peritonitis rate in continuous ambulatory peritoneal dialysis patients: a retrospective study. Medicine. 2016;95(49):e5569.

[14] Noppakun K, Kasemset T, Wongsawad U, et al. Changes in serum albumin concentrations during transition to dialysis and subsequent risk of peritonitis after peritoneal dialysis initiation: a retrospective cohort study. J Nephrol. 2020;33(6):1275–1287.

[15] Ram R, Swarnalatha G, Neela P, et al. Fungal peritonitis in patients on continuous ambulatory peritoneal dialysis: a single-centre experience in India. Nephron Clin Pract. 2008;110(4):c207–c212.

[16] Oygar DD, Altiparmak MR, Murtezaoglu A, et al. Fungal peritonitis in peritoneal dialysis: risk factors and prognosis. Ren Fail. 2009;31(1):25–28.

[17] ISPD peritonitis recommendations: 2016 update on prevention and treatment. Perit Dial Int. 2018;38(4):313.

[18] Htay H, Cho Y, Pascoe EM, et al. Multicenter registry analysis of center characteristics associated with technique failure in patients on incident peritoneal dialysis. Clin J Am Soc Nephrol. 2017;12(7):1090–1099.

[19] Chuang YW, Shu KH, Yu TM, et al. Hypokalaemia: an independent risk factor of Enterobacteriaceae peritonitis in CAPD patients. Nephrol Dial Transplant. 2009;24(5):1603–1608.

[20] Zanger R. Hyponatremia and hypokalemia in patients on peritoneal dialysis. Semin Dial. 2010;23(6):575–580.

[21] Ribeiro SC, Figueiredo AE, Barretti P, et al. Low serum potassium levels increase the infectious-caused mortality in peritoneal dialysis patients: a propensity-matched score study. PLoS One. 2015;10(6):e0127453.

[22] Newman LN, Weiss MF, Berger J, et al. The law of unintended consequences in action: increase in incidence of hypokalemia with improved adequacy of dialysis. Adv Perit Dial. 2000;16:134–137.

[23] Kwan BC, Szeto CC. Dialysis: hypokalaemia and cardiac risk in peritoneal dialysis patients. Nat Rev Nephrol. 2012;8(9):501–503.

[24] Davies SJ, Zhao J, Morgenstern H, et al. Low serum potassium levels and clinical outcomes in peritoneal Dialysis-International results from PDOPPS. Kidney Int Rep. 2021;6(2):313–324.

[25] Smit W, van den Berg N, Schouten N, et al. Free-water transport in fast transport status: a comparison

between CAPD peritonitis and long-term PD. Kidney Int. 2004;65(1):298–303.
[26] Coester AM, Struijk DG, Smit W, et al. The cellular contribution to effluent potassium and its relation to free water transport during peritoneal dialysis. Nephrol Dial Transplant. 2007;22(12):3593–3600.
[27] Khan MU, Komolafe BO, Weber KT. Cation interdependency in acute stressor states. Am J Med Sci. 2013;345(5):401–404.
[28] Udensi UK, Tchounwou PB. Potassium homeostasis, oxidative stress, and human disease. Int J Clin Exp Physiol. 2017;4(3):111–122.
[29] Shu KH, Chang CS, Chuang YW, et al. Intestinal bacterial overgrowth in CAPD patients with hypokalaemia. Nephrol Dial Transplant. 2008;24(4):1289–1292.
[30] Okuda J, Hayashi N, Okamoto M, et al. Translocation of *Pseudomonas aeruginosa* from the intestinal tract is mediated by the binding of ExoS to an Na,K-ATPase regulator, FXYD3. Infect Immun. 2010;78(11):4511–4522.
[31] Alharbi MA. Low serum albumin a predictor sign of the incidence of peritoneal dialysis-associated peritonitis? A quasi-systematic review. Saudi J Kidney Dis Transpl. 2020;31(2):320–334.
[32] Proia RL, Hla T. Emerging biology of sphingosine-1-phosphate: its role in pathogenesis and therapy. J Clin Invest. 2015;125(4):1379–1387.
[33] Zha Y, Qian Q. Protein nutrition and malnutrition in CKD and ESRD. Nutrients. 2017;9(3):208.
[34] Wu YC, Wu YH, Chang JY, et al. Anemia, hematinic deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody positivity in atrophic glossitis patients with vitamin B12 deficiency. J Formos Med Assoc. 2020;119(3):720–727.
[35] Kuwahara T, Kaneda S, Shimono K. Adding biotin to parenteral nutrition solutions without lipid accelerates the growth of *Candida albicans*. Int J Med Sci. 2016;13(9):724–729.
[36] Ohara H, Matsuzaki T, Ochiai T, et al. Biotin regulates colonization and growth of *Candida albicans* in the catheter lumen during nutrient infusions. Int J Pharm Compd. 2020;24(5):420–425.
[37] Anyanwu EC, Morad M, Campbell AW. Metabolism of mycotoxins, intracellular functions of vitamin B12, and neurological manifestations in patients with chronic toxigenic mold exposures. A review. ScientificWorldJournal. 2004;4:736–745.
[38] Moreira ES, Brasch NE, Yun J. Vitamin B12 protects against superoxide-induced cell injury in human aortic endothelial cells. Free Radic Biol Med. 2011;51(4):876–883.
[39] Manzanares W, Hardy G. Vitamin B12: the forgotten micronutrient for critical care. Curr Opin Clin Nutr Metab Care. 2010;13(6):662–668.
[40] Birch CS, Brasch NE, McCaddon A, et al. A novel role for vitamin B12: cobalamins are intracellular antioxidants in vitro. Free Radic Biol Med. 2009;47(2):184–188.
[41] Tyagi N, Sedoris KC, Steed M, et al. Mechanisms of homocysteine-induced oxidative stress. Am J Physiol Heart Circ Physiol. 2005;289(6):H2649–H2656.
[42] Frijhoff J, Winyard PG, Zarkovic N, et al. Clinical relevance of biomarkers of oxidative stress. Antioxid Redox Signal. 2015;23(14):1144–1170.
[43] Nowotny K, Jung T, Höhn A, et al. Advanced glycation end products and oxidative stress in type 2 diabetes mellitus. Biomolecules. 2015;5(1):194–222.
[44] Kosmadakis G, Da Costa Correia E, Carceles O, et al. Vitamins in dialysis: who, when and how much? Ren Fail. 2014;36(4):638–650.