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Original Article

Additional hemoperfusion for patients receiving maintenance hemodialysis: a retrospective analysis

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Abstract: Objective: To determine the efficacy of hemodialysis combined with hemoperfusion with acupuncture on calcium-phosphorus metabolism disorder (CPMD) of patients who had received maintenance hemodialysis and its effect on intact parathyroid hormone (iPTH) and nutritional status. Methods: Data from 142 patients who were treated and given maintenance hemodialysis in Baoji People's Hospital from March 2018 to February 2020 were analyzed retrospectively. Patients treated with hemodialysis and acupuncture-moxibustion adjuvant therapy were enrolled into the control group (n=58), while those treated with hemoperfusion in addition to hemodialysis and acupuncture-moxibustion adjuvant therapy were enrolled into the research group (n=84). The two groups were compared in terms of changes in iPTH, calcium-phosphorus product, serum calcium (Ca), serum phosphorus (P), β2 microglobulin (β2-MG), serum albumin (Alb), creatinine (Scr) and urea nitrogen (BUN). The clinical efficacy in the two groups was compared after therapy, and the two groups were also compared in the improvement of immune function-related indexes (IgG and IgM) and the changes of nutrition-related indexes (Alb, prealbumin (PA) and hemoglobin (Hb)) before and after treatment. A risk prediction model was constructed based on LASSO regression to evaluate the predictive value of the risk score for efficacy of patients. Results: After treatment, the research group presented significantly lower levels of P, iPTH, and calcium-phosphorus product than the control group, but a significantly higher Ca level than the control group (all $P<0.05$). In addition, after treatment, the research group showed significantly lower levels of β2-MG, Scr and BUN but a higher Alb level than the control group (all $P<0.05$). After treatment, the research group had a greater improvement in immune function-related indexes (IgG and IgM) than the control group (all $P<0.05$), while the control group had significantly decreased Alb, PA and Hb after treatment (all $P<0.05$), but the levels of these in the research group did not change greatly (all $P>0.05$). Risk scoring formula was constructed: risk score = (dialysis time * 0.057123881) + (Ca * -0.100413548) + (P * 0.100419363) + (calcium and phosphorus product * 0.03872268) + (iPTH * 0.000358779). According to inter-group comparison of risk score, the Improvement group got a lower risk score than the Non-improvement group ($P<0.0001$). Moreover, according to ROC curve-based analysis, the area under the curve of risk score in predicting the efficacy of patients was 0.991. Conclusion: Hemodialysis combined with acupuncture and blood perfusion can control the immune regulation by increasing the blood calcium content without affecting nutritional status, but it has no significant effect on the efficacy in patients.

Keywords: Hemodialysis, hemoperfusion, maintenance hemodialysis, calcium-phosphorus metabolism disorder, iPTH, nutritional status

Introduction

End-stage renal disease (ESRD) is the stage at which the kidney is no longer able to function at the level required in daily life [1]. Normally, the kidney is responsible for filtering waste and excess liquid in the blood, regulating electrolytes, and producing hormones to help control blood pressure and keep bones healthy [2]. However, for patients with ESRD, the kidneys are no longer able to perform these functions, resulting in an accumulation of waste and fluid in the body [3]. At present, with an annually increasing incidence worldwide, ESRD has become an unavoidable public health problem requiring prevention for many countries [4]. Currently, hemodialysis is the primary treatment for ESRD. Through dialysis, removal of toxins and metabolic wastes, maintenance of electrolyte and acid-base balance, and purification

of blood can be achieved to prolong the survival time of patients [5]. Reportedly, patients undergoing long-term maintenance hemodialysis often suffer complications, such as renal anemia, calcium-phosphorus metabolism disorder (CPMD), secondary hyperparathyroidism, renal osteopathy, malnutrition, low immune function and infection [6].

Due to the removal of minerals during dialysis, patients receiving hemodialysis often suffer CPMD [7]. The most common result is secondary hyperparathyroidism with features of a high parathyroid hormone (PTH) level, low calcium level and high phosphorus level in blood [8]. In patients with chronic kidney disease, the parathyroid gland may become overactive and then produce too much parathyroid hormone, triggering secondary hyperparathyroidism [9]. As time goes on, secondary hyperparathyroidism can trigger bone diseases, vascular calcification, and cardiovascular diseases [10]. According to many scholars [11, 12], hemoperfusion technology has been found to effectively remove toxic metabolic wastes, including medium and large molecules, from blood, which cannot be achieved by hemodialysis. Whether the combined dialysis regimen had a positive effect on the CPMD in patients receiving maintenance hemodialysis, and whether it affected the nutritional status of patients has not been studied yet.

This study aimed to determine the efficacy of additional hemoperfusion on CPMD of patients receiving maintenance hemodialysis and its effect on intact parathyroid hormone (iPTH) and nutritional status.

Materials and methods

Inclusion and exclusion criteria

Inclusion criteria: Patients meeting the diagnostic criteria of uremia stage of chronic renal failure [13]; patients who definitely received hemodialysis three times a week; patients whose continuous dialysis time was longer than 6 months; patients without a history of bleeding, infection, or operation in the last 3 months and with a stable condition, and patients with complete clinical data.

Exclusion criteria: Patients who had received immunosuppressants; patients with a history of surgery or severe trauma recently; patients with declined function of major internal organs, such as heart, brain, liver, and lung; patients comorbid with heart failure, respiratory failure or circulatory failure; patients comorbid with malignant tumor; patients who received radiotherapy or chemotherapy that affected the immune function of the body; patients whose primary diseases were autoimmune diseases including systemic lupus erythematosus and vasculitis; patients with relative contraindications; and patients who were unable to tolerate the treatment.

Sample selection

Data from 142 patients who were treated and given maintenance hemodialysis in Baoji People's Hospital from March 2018 to February 2020 were analyzed retrospectively. Patients treated with hemodialysis and acupuncture-moxibustion adjuvant therapy were enrolled as the control group (n=58), while those treated with additional hemoperfusion were enrolled as the research group (n=84). This study was approved by the Medical Ethics Committee of Baoji People's Hospital. A flow chart of this study is shown in **Figure 1**.

Therapeutic regimen

Patients underwent basic treatment for two weeks before dialysis, including antihypertensive drugs, insulin therapy, iron, folic acid, erythropoietin supplements, diet control, and nutritional supplements. The control group received hemodialysis and acupuncture-moxibustion adjuvant therapy, 4 hours/session, 3 times/week, while the research group underwent hemoperfusion based on hemodialysis. Acupuncture-moxibustion adjuvant therapy was conducted with the same duration in both groups. Hemoperfusion was conducted for 2 hours every two weeks.

In the acupuncture-moxibustion adjuvant therapy, patients were in a supine position and the Quchi, Hegu, Zusanli, Sanyinjiao, and Taixi acupoints in bilateral shoulders were stimulated. After disinfection, a 0.30 mm * 40 mm needle was inserted 20-30 mm deep. After getting Qi, a 15 mm moxa stick was used, with two moxibustions per acupoint. Needles were kept in for 30 minutes, with treatments three times/week.

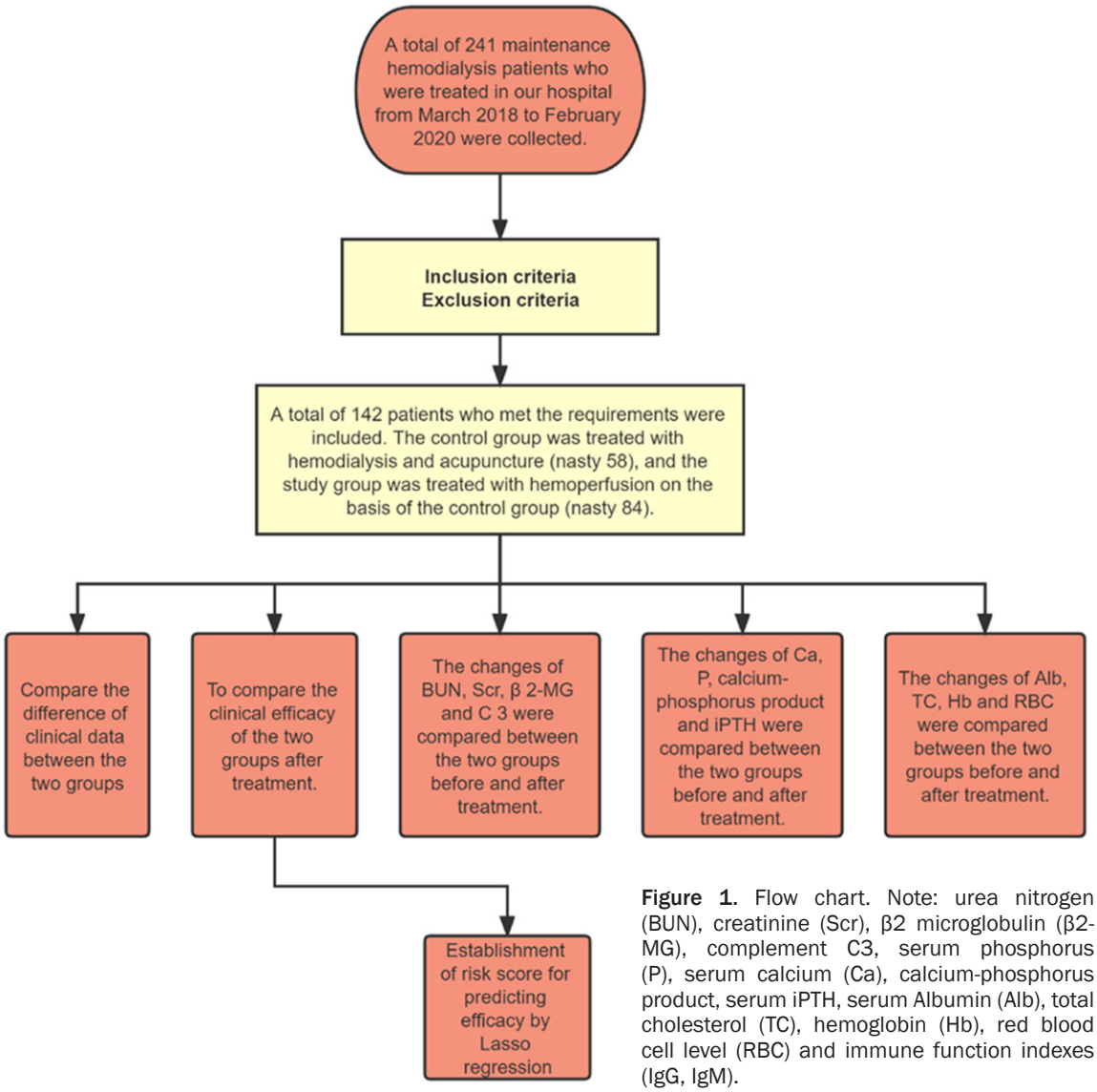

Figure 1. Flow chart. Note: urea nitrogen (BUN), creatinine (Scr), β2 microglobulin (β2-MG), complement C3, serum phosphorus (P), serum calcium (Ca), calcium-phosphorus product, serum iPTH, serum Albumin (Alb), total cholesterol (TC), hemoglobin (Hb), red blood cell level (RBC) and immune function indexes (IgG, IgM).

Dialysis was conducted using a Swedish Gambro AK200S dialyzer, with blood flow of 200 mL/min, low molecular weight heparin anticoagulant (3000 m/5000 IU), and dialysate calcium concentration of 1.5 mmol/L. The hemoperfusion treatment was conducted using a Zhuhai Jafron Biomedical HA130 device (produced by Zhuhai Jafron Biomedical Co., Ltd.) with a 65 mL capacity, and the device was rinsed with 5% glucose solution before being connected to the dialyzer. Heparin saline and aseptic saline were used for rinsing before connecting to the arteriovenous line for 2-hour continuous perfusion. The hemoperfusion device was then removed, and hemodialysis continued for 2 more hours. All operation procedures were conducted by strictly following machine operating instructions.

Collection of clinical data and detection indicators

The clinical data of enrolled patients were collected from the electronic medical record system of Baoji People's Hospital, including age, gender, dialysis time, causes of kidney injury, history of alcoholism and smoking. The detection indexes included urea nitrogen (BUN), creatinine (Scr), β2 microglobulin (β2-MG), complement C3, serum phosphorus (P), serum calcium (Ca), calcium-phosphorus product, serum iPTH, serum Albumin (Alb), total cholesterol (TC),

Table 1. Comparison of clinical data

Factors	Control group (n=58)	Research group (n=84)	x^2 value	*P* value
Age			2.016	0.155
≥60 years old	20	39		
<60 years old	38	45		
Gender			0.227	0.633
Male	35	54		
Female	23	30		
Dialysis history			0.284	0.593
≥3 years	19	24		
<3 years	39	60		
Causes of renal injury			0.448	0.978
Hypertension	10	13		
Diabetes	8	15		
Obstructive nephropathy	3	4		
Chronic glomerulonephritis	30	42		
Polycystic kidney	7	10		
Smoking history			0.227	0.633
Yes	35	54		
No	23	30		
History of alcoholism			0.033	0.854
Yes	5	8		
No	53	76		

hemoglobin (Hb), red blood cell level (RBC) and immune function indexes (IgG, IgM) before and 4 months after treatment. The clinical efficacy in the two groups after treatment was also compared.

Outcome measures

Primary outcome measures: The clinical efficacy in the two groups before and after treatment was compared. Markedly effective: The calcium and phosphorus metabolism of the patients returned to a normal state, and the symptoms disappeared completely [4]; Effective: The metabolism of calcium and phosphorus in the patient was improved, and the symptoms were alleviated; Ineffective: The metabolism of calcium and phosphorus in the patient was still in disorder, and the symptoms may have worsened. Potential indicators for prediction of the efficacy were screened.

Secondary outcome measures: The clinical data and collected clinical indicators were compared between the two groups. The overall response rate in patients of the two groups was compared: Overall response rate = (number of markedly effective cases + that of effective cases)/ total number of cases ×100%. A risk prediction model was constructed based on LASSO regression to evaluate the predictive value of the risk score for treatment efficacy.

Statistical analyses

SPSS 26.00 (IBM Corp, Armonk, NY) was used for analyses. The measured data with normal distribution and homogeneity of variance were expressed by mean ± SD and compared by the independent-samples T test or paired t test as appropriate (All the data in this study were normally distributed). The data in non-normal distribution were analyzed by nonparametric test and represented by Z. Counted data (rate) were analyzed using the chi-square test. Based on Lasso regression analysis, the influence of each index on the efficacy in patients was determined. The efficacy of risk score in predicting the efficacy in patients was analyzed through receiver operating characteristic (ROC) curves. P<0.05 was considered significantly different.

Results

Comparison of clinical data

The clinical data of the two groups were compared. According to the results, there were no significant differences between the two groups in age, sex, dialysis time, causes of kidney injury, history of alcoholism, or smoking (all P>0.05, **Table 1**).

Evaluation of renal function

Renal function was compared between the two groups before and after treatment. Before treatment, the levels of BUN, Scr, β2-MG and C3 were not markedly different between the two groups (all P>0.05, **Figure 2**); however, after treatment, the levels of BUN, Scr, and β2-MG in the two groups decreased significantly, while C3 increased notably (all P<0.001,

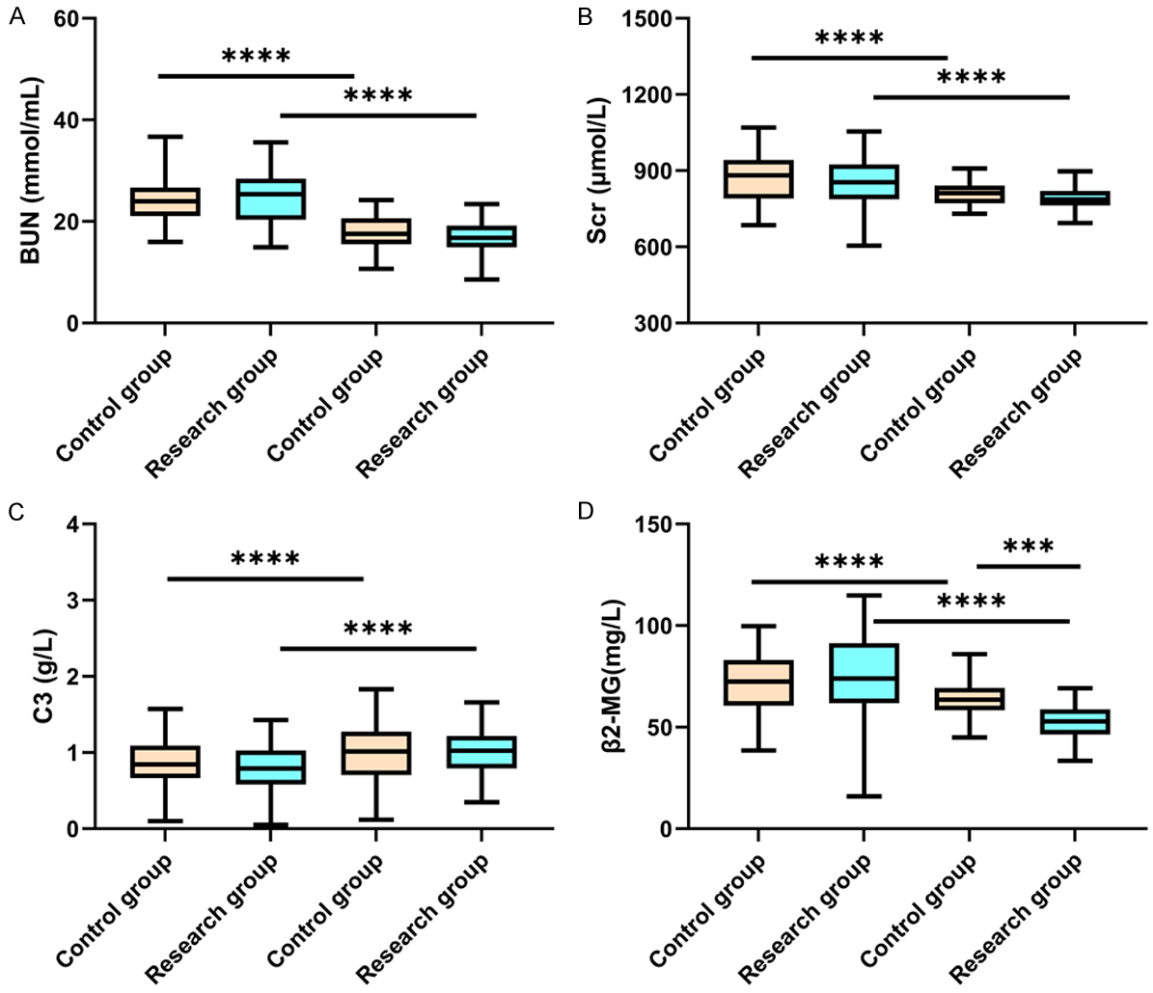

Figure 2. Comparison of the influences on renal function of patients before and after treatment. A. Changes of BUN in patients before and after treatment; B. Changes of Scr in patients before and after treatment; C. Changes of C3 in patients before and after treatment; D. Changes of β2-MG in patients before and after treatment. Note: BUN: Urea nitrogen; Scr: Serum creatinine; β2-MG: β2 microglobulin. ***P<0.001, ****P<0.0001.

Figure 2). Additionally, the research group showed a significantly lower β2-MG level than that in the control group after treatment (P<0.001, **Figure 2**).

Evaluation of calcium and phosphorus metabolism indexes

The changes in calcium and phosphorus metabolism were compared between the two groups. Before treatment, the two groups were not significantly different in the levels of Ca, P, calcium and phosphorus product and iPTH (all P>0.05, **Figure 3**); however, after the treatment, the levels of P, calcium-phosphorus product and iPTH in both groups decreased markedly, while the level of Ca increased markedly (all P<0.001, **Figure 3**). In addition, the research group showed significantly lower levels of Ca, P, calcium-phosphorus product and higher iPTH level compared with the control group (all P<0.001, **Figure 3**).

Evaluation of nutritional indexes

The changes of nutritional status were compared between the two groups. Before the treatment, the two groups were not significantly different in the levels of Alb, TC, Hb and RBC (all P>0.05, **Figure 4**); however, after the treatment, the levels of Alb, TC, Hb and RBC in the research group increased significantly (all P<0.001, **Figure 4**), but did not change greatly in control group (all P>0.05). Consequently, the research group showed significantly higher levels of Alb, TC, Hb, and RBC than the control

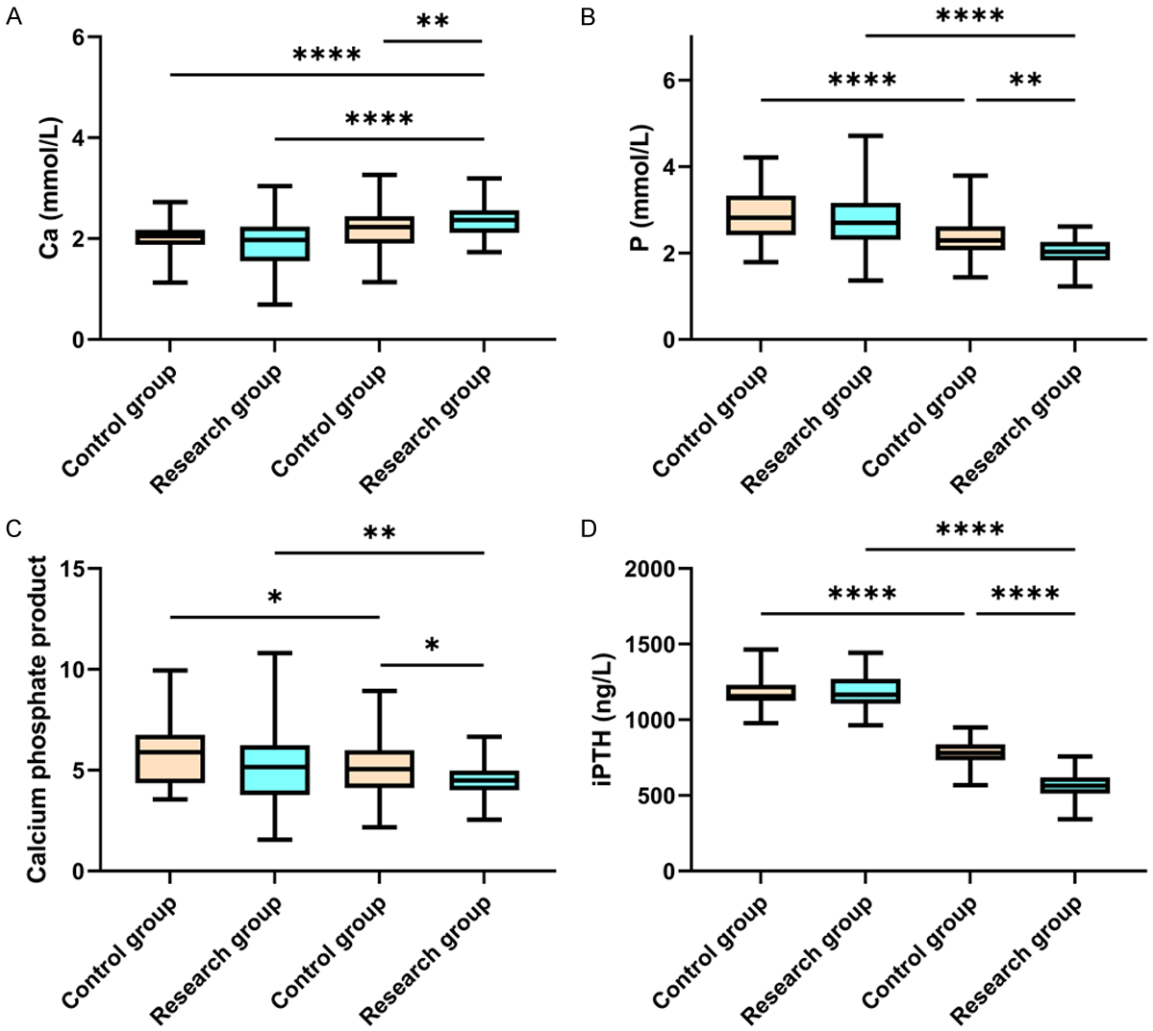

Figure 3. Comparison of the influences on calcium and phosphorus metabolism indexes of patients before and after treatment. A. Changes of Ca in patients before and after treatment; B. Changes of P in patients before and after treatment; C. Changes of calcium and phosphorus product in patients before and after treatment; D. Changes of iPTH in patients before and after treatment. Notes: Ca: Serum calcium; P: Serum phosphorus; iPTH: Intact parathyroid hormone. *P<0.05, **P<0.01, ****P<0.0001.

group after the treatment (all P<0.001, **Figure 4**).

Evaluation of clinical efficacy

According to the comparison of efficacy between the two groups, there was a markedly lower overall response rate in the control group than that in the research group (P<0.05, **Table 2**).

Establishment of risk score for efficacy prediction based on Lasso regression

In order to determine the factors affecting the efficacy, the patients with markedly effective treatment or effective treatment were assigned to an Improvement, and those with ineffective treatment were assigned to a Non-improvement. Lasso regression analysis was conducted to screen the factors affecting the treatment efficacy. According to analysis, dialysis time, Ca, P, calcium-phosphorus product and iPTH were the main factors affecting the efficacy in the patients (**Figure 5**), and 1se and min can accept the five indicators in the selection of lambda, so we closed lambda.1se (0.05161) for analysis (**Figure 5**). On the basis of lambda.1se, a risk scoring formula was constructed: risk score = (dialysis time * 0.057123881) + (Ca * -0.100413548) + (P *

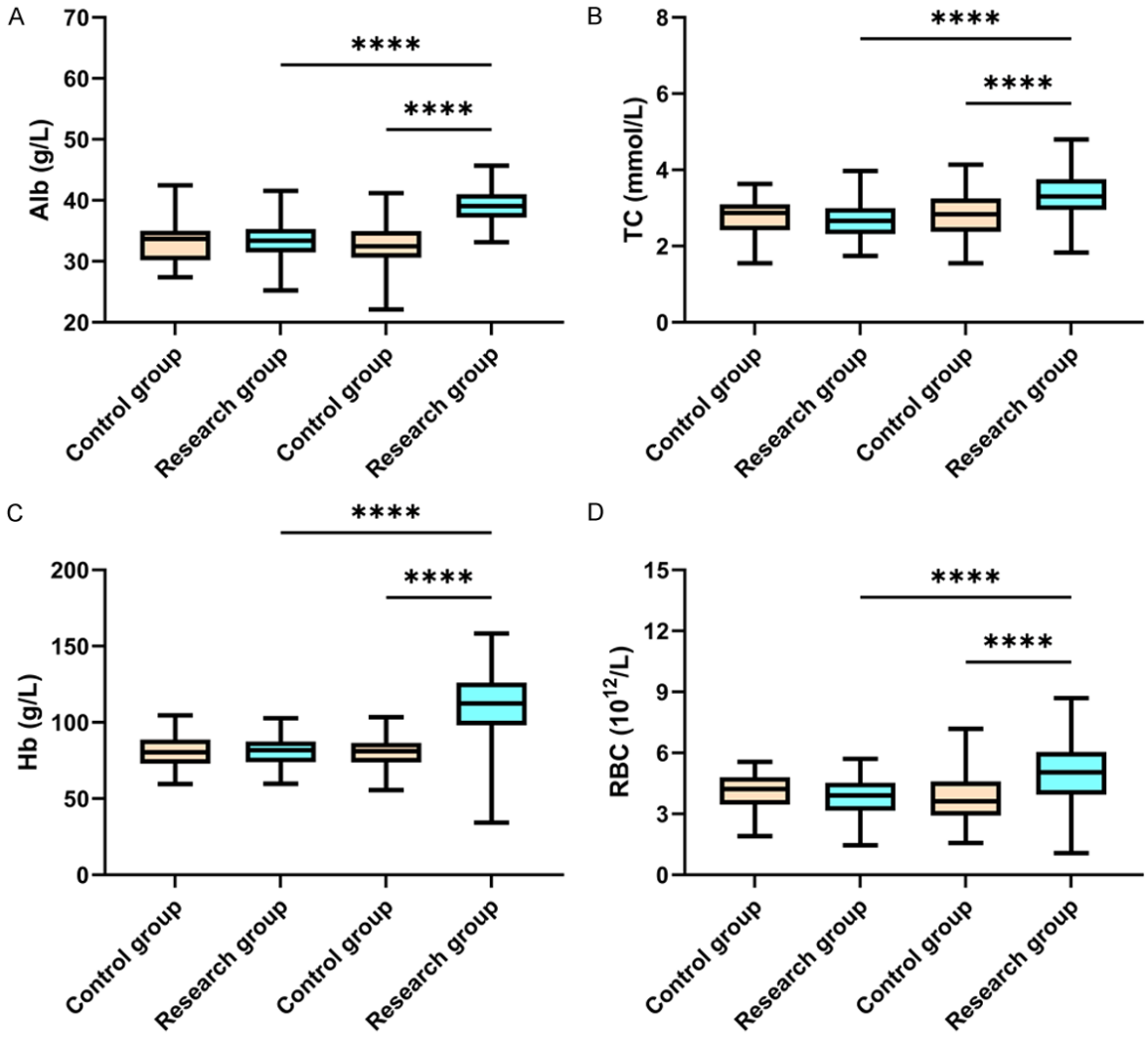

Figure 4. Comparison of the influences on nutritional status of patients before and after treatment. A. Changes of Alb in patients before and after treatment; B. Changes of TC in patients before and after treatment; C. Changes of Hb in patients before and after treatment; D. Changes of RBC in patients before and after treatment. Note: Alb: Serum Albumin; TC: Total cholesterol; Hb: Hemoglobin; RBC: Red blood cell. ****P<0.0001.

Table 2. Efficacy evaluation

Group	Markedly effective	Effective	Ineffective	Overall response rate
Control group (n=58)	28	18	12	46 (79.31)
Research group (n=84)	44	34	6	78 (92.86)
x^2 value		5.916		5.688
P value		0.052		0.017

0.100419363) + (calcium and phosphorus product * 0.03872268) + (iPTH * 0.000358779). According to the results, the Improvement got a notably lower risk score than the Non-improvement (**Figure 6A**, P< 0.0001). Moreover, according to ROC curve-based analysis, the area under the curve of risk score in predicting the efficacy in patients was 0.991 (**Figure 6B**).

Discussion

Hemoperfusion is a procedure to apply porous and loose adsorbents with larger surface area

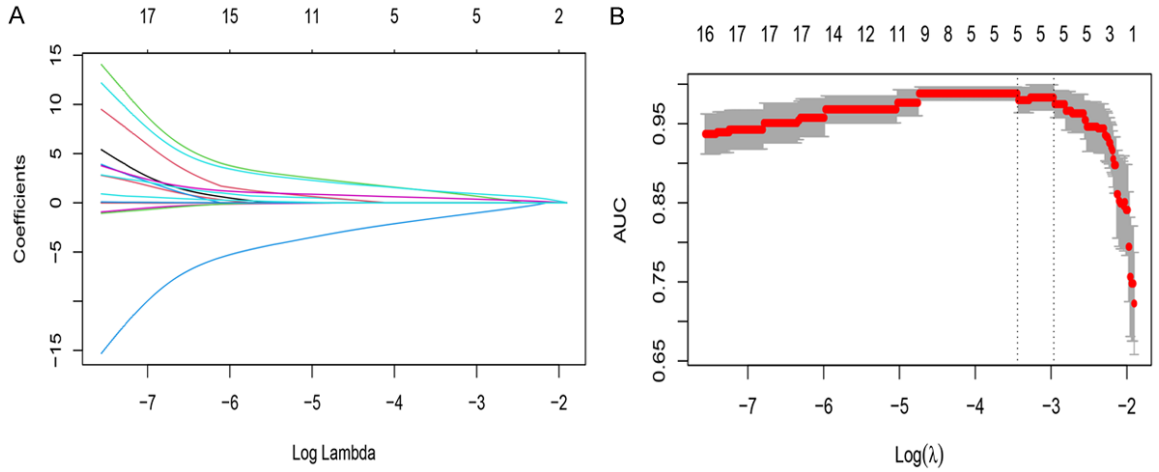

Figure 5. Lasso regression-based screening of factors affecting the efficacy. A. Coefficient distribution of regression analysis of minimum absolute contraction and selection operator (LASSO). B. Area under the curve of regression analysis of minimum absolute contraction and selection operator (LASSO).

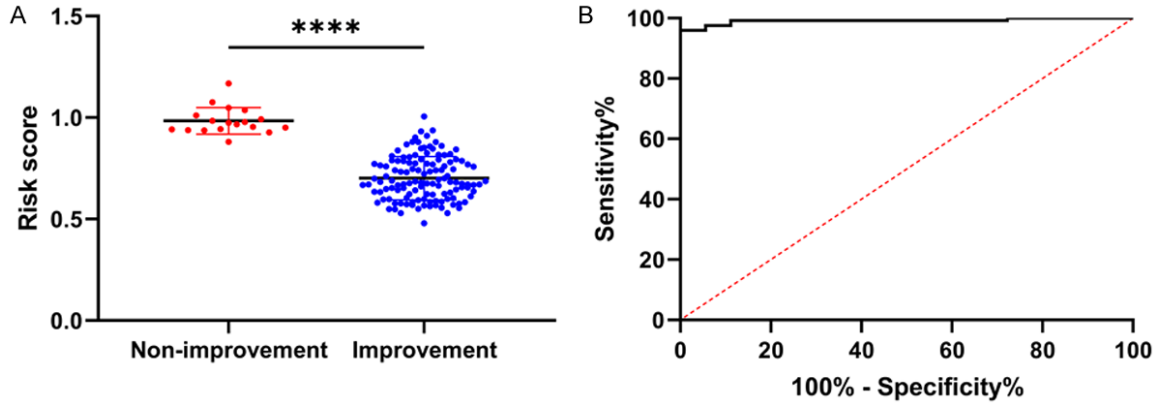

Figure 6. Risk score of two groups of patients and its predictive value for treatment efficacy. A. The risk score in patients in the Improvement group and the Non-improvement group; B. The predictive value of risk score for the efficacy in patients based on ROC curve. Note: ROC: Receiver operating characteristic curve; ****P<0.0001.

to remove macromolecular substances from the body during dialysis [14]. Reportedly, this method has advantages of high mechanical strength, fast adsorption rate and large adsorption capacity [15]. In the present study, the application of hemodialysis alone and hemodialysis combined with hemoperfusion in uremia patients with CPMD were compared. According to the results, after the treatment, the serum levels of BUN, Scr, β2-MG and C3 in the control group and the research group were significantly improved after treatment. The results suggest that both hemodialysis alone and hemodialysis combined with hemoperfusion can remove toxins in patients, and the combination did not improve the effect. Liu et al. [16] have revealed that hemodialysis combined with hemoperfusion has no obvious impact on the residual renal function of patients, but it exerts a significant effect compared with low-flux hemodialysis. In this study, however, the control group showed a higher β2-MG level than the research group. As a marker of renal function, β2-MG is adopted as an index for the evaluation of renal function. However, in addition to a renal function marker, β2-MG is also a marker of inflammation. We believe that improving the inflammatory response of patients can effectively improve the renal function of patients and eliminate toxins in the body, so that the decrease of β-2-MG in the study group is more significant than that in the control group [17, 18].

Serum calcium and phosphorus levels in blood are regulated through a complex system involving hormones, enzymes, and other factors [19]. In the cases of CPMD, the levels of the minerals in the blood are dysregulated, which can trigger a series of symptoms and health problems [20]. The levels of calcium and phosphorus product in the blood can provide useful information about the risk of certain health problems, especially in patients with chronic kidney disease [21]. Intact parathyroid hormone (iPTH) is also called PTH (1-84). When the content of calcium in the blood is too low or too high, the parathyroid gland will release or inhibit iPTH, exerting a regulatory effect [22]. In this study, the research group showed a greater improvement in the levels of Ca, P, calcium-phosphorus product and iPTH than the control group after treatment, indicating that additional hemoperfusion can better alleviate the CPMD in patients. We believe this is due to the fact that additional hemoperfusion is a blood purification technique that can effectively remove medium and large molecular toxins in the body, including parathyroid hormone that binds to proteins, providing a valuable treatment choice for patients with CPMD (such as patients with chronic kidney disease). Moreover, hemoperfusion can control calcium and phosphorus product within the normal range, which is beneficial for the prevention of complications such as bone disease and cardiovascular disease.

Nutritional status plays a crucial part in the regulation of calcium and phosphorus metabolism. Adequate dietary intake of calcium and phosphorus is necessary to maintain healthy bones, teeth, and other body functions [23]. Due to malnutrition, unbalanced diet and some medical conditions that affect nutrient absorption and metabolism, the mineral levels in the blood may be disordered [24]. In this study, the nutritional status of patients before and after hemodialysis combined with hemoperfusion was evaluated. According to the results, the levels of Alb, TC, Hb and RBC in the research group increased significantly after treatment, and were significantly higher than those in the control group. These findings indicate that additional hemoperfusion can better improve the nutritional status of patients. We believe that the improvement of nutritional status may be due to better diet control and increased intake of protein, which is crucial for maintaining adequate levels of Alb, TC, Hb and RBC. Additional hemoperfusion can effectively remove toxins such as medium and large molecules in the body, without damaging the immune system but promoting hematopoietic function, thus improving the nutritional status of patients [25]. Finally, the factors affecting the treatment efficacy in patients were screened based on lasso regression. According to the results, dialysis time, Ca, P, calcium-phosphorus product and iPTH were primary factors impacting the efficacy. Further, a risk scoring formula was contrsucted based on Lasso regression, and the Non-improvement group got a higher risk score than the Improvement group, and the area under the ROC curve was >0.9, indicating that the risk score is an ideal predictive tool.

This study has confirmed through experiments that additional hemoperfusion can alleviate the CPMD in patients who had received maintenance hemodialysis and improve their nutritional status. However, the study still has some limitations. First of all, the risk scoring formula we established in this study only demonstrated a high predictive ability in this study, but whether the model is universal in external data requires further verification. Secondly, in such a single-center study, few samples were collected, which may bias the statistical analysis results. Lastly, we were unable to follow up the long-term prognosis of patients, so the impact of the two treatment schemes on patients' long-term prognosis needs further verification. Therefore, we hope to carry out more experiments in the future to improve the conclusions.

To sum up, hemodialysis combined with acupuncture and blood perfusion can control its immune regulation by increasing the blood calcium content without affecting its nutritional status, but it has no significant effect on the efficacy in patients.

Disclosure of conflict of interest

None.

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