Review

# Effect of the Combination of Hemodialysis and Hemoperfusion on Clearing Interleukin-31: A Prospective, Randomized Crossover Trial in Patients under Maintenance Hemodialysis

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**Keywords.** Hemodialysis; Interleukin-31; Pruritus; Hemoperfusion

**Introduction.** Uremic pruritus (UP) is a disturbing symptom in a quite large proportion of hemodialysis (HD) patients. Recent studies have indicated a potential role of interleukin-31 (IL-31) in the pathophysiology of pruritus, and it is becoming a promising therapeutic target for UP. Hemoperfusion (HP) is an extracorporeal technique that has been shown to be effective in absorbing molecules which may be responsible for inducing pruritus. In this study, we conducted this study to explore whether additional HP could enhance the removal of IL-31 in UP patients.

**Methods.** The study was conducted in two parts. In Part A, the prevalence and intensity of UP were recorded and the basal serum IL-31 level was determined three times a week in HD patients. Patients with detectable serum IL-31 levels in part A were included in Part B. Each patient had two 4-h test sessions: conventional HD or HD plus HP (HDHP). The reduction ratio (RR) of IL-31 from HD and HDHP was compared.

**Results.** Forty patients completed part A and 40% of them were suffering from UP. Serum IL-31 was detected at significantly higher percentages in UP patients than in non-UP patients (50% vs 4.2%). Serum levels of IL-31 in UP patients were significantly higher than that in non-UP patients (median: 8.35pg/ml vs 7.8pg/ml). Serum IL-31 levels were significantly correlated with pruritus intensity in patients with UP($r = 0.55$, $P < .05$). Eight patients were enrolled and completed part B. The use of combined HD and HP treatment produced a better RR for IL-31 than HD alone ($34.26 \pm 1.43\%$ vs $15.28 \pm 2.11\%$, $P < .01$).

**Conclusions.** IL-31 may play an important role in the pathophysiology of uremic pruritus. The addition of hemoperfusion to conventional hemodialysis provides enhanced removal of IL-31.

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## INTRODUCTION

Uremic pruritus (UP) is a common symptom in patients undergoing hemodialysis (HD) that is linked to poor quality of life and increased mortality.[1-3] Since current anti-pruritic treatments are often ineffective, exploring novel therapeutic approaches has become a top research priority.

Interleukin 31 (IL-31) is a recently identified cytokine with a well-defined role in the pathogenesis of pruritus. IL-31 and its receptor, IL-31 receptor A (IL-31RA) and oncostatin M β, mediate itching signal via sensory neurons in the dorsal root

ganglion.[4-5] Overexpression of IL-31 or injection of IL-31 in animals or humans induces scratching behavior and itching sensation.[6-9] Emerging evidence indicates that IL-31 may play a role in the development and maintenance of UP.[10] In a study of 178 hemodialysis patients, significantly higher levels of IL-31 were recorded in patients with pruritic symptoms compared with those without the symptoms.[11] Patients with higher serum IL-31 levels experienced greater pruritus visual analogue scale (VAS) reductions following the treatment with nemolizumab (a humanized mAb against IL-31 receptor).[12] Thus, IL-31 is becoming a promising therapeutic target for UP.

Over the years, extracorporeal techniques to remove pruritogen from the blood have been in the focus of clinical research. With a molecular weight of approximately 24 kD,[13] IL-31 cannot be removed efficiently by conventional hemodialysis. One solution for a better IL-31 removal may be hemoperfusion (HP). The hemoadsorption (HA) 130 cartridges (Jafron, China) are resin-made polymers with highly biocompatible sorbents. The pore size distributions of the resin is 500 D-40 kD, allowing elimination of molecules up to 30 kD.[14] In theory, HA-130 is justified for IL-31 removal.

In this study, we hypothesized that adding HA130 hemoperfusion to conventional hemodialysis would improve IL-31 elimination. To test this hypothesis, we compared the efficiency of removal of IL-31 with two different extracorporeal therapies: conventional hemodialysis plus hemoperfusion (HDHP) and conventional hemodialysis (HD).

## MATERIAS AND METHODS

### Study Design

The study was conducted as a two-part study. In part A, the prevalence and intensity of UP

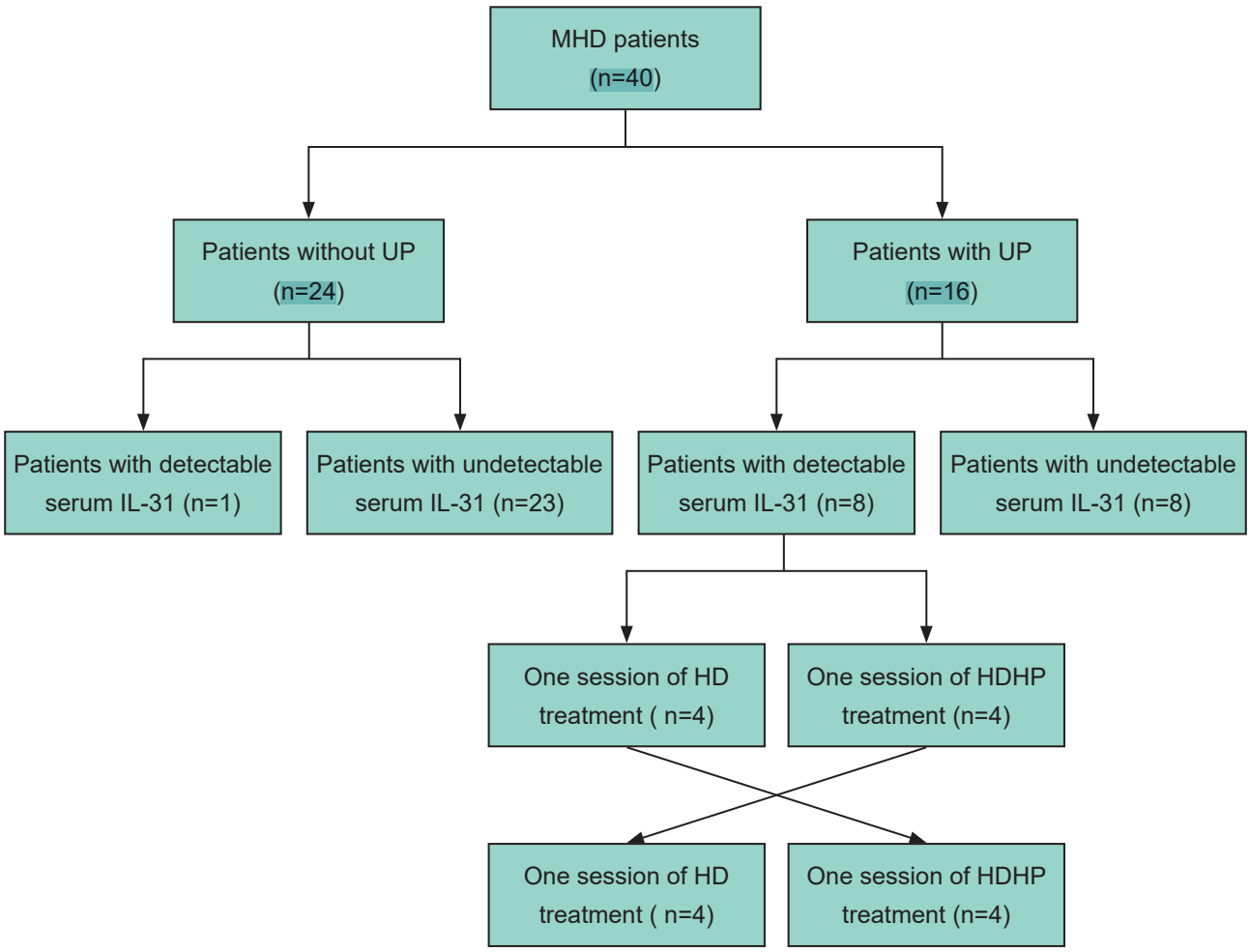


**Figure 1.** Study flowchart. MHD, maintenance hemodialysis; UP, uremic pruritus; HDHP: combined hemodialysis and hemoperfusion.

was investigated and the basal serum IL-31 was determined. Part B began after measuring the serum IL-31 levels of patients in part A. UP patients with detectable serum IL-31 levels were included in part B. Each patient had two 4-h test sessions, either HD or HDHP. The order of the two sessions was randomized by using a list created by a random number generator. The test sessions were performed two weeks apart, during the midweek day. Concentration of IL-31 in serum at the beginning and at the end of each session was measured (Figure 1).

### Patient Selection

The study participants were patients undergoing HD three times a week at Tongji Hospital, Shanghai, China. The eligible participants were those aged 18 years or older. For part A of the study, the participants were excluded if they had any of the following conditions: active infection; psychotic diseases; primary skin disorders; cholestatic liver disease or acute hepatitis; active malignancy; change in dialysis modality within the past three months; and participant refusal. For part B of the study, UP patients with detectable serum IL-31 levels were included, and excluded if they had contraindications for HP or refused to participate. The study was approved by the local Ethics Committee (Tongji Hospital, NO.2021-024) and was conducted in agreement with the Declaration of Helsinki and registered on chictr.org.cn (identification number ChiCTR20000038640). All participants provided informed consent.

### Patient Characteristics

Demographic data and baseline characteristics, including age, sex, etiology of end stage kidney disease (ESKD), the duration of HD, vascular access type, weekly dose of EPO, laboratory findings, the prevalence and intensity of UP of all participants were recorded.

### Pruritus Assessment

The patients were considered to have UP if they met the following criteria:[15] experiencing at least three episodes of pruritus within the past two weeks, with symptoms occurring a few times a day, lasting at least a few minutes, and causing discomfort for the patient; or the regular occurrence of pruritus within the past six months, but less frequently than those listed above. Visual analogue scale (VAS) for pruritus intensity was reported from 0 to 10 (0 = no itching, 10 = worst imaginable itching).[16]

### Laboratory Parameters

Laboratory measurements included concentration of IL-31 in serum at the beginning and at the end of each dialysis session. For collecting the blood samples at the end of the dialysis, the blood flow rate was reduced to 50 mL/min for 30 s and the samples were drawn from the arterial set. Serum specimens were collected and stored at −80° C. IL-31 concentration was measured by using a commercially available enzyme-linked immunosorbent assay with conventional kits according to the manufacturer's instructions (Human IL-31 ELISA Kit; Abcam, Cambridge, MA, USA). The detection limit was 7.8 pg/mL.

### Dialysis modality

HD was conducted by using Dialog$^+$ Machines (B.Braun, Germany) and low-flux dialyzers (Diacap LOPS 15; B. Braun, Melsungen, Germany). All patients were dialyzed with routine dialysis parameters (bicarbonate dialysate, blood flow of 250 ± 50 mL/min and dialysate flow of 500 mL/min, and dialysis time of 240 ± 15 min).

HDHP was conducted over 4hrs, which was divided into two parts. The HA130 resin cartridge (Jafron Biomedical Co., Ltd, Zhuhai, China) was connected in series prior to the dialyzers (Diacap LOPS 15) for the first 2h. This was followed by the exclusive use of Diacap LOPS 15 for the subsequent 2h. In China, HA130 cartridge is mainly used in chronic dialysis complications. It contains biocompatible, highly porous copolymers, capable of binding a broad spectrum of hydrophobic compounds with molecular weights ranging between 0.5 and 40 kDa.[14]

Anticoagulation was conducted by using low-molecular-weight heparin. Net fluid removal was set individually. For each patient, the dialysis prescription was kept constant throughout the study. The blood flow rate for HD and HDHP was 250 ± 50 mL/min and 180 mL/min, respectively.

### Reduction ratio (RR) of IL-31

Reduction ratio (RR) of IL-31 was compared

between HD and HDHP. RR was calculated with the equation: $RR = 100\times[1-(C_{post\text{-}corr}/C_{pre})]$. $C_{post\text{-}corr}$ was calculated using the following equation:[17] $C_{post\text{-}corr} = C_{post}/[1+(BW_{pre}-BW_{post})/(0.2\times BW_{post})]$. $BW_{pre}$ and $BW_{post}$ referred to pre- and post-dialysis body weight.

### Statistical Analysis

Data were presented as mean ± conventional deviation for normally distributed continuous variables, as median and quartile (P25, P75) for non-normally distributed continuous variables, and as number of participants (n) and percentage (%) for categorical variables. For descriptive analysis, univariate analyses were conducted by using the independent 2-sample *t* test, Wilcoxon rank-sum test, and Pearson $\chi^2$ test, respectively.IL-31 with values below limits of detection were graded as negative and the levels were assigned a numerical value of 7.8pg/ml for statistical analysis. Spearman's correlation coefficient test was used to assess the correlation between IL-31 levels and pruritus intensity. All statistical analyses were performed by using Prism v.8 (GraphPad Software). $P < 0.05$ was considered to be statistically significant. For practical reasons (low or non-adherence), we enrolled 40 patients in part A. Because of lack of appropriate data, a priori power analysis was not conducted to determine the appropriate sample size in part B. Based on feasibility, eight patients with detectable serum IL-31 levels were included in part B.

## RESULTS

### Baseline Characteristics

Forty patients were enrolled in part A. Among them, 40% of patients were suffering from pruritus. Serum IL-31 was detected at significantly higher

**Table 1.** Demographic and clinical characteristics of participants in part A

| Parameters | Without pruritus (n = 24) | With pruritus (n = 16) | *P* |
|---|---|---|---|
| Age (years) | 58.40 ± 20.30 | 60.70 ± 18.60 | .45 |
| Female (n (%)) | 11 (45.8) | 8 (50) | 1.00 |
| Dialysis vintage (months) | 69.90 ± 5.20 | 71.20 ± 13.80 | .79 |
| Cause of ESKD (n (%)) | | | |
| Glomerular disorders | 8 | 6 | 1.00 |
| Hypertension | 2 | 1 | 1.00 |
| Diabetic nephropathy | 10 | 7 | 1.00 |
| Polycystic kidney disease | 2 | 1 | 1.00 |
| Unknown | 2 | 1 | 1.00 |
| Vascular access type (AVF/AVG/Catheter) | 24/0/0 | 16/0/0 | .21 |
| Weekly dose of EPO (units) | 8500 ± 1694 | 8500 ± 2366 | .39 |
| Average ultrafiltration rate (mL/h) | 728 ± 133.84 | 682.89 ± 152.22 | .15 |
| Laboratory findings at baseline | | | |
| Hemoglobin (g/L) | 102.84 ± 11.67 | 100.98 ± 14.03 | .65 |
| Albumin (g/L) | 38.23 ± 3.86 | 39.42 ± 3.33 | .32 |
| Blood Urea (mmol/L) | 37.16 ± 6.96 | 38.28 ± 6.49 | .79 |
| Creatinine (μmol/L) | 936.41 ± 47.50 | 915.21 ± 71.33 | .77 |
| Calcium (mmol/L) | 2.33 ± 0.43 | 2.30 ± 0.23 | .78 |
| Phosphorus (mmol/L) | 1.96 ± 0.95 | 1.89 ± 0.85 | .82 |
| Bilirubin (μmol/L) | 11.46 ± 0.66 | 11.50 ± 0.98 | .09 |
| Intact parathyroid hormone (pg/ml) | 389.01 ± 105.33 | 324.51 ± 157.96 | .13 |
| β2-microglobulin (mg/L) | 30.74 ± 7.03 | 33.67 ± 10.14 | .11 |
| Residual kidney function (urine volume) | | | 1.00 |
| < 100 mL/24 h | 20 | 14 | |
| > 100 mL/24 h | 4 | 2 | |
| Kt/v | 1.7 ± 0.17 | 1.26 ± 0.14 | .71 |
| Serum IL-31 (pg/ml) | 7.8 (7.8,7.8) | 8.35 (7.8,11.30) | .0005 |
| Patients with detectable IL-31 (n (%)) | 1 (4.2) | 8 (50) | .02 |

Data were presented as mean ± conventional, median (P25, P75) and percentage (%). Independent 2-sample *t* test, Wilcoxon rank-sum test and Pearson $\chi^2$ test were conducted.IL-31 with values below limits of detection were graded as negative and the levels were assigned a numerical value of 7.8pg/ml for statistical analysis. IL-31: interleukin 31.

percentages in UP patients than in non-UP patients (50% vs 4.2%). Similar to the percent detectable results, serum levels of IL-31 were significantly higher in UP patients than in non-UP patients. No statistically significant differences were found in demographic and clinical characteristics. Baseline data in part A were listed in Table 1.

### The correlation between IL-31 levels and pruritus intensity

Pruritus intensity in patients with UP was significantly correlated with serum IL-31 levels (shown in Figure 2).

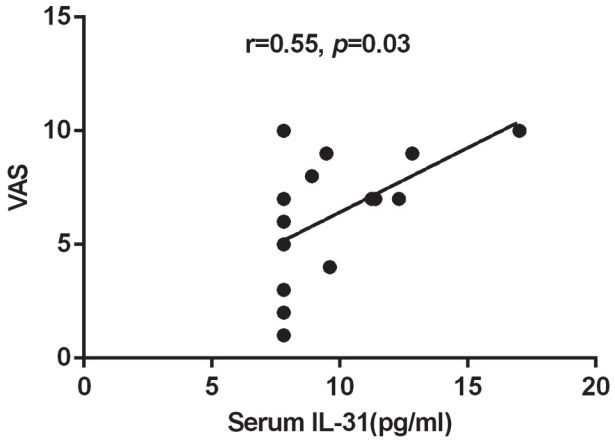


**Figure 2.** The correlation between serum IL-31 levels and pruritus intensity (n = 16). Spearman's correlation coefficient test was used to assess the correlation between IL-31 levels and pruritus intensity. IL-31 with values below limits of detection were assigned a numerical value of 7.8pg/ml for statistical analysis. IL-31: interleukin 31. VAS: pruritus visual analogue scale.

### Comparison of IL-31 removal

Eight patients were enrolled in part B. Baseline data are listed in Table 2. Initial serum levels of IL-31 were comparable between the two groups at the beginning of the treatment (Figure 3A). Figure 3B shows a box-plot graph of the IL-31 RR according to the dialysis modality. The use of combined HD and HP treatment produced a better RR for IL-31 than HD alone (34.26 ± 1.43% vs 15.28 ± 2.11%).

**Table 2.** Demographic and clinical characteristics of participants in part B (n = 8)

| Parameters | Total (n = 8) | HD (n = 8) | HDHP (n = 8) | *P* |
|---|---|---|---|---|
| Age (years) | 58.70 ± 16.40 | | | |
| Female (n (%)) | 4 (50) | | | |
| Dialysis vintage (months) | 68.20 ± 14.30 | | | |
| Cause of ESKD (n (%)) | | | | |
| Glomerular disorders | 3 | | | |
| Hypertension | 1 | | | |
| Diabetic nephropathy | 2 | | | |
| Polycystic kidney disease | 1 | | | |
| Unknown | 1 | | | |
| Vascular access type (AVF/AVG/Catheter) | 8/0/0 | | | |
| Weekly dose of EPO (units) | 9125 ± 1356 | | | |
| Average ultrafiltration rate (mL/h) | 2521.49 ± 623.24 | | | |
| Laboratory findings at baseline | | | | |
| Hemoglobin (g/L) | 102.67 ± 12.12 | | | |
| Albumin (g/L) | 39.24 ± 3.42 | | | |
| Blood Urea (mmol/L) | 41.64 ± 5.55 | | | |
| Creatinine (μmol/L) | 919.74 ± 69.22 | | | |
| Calcium (mmol/L) | 2.28 ± 0.22 | | | |
| Phosphorus (mmol/L) | 1.88 ± 0.84 | | | |
| Bilirubin (μmol/L) | 11.8 ± 1.24 | | | |
| Intact parathyroid hormone (pg/ml) | 327.51 ± 153.68 | | | |
| β2-microglobulin (mg/L) | 36.81 ± 5.83 | | | |
| Residual kidney function (urine volume) | | | | |
| < 100 mL/24 h | 8 | | | |
| > 100 mL/24 h | 0 | | | |
| Modality | | | | |
| Kt/v | | 1.24 ± 0.15 | 1.22 ± 0.18 | .43 |
| Serum IL-31 before treatment (pg/ml) | | 11.13 ± 2.79 | 12.10 ± 2.24 | .23 |

Data were presented as mean ± conventional and percentage (%). Independent 2-sample *t* test was conducted. IL-31: interleukin 31.

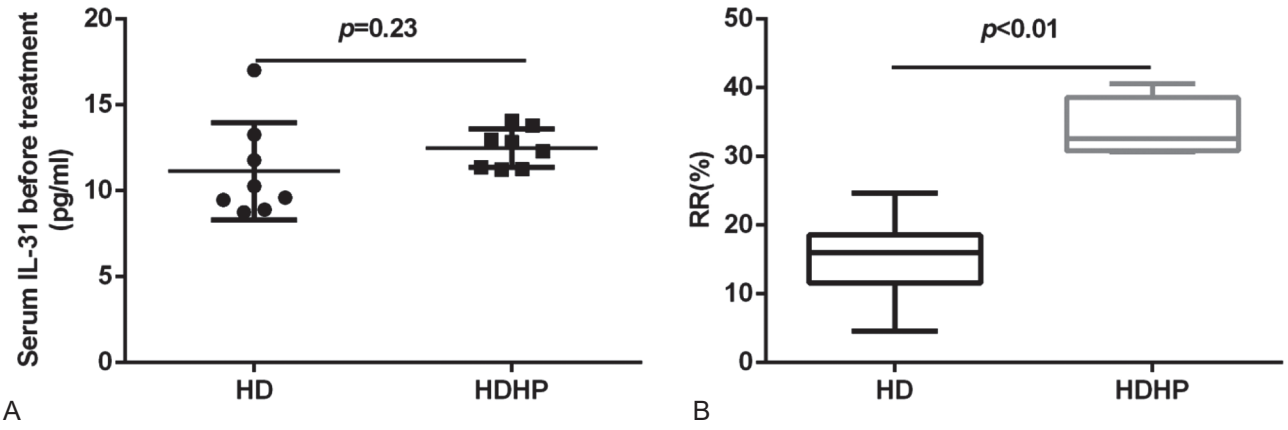


**Figure 3.** RR of IL-31 with HD and HDHP (n = 8). (a) Basal serum IL-31levels before HD and HDHP treatments. (b) RR for IL-31 between HD and HDHP. Independent 2-sample *t* test was conducted. IL-31: interleukin 31; RR: reduction ratio; HD: hemodialysis; HDHP: hemodialysis in combination with hemoperfusion.

## DISCUSSION

In the present study, we have shown that serum levels of IL-31 were significantly higher in UP patients compared to non-UP patients. Similar reports with presented results can also be found in the literature. In the study by Oweis *et al.*,[10] the serum level of IL-31 was found to be significantly elevated in maintenance hemodialysis (MHD) patients compared to healthy controls. In another study,[18] MHD patients with UP had significantly increased serum levels of IL-31 compared with the levels in those without UP. In line with the results of the above-mentioned studies, our findings further stressed the potential role of IL-31 in UP.

In this study we have shown a positive correlation between pruritus intensity and serum IL-31 levels. Similar to our findings, Ko MJ *et al.*[11] in their study demonstrated a positive exposure-response relationship between serum levels of IL-31 and pruritus intensity. However, Oweis *et al.*[10] obtained different results and did not observe any relationship between pruritus intensity and IL-31 levels in patients with UP. Overall, data from previous studies are less homogenous and further studies are needed in the future.

Due to the fact that we have practically no way to reduce the production of IL-31, blood purification techniques enhancing IL-31 removal might be a potential strategy. Major characteristics of HA130 have been introduced in the method section. Due to the interaction between toxins and the hydrophobic groups, as well as the physical adsorption of the 3-dimensional mesh structures of the resin molecules, HA130 has a high affinity for several uremic toxins in the range of the middle molecular weight molecules, such as β2-microglobulin, and parathyroid hormone (PTH).[14,19] Herein, to the best of our knowledge, we demonstrate for the first time that the addition of HP using HA130 cartridge to low-flux HD provides enhanced removal of IL-31. We postulate that HP using HA130 cartridge may improve pruritus in MHD patients by removing IL-31. Further studies will need to investigate the kinetics of IL-31 clearance during dialysis, including studies in which IL-31 levels are measured at several time points after treatment to assess for rebound. Formal kinetic modeling of IL-31 clearance will allow for estimation of generation rate and would be helpful for determining how many sessions should be prescribed, and how often HA130 cartridge should be changed.

### Study Limitations

Some limitations should be stressed. First, the sample size was small. Second, the aim of this study was to investigate the role of HDHP in IL-31 removal. It was not powered to assess an association with symptom improvement. Third, we selected IL-31 but did not measure other potential prurinogens, and thus our conclusions only apply to IL-31, and it is possible that other prurinogens are removed by HDHP. Finally, there were some patients with undetectable IL-31 concentration. Given the mechanistic nature of this study, we only included patients with detectable IL-31 when analyzing the RR.

## CONCLUSION

UP is a complex and multifactorial problem. In patients with UP the high levels of IL-31 indicates a possible role in pathogenesis. The addition of HP to conventional HD provides enhanced removal of IL-31. Further studies addressing the cause-effect relationship between IL-31 removal and UP improvment are needed.

## ETHICAL APPROVAL

The study was approved by the local Ethics committee (Tongji Hospital, NO.2021-024) and was conducted in agreement with the Declaration of Helsinki and registered on chictr.org.cn (identification number ChiCTR20000038640).

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ACKNOWLEDGMENTS

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## REFERENCES

1. Curtin RB, Bultman DC, Thomas-Hawkins C, Walters BA, Schatell D. Hemodialysis patients' symptom experiences: effects on physical and mental functioning. Nephrol Nurs J. 2022; 29(6): 562, 567-574.
2. Pisoni RL, Wikström B, Elder SJ, et al. Pruritus in haemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant. 2006; 21(12):3495-3505.
3. Kuypers DRJ. Skin problems in chronic kidney disease. Nat Clin Pract Nephro. 2009; 5(3):157-170.
4. Arai I, Tsuji M, Miyagawa K, Takeda H, Akiyama N, Saito S. Repeated administration of IL-31 upregulates IL-31 receptor A (IL-31RA) in dorsal root ganglia and causes severe itch-associated scratching behaviour in mice. Exp Dermatol. 2015;24(1):75-8.
5. Tseng PY, Hoon MA. Oncostatin M can sensitize sensory neurons in inflammatory pruritus. Sci Transl Med. 2021;13(619): eabe3037.
6. Dillon SR, Sprecher C, Hammond A, et al. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. Nat Immunol. 2004;5(7):752-60.
7. Gonzales AJ, Humphrey WR, Messamore JE, et al. Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. Vet Dermatol. 2013;24(1):48-53.
8. Oyama S, Kitamura H, Kuramochi T, et al. Cynomolgus monkey model of interleukin-31-induced scratching depicts blockade of human interleukin-31 receptor A by a humanized monoclonal antibody. Exp Dermatol. 2018; 27(1):14-21.
9. Hawro T, Saluja R, Weller K, Altrichter S, Metz M, Maurer M. Interleukin-31 does not induce immediate itch in atopic dermatitis patients and healthy controls after skin challenge. Allergy. 2014;69(1):113-7.
10. Oweis AO, Al-Qarqaz F, Bodoor K, et al. Elevated interleukin 31 serum levels in hemodialysis patients are associated with uremic pruritus. Cytokine. 2020; 138:155369.
11. Ko MJ, Peng YS, Chen HY, et al. Interleukin-31 is associated with uremic pruritus in patients receiving hemodialysis. J Am Acad Dermatol. 2014; 71(6):1151-9
12. Kinugasa E, Igawa K, Shimada H, et al. Anti-pruritic effect of nemolizumab in hemodialysis patients with uremic pruritus: a phase II, randomized, double-blind, placebo-controlled clinical study. Clin Exp Nephrol.2021;25(8):875-884.
13. Heike M Hermanns. Oncostatin M and interleukin-31: Cytokines, receptors, signal transduction and physiology. Cytokine Growth Factor Rev. 2015;26(5):545-58.
14. Ankawi G, Fan W, Pomarè Montin D, et al. A New Series of Sorbent Devices for Multiple Clinical Purposes: Current Evidence and Future Directions. Blood Purif. 2019;47(1-3),94-100.
15. Mistik S, Utas S, Ferahbas A, et al. An epidemiology study of patients with uremic pruritus. J Eur Acad Dermatol Venereol. 2006; 20(6):672-678.
16. Furue M, Ebata T, Ikoma A, et al. Verbalizing Extremes of the Visual Analogue Scale for Pruritus: A Consensus Statement. Acta Derm Venereol. 2013;93(2):214-215.
17. Bergstrom J, Wehle B. No change in corrected beta 2-microglobulin concentration after cuprophane haemodialysis. Lancet. 1987;(8533):628-629.
18. Rymsza A, Świerczyńska K, Piotrowska A, Dzięgiel P, Szepietowski JC. The Serum Level of IL-31 in Patients with Chronic Kidney Disease-Associated Pruritus: What Can We Expect? Toxins (Basel). 2022;14(3): 197.
19. Li WH, Yin YM, Chen H, et al. Curative effect of neutral macroporous resin hemoperfusion on treating hemodialysis patients with refractory uremic pruritus. Medicine (Baltimore). 2017 ;96(12): e6160.

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