



## Original Article

## Comparison of uremic pruritus between patients undergoing hemodialysis and peritoneal dialysis



Ji-Won Min<sup>1</sup>, Su-Hyun Kim<sup>2</sup>, Young Ok Kim<sup>1</sup>, Dong Chan Jin<sup>1</sup>, Ho Chul Song<sup>1</sup>, Euy Jin Choi<sup>1</sup>, Yong-Lim Kim<sup>3</sup>, Yon-Su Kim<sup>4</sup>, Shin-Wook Kang<sup>5</sup>, Nam-Ho Kim<sup>6</sup>, Chul Woo Yang<sup>1</sup>, Yong Kyun Kim<sup>1,\*</sup>

<sup>1</sup> Division of Nephrology, Department of Internal Medicine, Bucheon St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea

<sup>2</sup> Department of Internal Medicine, College of Medicine, Chung-Ang University, Seoul, Korea

<sup>3</sup> Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, Korea

<sup>4</sup> Department of Internal Medicine, College of Medicine, Seoul National University, Seoul, Korea

<sup>5</sup> Department of Internal Medicine, College of Medicine, Yonsei University, Seoul, Korea

<sup>6</sup> Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Korea

## A B S T R A C T

## Article history:

Received 4 November 2015

Received in revised form

10 January 2016

Accepted 7 February 2016

Available online 21 February 2016

## Keywords:

Hemodialysis

Peritoneal dialysis

Uremic pruritus

**Background:** Uremic pruritus is a common, but unpleasant, complication of end-stage renal disease. The uremic burden may differ between hemodialysis (HD) and peritoneal dialysis (PD) patients. This difference may also change the clinical characteristics of uremic pruritus between the 2 modalities. In this study, we investigated the uremic pruritus between patients on HD and PD.

**Methods:** A total of 425 HD and 223 PD patients from the Clinical Research Center registry in Korea were included. Patients were assessed for pruritus intensity, scratching activity, pruritus distribution, and frequency of pruritus-related sleep disturbance using the visual analog scale and questionnaire.

**Results:** The prevalence of uremic pruritus was higher in PD patients than that in HD patients (62.6% vs. 48.3%,  $P = 0.001$ ). In the multivariable logistic analysis, PD treatment was significantly associated with the prevalence of uremic pruritus (odds ratio, 1.76; 95% confidence interval, 1.20–2.57,  $P = 0.004$ ) after adjustment for clinical variables. The visual analog scale score, representing a subjective intensity of itchiness, was significantly higher in PD patients (PD  $2.11 \pm 2.32$  vs. HD  $1.65 \pm 2.28$ ,  $P = 0.013$ ) compared with HD patients. The intensity of uremic pruritus was independently related with serum albumin levels ( $\beta = -0.143$ ,  $P = 0.006$ ) in HD patients and total weekly Kt/V ( $\beta = -0.176$ ,  $P = 0.028$ ) in PD patients.

**Conclusion:** Our data demonstrate the difference in prevalence, intensity, and risk factors of uremic pruritus between HD and PD patients. These findings suggest that careful consideration for uremic pruritus might be needed in end-stage renal disease patients according to the dialysis modality.

Copyright © 2016. The Korean Society of Nephrology. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

\* Corresponding author. Division of Nephrology, Department of Internal Medicine, Bucheon St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea.

E-mail address: [drkimyk@catholic.ac.kr](mailto:drkimyk@catholic.ac.kr) (YK Kim).

<http://dx.doi.org/10.1016/j.krccp.2016.02.002>

2211-9132/Copyright © 2016. The Korean Society of Nephrology. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Uremic pruritus is a common and disabling complication that affects the quality of life in end-stage renal disease (ESRD) patients undergoing hemodialysis (HD) and peritoneal dialysis (PD) [1–5]. The prevalence of uremic pruritus has been reported from 22% to 84% in HD patients [2–9].

The degrees of intensity and the spatial distribution of uremic pruritus are influenced by multiple factors and vary over time [3,6]. Although its pathogenesis is not well understood, factors such as uremic burden (i.e., increased inflammation), secondary hyperparathyroidism, iron-deficiency anemia, neuropathy, and neurophysiological factors or allergic sensitization may contribute to the development of uremic pruritus [2–9]. Severe uremic pruritus negatively affects the quality of life and is associated with a poor outcome in HD patients [3].

The uremic burden may differ between HD and PD patients [10], which may make a difference in clinical characteristics of uremic pruritus between patients on HD and PD. Therefore, it may be postulated that clinical characteristics of uremic pruritus may be different between patients on HD and PD. A previous study reported a higher prevalence of uremic pruritus in PD patients than in HD patients [11]. However, the study is limited by a relatively small sample size.

In this study, we determined the differences in the prevalence and the clinical characteristics of uremic pruritus in patients with uremic pruritus undergoing PD and HD from the Clinical Research Center registry for ESRD, a multicenter cohort study in Korea.

## Methods

### Study population

Patients were selected from the Clinical Research Center registry for ESRD, which is a multicenter, observational, prospective cohort study on patients with ESRD in Korea. Adult patients (aged > 18 years) with ESRD undergoing PD or HD were included from 31 medical centers in Korea. The study was performed between April 2009 and April 2015. Only patients who had completed a questionnaire about uremic pruritus were included. A total of 648 patients from 9 medical centers were included in the final analysis. Of these, 425 patients were undergoing HD and 223 were undergoing PD. Demographic and clinical data were collected at enrollment. The study protocol was approved by the medical ethics committees of all participating hospitals. Written informed consent was obtained from all patients before inclusion.

### Pruritus assessment

A survey was used to measure uremic pruritus by 2 scoring systems. A detailed scoring system modified by Pauli-Magnus [12] was used to assess the characteristics of pruritus including intensity, scratching activity, pruritus distribution, and the frequency of pruritus-related sleep disturbances. The visual analog scale (VAS) was used to assess the subjective intensity of itchiness. A survey was done by trained investigators. These parameters were graded as follows:

#### 1. Pruritus scoring system modified by Pauli-Magnus

Severity: A slight itchy sensation without the need to scratch received 1 point. The necessity to scratch, but in the absence of excoriations received 2 points. Scratching accompanied by excoriation received 4 points. Finally, pruritus causing total restlessness received 5 points.

Distribution: Itching at fewer than 2 locations received 1 point, at 2 locations 2 points, and generalized itching 3 points. The scores for pruritus severity and distribution were recorded and multiplied separately based on those from the morning and afternoon. A maximum of 30 points could be achieved.

Sleep disturbance: Each arousal from sleep due to itching received 2 points (maximum 10 points). Every nighttime scratching episode that led to excoriations received 1 point (maximum 5 points). The final score was obtained by adding the sleep disturbance score and the severity–distribution product. There was a maximum of 45 points.

#### 2. Visual Analog Scale

In addition to the pruritus scoring system modified by Pauli-Magnus, we assessed uremic pruritus using the VAS. The VAS has been previously used to assess itching intensity in clinical trials [13,14]. Patients were asked to grade their itching intensity on a 10-cm VAS (0 = no pruritus to 10 = unbearable pruritus). Patients without uremic pruritus were defined by a score of 0.

### Data collection

The following baseline demographic and clinical data were recorded: age, sex, height, weight, body mass index (BMI), causes of ESRD, comorbidities, systolic blood pressure (BP), diastolic BP, laboratory investigations, and therapeutic characteristics. Blood samples were drawn to measure serum hemoglobin, albumin, creatinine, blood urea nitrogen, potassium, total cholesterol, calcium, phosphorous, high-sensitivity C-reactive protein, intact parathyroid hormone, and  $\beta_2$ -microglobulin.

### Statistical analysis

Continuous variables with normal distributions are expressed as means  $\pm$  standard deviations. Those without normal distributions are presented as medians and interquartile ranges. Student *t* tests were used to compare continuous variables. Categorical variables are presented as numbers with percentages. The Pearson chi-square test was used to compare the categorical variables. Univariate and multivariate logistic regression analyses were used to assess the clinical factors associated with uremic pruritus in HD patients. Multivariate logistic regression analysis was adjusted for significant or nearly significant ( $P < 0.05$ ) predictors of uremic pruritus in univariate logistic regression analysis including BMI and serum albumin levels. To achieve adequate confounder control, important covariates known to be influential based on prior studies and clinical insight were retained in the multivariate logistic regression model, regardless of their statistical significance. These covariates included age, sex, and diabetes mellitus (DM).

Survival curves were estimated by the Kaplan–Meier method and compared by the log-rank test according to the presence of uremic pruritus. A *P* value < 0.05 was considered

statistically significant. All statistical analyses were performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA).

## Results

### Patient characteristics

Baseline characteristics of the study population according to dialysis modality are shown in Table 1. PD patients were older than HD patients. PD patients had higher BMI, diastolic BP, serum levels of creatinine, phosphorus, calcium–phosphorus product, intact parathyroid hormone,  $\beta$ 2-microglobulin, and ferritin than HD patients. There was a lower prevalence of DM in the PD patients than in the HD patients. In addition, the systolic BP, serum albumin levels, and serum high-sensitivity C-reactive protein levels were lower in the PD patients than those in the HD patients. There were no significant differences in sex, duration of dialysis therapy, fasting blood glucose, hemoglobin, blood urea nitrogen, serum calcium, total cholesterol levels, or use of medications such as calcium-containing or non-calcium-containing phosphate binders, active vitamin D compounds, and calcimimetics between the HD and PD patients.

### Prevalence and characteristics of uremic pruritus

Table 2 shows the prevalence and characteristics of uremic pruritus according to the dialysis modality. There was a higher prevalence of uremic pruritus throughout the day, and it was higher in the PD patients than in the HD patients (62.6% vs. 48.3%,  $P = 0.001$ ). Uremic pruritus was more prevalent in PD patients than in HD patients in the morning (62.2% vs. 47.0%,  $P = 0.002$ ) and afternoon (57.7% vs. 44.3%,  $P < 0.001$ ).

**Table 2. Prevalence and characteristics of uremic pruritus by dialysis modality**

Characteristics	Hemodialysis (n = 425)	Peritoneal dialysis (n = 223)	P
Prevalence of pruritus (%)			
Morning	44.3	57.7	0.002
Afternoon	47.0	62.2	< 0.001
Throughout the day	48.3	62.6	0.001
Characteristics of uremic pruritus			
Detailed score (Pauli-Magnus scoring system)			
Severity			
Morning	1.32 ± 0.82	1.29 ± 0.77	0.654
Afternoon	1.46 ± 0.96	1.50 ± 1.02	0.288
Distribution			
Morning	1.17 ± 0.61	1.19 ± 0.65	0.790
Afternoon	1.17 ± 0.62	1.23 ± 0.68	0.272
Sleep disturbance			
Frequency of waking from sleep	0.24 ± 0.91	0.23 ± 0.74	0.925
Frequency of scratching during sleep	0.19 ± 0.96	0.12 ± 0.56	0.332
Total score by measuring system	4.54 ± 6.35	4.52 ± 5.35	0.356
VAS scoring system			
Morning	1.40 ± 2.10	1.73 ± 2.06	0.057
Afternoon	1.90 ± 2.66	2.51 ± 2.73	0.006
Average	1.65 ± 2.28	2.11 ± 2.32	0.013

Continuous variables are presented by means ± SD. VAS, visual analog scale.

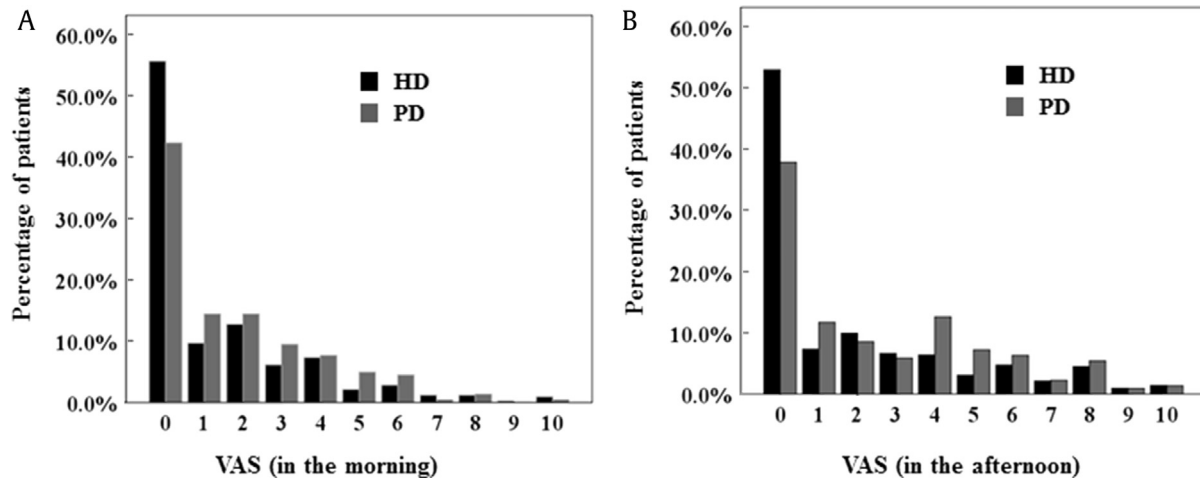
We also assessed the clinical characteristics of uremic pruritus according to the dialysis modality. There were no significant differences in pruritus intensity, scratching activity, pruritus distribution, or frequency of pruritus-related sleep disturbances between PD and HD patients.

**Table 1. Baseline characteristics of patients**

Characteristics	Hemodialysis (n = 425)	Peritoneal dialysis (n = 223)	P
Age (y)	58.0 ± 12.0	53.0 ± 11.0	< 0.001
Male	237 (55.8)	127 (59.2)	0.402
Body mass index (kg/m <sup>2</sup> )	22.6 ± 3.5	23.9 ± 3.4	< 0.001
Diabetes mellitus	215 (55.0)	91 (41.2)	0.001
Duration of dialysis therapy (mo)	50 (29–83)	55 (34–86)	0.377
Systolic BP (mmHg)	144.0 ± 21.0	133.0 ± 22.0	< 0.001
Diastolic BP (mmHg)	75.0 ± 14.0	80.0 ± 12.0	< 0.001
Fasting blood glucose (mg/dL)	146.0 ± 72.0	135.0 ± 75.0	0.082
BUN (mg/dL)	66.0 ± 24.0	63.0 ± 24.0	0.169
Serum creatinine (mg/dL)	9.0 ± 2.9	10.2 ± 3.7	< 0.001
Hemoglobin (g/dL)	10.3 ± 1.4	10.2 ± 1.5	0.373
Serum albumin (g/dL)	3.7 ± 0.5	3.6 ± 0.4	< 0.001
Serum calcium (mg/dL)	8.6 ± 1.0	8.5 ± 0.9	0.326
Serum phosphorus (mg/dL)	5.0 ± 1.0	5.3 ± 1.5	0.016
Serum calcium–phosphorus product (mg <sup>2</sup> /dL <sup>2</sup> )	42.7 ± 13.6	45.3 ± 13.6	0.027
Serum total cholesterol (mg/dL)	141.0 ± 65.0	150.0 ± 75.0	0.191
Serum intact PTH (pg/mL)	147 (65–273)	222 (110–412)	< 0.001
$\beta$ 2-microglobulin (mg/dL)	248 (135–414)	287 (137–569)	0.043
Serum ferritin (mg/dL)	62 (45–78)	67 (52–93)	0.010
hsCRP (mg/dL)	0.13 (0.00–1.57)	0 (0–0.02)	< 0.001
Using high-flux dialysis	116 (27.3)		
Single-pool Kt/V	1.6 ± 0.5		
Total weekly Kt/V		3.1 ± 1.3	
Medication			
Calcitriol or vitamin D analogues	100 (24)	53 (24)	0.946
Calcium-containing phosphorus binder	249 (59)	116 (52)	0.109
Non-calcium-containing phosphorus binders	40 (9)	16 (7)	0.336

Values for continuous variables are given as mean ± SD and variables without a normal distribution are given as median and interquartile range; values for categorical variables are given as n (%).

BP, blood pressure; BUN, blood urea nitrogen; hsCRP, high-sensitivity C-reactive protein; PTH, parathyroid hormone.



**Figure 1.** Distribution of patients in each range of VAS scores in HD and PD patients. VAS in the morning (A) and VAS in the afternoon (B) are shown. HD, hemodialysis; PD, peritoneal dialysis; VAS, visual analog scale.

The VAS score was significantly higher in PD patients than it was in HD patients, especially in the afternoon (average, PD  $2.11 \pm 2.32$  vs. HD  $1.65 \pm 2.28$ ,  $P = 0.013$ ; afternoon, PD  $2.51 \pm 2.73$  vs. HD  $1.90 \pm 2.66$ ,  $P = 0.006$ ; Table 2). Fig. 1 shows the distribution of patients with each range of VAS scores in the patients with HD and PD. There are few PD and HD patients with severe uremic pruritus (VAS score  $> 7$ ) in the morning. PD patients with moderate-to-severe uremic

pruritus (VAS score  $\geq 4$ ) were more common in the afternoon compared with HD patients (Fig. 1B).

#### Determinants of prevalence and intensity of uremic pruritus

First, we evaluated the clinical parameters to predict the prevalence of uremic pruritus. Table 3 shows the clinical and laboratory risk factors that influence the prevalence of uremic

**Table 3.** Logistic regression analysis for predicting prevalence of uremic pruritus

Risk factors	Univariate		Multivariate	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
PD (vs. HD)	1.79 (1.28–2.49)	0.001	1.76 (1.20–2.57)	0.004
Age (per 10 y)	1.01 (0.99–1.02)	0.429	1.01 (0.99–1.02)	0.412
Sex (male vs. female)	1.05 (0.77–1.44)	0.746	1.00 (0.71–1.41)	0.989
Body mass index (per 1 kg/m <sup>2</sup> )	1.07 (1.02–1.12)	0.006	1.06 (1.01–1.12)	0.017
DM (vs. non-DM)	1.11 (0.81–1.53)	0.512	1.07 (0.76–1.52)	0.695
Duration of dialysis (per 1 mo)				
Systolic BP (per 10 mmHg)	1.01 (1.00–1.01)	0.211		
Fasting blood glucose (mg/dL)	1.00 (1.00–1.00)	0.221		
HbA1c in patients with DM (per 1%)	1.03 (0.99–1.08)	0.155		
BUN (per 1 mg/dL)	1.00 (0.99–1.01)	0.607		
Serum creatinine (per 1 mg/dL)				
Hemoglobin (per 1 g/dL)	1.06 (0.96–1.19)	0.263		
Serum albumin (every 1 mg/dL)	0.69 (0.48–1.00)	0.050	0.77 (0.52–1.14)	0.190
Serum calcium (per 1 mg/dL)	0.98 (0.82–1.16)	0.779		
Serum phosphorus (per 1 mg/dL)	1.02 (0.92–1.13)	0.708		
Serum calcium–phosphorus product (per 1 mg <sup>2</sup> /dL <sup>2</sup> )	1.00 (0.99–1.01)	0.862		
Serum alkaline phosphatase (per 1 mg/dL)				
Total cholesterol (per 1 mg/dL)	1.00 (1.00–1.01)	0.236		
iPTH (per 100 pg/mL)	1.00 (0.98–1.03)	0.769		
$\beta$ 2-microglobulin (per 1 mg/dL)	1.00 (1.00–1.00)	0.448		
Serum ferritin (per 1 mg/dL)	1.00 (0.99–1.01)	0.917		
hsCRP (mg/dL)	1.00 (0.99–1.01)	0.795		
spKt/V $< 1.2$ in HD patients (vs. spKt/V $\geq 1.2$ )	1.07 (0.41–2.76)	0.892		
Total weekly Kt/V $< 1.7$ in PD patients (vs. total weekly Kt/V $\geq 1.7$ )	1.89 (0.44–8.16)	0.396		
Use of calcitriol or vitamin D analogues (vs. nonuser)	1.17 (0.81–1.68)	0.401		
Use of calcium-containing phosphorus binder (vs. nonuser)	1.11 (0.81–1.52)	0.508		
Use of non–calcium-containing phosphorus binders (vs. nonuser)	1.10 (0.63–1.90)	0.741		

BP, blood pressure; BUN, blood urea nitrogen; CI, confidence interval; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HD, hemodialysis; hsCRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; PD, peritoneal dialysis; spKt/V, single-pool Kt/V.

**Table 4. Spearman's correlation between the intensity of uremic pruritus using VAS and clinical parameters in HD and PD patients**

Clinical parameters	HD		PD	
	$\rho$	<i>P</i>	$\rho$	<i>P</i>
Age (per 10 y)	0.032	0.506	0.096	0.156
Duration of dialysis (per 1 mo)	-0.023	0.632	0.139	0.040
Body mass index (per 1 kg/m <sup>2</sup> )	0.070	0.172	0.063	0.356
Systolic BP (per 10 mmHg)	0.070	0.170	0.137	0.047
Fasting blood glucose (mg/dL)	-0.015	0.763	-0.043	0.523
HbA1c in patients with DM (per 1%)	0.074	0.172	-0.072	0.287
BUN (per 1 mg/dL)	0.004	0.931	-0.022	0.753
Serum creatinine (per 1 mg/dL)	0.030	0.557	0.088	0.198
Hemoglobin (per 1 g/dL)	-0.032	0.525	0.106	0.116
Serum albumin (every 1 mg/dL)	-0.156	0.002	-0.022	0.754
Serum calcium (per 1 mg/dL)	-0.081	0.111	0.096	0.173
Serum phosphorus (per 1 mg/dL)	0.022	0.665	0.014	0.841
Total cholesterol (per 1 mg/dL)	-0.014	0.783	0.153	0.036
iPTH (per 100 pg/mL)	0.168	0.143	0.114	0.514
$\beta$ 2-microglobulin (per 1 mg/dL)	0.008	0.876	-0.091	0.321
Serum ferritin (per 1 mg/dL)	-0.011	0.837	-0.096	0.247
hsCRP (mg/dL)	0.032	0.517	-0.096	0.307
spKt/V in HD patients	-0.048	0.376		
Total weekly Kt/V in PD patients			-0.206	0.002

BP, blood pressure; BUN, blood urea nitrogen; DM, diabetic mellitus; HbA1c; hemoglobin A1c; HD, hemodialysis; hsCRP, high-sensitivity C-reactive protein; PD, peritoneal dialysis; PTH, intact parathyroid hormone; spKt/V, single-pool Kt/V; VAS, visual analog scale.

pruritus in the entire patient cohort. In the univariate logistic analysis, PD treatment [odds ratio (OR), 1.79; 95% confidence interval (CI), 1.28–2.49; *P* = 0.001] and BMI (OR, 1.07; 95% CI, 1.02–1.12; *P* = 0.006) significantly influenced the prevalence of uremic pruritus. In multivariable logistic analysis, PD treatment and BMI were significant independent risk factors for the prevalence of uremic pruritus (OR, 1.76; 95% CI, 1.20–2.57; *P* = 0.004 and OR, 1.06; 95% CI, 1.01–1.12; *P* = 0.017, respectively) after adjustment for age, sex, BMI, dialysis modality, DM, and serum albumin level.

Next, we determined the clinical parameters associated with the intensity of uremic pruritus according to dialysis modality. Table 4 shows the Spearman correlation between the intensity of uremic pruritus and clinical parameters in HD and PD patients. The intensity of uremic pruritus was negatively correlated with serum albumin levels in HD patients. In PD patients, the intensity of uremic pruritus was negatively correlated with total weekly Kt/V and positively correlated with duration of dialysis, systolic BP, and serum total cholesterol levels.

To determine the independent predictor for the intensity of uremic pruritus, we performed multiple linear regression analysis using the model including age, sex, DM, and all univariate correlates of the intensity of uremic pruritus (Table 5). In HD patients, serum albumin levels ( $\beta$  = -0.143, *P* = 0.006) maintained an independent relationship with the intensity of uremic pruritus, whereas in PD patients, total weekly Kt/V ( $\beta$  = -0.176, *P* = 0.028) was independently associated with the subjective intensity of uremic pruritus.

#### Uremic pruritus and all-cause mortality

To determine the clinical impact of uremic pruritus in HD and PD patients, we performed the survival analysis. We divided the patients into 4 groups according to the intensity of uremic pruritus by using VAS as follows: group 1, patients with no pruritus (*n* = 304); group 2, mild pruritus with VAS scores < 4.0 (*n* = 207); group 3, moderate pruritus with

**Table 5. Multivariate linear regression analyses for intensity of uremic pruritus using VAS in HD and PD patients**

Clinical parameters	HD		PD	
	$\beta$ coefficient	<i>P</i>	$\beta$ coefficient	<i>P</i>
Age (per 10 y)	-0.062	0.244	0.108	0.172
Sex (male)	-0.003	0.950	0.086	0.274
Body mass index (per 1 kg/m <sup>2</sup> )	0.030	0.562	0.093	0.246
DM	-0.097	0.071	-0.041	0.620
Duration of dialysis (per 1 mo)	0.010	0.845	-0.026	0.755
Systolic BP (per 10 mmHg)	0.005	0.924	0.093	0.231
Fasting blood glucose, mg/dL	-0.102	0.069	-0.039	0.666
BUN (per 1 mg/dL)	0.030	0.562	0.051	0.545
Serum creatinine (per 1 mg/dL)	0.014	0.785	0.219	0.026
Hemoglobin (per 1 g/dL)	0.044	0.440	0.102	0.205
Serum albumin (every 1 mg/dL)	-0.143	0.006	-0.064	0.443
Serum calcium (per 1 mg/dL)	-0.006	0.921	0.056	0.523
Serum phosphorus (per 1 mg/dL)	0.037	0.482	0.120	0.163
Total cholesterol (per 1 mg/dL)	0.012	0.819	0.027	0.732
iPTH (per 100 pg/mL)	0.095	0.436	-0.447	0.181
$\beta$ 2-microglobulin (per 1 mg/dL)	-0.060	0.269	0.001	0.996
Serum ferritin (per 1 mg/dL)	0.017	0.758	-0.046	0.629
hsCRP (mg/dL)	-0.029	0.589	0.054	0.481
spKt/V in HD patients	-0.021	0.701		
Total weekly Kt/V in PD patients			-0.176	0.028

Adjusted for age, sex, DM, systolic BP, and serum albumin levels in HD patients.

Adjusted for age, sex, DM, duration of dialysis, systolic BP, serum total cholesterol levels, and total weekly Kt/V in PD patients.

BP, blood pressure; BUN, blood urea nitrogen; DM, diabetic mellitus; HbA1c, hemoglobin A1c; HD, hemodialysis; hsCRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; PD, peritoneal dialysis; spKt/V, single-pool Kt/V; VAS, visual analogue scale.

VAS score 4.0–6.9 (*n* = 106); and group 4, severe pruritus with VAS score  $\geq$  7 (*n* = 31). The Kaplan–Meier survival analysis showed that there was no significant difference in all-cause mortality among the groups in whole cohort including HD and PD patients (*P* = 0.249, log-rank test) as well as in HD patients (*P* = 0.055, log-rank test) and PD patients (*P* = 0.922, log-rank test).

## Discussion

In this study, we showed that there was a higher prevalence of uremic pruritus in PD patients than there was in HD patients. Furthermore, the subjective intensity of itchiness (assessed by VAS) was higher in PD patients than it was in HD patients. These findings indicate that prevalence and clinical characteristics of uremic pruritus differ according to the dialysis modality.

The prevalence of uremic pruritus in HD patients has been previously reported. However, there are limited data regarding uremic pruritus in PD patients. In their study of 113 continuous ambulatory peritoneal dialysis patients and 76 HD patients, Balaskas et al [11] found that the prevalence of uremic pruritus was 62% in continuous ambulatory peritoneal dialysis and 54% in HD. In this study, the prevalence of uremic pruritus over the course of the whole day was 62.6% in PD patients and 48.3% in HD patients. The PD patients had approximately 1.8-fold increased risk of uremic pruritus than did the HD patients.

Another interesting finding of this study is the different relationship between the intensity of uremic pruritus and clinical parameters according to dialysis modality. In this study, the intensity of uremic pruritus was negatively associated with serum albumin levels in HD patients, which suggests the

impact of the serum albumin as a negative acute-phase protein on uremic pruritus in HD patients [8]. Interestingly, in this study, single-pool Kt/V was not related with the intensity of uremic pruritus in HD patients, whereas total weekly Kt/V was independently associated with the intensity of uremic pruritus in PD patients. These findings are consistent with previous studies [4,15]. Pisoni et al [15] reported that Kt/V did not show any significant relationship with pruritus in HD patients in Dialysis Outcomes and Practice Patterns Study. Liakopoulos et al [4] demonstrated the beneficial effect of increased dialyzer volume on uremic symptoms in chronic PD patients. These findings support the idea that adequate dialysis may be critically important in reducing the intensity of uremic pruritus in PD patients.

One strength of this study was its relatively large sample size and multicenter design, which enhances the evidence of prevalence of uremic pruritus.

Another strength of this study is that we assessed the uremic pruritus by using a pruritus scoring system modified by Pauli-Magnus [12] and the VAS. The detailed characteristics of pruritus including intensity, scratching activity, pruritus distribution, and the frequency of pruritus-related sleep disturbances were assessed by Pauli-Magnus scoring system. The subjective intensity of itchiness was assessed by VAS scoring system. In this study, scratching activity, pruritus distribution, and the frequency of pruritus-related sleep disturbances were not significantly different according to dialysis modality. Interestingly, the VAS score was significantly higher in PD patients than it was in HD patients, especially in the afternoon. This finding suggests that PD patients have greater subjective itch intensity than do HD patients (Table 2). However, the intensity measured by VAS was not severe in general, and the difference of VAS score between HD and PD patients was relatively small (HD:  $1.65 \pm 2.28$  vs. PD:  $2.11 \pm 2.32$ ). Therefore, clinical significance of these findings needed to be cautiously interpreted.

It is unclear why PD patients had a higher prevalence and subjective intensity of uremic pruritus than did HD patients. However, there are several potential explanations. Uremic pruritus has been associated with the accumulation of middle molecular weight uremic toxins such as  $\beta_2$ -microglobulin [2,9]. Dialysis clearance of  $\beta_2$ -microglobulin with HD treatment using a high-flux membrane has been reported to be much higher than with PD treatment [16–18]. High-flux dialyzers are now widely used in clinical practice. The present study included approximately 30% of HD patients using the high-flux dialyzer. In concordance with this idea, PD patients had significantly higher serum levels of  $\beta_2$ -microglobulin than did HD patients in this study. Therefore, it is possible that increased accumulation of uremic toxins in PD patients may contribute to the higher prevalence and intensity of uremic pruritus compared to that in HD patients.

For the association between uremic pruritus and clinical outcomes in ESRD patients, Narita et al [3] reported that severe uremic pruritus (VAS score > 7) is associated with clinical poor outcomes including mortality in chronic HD patients. However, in this study, the presence of uremic pruritus was not associated with all-cause mortality not only in HD patients but also in PD patients. It may be due to the differences in the study population. In this study, the percentage of patients with severe uremic pruritus was much lower (4.5% in HD patients and 5.4% in PD patients) than that of the previous study (25.6% in HD

patients) [3], which may have resulted in the discrepancy between the studies. Despite the nonsignificant association between uremic pruritus and all-cause mortality in this study, uremic pruritus might be considered as an important risk factor for poor clinical outcomes in consideration of the relationship between uremic pruritus and quality of life or mortality in ESRD patients from previous studies [3,6].

Our study has several limitations. First, the design of our study was not a randomized controlled study but rather was an observational study. The choice of dialysis modality may have been influenced by clinicians and patients. Therefore, it is difficult to infer causality between dialysis modality and uremic pruritus. In addition, despite the study's multicenter nature, all patients were of Asian descent. Therefore, our results may not be generalizable to other ethnic groups with ESRD. Second, dry skin may be one of the major factors to exacerbate pruritus [19]. Unfortunately, it was not assessed in this study. Third, chronic inflammation had significant impact on uremic pruritus and mortality in dialysis patients [3]. To clarify the relationship between uremic pruritus and mortality, the patients with chronic inflammatory diseases may need to be excluded. However, they were not excluded at the time of enrollment in this study.

In conclusion, our data demonstrate the differences in prevalence, intensity, and risk factors of uremic pruritus between HD and PD patients. These findings suggest that careful consideration for uremic pruritus might be needed in ESRD patients according to the dialysis modality.

## Conflicts of interest

All authors have no conflicts of interest to declare.

## Acknowledgments

The authors thank the study coordinators Hye Young Lim, Nam Hee Kim, Mi Joung Moon, Hwa Young Lee, Mi Joung Kwon, Su Yeon An, Su Joung Oh, and Hye Young Kwak for contribution to this study.

This work was supported by a grant of the Korea Healthcare Technology R&D Project (HI10C2020), Ministry of Health and Welfare, Korea (HI10C2020).

## References

- [1] Mettang T, Kremer AE: Uremic pruritus. *Kidney Int* 87:685–691, 2015
- [2] Urbonas A, Schwartz RA, Szepietowski JC: Uremic pruritus—an update. *Am J Nephrol* 21:343–350, 2001
- [3] Narita I, Alchi B, Omori K, Sato F, Ajiro J, Saga D, Kondo D, Skatsume M, Maruyama S, Kazama JJ, Akazawa K, Gejyo F: Etiology and prognostic significance of severe uremic pruritus in chronic hemodialysis patients. *Kidney Int* 69:1626–1632, 2006
- [4] Liakopoulos V, Krishnan M, Stefanidis I, Savaj S, Ghareeb S, Musso C, Vas S, Bargman JM, Jassal SV, Oreopoulos DG: Improvement in uremic symptoms after increasing daily dialysate volume in patients on chronic peritoneal dialysis with declining renal function. *Int Urol Nephrol* 36:437–443, 2004
- [5] Narita I, Iguchi S, Omori K, Gejyo F: Uremic pruritus in chronic hemodialysis patients. *J Nephrol* 21:161–165, 2008
- [6] Mathur VS, Lindberg J, Germain M, Block G, Tumlin J, Smith M, Grewal M, McGuire D: A longitudinal study of uremic pruritus in hemodialysis patients. *Clin J Am Soc Nephrol* 5:1410–1419, 2010

- [7] Duque MI, Thevarajah S, Chan YH, Tuttle AB, Freedman BI, Yosipovitch G: Uremic pruritus is associated with higher kt/V and serum calcium concentration. *Clin Nephrol* 66:184–191, 2006
- [8] Melo NC, Elias RM, Castro MC, Romao Jr JE, Abensur H: Pruritus in hemodialysis patients: the problem remains. *Hemodial Int* 13:38–42, 2009
- [9] Lin HH, Liu YL, Liu JH, Chou CY, Yang YF, Kuo HL, Huang CC: Uremic pruritus, cytokines, and polymethylmethacrylate artificial kidney. *Artif Organs* 32:468–472, 2008
- [10] Capusa C, Stoian I, Rus E, Lixandru D, Barbulescu C, Mircescu G: Does dialysis modality influence the oxidative stress of uremic patients? *Kidney Blood Press Res* 35:220–225, 2012
- [11] Balaskas EV, Chu M, Uldall RP, Gupta A, Oreopoulos DG: Pruritus in continuous ambulatory peritoneal dialysis and hemodialysis patients. *Perit Dial Int* 13(Suppl 2):S527–S532, 1993
- [12] Pauli-Magnus C, Mikus G, Alscher DM, Kirschner T, Nagel W, Gugeler N, Risler T, Berger ED, Kuhlmann U, Mettang T: Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. *J Am Soc Nephrol* 11:514–519, 2000
- [13] Chen YC, Chiu WT, Wu MS: Therapeutic effect of topical gamma-linolenic acid on refractory uremic pruritus. *Am J Kidney Dis* 48:69–76, 2006
- [14] Ashmore SD, Jones CH, Newstead CG, Daly MJ, Chrystyn H: Ondansetron therapy for uremic pruritus in hemodialysis patients. *Am J Kidney Dis* 35:827–831, 2000
- [15] Pisoni RL, Wikström B, Elder SJ, Akizawa T, Asano Y, Keen ML, Saran R, Mendelssohn DC, Young EW, Port FK: Pruritus in haemodialysis patients: International results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 21:3495–3505, 2006
- [16] Evenepoel P, Bammens B, Verbeke K, Vanrenterghem Y: Superior dialytic clearance of beta(2)-microglobulin and p-cresol by high-flux hemodialysis as compared to peritoneal dialysis. *Kidney Int* 70:794–799, 2006
- [17] Yamashita AC: A kinetic model for peritoneal dialysis and its application for complementary dialysis therapy. *Contrib Nephrol* 177:3–12, 2012
- [18] Ko MJ, Wu HY, Chen HY, Chiu YL, Hsu SP, Pai MF, Ju Y, Lai CF, Lu HM, Huang SC, Yang SY, Wen SY, Chiu HC, Hu FC, Peng YS, Jee SH: Uremic pruritus, dialysis adequacy, and metabolic profiles in hemodialysis patients: a prospective 5-year cohort study. *PLoS One* 8:e71404, 2013
- [19] Zucker I, Yosipovitch G, David M, Gafter U, Boner G: Prevalence and characterization of uremic pruritus in patients undergoing hemodialysis: uremic pruritus is still a major problem for patients with end-stage renal disease. *J Am Acad Dermatol* 49:842–846, 2003