Original Paper

Uremic Pruritus is Associated with Two-Year Cardiovascular Mortality in Long Term Hemodialysis Patients

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Key Words

Uremic pruritus • Cardiovascular • Mortality • Hemodialysis

Abstract

Background/Aims: Uremic pruritus (UP) is an unpleasant complication in patients undergoing maintenance dialysis. Cardiovascular and infection related deaths are the major causes of mortality in patients undergoing dialysis. Studies on the correlation between cardiovascular or infection related mortality and UP are limited. **Methods:** We analyze 866 maintenance hemodialysis (MHD) patients in our hemodialysis centers. Clinical parameters and 24-month cardiovascular and infection-related mortality are recorded. **Results:** The associations between all-cause, cardiovascular and infection related mortality with clinical data including UP are analyzed. Multivariate Cox regression demonstrated that UP is a significantly predictor for 24-month cardiovascular mortality in the MHD patients (Hazard ratio: 3.164; 95% confidence interval, 1.743–5.744; $p < 0.001$). **Conclusion:** Uremic pruritus is one of the predictor of 24-month cardiovascular mortality in MHD patients.

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Introduction

Uremic pruritus (UP) is an unpleasant complication in patients undergoing maintenance dialysis (MHD) and the pathogenesis and etiology of UP are not well known and multifactorial [1-4]. The prevalence of UP is in a wide range (22% to 90%) [5-7]. It affects not only the patients' quality of life but also death [8-10]. Cardiovascular and infection related death are the major causes of mortality in patients undergoing dialysis [11]. Uremic pruritus has been noted to be a presentation of systemic inflammation [12]. Systemic inflammation is one of

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the etiologies of cardiovascular mortality in hemodialysis (HD) patients [13]. However, study on the correlation between pruritus and mortality of HD patients is limited. Study on the correlation between cardiovascular or infection related mortality and UP is also limited. Narita showed that severe renal itch is associated with 24-months all cause mortality [10]. Cardiovascular or infection related mortality is not mentioned in the study. The aim of this study is focused on the role of UP on cardiovascular and infection related mortality in patients undergoing MHD.

Materials and Methods

Patients

This is a retrospective study. The study patients were recruited from the 3 HD centers of Chang Gung Memorial Hospital, Lin-Kou Medical Center at both the Taipei and Taoyuan branches. Only MHD patients who were 18 years of age or older and had undergone HD for at least 6 months were enrolled in this study. Patients with malignancies or obvious infectious diseases, as well as those who had been hospitalized or had undergone surgery within 3 months of the investigation, were excluded. A total of 1216 HD patients were screened. Eight hundred and sixty six HD patients participated in this study. Most patients underwent 4 hours of HD, 3 times a week, which was performed using single-use hollow-fiber dialyzers equipped with modified cellulose, polyamide, or polysulfone membranes. The dialysate used in all cases had a standard ionic composition with a bicarbonate-based buffer. The cardiovascular diseases (CVDs) were defined as cerebrovascular disease, coronary artery disease, congestive heart failure, and peripheral vascular disease in these patients identified by chart reviews. Infection related mortality was defined as death that was attributed to an acute infectious disease. Infectious disease is defined as an illness caused by a specific infectious organism diagnosed by attending physicians based on various examinations for infectious organisms and clinical suspicions. Hypertension was defined as the regular use of antihypertensive drugs to control blood pressure or at least 2 blood pressure measurements of more than 140/90 mmHg measured after HD. Senior dermatologists diagnosed the presence of UP. The severity of pruritus was measured by visual analogue scale (VAS), which consisted of a 10-cm horizontal line with 0 point (no pruritus) to 10 points (maximum intensity of pruritus) and was given to patients after HD.

Laboratory, Nutritional, and Inflammatory Parameters

All blood samples were drawn from the arterial end of the vascular access immediately after the initial 2-day interval for HD and were then centrifuged and stored at -80°C until use. Serum creatinine (Cr) levels, normalized protein catabolism rate (nPCR), and serum albumin levels were assayed and recorded as nutritional markers. High-sensitivity C-reactive protein (hsCRP) levels were measured as indices of inflammation. All other biochemical indices were measured using a standard laboratory approach with an automatic analyzer. In the HD patients, dialyzer clearance of urea was measured using a method described by Daugirdas and was expressed as $\text{Kt}/V_{\text{urea}}$. The nPCR of the HD patients was calculated using validated equations and was normalized to the patients' body weight. Anuria was defined as a daily urine amount less than 100 mL measured by 24 hours urine and in recent 3 months at the time of chart review. Non-anuria was defined as a daily urine amount of ≥ 100 mL. The serum calcium level was adjusted using the serum albumin level with the following formula: corrected calcium level (mg/dL) = serum calcium level + $0.8 \times (4.0 - \text{serum albumin level})$. Twenty-four month cardiovascular and infection-related mortality were recorded.

Statistical Analysis

The Kolmogorov-Smirnov test was used to test if variables were normally distributed. A P value of > 0.05 was required to assume a normal distribution. Continuous variables are expressed as the mean $\pm$ standard deviation/median (interquartile range), and categorical variables are expressed as numbers or percentages. Chi-square or Fisher's exact test was used to analyze the correlation between categorical variables. Comparisons between 2 groups were performed using the Mann-Whitney U test or Student's t-test. Data involving hsCRP, intact parathyroid hormone (iPTH), and ferritin levels were log-transformed for analysis. Univariate and multivariate Cox regression analyses were performed to evaluate the variables

related to UP. Missing data were handled using list-wise deletion. Data were analyzed using SPSS, version 12.0 for Windows 95 (SPSS Inc., Chicago, IL, USA). The level of significance was set at a $P < 0.05$.

Results

In this 866 MHD patients-included observational study, 189 had UP (21.8%). The mean age was 56.18 year-old and the mean HD duration was 6.96 years. Between patients with and without UP, significant differences were seen in age (57.93 ± 12.437 vs 55.70 ± 13.867 years, $P = 0.046$), DM (13.2% vs 24.7%, $P = 0.001$), hepatitis C virus infection (HCV) (24.9% vs 17.9%, $P = 0.037$), HD duration (9.41 ± 5.43 vs 6.27 ± 5.13 years, $P < 0.001$), use of hemodiafiltration (HDF) (27.5% vs 19.9%, $P = 0.028$), Kt/V_{urea} (1.89 ± 0.34 vs 1.77 ± 0.32 , $P < 0.001$), nPCR (1.22 ± 0.27 vs 1.17 ± 0.26 g/kg/day, $P = 0.003$), non-anuria condition (11.6% vs 23%, $P < 0.001$), i-PTH levels [187.2 (63.8, 401.7) vs 121.3 (47.7, 284.1) pg/ml, $P = 0.003$], total cholesterol levels (176.93 ± 39.240 vs 169.73 ± 37.089 mg/dl, $P = 0.02$), LDL levels (100.36 ± 31.058 vs 93.26 ± 30.306 mg/dl, $P = 0.005$) and cardiovascular death (6.3% vs 5.6%, $P = 0.008$) respectively (Table 1). Patients with UP had significantly higher all-cause mortality in the 24-month period by Kaplan–Meier analysis (Fig. 1, log rank test, $r^2 = 4.698$, $p = 0.03$). Patients with UP also had significantly higher cardiovascular mortality in the 24-month period (Fig. 2, log rank test, $r^2 = 7.987$, $p = 0.005$). However, patients with UP did not have significantly higher proportion of infection related mortality in the 24-month period (Fig. 3; log rank test, $r^2 = 0.244$, $p = 0.622$).

In order to further investigate the significance of UP as an independent predictor for 24-month cardiovascular mortality, the univariate and multivariate Cox proportional hazard regression analysis was used. Univariate Cox regression showed age [odds ratio (OR): 1.066, 95% confidence interval (CI): 1.042 - 1.090, $P < 0.001$], DM (OR: 3.153, 95% CI: 1.816 - 5.475, $P < 0.001$), previous CVD history (OR: 3.339, 95% CI: 1.504 - 7.413, $P = 0.003$), log hsCRP (OR: 2.741, 95% CI: 1.593 - 4.718, $P < 0.001$), UP (OR: 2.217, 95% CI: 1.257 - 3.911, $P = 0.006$) and cardiomegaly (OR: 1.763, 95% CI: 1.013 - 3.069, $P = 0.045$) were associated with increased risk of 24-months cardiovascular mortality. On the other hand, fistula as blood access (OR: 0.344, 95% CI: 0.197 - 0.601, $P < 0.001$), nPCR (OR: 0.231, 95% CI: 0.076 - 0.703, $P = 0.01$), hemoglobin level (OR: 0.751, 95% CI: 0.611 - 0.923, $P = 0.006$), serum albumin level (OR: 0.233, 95% CI: 0.112 - 0.483, $P < 0.001$) and serum Cr level (OR: 0.736, 95% CI: 0.649 - 0.834, $P < 0.001$) were associated with reduced risk of 24-months cardiovascular mortality. VAS was not a significant factor to predict 24-month all-cause mortality (HR = 0.89, $p = 0.326$), cardiovascular-related (HR = 0.85, $p = 0.253$) mortality and infection-related (HR = 0.97, $p = 0.89$) mortality (Table 2). Despite UP patients having longer HD duration, HD duration was not a predictor of 24-months cardiovascular mortality by univariate Cox regression (OR: 0.97, 95% CI: 0.91 - 1.02, $P = 0.289$). An advanced multivariate Cox regression indicated that after adjusted above mentioned significant variables, age (OR: 1.053, 95% CI: 1.026 - 1.080, $P < 0.001$), DM (OR: 2.957, 95% CI: 1.664 - 5.256, $P < 0.001$), previous CVD history (OR: 2.845, 95% CI: 1.267 - 6.386, $P = 0.011$), log hsCRP (OR: 2.241, 95% CI: 1.269 - 3.958, $P = 0.005$), UP (OR: 2.217, 95% CI: 1.257 - 3.911, $P = 0.006$), fistula as blood access (OR: 0.538, 95% CI: 0.298 - 0.972, $P = 0.040$), and uremic pruritus (OR: 3.164; 95% CI: 1.743 - 5.744, $P < 0.001$) were significant predictors for 24-month cardiovascular mortality in the MHD patients (Table 3).

Univariate logistic regression showed that body mass index (OR: 1.07, 95% CI: 1.01 - 1.15, $P = 0.036$), DM (OR: 0.46, 95% CI: 0.29 - 0.73, $P = 0.001$), HCV (OR: 1.52, 95% CI: 1.03 - 2.23, $P = 0.032$), hemodialysis duration (OR: 1.11, 95% CI: 1.05 - 1.15, $P < 0.001$), hemodiafiltration (OR: 1.52, 95% CI: 1.05 - 2.20, $P = 0.026$), Kt/V_{urea} (Daugirdas) (OR: 2.94, 95% CI: 1.8 - 4.79, $P < 0.001$), nPCR (OR: 1.93, 95% CI: 1.06 - 3.51, $P = 0.03$), non-anuria (OR: 0.44, 95% CI: 0.27 - 0.71, $P = 0.001$), serum albumin (OR: 0.57, 95% CI: 0.36 - 0.91, $P = 0.02$), log iPTH (OR: 1.52, 95% CI: 1.14 - 2.02, $P = 0.004$), and LDL (OR: 1.01, 95% CI: 1.00 -

1.01, $P = 0.005$) were significant predictors for UP in the MHD patients. Multivariate logistic regression indicated that after adjusted for significant variables analysed by univariate logistic regression, hemodialysis duration (OR: 1.102, 95% CI: 1.069 – 1.137, $P < 0.001$), and LDL (OR: 1.008, 95% CI: 1.002 – 1.013, $P = 0.006$) were significant predictors for UP in the MHD patients (Table 4).

Table 1. Characteristics of studied MHD patients and patients with and without uremic pruritus. Abbreviations: SD: standard deviation; CVD: cardiovascular disease; HBV: hepatitis B virus infection; HCV: hepatitis C virus infection; nPCR: normalized protein catabolic rate; hsCRP: high-sensitivity C-reactive protein; LDL: low density lipoprotein; Kt/V_{urea} : dialysis clearance of urea. *Non-normal distribution data are presented as median (interquartile range)

Characteristics	Total (866) Mean $\pm$ SD/Median(Range)	Without pruritus (677) Mean $\pm$ SD/Median(Range)	With pruritus (189) Mean $\pm$ SD/Median(Range)	P
Demographics				
Age (years)	56.18 $\pm$ 13.59	55.70 $\pm$ 13.867	57.93 $\pm$ 12.437	0.046
Male sex, n (%)	440 (50.8%)	352 (52%)	88(46.6%)	0.18
Body mass index (kg/m ²)	22.19 $\pm$ 3.18	22.231 $\pm$ 3.1331	22.063 $\pm$ 3.3742	0.52
Smoking, n (%)	150(17.3%)	120(17.7%)	30(15.9%)	0.58
Dialysis Related Data				
Haemodialysis duration (years)	6.96 $\pm$ 5.35	6.27 $\pm$ 5.13	9.41 $\pm$ 5.43	<0.001
Erythropoietin (U/kg/week)	73.62 $\pm$ 47.37	75.0643 $\pm$ 47.71407	68.4568 $\pm$ 45.87704	0.09
Fistula as blood access, n (%)	689(79.6%)	532(78.6%)	157(83.1%)	0.18
Hemodiafiltration, n (%)	187(21.6%)	135(19.9%)	52(27.5%)	0.028
Kt/V_{urea} Daugirdes	1.79 $\pm$ 0.32	1.77 $\pm$ 0.32	1.89 $\pm$ 0.34	<0.001
nPCR (g/kg/day)	1.18 $\pm$ 0.26	1.17 $\pm$ 0.26	1.22 $\pm$ 0.27	0.03
Residual daily urine of >100 ml, n (%)	178(20.6%)	156(23%)	22(11.6%)	<0.001
Medications for itching, n (%)		33 (4.9%)	189 (100%)	<0.001
Biochemical Data				
Hemoglobin (g/dl)	10.51 $\pm$ 1.36	10.482 $\pm$ 1.3431	10.625 $\pm$ 1.4527	0.2
Albumin (g/dl)	4.06 $\pm$ 0.34	4.078 $\pm$ 0.3482	4.012 $\pm$ 0.3367	0.019
Creatinine (mg/dl)	10.88 $\pm$ 2.39	10.900 $\pm$ 2.4179	10.837 $\pm$ 2.2953	0.74
Ferritin (μ g/l)*	305.0(129.57, 504.45)	296(116.6, 505.4)	335.2(189.2, 499.4)	0.13
Corrected-calcium (mg/dl)	9.94 $\pm$ 0.93	9.912 $\pm$ 0.9188	10.059 $\pm$ 0.9779	0.055
Phosphate (mg/dl)	4.84 $\pm$ 1.35	4.844 $\pm$ 1.3395	4.843 $\pm$ 1.4128	0.99
Intact parathyroid hormone (pg/ml)*	130.1 (52.52, 319.2)	121.3(47.7, 284.1)	187.2(63.8, 401.7)	0.003
hsCRP (mg/l)*	2.95(1.4, 7.01)	2.89(1.38,7.39)	3.04(1.43,5.94)	0.87
Co-Morbidity				
Diabetes mellitus, n (%)	192(22.2%)	167(24.7%)	25(13.2%)	0.001
Hypertension, n (%)	339 (39.1%)	266(39.3%)	73(38.6%)	0.93
Previous CVD, n (%)	41(4.7%)	34(5%)	7(3.7%)	0.56
HBV, n (%)	98 (11.3%)	84(12.4%)	14(7.4%)	0.06
HCV, n (%)	168(19.4%)	121(17.9%)	47(24.9%)	0.037
Cardiovascular Risks				
Cholesterol (mg/dl)	171.3 $\pm$ 37.66	169.73 $\pm$ 37.089	176.93 $\pm$ 39.240	0.02
Triglyceride (mg/dl)	164.33 $\pm$ 115.8	167.11 $\pm$ 118.676	154.36 $\pm$ 104.573	0.18
LDL(mg/dl)	94.83 $\pm$ 30.59	93.26 $\pm$ 30.306	100.36 $\pm$ 31.058	0.005
Cardiomegaly, n (%)	383(44.2%)	310(45.8%)	73(38.6%)	0.083
24-month Mortality				0.043
Cardiovascular-related, n (%)	50(5.8%)	38 (5.6%)	12(6.3%)	0.008
Infection-related, n (%)	50(5.8%)	31(4.6%)	19(10.1%)	0.59
Cancer or others related, n (%)	4(0.4%)	4(0.6%)	0	0.58

Fig. 1. Comparison of the 24-month all-cause mortality between patients with and without uremic pruritus by Kaplan-Meier analysis. (Green line: patients with uremic pruritus, blue line: patients without pruritus).

Fig. 2. Comparison of the 24-month cardiovascular mortality between patients with and without uremic pruritus by Kaplan-Meier analysis. (Green line: patients with uremic pruritus, blue line: patients without pruritus).

Fig. 3. Comparison of the 24-month infection-related mortality between patients with and without uremic pruritus by Kaplan-Meier analysis. (Green line: patients with uremic pruritus, blue line: patients without pruritus).

Table 2. Univariate Cox Regression Analysis of 24-month cardiovascular related mortality. Abbreviations: CVD: cardiovascular disease; nPCR: normalized protein catabolic rate; WBC: white blood cell count; HBV: hepatitis B virus infection; HCV: hepatitis C virus infection; hsCRP: high-sensitivity C-reactive protein; iPTH: intact parathyroidhormone; Kt/V urea: dialysis clearance of urea; C-Ca: corrected calcium; LDL: low density lipoprotein; VAS: visual analogue scale

Variables	Odds ratio (OR) 95% confidence Intervals (CI)	p
Age (years)	1.066(1.042,1.090)	<0.001
Male sex	0.616(0.351,1.081)	0.091
Body mass index (kg/m ²)	1.074(0.99,1.16)	0.077
Smoking	1.008(0.49,2.07)	0.98
Diabetes mellitus	3.153(1.816, 5.475)	<0.001
Hypertension	0.932(0.52,1.64)	0.808
Previous CVD	3.339(1.504,7.413)	0.003
HBV	1.28(0.57,2.84)	0.544
HCV	0.77(0.362, 1.637)	0.497
Haemodialysis duration (years)	0.97(0.91,1.02)	0.289
Fistula as blood access	0.344(0.197,0.601)	<0.001
Hemodiafiltration	0.657(0.309, 1.397)	0.27
Kt/V _{urea} (Daugirdes)	1.054(0.459, 2.423)	0.901
nPCR (g/kg/day)	0.231(0.076, 0.703)	0.01
Non-Anuria	0.487(0.208, 1.141)	0.098
Hemoglobin (g/dl)	0.751(0.611, 0.923)	0.006
Serum Albumin (g/dl)	0.233(0.112, 0.483)	<0.001
WBC >10 ⁴	1.893(0.589, 6.078)	0.284
Creatinine (mg/dl)	0.736(0.649, 0.834)	<0.001
C-Ca	1.055(0.787, 1.414)	0.722
Phosphate (mg/dl)	0.84(0.679, 1.040)	0.109
Log ferritin	1.89(0.96, 3.69)	0.062
Log iPTH	0.685(0.454, 1.033)	0.071
Log hsCRP	2.741(1.593, 4.718)	<0.001
LDL (mg/dl)	1.007(0.998,1.015)	0.145
Triglyceride (mg/dl)	1.001(0.999, 1.003)	0.268
Pruritus	2.217(1.257, 3.911)	0.006
VAS	0.85(0.644,1.123)	0.253
Cardiomegaly	1.763(1.013, 3.069)	0.045

Table 3. Multivariate Cox regression analysis of predictors of 24 months cardiovascular mortality. Abbreviations: CVD: cardiovascular disease; hsCRP: high-sensitivity C-reactive protein

Variables	Odds ratio (OR) 95% confidence Intervals (CI)	p
Age (years)	1.053(1.026,1.080)	<0.001
Diabetes mellitus	2.957(1.664,5.256)	<0.001
Previous CVD	2.845(1.267,6.386)	0.011
Fistula as blood access	0.538(0.298,0.972)	0.040
Log hs-CRP	2.241(1.269, 3.958)	0.005
Pruritus	3.164(1.743,5.744)	<0.001

Discussion

The pathophysiology of uremic pruritus is not well clarified and multifactorial. The possible mechanisms include immune-hypothesis [14], opioid imbalance [15], histamine and other pruritogens hypothesis [15]. Different treatment modalities and medications such as phototherapy, thalidomide, calcineurin inhibitors, antihistamines and gabapentin have

Table 4. Univariate and multivariate logistic regression analysis of the predictors of UP in MHD patients. Abbreviations: UP: uremic pruritus; MHD: maintenance haemodialysis; HBV: hepatitis B virus infection; HCV: hepatitis C virus infection; nPCR, normalized protein catabolic rate; iPTH: intact-parathyroid hormone; hsCRP= high-sensitivity C-reactive protein; LDL= low density lipoprotein; Kt/V_{urea}=dialysis clearance of urea

Variables	Univariate logistic regression	P	Multivariate logistic regression	P
	Odds ratio (OR) 95% confidence Intervals (CI)		Odds ratio (OR) 95% confidence Intervals (CI)	
Body mass index (kg/m ²)	1.07(1.01-1.15)	0.036		
Diabetes mellitus	0.46(0.29-0.73)	0.001		
HCV	1.52(1.03-2.23)	0.032		
Haemodialysis duration (years)	1.11(1.05-1.15)	<0.001	1.102(1.069,1.137)	<0.001
Hemodiafiltration	1.52(1.05- 2.20)	0.026		
Kt/V _{urea} (Daugirdas)	2.94(1.8- 4.79)	<0.001		
nPCR (g/kg/day)	1.93(1.06-3.51)	0.03		
Non-Anuria	0.44(0.27-0.71)	0.001		
Serum Albumin (g/dl)	0.57(0.36-0.91)	0.02		
Log iPTH	1.52(1.14- 2.02)	0.004		
LDL (mg/dl)	1.01(1.00-1.01)	0.005	1.008(1.002,1.013)	0.006

been tested and used for UP. In this observational study, we found that after adjusted related variables, MHD patient with UP had greater odds for 24-month cardiovascular mortality. However, the severity of UP measured by VAS was not a predictor for cardiovascular mortality.

According to our review of the relevant literatures, studies of UP on mortality in MHD patients were limited. In early period between 1991 to 1995, Balaskas et al. [8] and Carmichael et al. [9] revealed the association between renal itch and mortality. In Balaskas's 24-month observation, the mortality in patients was 24% with pruritus and 4% without pruritus, respectively ($p < 0.025$). After following up 54 MHD patients for 3 years, Carmichael [9] revealed the significant association between high itch VAS and poor outcome. In Narita's study of 1773 MHD patients; severe UP (VAS > 7) was associated with poor outcome in these patients [10]. However, in subgroup analysis, instead of cardiovascular death, infection-related mortality was positively associated with itch severity [10]. In our study, Cox regression showed that VAS was not a significant factor to predict 24-month all-cause mortality, cardiovascular-related mortality and infection-related mortality. The severe UP (VAS > 7) was neither a significant predictor for all cause (HR = 0.85, $p = 0.71$), cardiovascular-related (HR = 0.77, $p = 0.65$) and infection-related (HR = 0.97, $p = 0.96$) mortality. From above cited and our studies, we found that renal itch was associated with higher mortality, but the role of VAS of renal itch on outcome should be further clarified. The different finding with VAS of UP on mortality between above cited and our studies may be due to the VAS was a subjective feeling by patients.

Most of the studies of the impact of UP on mortality were focusing on all-cause mortality [10, 16]. Our study showed that UP was a significant predictor of cardiovascular mortality in MHD patients. Systemic inflammation in dialysis has been noted to be the major etiology of UP[14]. In our study, after corrected with hsCRP, a surrogate of inflammation, uremic pruritus was still a predictor of cardiovascular mortality in hemodialysis patients. In a retrospective analysis of the DOPPS trial, congestive heart failure had also been noted to be one of the predictor of UP[7]. The DOPPS trial also states the pruritus/mortality relationship may be substantially attributed to poor sleep quality [7]. Mathur et al. showed that sleep disruption due to UP, assessed both by the Itch Medical Outcomes Study (MOS) composite score and the sleep interference question from the Brief Itching Inventory (BII), are significantly associated with the Self-Assessed Disease Severity [17]. Sleep disruption and disturbance have been noted to be associated with CVDs [18, 19] and will possible lead to cardiovascular mortality. Congestive heart failure (CHF) had been known to be a factor of cardiovascular mortality in hemodialysis patients [20]. Chronic inflammation has been noted to be a factor associated with CHF in MHD patients [21]. One of the possible mechanism of UP is systemic inflammation in MHD patients. Systemic inflammation, the common mechanism of UP and CHF, might be the reason that UP could predict or correlated with cardiovascular mortality in our study.

Histamine released by mast cell may also be a contributing factor to UP [16]. Mast cells also had been noted to be associated with eccentric cardiac hypertrophy [22], which had an important impact on mortality in hemodialysis patients [23]. Omae et al. showed that antihistamine therapy had a negative correlation with eccentric cardiac hypertrophy and could improve cardiovascular mortality in hemodialysis patients [24, 25]. Therefore, the possible correlation between UP and cardiovascular mortality might be due to the release of histamine from mast cell, which could induce both pruritus and eccentric cardiac hypertrophy.

Brain natriuretic peptide (BNP) has been noted to be expressed in a subset of transient receptor potential cation channel subfamily V member 1 (TRPV1) neurons, which triggered the itch sensation. BNP knocked out mice lose almost all behavioral responses to itch-inducing agents [26]. Shimizu et al. also demonstrated that serum brain BNP associates with the pruritus of hemodialysis patients [27]. Uremic pruritus might be a consequence of elevation of BNP induced by left ventricular pressure and volume overload due to salt and water retention and anemia, and increased blood volume and left ventricular end diastolic dysfunction caused by the arteriovenous vascular access in hemodialysis patients [28-30]. Cardiovascular events and death in hemodialysis patients had been noted to be associated with serum BNP [29].

Our data showed that HD duration was not a predictor of cardiovascular mortality in MHD patients, despite UP patients had longer HD duration. Li et al. showed that high neutrophil/ lymphocyte ratio can predict cardiovascular mortality in chronic hemodialysis patients [31]. The dialysis duration in their study was not correlated with cardiovascular mortality (correlation coefficient = 0.055, $P = 0.369$). In another study by Losito et al. demonstrated that dialysis duration was one of the predictor of cardiovascular mortality. But the OR was borderline (OR: 1.002, 95% CI: 1.001 – 1.004, $P = 0.006$) [31]. The controversy might be due to not enough duration of follow up and other confounding factors which were correlated with dialysis duration and masked its impact on cardiovascular mortality.

In our present study, Kt/V_{urea} (Daugirdas) was higher in UP patient as compared with patients without UP (1.89 ± 0.34 vs 1.77 ± 0.32 , $P < 0.001$). There were also controversial studies in this subject. Duque et al. showed that higher Kt/V was associated with UP [32]. Ko et al. showed the different result that $Kt/V \geq 1.5$ and use of high-flux dialyzer may reduce the intensity of pruritus in patients on chronic hemodialysis [33]. The possible explanation of higher Kt/V in our and Duque's study might be that doctors would increase the dialysis dosage in UP patients trying to reduce the intensity of itch.

Hepatitis C virus infection was significantly more common in patients with UP in this study. Pruritus due to HCV infection has been noted in several studies including HD patients with HCV infection [34-36]. The possible etiologies are HCV- induced cholestasis, increased production of cytokines and chemokines.

The prevalence of infection – related mortality in MHD was not different between patients with and without UP in our study. Narita et al. showed that mortality due to severe UP tended to be more prevalent [10], but the difference was not significant. Skin excoriations from scratching can lead to skin infections. Approximate 9% of infection episodes of long-term dialysis patients were skin and soft tissue infections [37]. The definite association between UP, skin infections, other infection sources and infection related mortality needed further investigations.

Conclusion

Uremic pruritus was one of the predictor of 24-month cardiovascular mortality in MHD patients. Nephrologists should be mindful of cardiovascular risks in hemodialysis patients, especially those with UP.

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Disclosure Statement

The authors declare no conflicts of financial interest.

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