Q J Med 2010; **103**:837–846
doi:10.1093/qjmed/hcq036 Advance Access Publication 29 March 2010

Original papers

QJM

Elevated C-reactive protein level in hemodialysis patients with moderate/severe uremic pruritus: a potential mediator of high overall mortality

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Received 8 October 2009 and in revised form 18 February 2010

Summary

Background: Dialysis patients with uremic pruritus have worse outcomes. However, the pathophysiology of the high mortality in these patients remains inconclusive except for links with calcium/phosphate imbalance and sleep disturbance. Whether inflammation, an outcome predictor in dialysis patients, plays a role is unknown.

Methods: This prospective study included 321 chronic hemodialysis (HD) patients (>3 months) for survival analysis. A visual analog scale (VAS) was used to measure the severity of itching, and the patients were divided into four groups: no pruritus (VAS = 0, $N = 118$), mild (VAS 1–3, $N = 76$), moderate (VAS 4–7, $N = 89$) and severe pruritus (VAS 8–10, $N = 38$). The Pittsburgh Sleep Quality Index (PSQI) was used to define sleep disturbance, while high-sensitive C-reactive protein (hs-CRP) and tumor necrosis factor α (TNF-α) were used to evaluate inflammation. The patients were followed-up for 30 months.

Results: Patients with moderate/severe pruritus had higher hs-CRP, but similar TNF-α levels; they also had a worse survival rate ($P = 0.0197$, log rank test). By stratifying hs-CRP levels, those with higher hs-CRP had worse survival regardless of the severity of uremic pruritus. In a Cox proportional hazard model, hs-CRP levels and moderate/severe uremic pruritus were independent predictors of mortality after adjusting for age, poor sleeper (PSQI > 5), diabetes, albumin, phosphate, hemoglobin and parathyroid hormone levels and (hs-CRP) × (moderate/severe uremic pruritus) (all $P < 0.05$).

Conclusion: In moderate/severe pruritic HD patients, those with higher hs-CRP suffer from worse overall mortality. Inflammation may bridge uremic pruritus to high mortality, and elevated hs-CRP predicts a worse outcome in this population.

Introduction

Uremic pruritus is a common complication in patients undergoing maintenance dialysis.[1,2] Our previous investigations confirmed that beyond metabolic factors and dialysis clearance,[1,3,4] inflammation is principally associated with uremic pruritus in hemodialysis (HD) patients, and that patients with severe uremic pruritus have higher high-sensitive C-reactive protein (hs-CRP) levels.[2] Other studies have indicated that several inflammatory cytokines promote the genesis of uremic pruritus, such as tumor necrosis factor α (TNF-α) or interleukin 2 (IL-2).[5,6]

High-degree uremic pruritus is associated with a worse outcome not only in terms of quality of life, but also with regards to overall survival in this population.[1,7,8] It independently predicts overall mortality even after adjustment for age, nutritional condition, and presence of diabetes mellitus (DM).[7,9] However, in the Dialysis Outcomes and Practice Patterns Study (DOPPS), the impact on mortality of moderate/severe uremic pruritus seems to be associated with sleep disturbance rather than uremic pruritus *per se*.[1,4] Interestingly, our previous studies have proven the close association between sleep disturbance and inflammation.[10–12] Therefore, a network among uremic pruritus, sleep disturbance, inflammation and mortality may be interactive; however, this is still not well understood.

Inflammation is considered a major contributor of cardio-vascular complications and overall mortality both in the general population and dialysis patients.[13–15] hs-CRP has been validated as a good surrogate of inflammation in dialysis patients and has independently predicted their overall mortality.[13,16] Although uremic pruritus is associated with higher hs-CRP levels and worse survival, whether or not hs-CRP or other inflammatory cytokines contribute to the mortality of HD patients with high-degree uremic pruritus remains unknown.

This study hypothesized that inflammation, measured by hs-CRP and TNF-α, would be a potential factor leading to a worse survival of HD patients with high-degree uremic pruritus and aimed to investigate if their high mortality is influenced by uremic pruritus per se, or by the interplay of inflammation. It also investigated the possible prognostic significance of uremic pruritus, inflammation and sleep disturbance for survival in this population.

Methods

Subjects and patients

There were 370 patients receiving maintenance HD at the Far Eastern Memorial Hospital in February, 2007. After excluding 49 patients, 321 patients aged >18 years (mean age 60 ± 12 years; 162 females) were recruited. The exclusion criteria were: (i) active infection; (ii) recent hospitalization within 3 months; (iii) psychotic illness or other communication problems; (iv) primary skin disorders; (v) cholestatic liver disease or acute hepatitis; (vi) active malignancy; and (vii) receiving HD for <3 months.

The study patients received 3.5–5 h of HD three times a week using bicarbonate dialysate and reverse osmosis purified water. In 71.3% of patients, a high-flux polysulfone membrane was used as the dialyzer, while the remaining 28.7% used a synthetic membrane low-flux dialyzer. The mean duration of HD before recruitment was 4.1 years (range 0.8–19.5 years). The hospital's Institutional Review Board approved this study and all of the participants provided written informed consent.

Baseline data and laboratory parameters

Baseline data, including gender, age, presence of hypertension or DM, underlying renal disease, HD regimen, duration of HD therapy, and concurrent medications of each patient, was recorded.

Venous blood was sampled in the morning, after an overnight fast >8 h before the patient's mid-week dialysis. All laboratory tests were performed by the hospital's central laboratory. Biochemistry data were determined using a Hitachi 747 auto-analyzer. The K_t/V_{urea} and normalized protein catabolic rate (nPCR) were calculated using a single-compartment model.

The hs-CRP levels were assayed by an Image autoanalyser using the nephelometric method (Beckman Coulter, Inc., CA, USA). Blood samples for measurement of TNF-α level were immediately centrifuged and stored at –70°C until assay. Serum TNF-α levels were measured by enzyme-linked immunosorbent assay (Biosource, Nivellas, Belgium).

Pruritus and sleep quality assessment

A visual analog scale (VAS) measuring the general severity of pruritus was reported from 0 to 10 (0, no pruritus to 10, intolerable pruritus). The patients were divided into four groups according to their VAS scores: Group 1 had no pruritus (VAS score 0); Group 2 had mild pruritus (VAS score 1–3); Group 3 had moderate pruritus (VAS score 4–7); and Group 4 had severe pruritus (VAS score 8–10).[7,17]

The Pittsburgh Sleep Quality Index (PSQI) includes seven indices: subjective sleep quality, latency, duration, efficiency, disturbances of sleep, use of sleep medication and daytime dysfunction.

The total score ranged from 0 to 21 points, with higher scores meaning poorer sleep quality. Patients with a total PSQI score >5 were defined as poor sleepers.

The VAS and PSQI of each patient were completed in March 2007 with the help of study nurses. We chose this study period in order to minimize the potential confounding effect of humidity on pruritus. The average relative humidity of the study months was 72–73%, which is nearly same as the annual average in Taiwan (75%).

Survival analysis

All patients were prospectively followed-up from 1 March 2007, until death or 1 September 2009. We first performed the survival analysis of patients in groups 1–4 and found the overall survival of patients in groups 1 and 2 (no/mild pruritus), groups 3 and 4 (moderate/severe pruritus) were similar, respectively (as shown in the Results section). Thereafter, we further sub-grouped patients with no/mild pruritus and moderate/severe pruritus according to their underlying inflammatory status by hs-CRP and TNF-α level. To date, the cut-off values of hs-CRP and TNF-α for the prediction of outcomes in HD patients have been inconclusive;[6,13,15,16,18–21] therefore, we sub-grouped the patients according to tertiles of their hs-CRP levels as performed in other investigations.[14,22] Patients were grouped with no/mild pruritus and first tertile of hs-CRP level; no/mild pruritus and second tertile of hs-CRP level; no/mild pruritus and third tertile of hs-CRP level; moderate/severe pruritus and first tertile of hs-CRP; moderate/severe pruritus and second tertile of hs-CRP; and moderate/severe pruritus and third tertile of hs-CRP. They were also sub-grouped by tertiles of TNF-α level. The survival analysis of subgroup patients were performed separately.

Statistical analysis

Normally distributed continuous variables were presented as mean (SD) while non-normally distributed continuous variables were presented as median (first and third quartiles). Categorical data were presented as percentages. Chi-square analysis was used to test the differences of categorical variables among Groups 1–4 and subgroups. Student's *t*-test and one-way ANOVA test was used for normally distributed variables while the non-parametric Mann–Whitney U and Kruskal–Wallis test was used for non-normally distributed continuous variables.

The Kaplan–Meier method and the Cox proportional hazard regression model were used to test the impact of pruritus severity and inflammation on overall survival. The Kaplan–Meier method (log rank test) was used to compare patient survival differences in Groups 1–4 and in subgroups. In the Cox proportional hazard model, covariates for multi-variable adjustment were selected based on the reported association with mortality in pruritic HD patients [i.e. age, albumin, hemoglobin, intact parathyroid hormone (iPTH), phosphate, hs-CRP, presence of diabetes, erythropoietin (EPO) dosage and poor sleeper] in previously published studies.[1,2,7,23] In addition, we also adjusted for (hs-CRP) × (uremic pruritus) in the model, in order to clarify the interaction between inflammation and uremic pruritus. All statistical analyses were performed using SPSS software, version 13.0 (SPSS Inc., Chicago, IL) and a *P*-value of <0.05 was considered statistically significant.

Results

Basic characteristics of patients with different severity of uremic pruritus and inflammation

The basic characteristics of the patients with different severities of pruritus (Groups 1–4) are demonstrated in Table 1. Patients with high-degree pruritus tended to have higher hs-CRP ($P=0.001$) and longer HD duration ($P=0.042$) than the other groups. Otherwise, there were no differences among the four groups. The TNF-α levels in the four groups were similar.

The basic characteristics of the patients in tertiles of hs-CRP and TNF-α levels are demonstrated in Table 2. Patients with higher hs-CRP tended to have lower albumin levels ($P=0.036$). Otherwise, there were no differences among patients in tertiles. The basic characteristics of the patients in tertiles of TNF-α level were similar.

Survival analysis

Overall, 57 of the 321 patients (17.8%) died during the 30-month follow-up. The major causes of death were cardiovascular disease ($N=35$, 61%), including nine cerebral vascular disease (16%), 16 coronary artery disease (28%) and 10 sudden death (17%); infection ($N=15$, 26%), malignancy ($N=2$, 4%), liver cirrhosis ($N=1$, 2%) and unknown ($N=4$, 7%). The average survival times in Groups 1–4 were 28.8, 28.8, 26.9 and 25.5 months, respectively; the overall survival of the patients in Groups 1–4 were significantly different ($\chi^2=9.87$, $P=0.0197$, log rank test) using the Kaplan–Meier method (Figure 1). By the Cox regression model, using Group 1 patients as the reference group, Group 2 had a hazard ratio

Table 1 Basic characteristics of patients in groups 1–4

	Severity of uremic pruritus ($N = 321$)					
	No/mild pruritus		Moderate/severe pruritus		*P*-value	
	Group 1 VAS = 0 $N = 118$	Group 2 VAS 1–3 $N = 76$	Group 3 VAS 4–7 $N = 89$	Group 4 VAS 8–10 $N = 38$	Among four groups	No/mild vs. moderate/severe
Male (%)	44	58	53	42	0.19	0.98
Age (year)	60 (11)	56 (12)	61 (12)	61 (12)	0.07	0.09
HD duration (year)	3.3 (3.9)	3.5 (3.7)	3.0 (3.2)	5.0 (5.5)	0.042	0.49
EPO user (%)	100	98.7	97.8	100	0.89	0.34
Dosage of EPO (Unit/month)	21 652 (12 777)	21 486 (13 397)	21 146 (13 066)	24 684 (12 951)	0.54	0.68
DM (%)	39.8	40.8	51.6	42.1	0.34	0.13
Poor sleeper (%)	47.9	51.2	58.1	50.6	0.93	0.54
K_t/V_{urea}	1.58 (0.3)	1.56 (0.2)	1.57 (0.3)	1.58 (0.3)	0.88	0.97
BUN (mg/dl)	71 (17)	72 (18)	72 (19)	74 (19)	0.64	0.22
Creatinine (mg/dl)	10.7 (2.5)	11.2 (2.1)	10.2 (2.3)	10.5 (2.5)	0.09	0.11
nPCR (g/Kg/day)	1.1 (0.2)	1.1 (0.2)	1.1 (0.3)	1.1 (0.3)	0.84	0.66
Hb (g/l)	10.7 (1.1)	10.8 (1.4)	10.9 (1.4)	11.1 (1.6)	0.60	0.93
Albumin (g/l)	4.1 (0.4)	4.1 (0.3)	4.0 (0.4)	4.1 (0.3)	0.08	0.036
Intact PTH (ng/l)	285 (207 412)	265 (269 448)	180 (224 394)	198 (98 817)	0.11	0.038
Calcium (mg/dl)	9.3 (0.7)	9.1 (0.7)	9.2 (0.8)	9.1 (0.5)	0.848	0.43
Phosphate (mg/dl)	5.0 (1.5)	5.4 (1.5)	5.4 (1.7)	5.4 (1.3)	0.234	0.29
hs-CRP (mg/l)	1.6 (1.1, 6.6)	2.8 (0.8, 9.5)	5.9 (1.4, 21.0)	7.7 (3.6, 26.9)	0.026	0.001
TNF-α[a] (ng/ml)	7.1 (6.0, 8.7)	7.2 (6.4, 8.5)	7.2 (6.5, 8.6)	7.5 (6.2, 10.9)	0.329	0.35

VAS, visual analog scale; HD, hemodialysis; EPO, erythropoietin; DM, diabetes mellitus; BUN, blood urea nitrogen; nPCR, normalized protein catabolic rate; Hb, hemoglobin; PTH, parathyroid hormone; hs-CRP, high-sensitive C-reactive protein; TNF-α, tumor necrosis factor alpha. For non-normally distributed continuous variables, values shown as median (first and third quartiles); for normally distributed continuous variables, values shown as mean (SD).

[a]TNF-α values were available in 235 patients.

Table 2 Basic characteristics of patients in tertiles of hs-CRP and TNF-α level

	hs-CRP tertiles ($N = 321$)				TNF-α tertiles ($N = 235$)			
	First ($N = 107$)	Second ($N = 107$)	Third ($N = 107$)	*P*-value	First ($N = 79$)	Second ($N = 78$)	Third ($N = 78$)	*P*-value
Male (%)	50	47	52	0.62	40	51	47	0.28
Age (year)	59 (12)	60 (12)	62 (12)	0.09	58 (12)	58 (13)	63 (11)	0.06
HD duration (year)	3.4 (4)	3.1 (3.3)	3.5 (4.2)	0.34	3.6 (4.1)	3.4 (3.9)	3.7 (4.4)	0.93
Dosage of EPO (Unit/month)	20 607 (11 458)	22 308 (13 147)	23 579 (14 087)	0.07	21 797 (12 238)	23 102 (13 738)	22 141 (14 962)	0.82
DM (%)	63	55	52	0.24	65	56	55	0.20
K_t/V_{urea}	1.59 (0.2)	1.59 (0.2)	1.54 (0.2)	0.30	1.6 (0.2)	1.56 (0.2)	1.61 (0.3)	0.43
BUN (mg/dl)	69 (17)	72 (19)	73 (19)	0.12	71 (18)	75 (16)	71 (21)	0.08
Creatinine (mg/dl)	10.8 (2.4)	10.7 (2.3)	10.6 (2.3)	0.72	10.4 (2.5)	11.1 (2.1)	10.6 (2.2)	0.12
nPCR (g/Kg/day)	1.1 (0.2)	1.1 (0.3)	1.1 (0.3)	0.36	1.1 (0.2)	1.2 (0.3)	1.0 (0.3)	0.07
Hb (g/l)	10.9 (1.3)	11.0 (1.4)	10.8 (1.5)	0.44	10.8 (1.5)	10.9 (1.4)	10.8 (1.4)	0.86
Albumin (g/l)	4.1 (0.4)	4.1 (0.3)	4.0 (0.3)	0.036	4.1(0.3)	4.1(0.4)	4.0 (0.4)	0.17
Intact PTH (ng/l)	304 (253 356)	347 (275 419)	367 (294 441)	0.40	327 (245 410)	338 (268 408)	348 (270 426)	0.94
Calcium (mg/dl)	9.3 (0.7)	9.2 (0.6)	9.1 (0.8)	0.32	9.2 (0.7)	9.1 (0.9)	9.2 (0.6)	0.21
Phosphate (mg/dl)	5.0 (1.4)	5.2 (1.6)	5.3 (1.6)	0.09	5.2 (1.6)	5.6 (1.4)	5.2 (1.5)	0.14

hsCRP, high-sensitive C-reactive protein; TNF-α, tumor necrosis factor alpha; HD, hemodialysis; EPO: erythropoietin; DM, diabetes mellitus; BUN, blood urea nitrogen; nPCR, normalized protein catabolic rate; Hb, hemoglobin; PTH, parathyroid hormone. For non-normally distributed continuous variables, values shown as median (first and third quartiles); for normally distributed continuous variables, values shown as mean (SD).

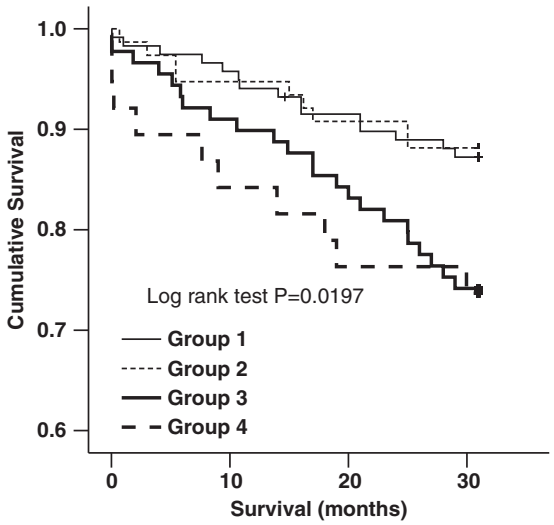

Figure 1. Hemodialysis patients with different severities of uremic pruritus had different overall survivals. Those with moderate (VAS 4–7) and severe (VAS 8–10) uremic pruritus seemed to have a worse survival than those with no (VAS = 0) or mild uremic pruritus (VAS 1–3).

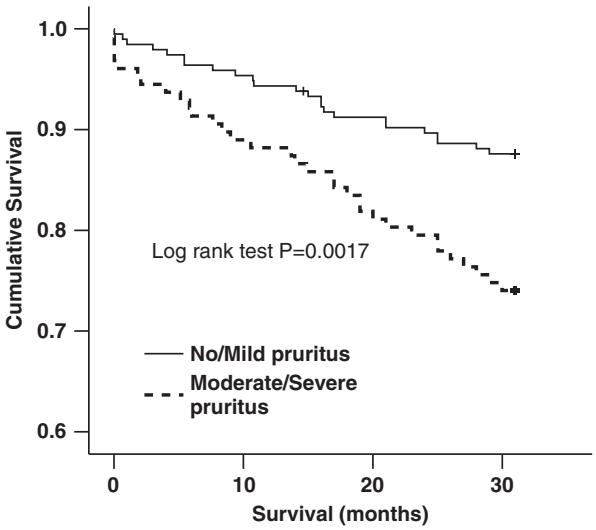

Figure 2. Hemodialysis patients with moderate/severe uremic pruritus had a worse overall survival than those with no/mild uremic pruritus.

(HR) = 0.93, $P = 0.861$, Group 3 HR = 2.2, $P = 0.021$ and Group 4 HR = 2.3, $P = 0.04$ for mortality.

Therefore, we compared the basic characteristics and survival of patients with no/mild pruritus (Groups 1 and 2) and those with moderate/severe pruritus (Groups 3 and 4). Patients with moderate/severe pruritus had lower albumin ($P = 0.036$) and iPTH ($P = 0.038$) and higher hs-CRP ($P = 0.001$) than those with no/mild pruritus (Table 1). In addition, patients with moderate/severe pruritus had a worse overall survival than those with no/mild pruritus ($\chi^2 = 9.80$, $P = 0.0017$, log rank test, Figure 2).

By the Kaplan–Meier method, patients in the third tertile of hs-CRP levels (higher hs-CRP level) had a worse overall survival than those in the second and first tertiles ($\chi^2 = 16.4$, $P = 0.0003$, log rank test); the overall survival of patients in tertiles of TNF-α levels were similar ($\chi^2 = 4.72$, $P = 0.193$, log rank test). Otherwise, patients with moderate/severe pruritus and higher hs-CRP levels also had the worse overall survival, and those with no/mild pruritus but higher hs-CRP also had worse survival (Figure 3).

By the Cox proportional hazard regression model, moderate/severe uremic pruritus ($P = 0.001$), poor sleeper ($P = 0.0012$), hs-CRP ($P < 0.001$), age ($P < 0.001$), albumin ($P < 0.001$), iPTH ($P = 0.028$) and phosphates ($P = 0.034$) predicted overall mortality, but not TNF-α ($P = 0.248$) in univariate analysis. After adjustments for age, presence of DM, EPO dosage, and metabolic factors (Model 1, Table 3), moderate/severe pruritus, hs-CRP and poor sleeper were still predictors. In the model of multivariable adjustment, hs-CRP and moderate/severe pruritus were still predictors of mortality (Models 2 and 3, Table 3). We found that there was interaction between the two predictors, moderate/severe pruritus and hs-CRP ($\chi^2 = 6.42$, $P = 0.011$). Therefore we also adjusted for (hs-CRP) × (moderate/severe pruritus) in Model 4: hs-CRP and moderate/severe pruritus were still independent predictors of mortality (Model 4, Table 3). By stratifying hs-CRP levels, patients in the third tertile of hs-CRP levels had 3.1 times the risk of mortality (confidence interval = 1.206–7.850, $P = 0.019$) than patients in the first tertile after adjustment for all covariates including moderate/severe pruritus and poor sleeper (Figure 4).

Discussion

This prospective study demonstrates that HD patients with moderate/severe uremic pruritus have a worse survival. Beyond uremic pruritus per se and poor sleep quality, a high hs-CRP level independently predicts all-cause mortality; hs-CRP may be the mediator of high all-cause mortality in HD patients with moderate/severe uremic pruritus.

We demonstrated that HD patients with moderate (Group 3) and severe (Group 4) uremic pruritus had similar all-cause mortality rates, but these were worse than those with no/mild pruritus (Figure 1). The results are similar to those shown in the DOPPS.[4] However, in another study conducted by Narita *et al.*,[7] they indicated that HD patients with moderate pruritus (VAS 4–7) did not have worse outcomes. We found that our patients with moderate uremic pruritus (Group 3) had significantly higher hs-CRP levels than those with no/mild

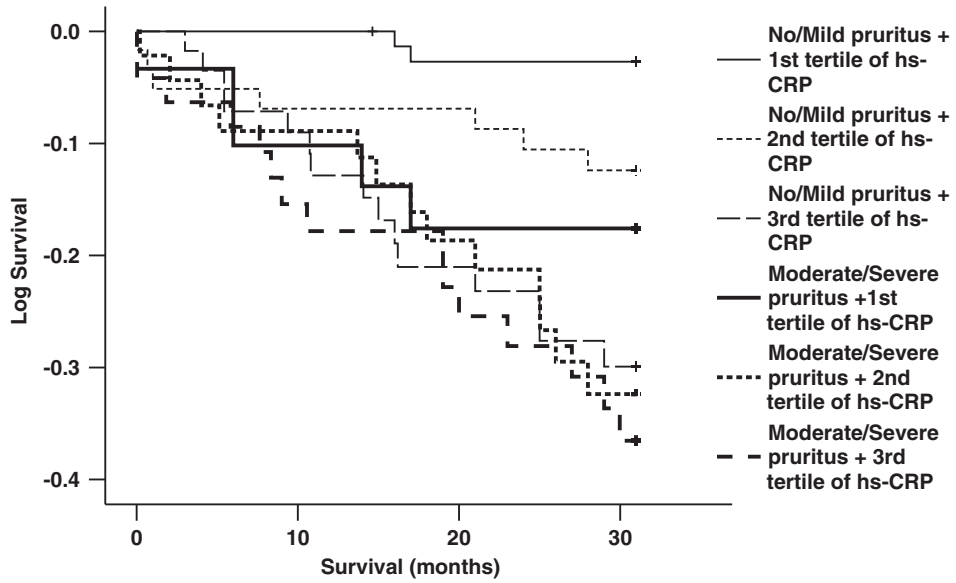

Figure 3. By the Cox regression model, using patients with no/mild pruritus and first tertile of hs-CRP level as the reference; patients with no/mild pruritus and second tertile hs-CRP had a hazard ratio (HR) = 4.7, $P = 0.065$; those with no/mild pruritus and third tertile hs-CRP HR = 11.1, $P = 0.001$; those with moderate/severe and first tertile hs-CRP HR = 6.8, $P = 0.022$; those with moderate/severe pruritus and second tertile hs-CRP HR = 11.8, $P = 0.001$ and those with moderate/severe pruritus and third tertile hs-CRP HR = 13.5, $P = 0.001$ for mortality.

Table 3 Predictors of all-cause mortality in hemodialysis patients by Cox proportional hazard models

Variables	HR	95% CI	*P*-value
Moderate/severe uremic pruritus			
Model 1	2.056	1.199–3.525	0.009
Model 2	1.899	1.107–3.256	0.02
Model 3	–	–	–
Model 4	3.125	1.596–6.122	0.001
hs-CRP			
Model 1	1.182	1.092–1.279	<0.001
Model 2	–	–	–
Model 3	1.175	1.083–1.275	<0.001
Model 4	1.261	1.155–1.376	<0.001
Poor sleeper (PSQI >5)			
Model 1	1.106	1.042–1.209	0.03
Model 2	1.089	1.040–1.104	0.039
Model 3	1.054	0.918–1.110	0.056
Model 4	1.038	0.888–1.212	0.061

CI, confidence interval; hs-CRP, high-sensitive C-reactive protein; PSQI, Pittsburgh sleep quality index. Model 1: adjustment of age, poor sleeper, DM, albumin, hemoglobin, EPO dosage, phosphate and iPTH level. Model 2: Model 1 + adjustment of hs-CRP level. Model 3: Model 1 + adjustment of moderate/severe uremic pruritus. Model 4: Model 2 + adjustment of (hs-CRP) × (moderate/severe uremic pruritus).

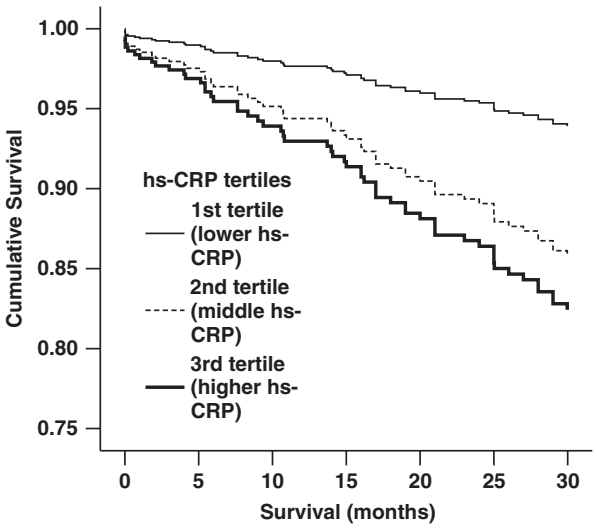

Figure 4. After adjustment for all covariates, patients in the third tertile of hs-CRP level had 3.1 times the risk [confidence interval (CI) = 1.206–7.850, $P = 0.019$] for mortality compared with patients in the first tertile; but those in second tertile (HR = 2.43, CI = 0.988–5.82, $P = 0.062$) did not.

pruritus (Table 1). Nevertheless, in the study performed by Narita *et al.*, the hs-CRP levels, which were not available in all participants, of patients with moderate uremic pruritus were similar or even lower than other patients. In this investigation, some patients had moderate pruritus but lower

hs-CRP levels and this is similar to the patients with moderate pruritus in Narita *et al.*'s study that also did not have a worse survival (Figure 3). This suggests that an underlying difference of inflammatory status might contribute to the survival discrepancy between the two studies. In addition, there were more poor sleepers in our Group 3 patients, which might also have lead to the worse outcomes.

The pathophysiology of uremic pruritus is associated with metabolic factors and inflammation,[24–26] however inflammation has yet to be confirmed as the cause leading to mortality in high-degree pruritic HD patients. In this investigation, patients were stratified into groups based on the hs-CRP level and severity of uremic pruritus. The results showed that the patients with higher hs-CRP had worse mortality, and patients with no/mild uremic pruritus but higher hs-CRP had even worse survival than moderate/severe pruritic patients with lower hs-CRP (Figure 3). HD patients with moderate/severe pruritus without higher hs-CRP may have pruritus related to abnormal opioid signaling or purely xerosis,[27–29] which are less significant factors associated with survival. These results strengthened the hypothesis that inflammation contributes to the mortality in pruritic HD patients rather than simply uremic pruritus *per se*.

Furthermore, in Cox multi-variable survival analysis, uremic pruritus and hs-CRP were survival predictors after adjustment for (hs-CRP) × (moderate/severe uremic pruritus) (Table 3, Models 2, 3 and 4), which implies that inflammation bridges moderate/severe uremic pruritus to high mortality. Interestingly, Narita *et al.*, demonstrated that higher β2-microglobulin independently predicts uremic pruritus and worse survival of HD patients because it stimulates local or systemic inflammatory reactions.[7] Chronic inflammation induces the accumulation of β2-microglobulin in dialysis patients.[30,31] This may further indicate a connection between uremic pruritus and poor survival via the inflammatory process.

Sleep disturbance may be substantially attributed to the pruritus/mortality relationship as mentioned in the DOPPS.[1,4] We have previously found a strong association between inflammation, measured by hs-CRP or inflammatory cytokines, and sleep disturbance in dialysis patients.[10–12] In the results of the current study, being a poor sleeper was only a marginal mortality predictor after adjusting for pruritus and (hs-CRP) × (moderate/severe uremic pruritus) (Table 2). However, there was no obvious interaction between hs-CRP and poor sleeper ($\chi^2 = 1.82$, $P = 0.42$, data not shown). Hence, hs-CRP itself remains a strong predictor of survival in high-degree pruritic HD patients regardless of either uremic pruritus per se or sleep disturbance.

Serum TNF-α levels have not been proven to be associated with uremic pruritus, and only intra-cytoplasmic TNF-α level is considered to be associated with it based on the clinical effects of thalidomide and tacrolimus on treatment of uremic pruritus.[6,32] In addition, TNF-α is not a survival predictor in HD patients.[19] Similarly, our results demonstrated that no association between TNF-α levels and either overall survival and severity of uremic pruritus. Although TNF-α level is strongly associated with hs-CRP level, TNF-α may not play a crucial role in the inflammatory process in pruritic HD patients.

The results showed similar annual mortality rates compared to HD patients both in Asian and in Western countries,[33,34] as well as HD patients with severe uremic pruritus[7] compared to previous investigations. In addition, the level of hs-CRP, calcium/phosphate control, and prevalence of poor sleepers in the study patients are equivalent to those in previous studies.[6,13,14,16] However, this study has limitations. This investigation is limited to the Taiwanese population and in the DOPPS, ethnic differences may interfere with the severity of uremic pruritus. Uremic pruritus and its underlying pathophysiology may be an issue linked to ethnic phenotype. In addition, we only used the VAS to evaluate of the severity of uremic pruritus. VAS is well validated and has been widely used for evaluation of uremic pruritus, but it may be influenced by the local temperature and humidity. We tried to lessen the impact by choosing spring as the study period, which is the mildest season in Taiwan. However, secondary tools for evaluation should be considered. Regarding inflammatory markers, other reported inflammatory cytokines associated with uremic pruritus, such as interleukin 6 (IL-6) or IL-2,[6,24] were not measured in this study. Despite this, hs-CRP is considered to be the most reliable inflammatory marker in HD patients.[19,20] Finally, this prospective observational study cannot resolve the causal relationship between the variables.

In conclusion, in this large-scale investigation, higher hs-CRP independently predicts worse all-cause mortality in HD patients with high-degree uremic pruritus, and it may be the mediator between uremic pruritus and mortality. Inflammation interplays with uremic pruritus and sleep disturbance, and consequently leads to worse outcomes. Clinicians should resolve the underlying inflammatory status to improve patient survival instead of focusing only on symptomatic treatment of uremic pruritus.

Acknowledgements

The authors express their thanks to the Ta-Tung Kidney Foundation and the Mrs Hsin-Chin Lee Kidney Research Fund for supporting this study.

Conflict of interest: None declared.

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