

Original Article

Factors contributing to pruritus in maintenance hemodialysis patients and establishment of a predictive model

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Abstract: Objective: Uremic pruritus represents a frequent and distressing condition among individuals receiving maintenance hemodialysis (MHD). This study aimed to identify risk factors for pruritus and to develop a predictive nomogram. Methods: This retrospective investigation enrolled 445 MHD patients treated at The Second People's Hospital of Hefei, Guangde Road Campus between January 2022 and December 2025. Patients were classified into pruritus and non-pruritus groups according to the Visual Analog Scale (VAS). They were further allocated into a training set (n=312) and a validation set (n=133) based on the timing of dialysis initiation. Pre-dialysis demographic data, dialysis-related parameters, and laboratory markers including serum phosphorus, β 2-microglobulin (β 2-MG), parathyroid hormone (PTH), interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor- α (TNF- α) were collected. Results: Of the 445 patients, 261 (58.7%) experienced pruritus. A multivariate logistic regression analysis revealed nine distinct risk factors that were independently associated with pruritus (all $P < 0.05$): longer dialysis duration (odds ratio [OR] 1.190), low-flux hemodialysis (OR 2.166), inadequate dialysis ($K_t/V < 1.2$; OR 2.537), higher serum phosphorus (OR 3.575), elevated β 2-MG (OR 1.269), higher PTH (OR 1.023), increased IL-6 (OR 1.203), elevated CRP (OR 1.627), and higher TNF- α (OR 1.087). The nomogram showed outstanding discrimination capability, with an area under the curve (AUC) of 0.955 in the training set and 0.950 in the validation set. Conclusion: Pruritus in MHD patients is independently associated with inadequate dialysis, disturbed mineral metabolism, and systemic inflammation, and the suggested nomogram serves as a dependable method for predicting individual risk.

Keywords: Pruritus, renal dialysis, risk factors, nomograms, retrospective studies

Introduction

Chronic kidney disease (CKD) represents an increasing worldwide health challenge, with a substantial proportion of individuals advancing to end-stage renal disease (ESRD) and necessitating maintenance hemodialysis (MHD) for survival [1]. Despite advances in dialysis technology and patient management, uremic pruritus remains a frequent and bothersome complication, affecting around 20% to 40% of individuals undergoing long-term hemodialysis, depending on the population studied and assessment methods [2, 3]. The symptom is often persistent and intensely distressing, leading to severe sleep disturbances, skin damage from repetitive scratching, depressive

symptoms, and a markedly reduced health-related quality of life [4, 5]. Importantly, uremic pruritus has been independently associated with increased all-cause and cardiovascular mortality, underscoring its role as a marker of poor prognosis [6].

The pathogenesis of uremic pruritus is multifactorial and incompletely understood, which continues to impede the development of targeted therapies [7]. Accumulation of uremic toxins, especially middle molecules such as β 2-microglobulin (β 2-MG) that are poorly removed by conventional low-flux dialysis, is thought to play a central role [8]. Concurrent mineral metabolism disorders, including hyperphosphatemia and secondary hyperparathy-

roidism with elevated parathyroid hormone (PTH) levels, are frequently observed in affected patients. Elevated serum phosphorus can facilitate cutaneous microcalcification and stimulate mast cell degranulation, releasing pruritogenic mediators such as histamine [9]. A chronic systemic microinflammatory state, marked by elevated levels of interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor- α (TNF- α), has been repeatedly linked to the severity and occurrence of pruritus, possibly through direct neuronal sensitization and immune cell infiltration in the skin [10]. Chronic inflammation, in turn, can heighten cutaneous nerve excitability and perpetuate the itch-scratch cycle, further aggravating skin barrier dysfunction [11]. Other proposed contributing factors include inadequate dialysis dose, skin xerosis, altered opioid receptor balance in the skin and central nervous system, and peripheral neuropathy [12]. Given this complexity, pruritus likely represents a clinical manifestation of the cumulative effect of retained metabolic waste products, mineral dysregulation, and immune activation. However, the relative importance of these factors as independent predictors has varied across studies, and a comprehensive, integrated risk assessment tool is still lacking in clinical practice.

A thorough understanding of modifiable and non-modifiable determinants of pruritus is essential for risk stratification and early intervention. While previous research has identified several associated variables, few studies have attempted to translate these findings into a practical predictive model that can be readily applied at the bedside [12, 13]. A nomogram, as a visual representation of a regression model, can integrate multiple risk factors and provide an individualized estimate of probability, thereby facilitating shared decision-making. Therefore, this study was designed to systematically assess a broad panel of demographic, dialysis-related, biochemical, and inflammatory parameters in MHD patients, to identify the independent risk factors for uremic pruritus, and to develop and validate a nomogram model for predicting its occurrence.

Materials and methods

Patient inclusion

In this retrospective study, we analyzed the clinical records from 445 patients who received

MHD at The Second People's Hospital of Hefei, Guangde Road Campus between January 2022 and December 2025.

Inclusion criteria: (1) meeting the diagnostic criteria for CKD [14] and reaching the end-stage of the disease; (2) receiving regular MHD treatment for ≥ 3 months; (3) age ≥ 18 years; and (4) availability of complete and valid clinical data. Exclusion criteria: (1) presence of primary skin diseases or other causes of pruritus not related to uremia; (2) presence of severe peripheral neuropathy, thyroid disease, leukemia, lymphoma, cholestasis, or chronic liver disease; (3) presence of severe infections or active inflammatory diseases; (4) presence of malignancy; (5) individuals who were pregnant or lactating; (6) presence of cognitive dysfunction, severe mental illness, or communication difficulties.

This retrospective study was conducted in accordance with the protocols of the Declaration of Helsinki and was approved by the Medical Ethics Committee of The Second People's Hospital of Hefei, Guangde Road Campus. Due to the retrospective study design using de-identified data from routine clinical practice, the requirement of written informed consent from individual patients was waived by the Ethics Committee.

Pruritus assessment

The Second People's Hospital of Hefei, Guangde Road Campus routinely used the Visual Analog Scale (VAS) to assess the occurrence and severity of pruritus [15]. Patients were asked to mark the intensity of their pruritus on a numerical scale ranging from 0 to 10, with 0 representing no pruritus and 10 denoting the most severe pruritus. Based on the patients' scores, the severity was classified as follows: 1-3 for mild pruritus, 4-6 for moderate pruritus, and 7-10 for severe pruritus.

Depending on the presence or absence of pruritus, 445 MHD patients were categorized into two groups: a non-pruritus group ($n=184$) and a pruritus group ($n=261$). Patients were categorized into the pruritus group if they presented with a VAS score ≥ 1 at any assessment point during a continuous 3-month MHD period. Conversely, patients with persistent VAS scores of 0 throughout the 3-month observation window were assigned to the non-pruritus group. Based on the timing of dialysis start, the 445

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MHD patients were divided into a training set (n=312) and a validation set (n=133). The training set comprised 127 patients without pruritus and 185 patients with pruritus, which was used for constructing the predictive model. The validation set included 57 patients without pruritus and 76 patients with pruritus, which was used for model verification.

Data collection

Patient data were collected from the hospital electronic medical record (EMR) system: (1) General information: including gender, age, body mass index (BMI), diabetic kidney disease (DKD), education level, duration of dialysis, dialysis modality, type of vascular access, and inadequate dialysis (urea clearance index [Kt/V] <1.2); (2) Laboratory tests: including biochemical and inflammatory markers before the initiation of dialysis. Biochemical indicators such as albumin (ALB), total cholesterol (TC), triglycerides (TG), total bilirubin (TBil), serum creatinine (Scr), blood urea nitrogen (BUN), uric acid (UA), phosphorus (P), calcium (Ca), and potassium (K) were assessed using an automated biochemical analyzer (AU5800, Beckman Coulter, USA). β 2-MG, PTH, IL-6, CRP, and TNF- α were assessed using an electrochemiluminescence immunoassay analyzer (Cobas e 602, Roche Diagnostics, Switzerland).

Statistical analysis

SPSS 25.0 software was used for data analysis. Categorical data were described as n (%), with group comparisons conducted using the χ^2 test. Continuous data were expressed as mean $\pm$ standard deviation (SD), and inter-group comparisons were conducted using independent samples t-tests. Logistic regression analysis was performed to identify factors influencing pruritus in individuals undergoing MHD. Receiver operating characteristic (ROC) curves were plotted to analyze the predictive value of each influencing factor on pruritus in MHD patients. The optimal cutoff values for continuous variables were determined using ROC curve analysis, selecting the points that maximized the Youden index. To ensure the stability of the regression model, multicollinearity was assessed using the variance inflation factor (VIF). Variables with a VIF <5 were considered to have no significant collinearity issues. The identified independent risk factors were incorporat-

ed into R 4.3.3 software to construct a nomogram model for predicting pruritus in MHD patients. Model performance was evaluated using ROC curves, calibration plots, decision curve analysis, and a validation cohort. A P-value <0.05 was considered significant.

Results

Baseline characteristics between the two datasets

To assess the comparability of the training and validation sets generated by the time-splitting method, we compared all general information and laboratory tests between the two cohorts (**Table 1**). No significant differences were observed in any of the variables examined (all P>0.05). These findings indicate that the training and validation sets were highly homogeneous in their baseline characteristics.

Establishment of model

General information in the training set: The training cohort included 312 patients, 127 without pruritus and 185 with pruritus (**Table 2**). The pruritus group had a markedly greater proportion of patients aged 60 years or older ($\chi^2=6.642$, P=0.010), a longer dialysis vintage (t=8.611, P<0.001), a greater reliance on low-flux hemodialysis (LFHD) ($\chi^2=8.806$, P=0.003), and a markedly higher rate of inadequate dialysis, defined as Kt/V<1.2 ($\chi^2=24.435$, P<0.001). The two groups were comparable with respect to gender (P=0.326), BMI (P=0.311), DKD (P=0.476), education level (P=0.105), and type of vascular access (P=0.403).

Laboratory tests in the training set: Among the biochemical indices, serum P (t=4.672, P<0.001), β 2-MG (t=8.241, P<0.001), and PTH (t=9.731, P<0.001) were markedly higher in patients with pruritus. ALB, TC, TG, TBil, SCr, BUN, UA, Ca, and K did not differ between groups (all P>0.05, **Table 3**).

With regard to inflammatory markers, the pruritus group demonstrated markedly higher circulating levels of IL-6 (t=6.636, P<0.001), CRP (t=7.485, P<0.001), and TNF- α (t=5.591, P<0.001, **Figure 1**).

Influencing factors analysis: Univariate logistic regression identified ten significant predictors (**Table 4**). Age $\geq$ 60 years was linked to increased

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Table 1. Comparative analysis of baseline characteristics between the two datasets

Variable	Training set (n=312)	Validation set (n=133)	t/ χ^2	P
General information				
Gender, n (%)			0.008	0.930
Male	175 (56.09%)	74 (55.64%)		
Female	137 (43.91%)	59 (44.36%)		
Age, n (%)			0.059	0.809
≥60 years	165 (52.88%)	72 (54.14%)		
<60 years	147 (47.12%)	61 (45.86%)		
BMI, kg/m ²	20.60 ± 1.58	20.57 ± 1.57	0.168	0.867
DKD, n (%)	155 (49.68%)	59 (44.36%)	1.057	0.304
Education level, n (%)			0.179	0.672
Junior high school and below	120 (38.46%)	54 (40.60%)		
High school and above	192 (61.54%)	79 (59.40%)		
Dialysis duration, months	35.18 ± 7.43	35.25 ± 7.47	0.085	0.932
Dialysis modality, n (%)			0.013	0.908
LFHD	152 (48.72%)	64 (48.12%)		
HFHD	160 (51.28%)	69 (51.88%)		
Vascular access type, n (%)			0.004	0.953
AVF	205 (65.71%)	87 (65.41%)		
CVC	107 (34.29%)	46 (34.59%)		
Kt/V<1.2, n (%)	168 (53.85%)	74 (55.64%)	0.121	0.728
Laboratory tests				
ALB, g/L	38.84 ± 2.98	38.85 ± 2.94	0.025	0.980
TC, mmol/L	3.25 ± 0.60	3.26 ± 0.59	0.232	0.816
TG, mmol/L	1.71 ± 0.59	1.71 ± 0.56	0.121	0.904
TBiL, μ mol/L	5.81 ± 0.78	5.79 ± 0.76	0.271	0.786
Scr, μ mol/L	706.78 ± 67.79	705.19 ± 67.11	0.228	0.820
BUN, mmol/L	24.25 ± 2.80	24.02 ± 2.71	0.783	0.434
UA, μ mol/L	428.54 ± 35.69	428.69 ± 35.97	0.039	0.969
Ca, mmol/L	2.20 ± 0.23	2.21 ± 0.24	0.498	0.619
P, mmol/L	2.37 ± 0.45	2.39 ± 0.43	0.477	0.634
K, mmol/L	5.88 ± 0.61	5.89 ± 0.58	0.193	0.847
β 2-MG, mg/L	22.79 ± 3.65	22.71 ± 3.71	0.202	0.840
PTH, pg/mL	375.89 ± 64.22	375.57 ± 65.84	0.048	0.962
IL-6, pg/mL	16.77 ± 3.40	16.81 ± 3.39	0.135	0.893
CRP, mg/L	9.61 ± 2.27	9.56 ± 2.25	0.190	0.850
TNF- α , pg/mL	41.34 ± 5.15	41.26 ± 5.00	0.158	0.874

Notes: MHD, Maintenance Hemodialysis; BMI, Body Mass Index; DKD, Diabetic Kidney Disease; LFHD, Low-flux Hemodialysis; HFHD, High-flux Hemodialysis; AVF, Arteriovenous Fistula; CVC, Central Venous Catheter; Kt/V, Urea Clearance Index; ALB, Albumin; TC, Total Cholesterol; TG, Triglyceride; TBiL, Total Bilirubin; Scr, Serum Creatinine; BUN, Blood Urea Nitrogen; UA, Uric Acid; Ca, Calcium; P, Phosphorus; K, Potassium; β 2-MG, β 2-Microglobulin; PTH, Parathyroid Hormone; IL-6, Interleukin-6; CRP, C-Reactive Protein; TNF- α , Tumor Necrosis Factor-alpha.

odds of pruritus (odds ratio [OR] =1.818, P=0.010). Each additional month of dialysis increased the odds by 16% (OR=1.164, P<0.001). LFHD doubled the risk (OR=2.000, P=0.003). A Kt/V<1.2 carried an OR of 3.218 (P<0.001). Higher levels of P (OR=3.338, P<0.001), β 2-MG (OR=1.334, P<0.001), PTH

(OR=1.021, P<0.001), IL-6 (OR=1.283, P<0.001), CRP (OR=1.509, P<0.001), and TNF- α (OR=1.142, P<0.001) were all significant risk factors.

In the subsequent multivariate analysis (**Table 5**), age ≥60 years was no longer a significant

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Table 2. General information of MHD patients with and without pruritus in the training set

Variable	Non-pruritus group (n=127)	Pruritus group (n=185)	t/ χ^2	P
Gender, n (%)			0.967	0.326
Male	67 (52.76%)	108 (58.38%)		
Female	60 (47.24%)	77 (41.62%)		
Age, n (%)			6.642	0.010
≥ 60 years	56 (44.09%)	109 (58.92%)		
<60 years	71 (55.91%)	76 (41.08%)		
BMI, kg/m ²	20.71 $\pm$ 1.48	20.53 $\pm$ 1.65	1.015	0.311
DKD, n (%)	60 (47.24%)	95 (51.35%)	0.508	0.476
Education level, n (%)			2.630	0.105
Junior high school and below	42 (33.07%)	78 (42.16%)		
High school and above	85 (66.93%)	107 (57.84%)		
Dialysis duration, months	31.24 $\pm$ 6.76	37.88 $\pm$ 6.64	8.611	<0.001
Dialysis modality, n (%)			8.806	0.003
LFHD	49 (38.58%)	103 (55.68%)		
HFHD	78 (61.42%)	82 (44.32%)		
Vascular access type, n (%)			0.700	0.403
AVF	80 (62.99%)	125 (67.57%)		
CVC	47 (37.01%)	60 (32.43%)		
Kt/V<1.2, n (%)	47 (37.01%)	121 (65.41%)	24.435	<0.001

Notes: MHD, Maintenance Hemodialysis; BMI, Body Mass Index; DKD, Diabetic Kidney Disease; LFHD, Low-flux Hemodialysis; HFHD, High-flux Hemodialysis; AVF, Arteriovenous Fistula; CVC, Central Venous Catheter; Kt/V, Urea Clearance Index.

Table 3. Biochemical indicators of MHD patients with and without pruritus in the training set

Variable	Non-pruritus group (n=127)	Pruritus group (n=185)	t	P
ALB, g/L	39.12 $\pm$ 2.58	38.64 $\pm$ 3.21	1.460	0.145
TC, mmol/L	3.31 $\pm$ 0.52	3.21 $\pm$ 0.65	1.555	0.121
TG, mmol/L	1.68 $\pm$ 0.54	1.73 $\pm$ 0.62	0.820	0.413
TBiL, μ mol/L	5.82 $\pm$ 0.81	5.79 $\pm$ 0.76	0.392	0.695
Scr, μ mol/L	700.45 $\pm$ 75.73	711.12 $\pm$ 61.38	1.318	0.189
BUN, mmol/L	23.97 $\pm$ 2.75	24.45 $\pm$ 2.83	1.475	0.141
UA, μ mol/L	424.56 $\pm$ 38.22	431.28 $\pm$ 33.67	1.638	0.102
Ca, mmol/L	2.19 $\pm$ 0.21	2.21 $\pm$ 0.24	0.617	0.537
P, mmol/L	2.23 $\pm$ 0.38	2.46 $\pm$ 0.47	4.672	<0.001
K, mmol/L	5.84 $\pm$ 0.56	5.91 $\pm$ 0.64	1.052	0.294
β 2-MG, mg/L	20.92 $\pm$ 3.42	24.07 $\pm$ 3.23	8.241	<0.001
PTH, pg/mL	338.47 $\pm$ 52.84	401.54 $\pm$ 58.47	9.731	<0.001

Notes: MHD, Maintenance Hemodialysis; ALB, Albumin; TC, Total Cholesterol; TG, Triglyceride; TBiL, Total Bilirubin; Scr, Serum Creatinine; BUN, Blood Urea Nitrogen; UA, Uric Acid; Ca, Calcium; P, Phosphorus; K, Potassium; β 2-MG, β 2-Microglobulin; PTH, Parathyroid Hormone.

predictor (P=0.271). Nine variables emerged as independent risk factors for pruritus: longer dialysis duration (OR=1.190, P<0.001), LFHD (OR=2.166, P=0.049), inadequate dialysis (Kt/V<1.2; OR=2.537, P=0.018), higher serum P (OR=3.575, P=0.007), higher β 2-MG (OR=1.269, P<0.001), higher PTH (OR=1.023, P<0.001), higher IL-6 (OR=1.203, P=0.004),

higher CRP (OR=1.627, P<0.001), and higher TNF- α (OR=1.087, P=0.037).

The ROC analysis indicated that PTH had the highest AUC of 0.792, followed by dialysis duration (AUC=0.753), β 2-MG (AUC=0.750), CRP (AUC=0.736), IL-6 (AUC=0.705), TNF- α (AUC=0.676), P (AUC=0.646), Kt/V<1.2 (AUC=0.642),

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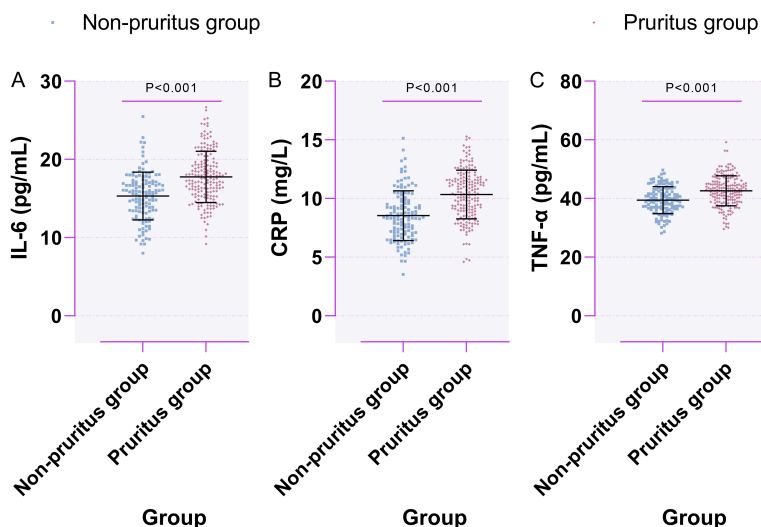


Figure 1. Comparison of inflammatory marker levels between MHD patients with and without pruritus in the training set. Notes: (A) IL-6, pg/mL; (B) CRP, mg/L; (C) TNF- α , pg/mL; MHD, Maintenance Hemodialysis; IL-6, Interleukin-6; CRP, C-Reactive Protein; TNF- α , Tumor Necrosis Factor-alpha.

LFHD (AUC=0.585), and age ≥ 60 years (AUC=0.574, **Table 6**).

Model construction: A predictive model for pruritus in MHD patients was established using a nomogram. The nomogram (**Figure 2A**) incorporated several clinical and biochemical variables, including dialysis duration, LFHD status, Kt/V <1.2 , serum P, $\beta 2$ -MG, PTH, IL-6, CRP, and TNF- α , each contributing to a total risk score that predicted the likelihood of pruritus. The ROC curve (**Figure 2B**) demonstrated excellent discriminatory power, with an AUC of 0.955, indicating high accuracy in distinguishing MHD patients with and without pruritus. The calibration curve (**Figure 2C**) showed excellent agreement between predicted and observed pruritus probabilities. The 1000-bootstrap-corrected AUC was 0.938, confirming that our model has low overfitting risk and stable internal performance. The DCA (**Figure 2D**) demonstrated that the nomogram yielded a higher net benefit than the extreme strategies of treating all patients as pruritus-positive or treating all patients as pruritus-negative within the threshold probability range of 10% to 85% for defining high pruritus risk.

Validation of model

The predictive model for pruritus in MHD patients was validated in an independent vali-

dation cohort, as demonstrated by the ROC curve (**Figure 3**). The AUC was 0.950, indicating strong discriminatory capability in differentiating between MHD patients with and without pruritus.

Discussion

The present study examined the clinical and laboratory determinants of pruritus in a cohort of maintenance hemodialysis patients and integrated these factors into a predictive nomogram. Uremic pruritus was highly prevalent in this population, and its occurrence was independently associated with a cluster of variables reflecting dialysis adequacy, mineral metabolism

disturbance, and systemic inflammation. The nomogram, incorporating dialysis duration, LFHD modality, inadequate urea clearance, serum P, $\beta 2$ -MG, PTH, IL-6, CRP, and TNF- α , demonstrated excellent discriminative ability in both the training and validation sets.

Longer dialysis vintage emerged as an independent risk factor for pruritus. This finding is consistent with the concept that cumulative retention of poorly dialyzable uremic solutes and progressive deterioration of residual renal function over time may intensify pruritogenic stimulation [16]. Several observational studies have similarly noted a positive correlation between time on dialysis and the prevalence of pruritus, although some investigations did not confirm this link, possibly due to differences in patient selection or dialysis vintage cutoff values [17]. Elderly age was more common in the pruritus group in univariate comparisons, but its effect was attenuated and no longer independently predictive after adjustment for other variables, suggesting that age-related susceptibility to pruritus may be mediated through longer dialysis history, altered mineral metabolism, or heightened inflammatory tone rather than aging *per se* [18, 19].

The dialysis-related parameters-LFHD and Kt/V below 1.2-were both independently linked to a higher probability of pruritus [20]. Low-flux

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Table 4. Univariate logistic regression analysis of factors contributing to pruritus in MHD patients

Variable	Coefficient	Std Error	Wald	P	OR	95% CI
Age ≥60 years	0.598	0.233	2.567	0.010	1.818	1.154-2.879
Dialysis duration	0.152	0.022	6.987	<0.001	1.164	1.118-1.217
LFHD	0.693	0.235	2.951	0.003	2.000	1.266-3.181
Kt/V<1.2	1.169	0.240	4.867	<0.001	3.218	2.019-5.183
P	1.205	0.284	4.251	<0.001	3.338	1.940-5.912
β2-MG	0.288	0.042	6.851	<0.001	1.334	1.232-1.454
PTH	0.021	0.003	7.589	<0.001	1.021	1.016-1.027
IL-6	0.249	0.043	5.819	<0.001	1.283	1.183-1.400
CRP	0.412	0.064	6.436	<0.001	1.509	1.337-1.719
TNF-α	0.132	0.026	5.120	<0.001	1.142	1.087-1.203

Notes: MHD, Maintenance Hemodialysis; OR, Odds Ratio; CI, Confidence Interval; LFHD, Low-flux Hemodialysis; Kt/V, Urea Clearance Index; P, Phosphorus; β2-MG, β2-Microglobulin; PTH, Parathyroid Hormone; IL-6, Interleukin-6; CRP, C-Reactive Protein; TNF-α, Tumor Necrosis Factor-alpha.

Table 5. Multivariate logistic regression analysis of factors contributing to pruritus in MHD patients

Variable	Coefficient	Std Error	Wald Stat	P	OR	OR CI Lower	OR CI Upper
Age ≥60 years	0.436	0.396	1.101	0.271	1.547	0.712	3.363
Dialysis duration	0.174	0.036	4.845	<0.001	1.190	1.109	1.276
LFHD	0.773	0.393	1.969	0.049	2.166	1.003	4.676
Kt/V<1.2	0.931	0.393	2.367	0.018	2.537	1.174	5.485
P	1.274	0.470	2.711	0.007	3.575	1.423	8.980
β2-MG	0.238	0.061	3.869	<0.001	1.269	1.125	1.431
PTH	0.023	0.005	4.977	<0.001	1.023	1.014	1.033
IL-6	0.185	0.063	2.916	0.004	1.203	1.062	1.362
CRP	0.487	0.103	4.730	<0.001	1.627	1.330	1.991
TNF-α	0.084	0.040	2.082	0.037	1.087	1.005	1.177

Notes: MHD, Maintenance Hemodialysis; OR, Odds Ratio; CI, Confidence Interval; LFHD, Low-flux Hemodialysis; Kt/V, Urea Clearance Index; P, Phosphorus; β2-MG, β2-Microglobulin; PTH, Parathyroid Hormone; IL-6, Interleukin-6; CRP, C-Reactive Protein; TNF-α, Tumor Necrosis Factor-alpha.

Table 6. ROC analysis of factors contributing to pruritus in MHD patients

Variable	Best_threshold	Sensitivities	Specificities	AUC	Youden_index	F1_score
Age ≥60 years	0.500	0.589	0.559	0.574	0.148	0.623
Dialysis duration	31.720	0.838	0.559	0.753	0.397	0.783
LFHD	0.500	0.557	0.614	0.585	0.171	0.611
Kt/V<1.2	0.500	0.654	0.630	0.642	0.284	0.686
P	2.425	0.557	0.669	0.646	0.226	0.624
β2-MG	22.425	0.676	0.740	0.750	0.416	0.729
PTH	364.680	0.762	0.717	0.792	0.479	0.779
IL-6	16.990	0.578	0.74	0.705	0.318	0.658
CRP	8.905	0.762	0.622	0.736	0.384	0.754
TNF-α	41.015	0.649	0.646	0.676	0.295	0.686

Notes: MHD, Maintenance Hemodialysis; ROC, Receiver Operating Characteristic; AUC, Area Under the Curve; LFHD, Low-flux Hemodialysis; Kt/V, Urea Clearance Index; P, Phosphorus; β2-MG, β2-Microglobulin; PTH, Parathyroid Hormone; IL-6, Interleukin-6; CRP, C-Reactive Protein; TNF-α, Tumor Necrosis Factor-alpha.

membranes have limited clearance of middle-molecular-weight uremic toxins, such as β2-MG,

which are increasingly recognized as key pruritogens [21]. In contrast, HFHD or hemodiafiltration

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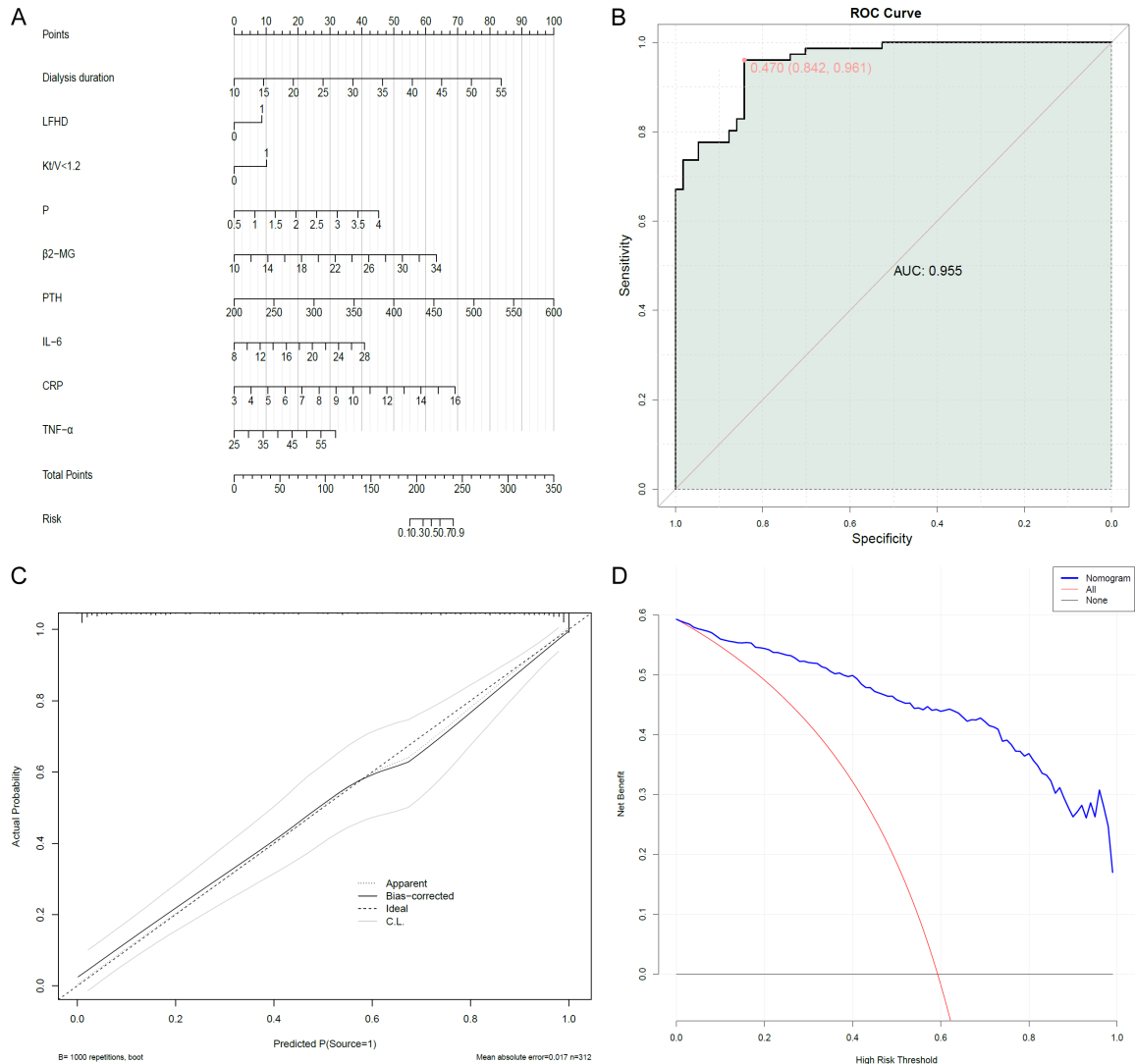


Figure 2. Development of a predictive model for pruritus in MHD patients in the training Set (A) Nomogram; (B) ROC curve; (C) Calibration plot; (D) DCA. Notes: MHD, Maintenance Hemodialysis; ROC, Receiver Operating Characteristic; DCA, Decision Curve Analysis; AUC, Area Under the Curve; LFHD, Low-flux Hemodialysis; Kt/V, Urea Clearance Index; P, Phosphorus; β 2-MG, β 2-Microglobulin; PTH, Parathyroid Hormone; IL-6, Interleukin-6; CRP, C-Reactive Protein; TNF- α , Tumor Necrosis Factor-alpha.

tion can enhance the removal of these molecules and have been associated with lower pruritus severity in several studies [22]. The independent role of inadequate dialysis dose, reflected by Kt/V, underscores the importance of optimizing small-solute clearance. Suboptimal dialysis delivery may permit the accumulation of a broad spectrum of metabolites that directly or indirectly activate itch pathways. Current guidelines emphasize maintaining a minimum Kt/V, and the present data suggest that achieving adequate dialysis may also confer a benefit in reducing pruritus burden [23, 24].

Disordered mineral metabolism was prominently represented among the independent predictors, with elevated serum phosphorus yielding the largest effect size in the multivariate model and PTH achieving the highest single-variable discriminative ability. These findings are mechanistically coherent with recent advances in chronic kidney disease-associated pruritus (CKD-aP) pathogenesis [25]. Hyperphosphatemia acts not merely as a biomarker but as a direct pruritogen. Beyond promoting cutaneous calcium-phosphate microdeposition that mechanically irritates dermal nerve endings, inorganic phosphate has been shown to acti-

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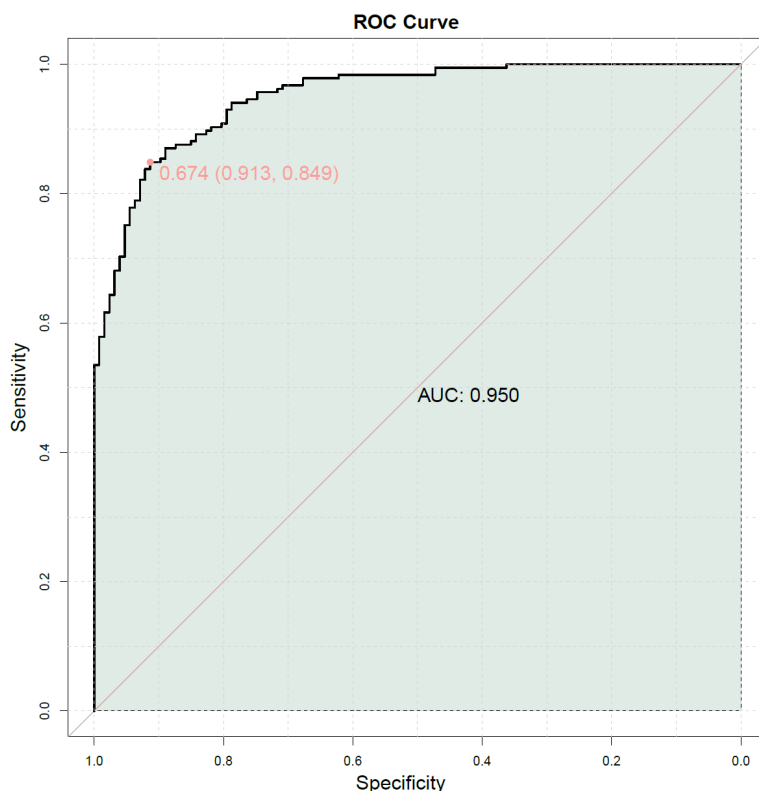


Figure 3. ROC curve analysis of the predictive model for pruritus in MHD patients in the validation set. Notes: MHD, Maintenance Hemodialysis; ROC, Receiver Operating Characteristic; AUC, Area Under the Curve.

vate Mas-related G protein-coupled receptor X4 (MRGPRX4), a primate-specific sensory neuron receptor that recognizes phosphate-containing ligands and drives histamine-independent itch [26]. Phosphate also potentiates mast cell degranulation and synergizes with IL-6 to amplify Th2-skewed responses, increasing IL-31 production - a canonical “pruritokine” now recognized as central to CKD-aP [27, 28]. PTH operates through both peripheral and central nodes. PTH1 receptors are expressed on dorsal root ganglion neurons, where PTH lowers pruriceptor excitation thresholds. PTH also stimulates cutaneous mast cell activity and fibroblast growth factor 23 (FGF23) secretion, the latter capable of crossing the blood-brain barrier to modulate central itch circuits [22]. This peripheral-to-central amplification loop helps explain why PTH emerged as the strongest single discriminator in our ROC analysis.

β2-MG-as a representative middle-molecule uremic toxin-retained independent predictive value despite adjustment for dialysis modality and Kt/V. β2-MG deposition potentiates der-

mal microinflammation and upregulates transient receptor potential vanilloid 1 (TRPV1) and Cav3.2 channels on sensory neurons, lowering itch thresholds through non-histaminergic pathways [29]. This aligns with the observed association between LFHD (limited middle-molecule clearance) and higher pruritus risk in our cohort, and supports the rationale for high-flux or hemodiafiltration in refractory cases.

The inflammatory signature (IL-6, CRP, TNF-α) maps onto defined neuro-immune pathways. IL-6 drives IL-31 production from Th2 cells and group 2 innate lymphoid cells; IL-31 acts on IL-31RA/OSMR complexes on sensory neurons to evoke sustained itch [28]. TNF-α sensitizes neurons by upregulating TRPV1 channel expression, amplifying responsiveness to both histaminergic and non-histaminergic

pruritogens. CRP, beyond serving as a biomarker, activates the complement alternative pathway to generate C3a/C5a anaphylatoxins that recruit and degranulate mast cells and potentiate keratinocyte-to-neuron signaling [30]. These inflammatory cascades form a feed-forward loop with mineral dysregulation-hyperphosphatemia and excess PTH themselves promote IL-6/TNF-α release-which is precisely why our nomogram’s integration of dialysis adequacy, mineral, and inflammatory domains achieved excellent discrimination [19, 31, 32].

Compared to previously published predictive models, our nomogram incorporates a more comprehensive panel of both traditional and emerging biomarkers. A recent study by Gu et al. developed and validated a nomogram for CKD-aP risk assessment in end-stage renal disease patients undergoing peritoneal dialysis, identifying age, IL-6, hemoglobin, residual urine volume, and renal Kt/V as key predictors [33]. Our model extends these findings by simultaneously integrating nine predictors across three core domains (dialysis adequacy, mineral

metabolism, and systemic inflammation), with a training-set AUC of 0.955 and validation-set AUC of 0.950, suggesting that multidimensional risk assessment may offer superior discrimination. However, direct head-to-head comparisons are limited by differences in study populations (hemodialysis vs. peritoneal dialysis), outcome definitions, and geographic settings.

Several limitations should be acknowledged. First, the retrospective, single-center design restricts generalizability and introduced potential selection and information biases. Information bias may have arisen from inconsistent documentation in the EMR system: details of pruritus attack frequency, diurnal variation, and concomitant skin xerosis were variably recorded across different providers, and VAS scores were occasionally extracted from nursing flow sheets completed by different assessors, introducing inter-rater variability. Additionally, although we excluded patients with severe cognitive impairment, mild cognitive decline in some elderly patients may have led to inaccurate self-reporting of pruritus severity, further contributing to information bias. Second, pruritus assessment relied on a single VAS measurement rather than a comprehensive multidimensional evaluation. We did not collect data on itch duration, attack frequency, nocturnal worsening, or validated pruritus-specific quality-of-life instruments such as the 5-D Itch Scale or Skindex-10. The absence of these dimensions may have led to misclassification of patients with intermittent but severe pruritus or those whose symptoms were predominantly nocturnal. Beyond the lack of multidimensional assessment, the use of VAS as a subjective patient-reported outcome introduces inherent scoring bias: VAS relies on patients' self-perception of itch intensity, which varies widely across individuals (e.g., elderly patients may have blunted sensory perception of pruritus, while patients with lower health literacy may misinterpret the 0-10 scoring system). Moreover, retrospective extraction of VAS data may be subject to recall bias, particularly in patients with intermittent pruritus who may underreport symptoms if assessed during asymptomatic periods. Future prospective studies will integrate validated multidimensional pruritus assessment tools, systematically document xerosis and temporal symptom patterns, and perform subgroup analyses across these dimensions to improve outcome classification accu-

racy and support more nuanced clinical interpretation. Third, variable inclusion was incomplete, introducing potential omission bias. Recognized confounding factors such as xerosis (skin dryness), opioid system dysregulation, dietary phosphorus intake, and detailed phosphate binder use were not captured in our retrospective EMR dataset. While our model incorporates serum phosphorus and inflammatory markers that partially correlate with xerosis and phosphate binder efficacy, future prospective studies should integrate these additional covariates to improve model accuracy and generalizability. Fourth, the temporal split-sample validation, although commonly used, does not fully account for potential temporal changes in dialysis practices and treatment protocols. Variations in dialysis prescription, membrane technology, and adjunctive therapies over the study period may have influenced pruritus outcomes independently of the included predictors. Future prospective studies with rigorous baseline equilibrium adjustment are needed to confirm the robustness of our model. Fifth, the generalizability of our nomogram is constrained by the lack of external multicenter validation. Although internal validation demonstrated robust discriminative ability, our study was conducted at a single tertiary care center in Hefei, China, and variations in dialysis protocols, laboratory testing standards, and pruritus assessment practices across different regions and institutions may influence the model's performance. External validation using independent cohorts from diverse geographic and clinical settings is therefore required to confirm the model's utility before widespread clinical implementation. Sixth, we did not evaluate the performance of the nomogram across key clinical subgroups, limiting conclusions about its differential applicability. Specifically, we did not stratify patients by age (<60 years vs. ≥ 60 years) or dialysis vintage (<36 months vs. ≥ 36 months, the median in our cohort) to assess calibration and discrimination within these subgroups. Future validation studies should specifically assess model performance in these high-risk subgroups to guide individualized clinical application.

Conclusion

In this retrospective analysis, uremic pruritus was independently associated with a constellation of modifiable and non-modifiable factors,

including longer dialysis vintage, LFHD, inadequate dialysis dose, and disturbances in mineral metabolism and systemic inflammation. The nomogram constructed from these nine predictors exhibited strong discrimination in both the derivation and validation cohorts, providing a practical and intuitive tool for individualized risk assessment in maintenance hemodialysis patients. These findings underscore the multifactorial nature of dialysis-associated pruritus and highlight the value of optimizing dialysis adequacy, controlling hyperphosphatemia and secondary hyperparathyroidism, and mitigating chronic inflammation as preventive strategies. Prospective, multicenter validation with comprehensive outcome measures is warranted to further establish the clinical utility of this predictive model.

Disclosure of conflict of interest

None.

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