

# The Severity, Quality of Life, and Correlated Factors of Chronic Kidney Disease-associated Pruritus between Hemodialysis and Kidney Transplant Patients: A Cross-sectional Study

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## ABSTRACT

**Background:** Chronic kidney disease-associated pruritus (CKD-aP) mainly occurs in hemodialysis (HD) patients and could persist in kidney transplant (KT) recipients. This study aims to compare the severity, correlation of various biochemical factors, and quality of life (QoL) concerning pruritus in CKD. **Methods:** A cross-sectional study was conducted on HD and KT recipients with chronic pruritus, where the 5-Dimensional (5-D) Itch Scale and Dermatology Life Quality Index (DLQI) were used to evaluate pruritus severity and QoL. **Results:** Among the 60 subjects, 76.7% of HD patients had moderate-to-severe pruritus, whereas in the KT group, 83.3% experienced mild pruritus ( $p < 0.001$ ). The median DLQI score was 5 (3–6) and 3 (2–4), respectively ( $p < 0.001$ ). There was a correlation between hs-CRP and the 5-D itch score in the HD group ( $r = 0.443$ ;  $p < 0.05$ ), whereas e-GFR was correlated with the 5-D itch score in the KT group ( $r = -0.424$ ;  $p < 0.05$ ). **Conclusion:** Moderate-to-severe pruritus was more common in HD patients. While pruritus in KT recipients had a mild effect on QoL, pruritus in the HD group had a mild-moderate impact on QoL. There was a correlation between hs-CRP and e-GFR and the severity of pruritus in HD and KT recipients, respectively.

**Keywords:** chronic kidney disease, hemodialysis, kidney transplant, pruritus, quality of life.

## INTRODUCTION

Pruritus is an unpleasant sensation that prompts the urge to scratch and could be induced by chronic kidney disease (CKD).<sup>1,2</sup> Approximately 69% of clinicians were not proactively searching for the possibility of CKD-associated pruritus (CKD-aP).<sup>3,4</sup> Where

the prevalence of pruritus in patients who underwent hemodialysis (HD) varies between 26% in Germany and 48% in England,<sup>4</sup> studies in Indonesia reported that 46.2%–75.8% of HD patients experienced pruritus,<sup>5-7</sup> which may be persistent in kidney transplant (KT) recipients. The incidence of pruritus in KT recipients was

12%–32%.<sup>8-10</sup>

In general, CKD-aP occurs over large areas of the skin, usually symmetrical and generalized in 25–50% of cases.<sup>3</sup> Additionally, xerosis mostly occurs in conjunction and exacerbates the symptoms.<sup>4-6</sup> Complications of pruritus include erosion, excoriation, ulceration, prurigo nodularis, lichen simplex chronicus, and secondary infection,<sup>11</sup> and additionally, pruritus in HD and KT recipients may contribute to a lower quality of life (QoL).<sup>8</sup>

Studies have reported various factors related to CKD-aP but with varying results.<sup>12</sup> While hypotheses regarding the pathogenesis of CKD-aP include inflammation, which may cause an imbalance of calcium and phosphate, and decreased kidney function leading to severe symptoms of pruritus,<sup>13,14</sup> xerosis, increased histamine, uremic toxins, endogenous opioid imbalance, neuropathy, and hyperparathyroidism further contribute to the pathogenesis of CKD-aP.<sup>15,16</sup> The objective of this study was to compare the severity of pruritus, and QoL, and to assess various biochemical factors between CKD-aP patients who underwent HD and KT.

## METHODS

### Study Design

Non-interventional cross-sectional study was carried out in the Department of Dermatology and Venereology and the Hemodialysis Unit at Dr. Cipto Mangunkusumo National Hospital Jakarta, Indonesia, from September 2022 to April 2023.

### Sample Size and Study Population

Based on the correlation sample size formula, the minimum sample size required was 30 subjects for each group, with a 95% level of confidence and 80% power. The target population included all patients with CKD stage V and pruritus, who underwent HD and KT recipients. The study population consisted of CKD patients with pruritus who underwent HD and KT recipients registered in the Hemodialysis Unit, Dermatology and Venereology Clinic, or Internal Medicine Clinic, Dr. Cipto Mangunkusumo National Hospital Jakarta, Indonesia.

### Patient Recruitment Criteria

Subjects were recruited consecutively based on inclusion and exclusion criteria. Inclusion criteria were as follows: CKD patients receiving HD twice a week, KT recipients  $\geq 3$  months post-surgery, chronic pruritus ( $\geq 6$  weeks), and age  $\geq 18$  years. The exclusion criteria were: patients with systemic diseases such as hepatobiliary, thyroid, psychiatric, or neurological disease; patients with primary skin diseases (e.g., autoimmune dermatosis, skin infection, genodermatosis, dermatosis in pregnancy); and malignancy.

### Patients Assessment

Patient data were collected from medical records, interviews, and physical examinations. Sociodemographic and clinical characteristics data included age, gender, duration of CKD ( $< 3$  years or  $\geq 3$  years), dialysis vintage ( $\leq 1$  year or  $> 1$  year), etiology of CKD (hypertension, diabetes mellitus, glomerulonephritis, cystic/congenital disease, or unknown), comorbidities (hypertension, diabetes mellitus, or other), body mass index (BMI), cutaneous findings (xerosis, scratch lesion, and discoloration), and laboratory parameters (hs-CRP, calcium, phosphate, e-GFR, urea, and creatinine). A skin examination was conducted by a dermatologist. Body mass index was calculated using the formula  $BMI = \text{weight (kg)}/\text{height (m}^2\text{)}$ .

### Assessment of Pruritus and Quality of Life

Pruritus was assessed using the 5-D Itch Scale questionnaire, a multidimensional tool covering five domains (duration, degree, direction, disability, and distribution). Patients with scores  $< 5$  points were defined as having no itch; a score of 6–10 points indicated mild pruritus, 11–20 points moderate pruritus, and 21–25 points indicated severe pruritus.<sup>17</sup> In this study, pruritus severity was categorized into mild pruritus (6–10) and moderate-to-severe pruritus (11–25) groups.

The Dermatology Life Quality Index (DLQI), which has proven to be a dependable and valid assessment tool for measuring QoL across various skin conditions, was used

to assess the quality of life.<sup>18</sup> The DLQI, comprising ten questions categorized into six groups: symptoms/feelings, daily activities, leisure, work/school, personal relationships, and treatment, is interpreted as having no effect at all on the patient's life (0–1), small effect (2–5), moderate effect (6–10), very large effect (11–20), and extremely large effect on the patient's life (21–30).<sup>19</sup>

### Laboratory Test

The laboratory parameters assessed were as follows: high-sensitivity C-reactive protein (hs-CRP), calcium, phosphate, urea, creatinine, and estimated glomerular filtration rate (e-GFR). According to the standard laboratory assessment guideline, blood samples (5 ml) were drawn from the vein using sterile equipment by trained laboratory personnel to assess hs-CRP, urea, calcium, and phosphate. Blood samples were then placed in labeled vacuum tubes. Before analysis, blood was allowed to clot at room temperature for 10 minutes, then centrifuged at 3000–10.000 rpm for 15 minutes to separate the serum. The serum was separated and analyzed on the same day. The e-GFR and creatinine within the last three months from the assessment day were also collected from the patient's medical record.

### Ethical Consideration

Ethical clearance was obtained from the Research Ethics Committee Faculty of Medicine Universitas Indonesia (clearance number: KET-725/UN2.F1/ETIK/ PPM.00.02/2022). Informed consent was requested from all participants.

### Statistical Analysis

Statistical analysis was performed using IBM® SPSS software (version 27; SPSS Inc., Chicago, IL, USA). Qualitative variables were presented as percentages and quantitative variables were expressed as mean  $\pm$  standard deviation or as median (interquartile range) for data with an abnormal distribution. The normality of data distribution was assessed using the Shapiro-Wilk test. Results were considered statistically significant at  $p < 0.05$ . Correlations between laboratory variables and the 5-D itch scores for each

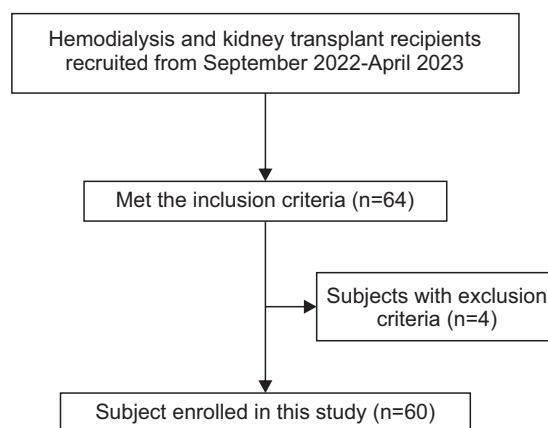
group were analyzed using Spearman's rho test. Differences in the proportion of pruritus severity across groups were examined using the Chi-square test, while differences in the mean of Dermatology Life Quality Index (DLQI) scores between groups were assessed using the nonparametric Mann–Whitney U-test.

## RESULTS

Sixty-four subjects met the inclusion criteria, while, after further assessment, four patients were excluded because of thyroid disease and pruritus related to dermatological disorders (psoriasis vulgaris, irritant contact dermatitis, or fungal skin disease). This led to a total of 60 subjects being included in our study (**Figure 1**).

### Sociodemographic and Clinical Characteristics

The sociodemographic and clinical characteristics are presented in **Tables 1** and **2**. Skin manifestations are documented in **Figure 2**.



**Figure 1.** Flow chart of patient recruitment.

**Table 1.** Sociodemographic characteristics of subjects in hemodialysis and kidney transplant groups (n = 60)

Variables	Hemodialysis (n = 30)	Kidney Transplant (n = 30)
Age (years)*	46.63 $\pm$ 16.33	38.0 $\pm$ 10.66
Gender (n, %)		
Male	17 (56.7)	18 (60)
Female	13 (43.3)	12 (40)

\*Data shown in means (standard deviation), n: number of subjects

**Table 2.** Clinical characteristics of subjects in hemodialysis and kidney transplant groups (n = 60)

Variables	Hemodialysis (n = 30)	Kidney Transplant (n = 30)
Duration of CKD (n, %)		
<3 years	10 (33.3)	10 (33.3)
≥3 years	20 (66.7)	20 (66.7)
Dialysis vintage (n, %)		
≤1 year	5 (16.7)	7 (23.3)
>1 years	25 (83.3)	23 (76.7)
Etiology of CKD (n, %)		
Hypertension	22 (73.3)	18 (60)
Diabetes mellitus	5 (16.7)	1 (3.3)
Glomerulonephritis	1 (3.3)	5 (16.7)
Cystic or congenital	0 (0)	2 (6.7)
Unknown	2 (6.7)	4 (13.3)
Comorbidities (n, %)		
Hypertension	27 (90)	23 (76.7)
Diabetes mellitus	8 (26.7)	4 (13.3)
Other	7 (23.3)	2 (6.7)
Body mass index (kg/m <sup>2</sup> )*	22.92 ± 4.34	23.50 ± 4.64
Cutaneous findings (n, %)		
Xerosis	24 (80)	5 (16.7)
Secondary scratch lesion	15 (50)	3 (10)
Discoloration	9 (30)	3 (10)
Laboratory parameters		
hs-CRP (mg/L)**	3.07 (0.93–7.60)	1.07 (0.38–2.40)
Calcium (mg/dl)*	8.51 ± 0.64	9.25 ± 0.54
Phosphate (mg/dl)*	5.17 ± 1.75	2.69 ± 0.47
e-GFR (ml/min/1.73 m <sup>2</sup> )*	4.94 ± 2.07	67.07 ± 21.60
Urea (mg/dl)*	154.73 ± 48.69	41.33 ± 17.59
Creatinine (mg/dl)*	11.62 ± 4.65	1.32 ± 0.41

\*Data shown in means (standard deviation), \*\*Data shown in median (interquartile range)

CKD: chronic kidney disease, e-GFR: estimated glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein, n: number of subjects



**Figure 2.** Clinical appearance of skin lesions in subjects (A) Xerosis cutis and excoriation on the leg. (B) Prurigo nodularis and postinflammatory hyperpigmentation on the lower back. (C) Hyperpigmentation on the lower legs

### Pruritus Severity

Moderate-to-severe pruritus, with HD patients being 4.6 times more likely to experience it than KT recipients (RR = 4.6, 95% CI = 2.02–10.49), was significantly higher

in HD group than in the KT recipients group ( $p < 0.001$ ) (Table 3). HD patients are 4.6 times more likely to experience moderate-to-severe pruritus than KT recipients (RR = 4.6, 95% CI = 2.02–10.49).

**Table 3.** The severity of pruritus between hemodialysis and kidney transplant group (n = 60)

Group	Pruritus		RR (95% CI)	p-value
	Moderate-severe	Mild		
Hemodialysis	23 (76.7%)	7 (23.3%)	4.6 (2.02–10.5)	<0.001 <sup>a</sup>
Kidney transplant	5 (16.7%)	25 (83.3%)		

<sup>a</sup>Chi-Square test, significant if  $p < 0.05$ , 95% CI: confidence interval 95%, RR: relative risk

### Quality of Life

The median DLQI score in the HD group was 5 (3–6) points, whereas in the KT group was 3 (2–4) points ( $p < 0.001$ ). The DLQI score in the HD group was slightly higher than in the KT group.

### Correlation of Biochemical Parameters

High-sensitivity CRP positively correlated with the 5-D itch score in the HD group ( $r = 0.443$ ,  $p = 0.014$ ). In the KT group, e-GFR showed a negative correlation ( $r = -0.424$ ,  $p = 0.02$ ) (Table 4).

### DISCUSSION

In the present study, moderate-to-severe pruritus was more common in HD compared to the KT group. Hemodialysis patients are 4.6 times more likely to experience moderate-to-severe pruritus than KT recipients, with the majority in the KT recipients group experiencing mild pruritus. Based on a study in Turkey, pruritus was also more common in HD patients and less in KT recipients.<sup>20</sup> A study in Germany reported that pruritus in KT recipients is mild, with an average Visual Analog Scale (VAS) of 3.2 points.<sup>9</sup> Persistent pruritus in KT could be caused by persistent pruritic stimuli or sensitization of pruritus signaling pathways, with kidney transplantation eliminating the

need for dialysis and reducing factors that trigger pruritus.<sup>8</sup> In addition, xerosis, systemic disease, or various biochemical factors could potentially trigger pruritus in KT recipients. While a study in Poland reported no difference in the prevalence and intensity of pruritus between various immunosuppressants used in KT recipients,<sup>10</sup> immunosuppressants for KT recipients could influence the incidence and severity of pruritus, with examples of these recipients being calcineurin inhibitors, cyclosporine, or tacrolimus.

Based on DLQI, there was a mild-to-moderate impact on the QoL in the HD group, while in the KT group pruritus had a mild effect on QoL ( $p < 0.001$ ). A study in Pakistan reported a DLQI score of  $9.8 \pm 1.7$  points in HD patients (moderately affected QoL). The study only included male subjects.<sup>19</sup> A study in South Korea reported higher means of DLQI score in HD patients with pruritus ( $10.4 \pm 6.46$  points).<sup>21</sup> No other studies have assessed QoL using DLQI in the KT population.

A positive correlation was found between hs-CRP and the 5-D itch scale in the HD group ( $r = 0.443$ ;  $p = 0.014$ ). This result is similar to that of a study in China and Cairo.<sup>13,14</sup> A study in China reported a significant relationship between hs-CRP and the severity of pruritus based on the 5-D itch scale. The hs-CRP of HD

**Table 4.** Correlation analysis of hs-CRP, calcium, phosphate, and e-GFR with 5-D itch score in hemodialysis and kidney transplant recipients (n = 60).

Variables	Hemodialysis (n = 30)		Kidney Transplant (n = 30)	
	R	p-value	R	p-value
hs-CRP (mg/L)	0.443	0.014	0.132	0.486
Calcium (mg/dl)	-0.016	0.932	-0.001	0.994
Phosphate (mg/dl)	0.232	0.218	0.114	0.550
e-GFR (ml/min/1.73 m <sup>2</sup> )	0.186	0.325	-0.424	0.020

Spearman's rho test, significant if  $p < 0.05$ , R: correlation coefficient.

e-GFR: estimated glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein, n: number of subjects.

patients with moderate-to-severe pruritus was significantly higher.<sup>13</sup> A study in Cairo reported a significant increase in hs-CRP in the HD group with pruritus compared to those without pruritus. High-sensitivity CRP positively correlated with the severity of pruritus both by measurement using the VAS ( $r = 0.34$ ;  $p < 0.001$ ) and the Pruritus Scoring System ( $r = 0.33$ ;  $p < 0.001$ ), indicates that on average KT recipients have a well-controlled inflammatory status, in the KT group there was a positive correlation between hs-CRP and the 5-D itch scale but it was statistically insignificant ( $r = 0.132$ ;  $p = 0.486$ ).<sup>14</sup> The role of inflammation in the KT group was less dominant in the severity of pruritus, with the means of hs-CRP levels in the KT group being lower compared to the HD group.

Microinflammation plays a role in the pathogenesis of pruritus. In CKD, there is an increase in pro-inflammatory cytokines, especially interleukin (IL)-6 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>22</sup> C-reactive protein, which is produced by liver cells in response to stimulation by IL-6 under inflammatory conditions, is closely related to IL-6.<sup>23</sup> Where it is seen that high CRP levels can reflect high IL-6 levels,<sup>23</sup> Hemodialysis patients have higher IL-6 than healthy patients up to 15-fold, especially those with pruritus,<sup>24</sup> with interleukin-6 playing a pivotal role in the differentiation of T helper (Th)-2 and Th-17 cells. Th-2 cell predominance causes an increase in cytokine, which is crucial in the pathogenesis of pruritus. These cytokines include IL-31, IL-4, IL-13, and IL-2. IL-31 cytokines can induce pruritus directly by binding to IL-31R $\alpha$  and Oncostatin M receptor (OSMR  $\beta$ ) on sensory neurons. Other cytokines (IL-4, IL-13, and IL-2) indirectly act as neuronal enhancers by activating other pruritus pathways.<sup>25</sup>

The results in the KT group showed a moderately negative correlation between e-GFR and the 5-D itch scale ( $r = -0.424$ ;  $p = 0.02$ ). Decreased kidney function results in inadequate excretion of toxic substances and metabolic waste products, leading to an accumulation and imbalance of biochemical factors that increase the severity of pruritus.<sup>26</sup> In nondialysis CKD patients, a decrease in e-GFR of 5 ml/minute/1.73 m<sup>2</sup> was associated with significantly

worsening pruritus ( $p < 0.01$ ).<sup>27</sup> A study in Turkey reported that e-GFR was associated with pruritus in both HD and KT recipients ( $p = 0.024$ ).<sup>20</sup> However, in the present study, there was no significant correlation between e-GFR, which is thought not to correlate with the severity of pruritus because in HD pruritus is more influenced by the adequacy of dialysis and the levels of various uremic toxin substances in the body as well as the severity of pruritus in this group. A study in Taiwan reported that low dialysis adequacy (Kt/V) and the usage of a low-flux dialyzer were significantly associated with severe pruritus. Reducing the severity of pruritus in hemodialysis patients, optimizing dialysis with a target Kt/V  $\geq 1.5$ , and using a high-flux dialyzer could increase the clearance of pruritogen molecules.<sup>28</sup> The results in the KT group also showed differences from studies in Italian and Polish populations, with these results reporting that there was no association between e-GFR and pruritus severity.<sup>8,10</sup>

Increased phosphate and calcium in the blood could trigger the formation of calcium-phosphate products deposited in the basal layer of the epidermis and other tissues. As a result, activation of local nerve fibers occurs and triggers pruritus, and, although we did not find a significant correlation between calcium and phosphate with pruritus, high calcium and phosphate were associated with the severity of pruritus.<sup>29</sup> This result was similar to the study in China. No significant relationship was found between calcium and phosphate and the severity of pruritus in HD patients ( $p = 0.485$  and  $0.227$ , respectively).<sup>13</sup> A study in Italy also reported no significant difference between calcium and phosphate, which are influenced by nutritional intake, supplementation, and malnutrition, in HD patients and KT with pruritus.<sup>8</sup> In this study, we found that calcium and phosphate did not correlate with the severity of pruritus because most subjects in both groups displayed well-controlled calcium and phosphate levels. **Table 5** summarizes the key findings from diverse studies.

Our study has several limitations as well. Data were collected over a period using a cross-sectional design; therefore we could

not determine the causal relationship between factors associated with pruritus in CKD. Immunosuppressant therapy to prevent organ rejection may affect the severity of pruritus in

KT recipients; however, we did not analyze other factors that could influence the severity of pruritus, for example, other uremic toxins and oxidative stress.

**Table 5.** Summary of Key Findings from Different Studies

Author (Year)	Type of Study	Participants	Key Findings
Schricker S, et al (2020) <sup>9</sup>	Cohort	- 132 KT patients - Male and female	- Mean pruritus VAS = 3.2 - A moderate correlation between the intensity of pruritus and transplant function ( $r = 0.3$ ; $p = 0.018$ )
Krajewski PK, et al (2020) <sup>10</sup>	Cohort	- 197 KT patients - Male and female	- 21.3% KT recipients had pruritus - The majority reported symptoms relieved after successful transplantation, the rest had residual itch. - WI-NRS itch was $5.98 \pm 2.17$ points - No significant correlation between hs-CRP, calcium, phosphate, and e-GFR levels with the severity of pruritus
Satti MZ, et al (2019) <sup>19</sup>	Cross-sectional	- 173 HD patients - Male only	- Prevalence of pruritus was 49.1% - Mean DLQI score $9.8 \pm 1.7$ points
Guvercin B, et al (2019) <sup>20</sup>	Cohort	- HD group (n = 30), PD group (n = 26), KT group (n = 30), CKD stage I-V group (n = 29), control (n = 30) - Male and female	- Pruritus inversely correlated with GFR, Hb, and albumin levels ( $p < 0.005$ ) - No differences in serum IL-31 and UGCG levels among study groups - Pruritus was highest in the dialysis group and less frequent in the KT group.
Noh SH, et al (2018) <sup>21</sup>	Cross-sectional	- 83 HD patients - Male and female	- Mean pruritus VAS score $6.17 \pm 2.62$ - Mean DLQI score $10.40 \pm 6.46$ (moderate to extreme large effect of QoL) found in 78.3% of subjects - Higher calcium levels were associated with pruritus
Zhao JH, et al (2021) <sup>13</sup>	Cross-sectional	- 148 HD patients - Male and female	- Incidence rate of pruritus 40.54% - Patients with pruritus had higher levels of iPTH, Hb, BUN, nPCR, and hs-CRP - A higher level of hs-CRP was associated with more severe pruritus (OR = 9.440; 95% CI = 3.547–25.124; $p < 0.01$ )
Sarhan II, et al (2020) <sup>14</sup>	Case-control	- 100 HD patients - Male and female	- Mean VAS $2.41 \pm 2.99$ points - Significant increase level of hs-CRP ( $p < 0.001$ ), phosphate ( $p < 0.05$ ), and bilirubin ( $p < 0.05$ ), in a pruritic group compared to non-pruritic group - Significant correlation between hs-CRP with intensity and severity of pruritus using VAS ( $r = 0.339$ and $0.325$ , respectively)
Panuccio V, et al (2017) <sup>8</sup>	Cohort	- KT group (n = 133), HD group (n = 29), control group (n = 62) - Male and female	- The prevalence of pruritus was 62% in HD patients and 32% in KT patients - No association was found between pruritus score and GFR

BUN: blood urea nitrogen, CKD: chronic kidney disease, GFR: glomerular filtration rate, Hb: hemoglobin, HD: hemodialysis, Hs-CRP: high-sensitivity C-reactive protein, IL-31: interleukin-31, iPTH: parathyroid hormone, KT: kidney transplant, nPCR: normalized protein catabolic rate, PD: peritoneal dialysis, UGCG: uridine diphosphate glucose ceramide glucosyltransferase, VAS: visual analog scale, WI-NRS: worst-itch numerical rating scale

## CONCLUSION

Hemodialysis patients are more prone to moderate-to-severe pruritus, whereas pruritus in KT recipients is mostly mild. In HD patients, itch had a mild-to-moderate influence on QoL, whereas in KT recipients, pruritus had a minor impact. There was a positive correlation between hs-CRP and pruritus in HD patients, and a negative correlation between e-GFR and pruritus in KT recipients.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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