

Comparative Analysis of Chronic Kidney Disease-Associated Pruritus: A Multi-Ethnic Study among Patients on Hemodialysis

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Abstract

To date, no study has compared the prevalence of chronic kidney disease-associated pruritus (CKD-aP) among patients on hemodialysis in Pakistan (a developing country with poor health resources) and Malaysia (a newly industrialized country with adequate health resources). The aim was to compare CKD-aP between Pakistani and Malaysian patients on hemodialysis and factors associated with CKD-aP. Pakistani patients were recruited from July 2016 to April 2017 from two tertiary hospitals in Peshawar and Rawalpindi. Whilst Malaysian patients were recruited from February to September 2017 from a tertiary hospital and its affiliated dialysis centers in Kuala Lumpur.

A total of 354 Pakistani and 334 Malaysian patients were recruited (response rate=100%). The CKD-aP prevalence was 74% and 61.3% in Pakistan and Malaysia, respectively. Pakistani patients had poorer PSQI and health-related quality of life (HRQOL) scores compared to Malaysian patients. The prevalence of CKD-aP and the PSQI score was slightly higher in Pakistan than in Malaysia. CKD-aP was significantly associated with PSQI score and HRQOL in both populations.

Keywords: Malaysia, Sleep, Hemodialysis, Quality of life, CKD-associated pruritus, Pakistan

INTRODUCTION

Among patients with hemodialysis, there is a common called Chronic kidney disease-associated pruritus (CKD-aP). The CKD-aP prevalence ranges from as low as 18% to as high as 97% [1]. CKD-aP can be mild or severe and affects a person's well-being and quality of life (QOL) [2, 3]. Studies have shown that the quality of sleep and sleep deprivation are affected by the severity of CKD-aP [2, 3].

Pakistan has been classified as a developing country and is the 6th most densely populated country and has limited health-related infrastructure as there is insufficient allocation of resources for health care [4]. Recent reports have suggested that the prevalence of CKD in Pakistan can be as high as 12.5% [5]. To date, there is a paucity of studies to improve outcomes among patients with CKD [4].

Malaysia has recently been recognized as a newly industrialized economy; a socioeconomic classification applied to countries whose economic status is not as good as developed countries but has outpaced their developing counterparts [6]. As a former Commonwealth nation, the health sector in Malaysia has benefitted from procedural guidelines outlined by the British, and patient-driven outcomes are well-practiced in Malaysia [7]. In Malaysia, the exact estimation of CKD is unknown. However, the

prevalence of CKD in West Malaysia was reported to be 9.0% [8], and the prevalence of CKD stages 1 to 5 were 4.1%, 2.0%, 2.2%, 0.2%, and 0.3%, respectively [8]. Approximately 90% of patients with end-stage renal failure (ESRD) refer to hemodialysis centers, where they are accepted for treatment. However, despite all the advances in medical care, the prevalence of CKD-aP was reported to be 64.2% [9].

To date, no study has compared the CKD-aP prevalence among patients on hemodialysis between Pakistan (a country with limited medical resources) and Malaysia (a country with adequate health resources). Therefore, this study aimed to perform a comparative analysis of CKD-aP between

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Pakistani and Malaysian patients on hemodialysis and to determine the factors associated with CKD-aP.

MATERIALS AND METHODS

This cross-sectional study was performed in Pakistan and Malaysia. Pakistani patients were recruited from July 2016 to April 2017, from two tertiary-care hospitals in Peshawar and Rawalpindi as mentioned previously [10]; whilst Malaysian patients were recruited from February 2017 to September 2017, from a tertiary hospital and its affiliated dialysis centers in Kuala Lumpur [11].

Instruments used

- **Baseline demographic questionnaire**

To collect demographic data from patients, a baseline demographic questionnaire was used. This questionnaire was prepared in Urdu and Malay.

- **The 5D-itch scale (5D-IS)**

The validated Urdu 5D-itch scale [12] and Malay 5D-itch scale [13] were used to assess CKD-aP.

- **The Pittsburgh sleep quality index (PSQI)**

The validated Urdu PSQI [14] and Malay PSQI [15] tools were used to measure self-rated sleep quality over the past month. PSQI <5 categorized were as good sleepers and scores ≥5 was categorized as bad sleepers [16].

- **Functional Assessment for non-life-threatening Conditions (FANLTC) tool**

To measure HRQOL, the Urdu [17] and Malay [18] FANLTC tool was used. The FANLTC has 26 items with four domains:

functional well-being, emotional well-being, social/family well-being, and physical well-being, and responses were rated on a 4-point Likert scale. For positively stated items, the said response categories yielded scores of 4, 3, 2, 1, and 0, respectively. The scores were reversed for negatively stated items. Then, the sum of items was multiplied by the number of items in the domain and divided by the number of items answered; which gave the domain score. The domain scores were added to derive the overall HRQOL score. A higher score indicates better HRQOL.

Statistical Analysis

Using SPSS v.20.0, a comparative analysis of data was carried out (SPSS Inc., Chicago, IL). Categorical variables were presented as frequency and number. Continuous variables were presented as interquartile and median ranges. The association between CKD-aP and sleep and QOL was only assessed in those with CKD-aP. Associations between categorical variables were analyzed by using chi-square tests, whereas associations between continuous variables were assessed using Spearman’s rho. Using the Mann–Whitney U-test, associations between continuous and categorical variables were measured.

RESULTS AND DISCUSSION

A total of 354/354 Pakistani and 334/334 Malaysian patients were included in this study (response rate=100%). The demographic characteristics of patients included are shown in **Table 1**. The flow-on how patients were recruited (**Figure 1**). Pakistani patients with pruritus were significantly younger than Malaysian patients (42 years versus 58 years, $p < 0.001$).

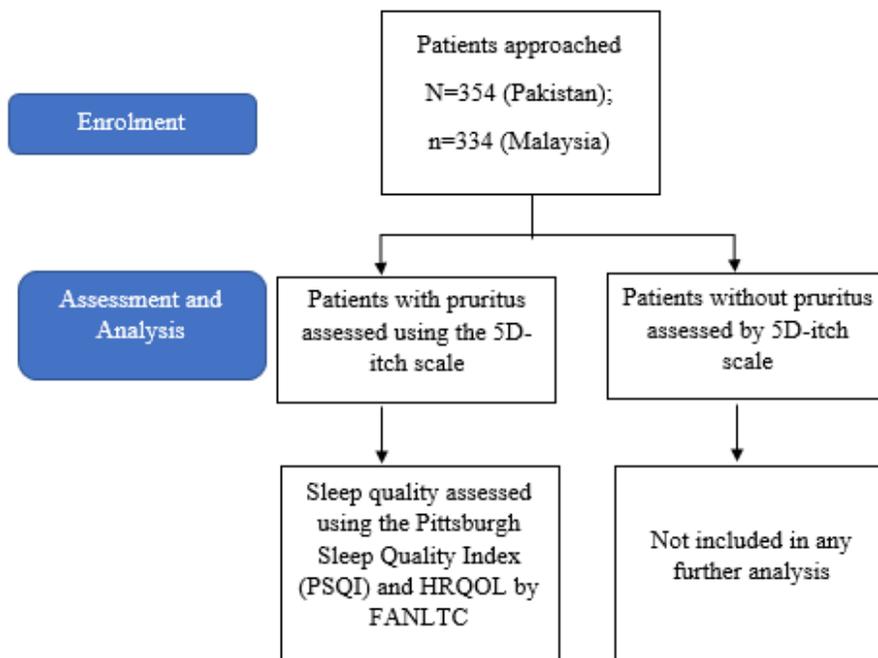


Figure 1. The flow of how patients were recruited

The CKD duration and duration of being on hemodialysis were also significantly shorter in Pakistani patients when compared to Malaysian patients in **Table 1**. All Pakistani patients (100%) received hemodialysis twice/week, while the

majority (99.4%) of Malaysian patients received hemodialysis three times/week. Hypertension, diabetes mellitus, and hyperlipidemia were the most common comorbidities found in CKD patients that have pruritus.

Table 1. Demographic characteristics of patients in Pakistan and Malaysia undergoing hemodialysis

	Pakistani patients (n=354)	Malaysian patients (n=334)	Difference between Pakistani and Malaysian patients with pruritus
	Total no. of Pakistani patients (n=354) N (%)	Total no. of Malaysian patients (n=334) N (%)	p-value
Gender			
Male	234 (66.1)	199 (59.6)	0.033 a
Female	120 (33.9)	135 (40.4)	
Median age [IQR] in years	42.0 [34.0-50.0]	58.0[47.8-68.0]	<0.001 c
Median duration of CKD [IQR] in months	36.0 [12.0-48.0]	48.0 [24.0-108.0]	<0.001 c
Median duration on hemodialysis [IQR] in months	24.0 [12.0-36.0]	48.00 [24.0-84.0]	<0.001 c
Frequency of hemodialysis			
Twice a week	354 (100)	2 (0.6)	<0.001 a
Three times a week	0	332 (99.4)	
Presence of co-morbidities **			
Cardiovascular diseases	7	6	
Diabetes mellitus	47	110	
Goiter	-	5	
Gout	-	7	
Hyperlipidemia	25	40	
Hypertension	215	170	

a: Chi-square test; **b:** Fisher exact test; **c:** Mann-Whitney U test; *p<0.05; **Abbreviations:** IQR: interquartile range. ** (Diabetes mellitus, hypertension, hyperlipidemia) were the most common comorbidities observed in a current cohort of patients. Figures were >100% as patients may be suffering from more than one chronic condition.

Prevalence and characteristics of CKD-aP

CKD-aP was 74% (262/354) and 61.3% (205/334) in Pakistan and Malaysia, respectively. The overall 5D-IS median score was significantly higher in Pakistani patients than Malaysian patients (10.0 [8.0-12.0] vs. 8.0 [6.0-9.0] p<0.001). Significant differences were found between Pakistani and Malaysian patients in all domains of the 5D-IS except for the “distribution bin score” (**Table 2**).

Sleep disturbance due to CKD-aP

The overall PSQI median score [IQR] was significantly higher in Pakistan 8.0 [7.0-10.0] when compared to Malaysian patients 6.0 [5.0-9.0], p<0.001). This difference was seen for all domains of the PSQI, indicating that Pakistani patients had poorer sleep quality when compared to Malaysian patients (**Table 3**).

Table 2. Responses obtained from Pakistani and Malaysian patients regarding CKD-associated pruritus

Domain	Statement	Responses	Pakistan (n=262)	Malaysia (n=205)	Difference between Pakistani and Malaysian patients with pruritus
			N (%)	N (%)	p-value
		Median [IQR]	1.0 [1.0-2.0]	1.0 [1.0-1.0]	
Duration	During the last 2 weeks, how many hours a day have you been itching?	<6 hours/day	169 (64.5)	182 (88.1)	<0.001 a
		6-12 hours/day	58 (22.1)	17 (8.3)	
		12-18 hours/day	27 (10.3)	1 (0.5)	
		18-23 hours/day	3 (1.1)	1 (0.5)	
		All day	5 (1.9)	4 (2.0)	

Degree	Please rate the intensity of your itching over the past 2 weeks	Median [IQR]	2.0[2.0-3.0]	2.0[1.0-2.0]	<0.001 a
		Not present	31 (11.8)	53 (25.9)	
		Mild	140 (53.4)	130 (63.4)	
		Moderate	70 (26.7)	16 (7.8)	
		Severe	15 (5.7)	6 (2.9)	
		Unbearable	6 (2.3)	0	
Direction	Over the past 2 weeks has your itching gotten better or worse compared to the previous month?	Median [IQR]	2.0[1.0-3.0]	1.0[1.0-2.0]	<0.001 a
		Completely resolved	106 (40.5)	133 (64.9)	
		Much better but still present	75 (28.6)	61 (29.8)	
		A little bit better but still present	70 (26.7)	7 (3.4)	
		Unchanged	9 (3.4)	3 (1.5)	
		Getting worse	2 (0.8)	1 (0.5)	
Disability: Sleep	Rate the impact of your itching on the following activities over the last 2 weeks	Median [IQR]	3.0[2.0-3.0]	2.0[1.0-2.0]	<0.001 a
		Never affects sleep	49 (18.7)	78 (38.0)	
		Occasionally delays falling asleep	81 (30.9)	100 (48.8)	
		Frequently delays falling asleep	76 (29)	20 (9.8)	
		Delays falling asleep and occasionally wakes me up at night	33 (12.6)	5 (2.4)	
		Delays falling asleep and frequently wakes me up at night	23 (8.8)	2 (1.0)	

Domain	Statement	Responses	Pakistan (n=262)	Malaysia (n=205)	Difference between Pakistani and Malaysian patients with pruritus
			N (%)	N (%)	p-value
Disability: Leisure/Social	Rate the impact of your itching on the following activities over the last 2 weeks	Median [IQR]	1.0[1.0-3.0]	1.0[1.0-1.0]	<0.001 a
		Never affect activity	141 (53.8)	159 (77.6)	
		Rarely affects activity	46 (17.6)	24 (11.7)	
		Occasionally affects activity	49 (18.7)	9 (4.4)	
		Frequently affects activity	24 (9.2)	6 (2.9)	
		Always affects activity	2 (0.8)	7 (3.4)	
Disability: Housework/Errands	Rate the impact of your itching on the following activities over the last 2 weeks	Median [IQR]	1.0[1.0-2.0]	1.0[1.0-1.0]	<0.001 a
		Never affect activity	147 (56.1)	161 (78.5)	
		Rarely affects activity	52 (19.8)	22 (10.7)	
		Occasionally affects activity	45 (17.2)	11 (5.4)	
		Frequently affects activity	12 (4.6)	7 (3.4)	
		Always affects activity	6 (2.3)	4 (2.0)	
Disability: Work/School	Rate the impact of your itching on the following activities over the last 2 weeks	Median [IQR]	1.0[1.0-2.0]	1.0[1.0-1.0]	<0.001 a
		Never affect activity	175 (66.8)	178 (86.8)	
		Rarely affects activity	38 (14.5)	14 (6.8)	
		Occasionally affects activity	35 (13.4)	6 (2.9)	
		Frequently affects activity	12(4.6)	3 (1.5)	
		Always affects activity	2 (0.8)	4 (2.0)	
Distribution bin score	Mark whether itching has been present	Median [IQR]	2.0[1.0-2.0]	1.0[1.0-1.0]	0.706 a
		Score bin 1	130 (49.6)	106 (51.7)	
		Score bin 2	104 (39.7)	85 (41.5)	

	in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically	Score bin 3	21 (8)	10 (4.9)	
		Score bin 4	2 (0.8)	1 (0.5)	
		Score bin 5	5 (1.9)	3 (1.5)	
		Median [IQR]	10.0[8.0-12.0]	8.0[6.0-9.0]	<0.001 b
Total score of 5D itch scale	Ranged from 5-25	5-10 (Mild pruritus)	136 (52.0)	117 (86.3)	
		11-19 (Moderate pruritus)	125 (47.7)	26 (12.7)	<0.001 a
		20-25 (severe pruritus)	1 (0.3)	2 (1.0)	

a: Chi-square test; b: Mann-Whitney U test; *p<0.05; **Abbreviations:** IQR: interquartile range.

Table 3. Responses obtained from Pakistani and Malaysian patients regarding sleep quality

Domains	Responses	Pakistan (n=262) N (%)	Malaysia (n=205) N (%)	Difference between Pakistani and Malaysian patients with pruritus having disturbed sleep p-value
Sleep duration	> 7 hours	41 (15.6)	24 (11.7)	<0.001 a
	6-7 hours	54 (20.6)	88 (42.9)	
	5-6 hours	135 (51.5)	47 (22.9)	
	<5 hours	32 (12.2)	46 (22.4)	
Sleep disturbances	0	2 (0.8)	23 (11.2)	<0.001 a
	1	185 (70.6)	168 (82.0)	
	2	67 (25.6)	14 (6.8)	
	3	8 (3.1)	0 (0)	
sleep latency	0	19 (7.3)	24 (11.7)	0.243a
	1	131 (50.0)	107 (52.2)	
	2	80 (30.5)	50 (24.4)	
	3	32 (12.2)	24 (11.7)	
Daytime dysfunction	0	27 (10.3)	49 (23.9)	<0.001 a
	1	177 (67.6)	144 (70.2)	
	2	46 (17.6)	10 (4.9)	
	3	12 (4.6)	2 (1.0)	
Sleep efficiency	>85%	121 (46.2)	85 (41.5)	0.438 a
	75-84%	76 (29.0)	71 (34.6)	
	65-74%	38 (14.5)	33 (16.1)	
	<65%	27 (10.3)	16 (7.8)	
Sleep quality	Very good	13 (5.0)	7 (3.4)	<0.001 a
	Fairly good	98 (37.4)	134 (65.4)	
	Fairly bad	131 (50.0)	57 (27.8)	
	Very bad	20 (7.6)	7 (3.4)	
Sleep medication	Not during the past month	216 (82.4)	202 (98.5)	<0.001 a
	Less than once a week	27 (10.3)	1 (0.5)	

	<i>Once or twice a week</i>	5 (1.9)	1 (0.5)	
	<i>Three or more times a week</i>	14 (5.3)	1 (0.5)	
Global PSQI score	Median [IQR]	8.0 [7.0-10.0]	6.0 [5.0-9.0]	<0.001 b

a: Chi-square test; b: Mann-Whitney U test; *p<0.05; **Abbreviations:** IQR: interquartile range.

Quality of life of patients with CKD-aP

The overall HRQOL score was significantly lower in Pakistani patients compared to Malaysian patients (p<0.001)

(**Table 4**). Pakistani patients reported HRQOL scores in the physical and emotional well-being domains, but higher HRQOL scores in the social/family wellbeing when compared to Malaysian patients (**Table 4**).

Table 4. Health-related quality of life scores of Pakistani and Malaysian patients undergoing hemodialysis

FANLTC scale	Pakistan n=262	Malaysia n=205	Mann Whitney U test to determine the difference between Pakistani and Malaysian patients
<i>Physical well-being</i>	17.0 [13.0-21.0]	19.0 [15.0-22.0]	<0.001*
<i>Social/family well-being</i>	16.0 [13.0-19.2]	11.0 [8.0-15.0]	<0.001*
<i>Emotional well-being</i>	11.0 [8.0-13.0]	13.0 [11.0-14.5]	<0.001*
<i>Functional well-being</i>	14.0 [10.0-17.0]	13.0 [9.0-16.0]	0.531
Total HRQOL score	52.0 [43.0-58.0]	55.0 [50.0-62.0]	<0.001*

Mann-Whitney test was used. *Statistical significance p <0.05. Values presented in Median [IQR].

A longer duration of CKD and the age of patients were associated with CKD-aP in Pakistani patients [10]. However, no factors were found to be correlated with CKD-aP in Malaysian patients [11]. The pruritus intensity was significantly associated with poorer sleep quality and HRQOL among both population patients [17, 18].

The prevalence of CKD-aP, pruritus score, and severity of pruritus were higher in Pakistan than in Malaysia. PSQI and HRQOL scores were also found to be worse in Pakistan when compared to Malaysia. The severity of pruritus was significantly associated with poorer sleep quality [10, 11] and HRQOL [17, 18] among both population patients. A longer duration of CKD and the age of patients were associated with CKD-aP in Pakistani patients [10]. However, no correlation between any of the factors and CKD-aP in Malaysian patients [11].

The prevalence of CKD-aP was slightly higher in Pakistani patients (74%) when compared to Malaysian patients (63.1%). Our findings are aligned with other studies in Pakistan, which reported rates of 64.0% to 77.7% [12], and in Malaysia, which reported rates of 58.6% to 64.2% [11]. The pruritus median score was also significantly higher in Pakistani 10.0 [8.0-12.0] compared to Malaysian patients 8.0 [6.0-9.0]; p<0.001. In our study, we discovered that longer CKD duration and the age-associated with CKD-aP in Pakistani patients [10]. However, no correlation between any of the factors and CKD-aP in Malaysian patients [11]. Previous studies reported a significant association between serum levels of parathyroid hormone (PTH) [11], blood urea nitrogen (BUN) [11], CKD duration; hyperphosphatemia [11, 19], serum calcium, and being on dialysis (more than 2 years) [20]; while other studies found no association of CKD-aP

with PTH and serum P levels [21], and also the age of patients [19]. The possible reasons for the variation in the prevalence of CKD-associated pruritus between Pakistani and Malaysian data may be because patients in Pakistan receive hemodialysis twice/week, whilst in Malaysia, it is three times/week. Additionally, low to medium flux dialyzers were used in Pakistan, whilst high flux dialyzers (which remove average-sized molecules more effectively – thus reducing the severity of uremic pruritus) were used in Malaysia. CKD-aP is believed to be caused by middle-molecule uremic toxins which are not dialyzed properly when using low flux dialyzer [19]. Worldwide, high-flux hemodialysis is the most commonly-used blood purification method. However, in Pakistan low-flux dialysis is mainly used and hemodialysis centers are also limited in Pakistan as in 2009 there were only 175 hemodialysis centers [22]. Patients have limited access to treatment as out of the available dialysis centers 10-15% are non-functional [22].

Pakistani patients were significantly younger than Malaysian patients, and had a shorter median duration of CKD and being on hemodialysis. This may be due to poorer management of chronic conditions (such as diabetes mellitus or hypertension) which predisposes an individual to renal damage in younger individuals. Additionally, the knowledge about chronic conditions and their complications is lower in Pakistani patients and therefore may not have known to take any preventive measures i.e., control of hypertension and dietary modifications [23]. One study found that Malaysian participants had higher knowledge levels regarding diabetes and hypertension [24, 25], which was, however, quite different for the Pakistani population [26, 27]. Moreover, awareness and attitude also play a decisive role in the actions of patients with diabetes and hypertension. Furthermore, in

Pakistan, multiple factors may account for poorer dialysis outcomes; such as anemia, malnutrition, late referral, and lacking qualified nephrologists at the centers for dialysis [28].

In our study, the overall PSQI score was significantly different between Pakistan (8.0) and Malaysia (6.0), which may be because 52.0% of Pakistani patients versus 86.3% of Malaysian patients reported “mild” pruritus. Moreover, hemodialysis patients having moderate to the extreme intensity of CKD-aP suffer from nocturnal awakenings and difficulty falling asleep [29].

The quality of patients’ life and the medical outcomes can be adversely affected by CKD-aP [2, 3]. Pruritus was associated with poorer HRQOL in both Pakistani and Malaysian patients [17, 18]. This was similar to previous studies, which found that 54% of patients on hemodialysis with CKD-aP in the UK had CKD-aP that affected their life quality [30]. Other studies found that social function, emotion, and symptoms were affected by CKD-aP [31]. Moreover, the lack of clinical practice guidelines (CPG) in Pakistan directly translates to a lack of procedures facilitating timely referrals for specialist support. The finding is opposite to that of Malaysia where physicians are equipped with CPG [32] thereby making them comfortable with the cutoff limit for a referral from where take-up of the case by the specialist leads to a well-preserved prognosis. Nevertheless, Malaysia being NIC has definite advantages to build up a system, which is absent in the case of Pakistan.

To the best of our knowledge, there has been no study comparing the prevalence of chronic kidney disease CKD-aP among patients on hemodialysis between Pakistan and Malaysia. However, a limitation of our study was that findings are not generalizable because only two centers from Malaysia and Pakistan provided the data. Future research should focus on pharmacological or non-pharmacological interventions to develop CKD-aP management.

CONCLUSION

The CKD-aP prevalence was slightly higher in Pakistan in comparison with Malaysia. Similarly, the pruritus score and PSQI score were also higher in the Pakistani population. However, the HRQOL for social and mental wellbeing was improved in the Malaysian population as compared to the Pakistani population. Furthermore; a statistically significant association between CKD-aP and PSQI score, as well as CKD-aP and HRQOL life, was observed among both populations.

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Informed consent was obtained from all individual participants included in the study.

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