Health-related Quality of Life Among Patients With Chronic Kidney Disease of Unknown Etiology (CKDu) of an Agricultural Community in Kebithigollawa, Sri Lanka

Vindika Suriyakumara (vsuriyakumara@yahoo.com)
Ministry of Health and Indigenous Medical Services, Sri Lanka
Thilina Anuradha Samarathunga
Institute of Ayurveda and Alternative Medicine, Sri Lanka
Dhanuja Gunaratne
Institute of Ayurveda and Alternative Medicine, Sri Lanka
Chaminda Karunarathne
General Sir John Kotelawala Defence University
Raveena Gajanayaka
Institute of Ayurveda and Alternative Medicine, Sri Lanka
Nishantha Kumarasinghe
Faculty of Medicine, Department of Anatomy, General Sir John Kotelawala Defence University, Sri Lanka
https://orcid.org/0000-0002-3230-9120

Research

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Abstract

BACKGROUND – The significant increase in the burden of chronic kidney disease of unknown etiology (CKDu) of Sri Lanka has led to evaluate the factors related to physical, social and mental aspects of health related quality of life (HRQOL) in CKDu patients.

METHOD – The quality of life of 84 CKDu patients (stages 1-5) were assessed by means of the Kidney Disease Quality of Life Short-Form survey (KDQOL™-36) Version 1.3 along with biomarkers and patient demographics. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula. Patients were divided into four groups according to their eGFR; group A with eGFR range 90-60 ml/min/1.73 m^2, group B with eGFR range 30–59 ml/min/1.73m^2, group C with eGFR range 15–29 ml/min/1.73m^2 and group D with eGFR<15 ml/min/1.73m^2.

RESULTS – The KDQOL™-36 scores impaired substantially across all stages of CKDu and comparatively lower scores were present in latter stages of the disease than the initial stages. The mental composite summary (MCS) scores were more impaired when compared to physical composite summary (PCS) scores during the early stage of disease. Poor KDQOL™-36 scores were present in males than in females. A significant variance in scores was not observed between the gender and younger (<65 years) and elderly (≥65 years) populations. Biochemical parameters showed a statistically significant correlation with majority of KDQOL™-36 dimensions while interestingly urine albumin to creatinine ratio did not.

CONCLUSION - Our findings reveals that CKDu patients in any stage of the disease despite their age and gender have a significant physical and mental health burden, and this burden is alarmingly increased among patients as the disease worsens. Thereby, early assessment of health related quality of life will help to identify high risk patients and modifying these factors may provide better active and a healthy lifestyle.

Introduction

Sri Lanka has a population of approximately 20 million with agriculture as the major economic force in the nation [1]. Over the past decades non-communicable diseases have become a major health burden advancing to a leading cause of premature deaths in the country. Since the early 1990s an epidemic of chronic kidney disease (CKD) has been reported clustering in the rural agricultural communities of Sri Lanka, characterized by the absence of identified conditions which cause chronic renal disease. This new condition has been coined the term *chronic kidney disease of unknown etiology* (CKDu). It is a slowly progressive disease most likely to occur in the second decade of life, and asymptomatic until advanced with late-onset peripheral oedema and hypertension [1–3]. Geographical distribution of CKDu in Sri Lanka is observed more commonly in the North Central Province (NCP) with prevalence between 4–21%, mainly in Medawachchiya, Girandurukotte, Kebithigollawa, Padaviya, Medirigiriya, Dehiattakandiya and Nikawewa populated with farming communities of low socioeconomic status who rely heavily on agrochemicals [1, 4–7]. Moreover, 11 districts in the country, Anuradhapura, Polonnaruwa, Kurunegala, Ampara, Trincomalee, Badulla, Mullaitivu, Vavuniya, Matale, Monaragala, Hambanthota have been identified as ‘at risk’ for the occurrence of CKDu at present [8].

A majority of the disease manifests in lower income male agricultural workers aged 30 to 60 years with more than 10 years of work experience in the agricultural sector. Furthermore, patients with a family history of CKDu have also been considered as at risk of developing the disease [7]. As this disease mainly affects the males in their second decade of life, the progressive impairment in renal function along with decreased quality of life (QOL) impacts the sufferers by reducing their earning potential. Subsequently it causes a loss in productivity, economic status and inability to support their families. For Sri Lanka as a developing nation with agriculture as its driving force of economy would result in a negative impact on the national income with fewer productive workers and lower agricultural productivity.

With the increase in disease burden, it is a growing need to understand patients' perception of their well-being and patient-reported outcomes (PROs). This might aid clinicians to portray the patients' state of living better than the biochemical parameters [9, 10]. World Health Organization (WHO) defines QOL as "the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [11]. The patients' psychological adaptation to the disease is strongly influenced by the QOL, thus a low QOL can adversely impact the course of the disease. Thereby, attempts to modify patients' attitudes related to the disease and coping strategies might cause cognitive and behavioral changes leading to a positive impact on the QOL of the patient [12]. Patients with end stage renal disease (ESRD) are particularly at high risk for impaired QOL. Thereby, studying the extent to which factors related to physical, social and mental aspects of health related quality of life (HRQOL) affect in CKDu patients is crucial in recognizing risk and protective factors that can be exploited in programs aiming to improve QOL [13–16]. Moreover, lifestyle interventions especially in primary care are a cost-effective way to improve QOL compared to standard interventions [17].

A limited number of studies have evaluated the association between HRQOL in different stages of CKD [9, 13, 16, 18–20], including fewer studies done in Sri Lanka on CKD/CKDu patients [21, 22]. CKDu has been perceived a disease of high prevalence with trends of increasing prevalence. Yet, there is a limited data in the country which allows for accurate estimation of the disease burden and management [8]. Therefore, early assessment of the components affecting HRQOL in patients could lead to a better overall outcome of CKDu in the country. The objective of this study was to assess HRQOL using the Kidney Disease Quality of Life Short-Form survey (KDQOL™-36) Version 1.3 [23], of patients with different stages of CKDu in a rural farming community of an endemic region and to assess the relationship of HRQOL with commonly used biomarkers at primary care setting.

Materials And Methods

Study Setting

A descriptive cross-sectional study was carried out at the CKD clinic conducted by Kebithigollewa Ayurvedic Community Health Centre for a duration of 6 months, from February 2019 to August 2019. Patients currently on conventional medicine were included for the study (patients who were present for their first visit to the clinic and who have not taken any native treatments). Patient's whose main place of residence for the past 6 months in the Anuradhapura district was recruited for the study. Informed written consent was taken prior to

the data collection. A total of randomly selected 134 patients were interviewed during this period. Patients who are ≥ 18 and ≤ 80, pregnant females, and individuals with psychiatric disorders, or cognitive dysfunction were excluded from the study. All known causes of CKD including diabetes mellitus, long standing hypertension, glomerulonephritis, persistent albuminuria and having a past history of snake bite and leptospirosis were excluded from the study. A total of 93 CKDu patients were confirmed by inspecting the medical records or taking their clinical history by clinicians according to the Health Ministry guidelines [8].

QOL was assessed by means of the KDQOL™-36, a tool for assessment of HRQOL from the RAND Corporation [23]. Sinhala language is the most prominent spoken language in the region; hence the culturally adapted and validated KDQOL™-36 Sinhala version was employed in the present study [24]. However, from the 93 CKDu patients only 84 patients completed the KDQOL-36™ questionnaire.

Sample collection

Blood and urine samples were collected from CKDu patients by a trained phlebotomist to analyze serum creatinine and urine albumin markers respectively. A 3 ml venous blood sample was collected to plain tubes under universal precautions. The serum was separated by using bench-top centrifuge at rpm 3200 for five minutes and serum was stored in 1.5 ml Eppendorf tubes and transported to laboratory at 4˚C.

The samples were analyzed using the TECOM TC-220 fully automated blood analyzer by a qualified laboratory technician. A 5–10 ml of urine was collected from the patients into clean urine containers and sealed and stored in temperature lower than 4˚C. Patients were instructed to collect the mid-stream urine samples with minimum contamination. Samples were analyzed using MALB-KIT and QR-100 specific protein analyzer by a qualified laboratory technician.

The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula [25]. Patients were divided into four groups according to their eGFR; group A (stage 1–2) with eGFR range 90 – 60 ml/min/1.73 m^2 (n = 9), group B (stage 3) with eGFR range 30–59 ml/min/1.73 m2 (n = 36), group C (stage 4) with eGFR range 15–29 ml/min/1.73 m2 (n = 26) and group D (stage 5) with eGFR < 15 ml/min/ 1.73 m2 (n = 13) [13]. KDQOL-36™ scale is the most preferentially used tool for routine measurements of HRQOL among patients with chronic kidney disease [26]. The KDQOL-36™ is comprised of 2 components; kidney disease specific component and the SF-36. It contains 19 domains with total 81 questions; in which 43 questions assess 11 kidney disease specific components of QOL and the SF-36 questionnaire which assess the generic measure of HRQOL in 8 domains. The 11 domains of kidney disease specific components include, symptoms and problems of kidney disease (SPKD) (12 items), effects of kidney disease (EKD) (8 items), burden of kidney disease (BKD) (4 items), cognitive function (3 items), quality of social interaction (3 items), sexual function (2 items), sleep (4 items), social support (2 items), work status (2 items), patient satisfaction (1 item), and dialysis staff encouragement (2 items). The SF-36 includes 36 items; physical function (PF) (10 items), role limitations caused by physical problems (RP) (4 items), role limitations caused by emotional problems (RE) (3 items), pain (BP) (2 items), general health perceptions (GH) (5 items), social function (SF) (2 items), mental health/emotional well-being (MH) (5

items), and energy/fatigue (VT) (4 items). The PF, RP, BP and GH dimensions are generally summarized into physical component summary (PCS) and the VT, SF, MH and RE dimensions are summarized to mental component summary (MCS). The final item, the overall health rate item, asks the respondents to rate their health on a 0–10 response scale. Different answer options are available for different questions ranging from two to seven, and each question is scored in a scale ranging from 0 (worst health) to 100 (best health). Finally, all items in a domain are summed up and averaged to give a mean score for each domain which ranges from 0 to 100 [23].

Statistical Analysis

The collected data obtained using the KDQOL™-36 are presented as mean and standard deviation. Statistical analysis was performed using IBM SPSS statistics software version 21. ANOVA was used to determine if there were statistical differences in KDQOL™-36 baseline scores across the CKDu stages and gender. Independent t-test was used to compare mean KDQOL™-36 scores related to categorized correlates. Pearson's correlation test was employed to compare the relationship between biochemical parameters and KDQOL™-36 scores. Statistical significance was set at $P < 0.05$, and all tests performed were two-tailed.

Results

The demographic and biochemical parameters of patients are presented in (Table 1). Out of the 84 patients who participated in the study 57 were male and 27 were female. The mean age of the patients was 57.56 ± 10.90 years. The mean age of males was 58.37 ± 9.79 and females had a mean age of 55.85 ± 12.98. The average eGFR value was 33.88 ± 18.41 ml/min/1.73 m^2 and majority of the patients diagnosed were stage 3 (42.9%). Biomarkers including eGFR, serum creatinine (S.Cr), and urine albumin (U.Alb) showed significant difference ($P \leq 0.05$) across the CKDu stages.

Table 1
Baseline demographic and biochemical parameters of patients

Parameter	Group A (n = 9) Stages 1 and 2	Group B (n = 36) Stage 3	Group C (n = 26) Stage 4	Group D (n = 13) Stage 5	p value
Age	51.89 ± 5.06	57.19 ± 11.19	57.92 ± 11.96	61.77 ± 9.91	0.22
Male	8	22	15	12	-
Female	1	14	11	1	-
S.Cr (mg/dL)	1.16 ± 0.13	1.69 ± 0.35	3.06 ± 0.79	5.70 ± 1.06	**0.00**
eGFR (ml/min/1.73 m^2)	69.19 ± 7.42	42.49 ± 7.78	21.32 ± 4.67	10.70 ± 2.17	**0.00**
Urine Creatinine (U.Cr) (mg/dL)	40.78 ± 19.53	75.37 ± 62.81	55.30 ± 27.41	82.64 ± 41.02	0.11
U. Alb (mg/L)	52.92 ± 25.46	82.87 ± 51.15	104.09 ± 70.93	180.82 ± 87.46	**0.00**
U. Alb/Cr ratio mg/g	153.76 ± 105.60	179.44 ± 143.22	205.03 ± 127.06	242.2 ± 120.42	0.42

In the study population none of the patients were under dialysis treatment, therefore the dialysis specific components of KDQOL™-36 were excluded. As shown in (Table 2), the KDQOL™-36 scores of all dimensions impaired significantly ($P \leq 0.05$) across the CKDu stages, although a progressive impairment wasn't observed in "*quality of social interaction*", "*role limitations – emotional*", and *"emotional well-being"*. Lower scores could be seen in CKDu groups C and D compared to groups A and B. However, the KDQOL™-36 scores in "*role limitations—emotional"* of group A (33.33 ± 0.00) was lower than groups B (49.07 ± 20.30) and C (41.03 ± 25.49). Among all four groups, comparatively lowest impairment was observed in the "*social support"* component whereas a higher impairment was observed in the "*general health"* component.

Table 2
KDQOL™-36 dimensions scores in different stages of CKDu

KDQOL™-36 dimensions	Group A Stage 1 and 2	Group B Stage 3	Group C Stage 4	Group D Stage 5	p value
Kidney disease specific components					
Symptom/problem list	97.73 ± 0.00	88.57 ± 11.78	53.32 ± 18.06	41.26 ± 15.73	**0.00**
Effects of kidney disease	93.75 ± 0.00	92.36 ± 4.12	74.64 ± 13.03	66.11 ± 11.11	**0.00**
Burden of kidney disease	68.75 ± 0.00	68.75 ± 15.16	30.05 ± 21.43	13.94 ± 14.47	**0.00**
Work status	100.00 ± 0.00	52.78 ± 49.20	9.62 ± 20.10	7.69 ± 27.73	**0.00**
Cognitive function	86.67 ± 0.00	85.56 ± 9.49	62.56 ± 12.38	52.82 ± 10.35	**0.00**
Quality of social interaction	73.33 ± 0.00	65.92 ± 7.26	55.38 ± 3.14	56.40 ± 5.85	**0.00**
Sexual function	100.00 ± 0.00	89.39 ± 12.15	63.19 ± 22.88	60.43 ± 21.30	**0.00**
Sleep	65.00 ± 0.00	64.93 ± 3.76	54.52 ± 5.34	52.69 ± 4.39	**0.00**
Social support	100.00 ± 0.00	99.07 ± 3.87	82.05 ± 14.08	66.67 ± 13.61	**0.00**
Physical component summary					
Physical functioning	95.00 ± 0.00	60.14 ± 29.96	20.38 ± 8.36	18.08 ± 19.42	**0.00**
Role limitations–physical	100.00 ± 0.00	66.67 ± 31.05	21.15 ± 25.19	11.54 ± 29.95	**0.00**
Pain	77.50 ± 0.00	67.92 ± 11.66	35.10 ± 14.53	23.84 ± 14.63	**0.00**
General health	55.00 ± 0.00	51.39 ± 7.89	30.58 ± 11.25	17.31 ± 9.27	**0.00**
Mental component summary					
Emotional well-being	56.00 ± 0.00	59.11 ± 4.70	44.77 ± 14.88	28.92 ± 11.56	**0.00**
Role limitations–emotional	33.33 ± 0.00	49.07 ± 20.30	41.03 ± 25.49	30.77 ± 21.35	**0.01**

KDQOL™-36 dimensions	Group A Stage 1 and 2	Group B Stage 3	Group C Stage 4	Group D Stage 5	p value
Social function	62.50 ± 0.00	59.72 ± 9.02	54.33 ± 16.18	43.27 ± 10.96	**0.00**
Energy/fatigue	50.00 ± 0.00	46.25 ± 6.25	36.54 ± 9.46	33.84 ± 8.20	**0.00**
Overall health	70.00 ± 0.00	56.67 ± 10.14	37.31 ± 6.67	30.77 ± 10.38	**0.00**

Apart from "*role limitations- emotional health"* scale, eGFR and S.Cr showed strong positive and negative correlations ($P < 0.05$) across the KDQOL™-36 scales respectively **(**Table 3**).** A negative correlation was observed between U.Cr, U.Alb, U. Alb/Cr ratio (ACR) and the HRQOL scores of KDQOL™-36. A strong correlation ($P < 0.05$) was seen in U.Alb and S.Cr between most of the KDQOL™-36 dimensions. However, a substantial correlation wasn't observed with ACR and the KDQOL™-36 dimensions.

Table 3
Correlation between parameters and KDQOL™-36 dimensions

KDQOL™-36 dimensions	Pearson correlation	Age	S.Cr	eGFR	U.Cr	U.Alb	U. Alb/Cr ratio
Kidney disease specific components							
Symptom/problem list	Correlation coefficient	-0.11	-0.91	0.84	-0.17	-0.34	-0.19
	p value	0.31	**0.00**	**0.00**	0.14	**0.00**	0.10
Effects of kidney disease	Correlation coefficient	-0.05	-0.83	0.76	-0.18	-0.35	-0.20
	p value	0.66	**0.00**	**0.00**	0.12	**0.00**	0.09
Burden of kidney disease	Correlation coefficient	-0.08	-0.70	0.65	-0.28	-0.39	-0.15
	p value	0.48	**0.00**	**0.00**	**0.01**	**0.00**	0.18
Work status	Correlation coefficient	-0.15	-0.76	0.67	-0.09	-0.20	-0.10
	p value	0.18	**0.00**	**0.00**	0.45	0.08	0.39
Cognitive function	Correlation coefficient	-0.10	-0.70	0.65	-0.28	-0.40	-0.16
	p value	0.38	**0.00**	**0.00**	**0.02**	**0.00**	0.16
Quality of social interaction	Correlation coefficient	-0.17	-0.82	0.73	-0.06	-0.24	-0.18
	p value	0.13	**0.00**	**0.00**	0.61	**0.04**	0.12
Sexual function	Correlation coefficient	0.01	-0.74	0.66	-0.14	-0.25	-0.12
	p value	0.91	**0.00**	**0.00**	0.26	**0.04**	0.34
Sleep	Correlation coefficient	-0.05	-0.62	0.58	-0.18	-0.31	-0.16
	p value	0.64	**0.00**	**0.00**	0.11	**0.01**	0.16
Social support	Correlation coefficient	-0.18	-0.83	0.74	-0.24	-0.41	-0.19
	p value	0.10	**0.00**	**0.00**	**0.04**	**0.00**	0.09
Physical component summary							
Physical functioning	Correlation coefficient	-0.05	-0.91	0.83	-0.22	-0.36	-0.16

KDQOL™-36 dimensions	Pearson correlation	Age	S.Cr	eGFR	U.Cr	U.Alb	U. Alb/Cr ratio
	p value	0.67	**0.00**	**0.00**	0.06	**0.00**	0.16
Role limitations–physical	Correlation Coefficient	-0.02	-0.85	0.75	-0.17	-0.32	-0.17
	p value	0.87	**0.00**	**0.00**	0.14	**0.00**	0.14
Pain	Correlation coefficient	-0.12	-0.94	0.87	-0.24	-0.40	-0.19
	p value	0.29	**0.00**	**0.00**	**0.04**	**0.00**	0.10
General health	Correlation coefficient	-0.13	-0.87	0.81	-0.29	-0.42	-0.17
	p value	0.23	**0.00**	**0.00**	**0.01**	**0.00**	0.14
Mental component summary							
Emotional well-being	Correlation coefficient	-0.14	-0.59	0.54	-0.24	-0.37	-0.16
	p value	0.22	**0.00**	**0.00**	**0.04**	**0.00**	0.17
Role limitations-emotional	Correlation coefficient	0.19	-0.14	0.10	-0.18	-0.16	-0.01
	p value	0.08	0.19	0.37	0.11	0.18	0.97
Social Function	Correlation coefficient	0.12	-0.38	0.38	-0.16	-0.29	-0.15
	p value	0.28	**0.00**	**0.00**	0.16	**0.01**	0.18
Energy/Fatigue	Correlation coefficient	-0.10	-0.75	0.63	-0.10	-0.26	-0.16
	p value	0.35	**0.00**	**0.00**	0.39	**0.02**	0.17
Overall health	Correlation coefficient	-0.11	-0.95	0.86	-0.22	-0.39	-0.19
	p value	0.34	**0.00**	**0.00**	0.06	**0.00**	0.11

The association between categorized correlates (eGFR, age, gender) and KDQOL™-36 dimensions are shown in (Table 4). All the KDQOL™-36 dimensions were substantially impaired ($P < 0.05$) between stages 4 & 5 (eGFR < 30 ml/min/1.73 m2) and stages 2 & 3 (eGFR ≥ 30 ml/min/1.73 m2). However, within the age category (≥ 65 and < 65) there wasn't any significant difference observed among the KDQOL™-36 dimensions. Females presented higher mean scores for all KDQOL™-36 scales than males. A significant difference between "*social support*" and "*MCS*" scores could be seen among each gender ($P < 0.05$).

Table 4
Categorized correlates and composite summary scores

KDQOL™-36 dimensions	eGFR (ml/min/1.73 m^2)		p value	Age (years)		p value	Gender		p value
	≥ 30	< 30	-	≥ 65	< 65	-	M	F	-
No. of patients	45	39	-	23	61	-	57	27	-
Kidney disease specific components									
Symptom/problem list	90.41 ± 11.14	49.65 ± 17.90	**0.00**	64.92 ± 26.44	73.95 ± 24.36	0.30	68.50 ± 26.46	77.78 ± 21.08	0.14
Effects of kidney disease	92.64 ± 3.72	71.80 ± 12.93	**0.00**	81.25 ± 14.53	83.61 ± 13.72	0.41	80.98 ± 15.08	87.15 ± 10.00	0.13
Burden of kidney disease	68.75 ± 13.52	24.68 ± 20.68	**0.00**	41.30 ± 29.12	50.92 ± 27.29	0.28	45.39 ± 29.71	54.40 ± 23.18	0.18
Work status	62.22 ± 47.86	8.97 ± 22.57	**0.00**	30.43 ± 47.05	40.16 ± 46.39	0.36	34.21 ± 46.44	44.44 ± 46.68	0.32
Cognitive function	85.78 ± 8.48	59.31 ± 12.50	**0.00**	69.27 ± 17.14	75.08 ± 16.68	0.21	71.70 ± 17.83	77.28 ± 14.35	0.12
Quality of social interaction	67.41 ± 7.14	55.72 ± 4.19	**0.00**	59.99 ± 8.53	62.73 ± 8.20	0.11	61.60 ± 8.33	63.21 ± 8.34	0.30
Sexual function	91.67 ± 11.60	65.50 ± 22.36	**0.00**	78.57 ± 23.73	82.78 ± 19.95	0.65	80.05 ± 19.62	86.25 ± 22.91	0.17
Sleep	64.94 ± 3.35	53.91 ± 5.06	**0.00**	58.48 ± 7.06	60.33 ± 6.90	0.33	59.21 ± 7.28	61.11 ± 6.14	0.24
Social support	99.26 ± 3.47	76.92 ± 15.58	**0.00**	84.78 ± 15.82	90.44 ± 15.35	0.10	86.26 ± 16.99	94.44 ± 10.34	**0.03**
Physical component summary (PCS)	65.60 ± 18.00	23.77 ± 14.88	**0.00**	42.31 ± 25.66	47.64 ± 27.17	0.55	42.95 ± 27.74	52.99 ± 23.46	0.07
Mental component summary (MCS)	52.92 ± 4.86	40.85 ± 12.59	**0.00**	46.96 ± 11.53	47.07 ± 10.94	0.71	45.15 ± 11.87	51.88 ± 7.30	**0.04**
Overall health	59.33 ± 10.53	35.13 ± 8.54	**0.00**	45.22 ± 15.04	49.18 ± 15.63	0.28	46.32 ± 15.99	51.85 ± 13.88	0.08

Discussion

The present study assessed prospectively the HRQOL in 84 CKDu patients residing in Kebithigollawa, a high prevalent region of CKDu in NCP of Sri Lanka [27, 28]. Amongst the study population identified for CKDu, the male prevalence was found to be almost twice than that of the female (male – 67.9%, female – 32.1%). Similar ratios were present in which the preponderance of the disease was 19.9% in males and 10.5% in females in the same district (Anuradhapura), according to the study done by the Epidemiology Unit of Ministry of Health, Sri Lanka and the WHO. The study also showed that the prevalence of suspected CKDu in the Anuradhapura district is of 13.3% with a decreasing trend in eGFR of the farming communities [8].

Significant constraints and restrictions on CKDu patients may possibly have an impaired psychosocial and physical well-being throughout the disease course. QOL is an independent risk factor for mortality and morbidity in CKD patients particularly in ESRD [18]. With disease progression complications including malnutrition, anemia, cognitive dysfunction, decreased physical and sexual functioning and co-morbidities including diabetes and cardiovascular disease (CVD) are associated with impaired QOL [13].

A clear decrement in the KDQOL^{TM}-36 sub scales is evident in the present study, implying reduced QOL across all stages of CKDu (Table 2), and the findings are consistent with previous studies conducted with CKD/CKDu patients [9, 13, 18–22]. Interestingly, *"MCS"* scores were found to be much lower compared to *"PCS"* scores in the early stage of the disease (group A). However, the mean scores of "*kidney disease specific components", "PCS"* and "*MCS"* in stages 4 and 5 were relatively impaired from stages 1–2 and 3, (Table 2). Hence raising an alarm on the complications particular to advanced stages which may associate with the rate of disease progression, and also indicating the need of addressing those issues for better QOL of CKDu patients. The worst results were registered in the "*general health"* scale of the physical health component and similar findings were demonstrated in the study done by Fructuoso et al., (2011) [20].

In accordance with the lower scores associated with mental health from early stages and worsening towards the end stages, our findings suggests that apparently patients in all stages of CKDu experience a significant perceptible mental health burden (Table 2). As evident from previous studies psychosocial factors on behavioral compliance were influenced as patients undergo numerous restrictions in their diet, fluid intake and lifestyle [29]. Furthermore, depressive symptoms in patients with chronic kidney disease are most likely to be associated with an increased risk of ESRD progression, dialysis initiation, hospitalization and mortality [30]. In a recent study done in Girandurukotte, Sri Lanka, a rural, endemic region for CKDu, the authors had argued that the *"MCS"* scores in CKDu patients are relatively preserved despite the worsening of *"PCS"* scores. However, our findings suggest the contrary. In the present study *"MCS"* scores were more impaired when compared to *"PCS"* scores during the early stages of CKDu. Nevertheless, towards advanced stages the rate of deterioration of *"MCS"* scores was comparatively lower than the *"PCS"* scores (Table 2). Thereby, the psychological adaptation of the sick person to the chronic illness during the disease course with a declining repercussion of the disease on the mental health could be an explanation to the above findings [20]. Moreover, the lower scores in *"role limitations—emotional"* of stages 1 & 2 than stages 3 & 4 could be due to the lack of adaptability to the disease during the initial stages.

Moreover, depression, anxiety, suicide and delirium are common mental complications observed in patients with renal failure [31]. Thereby, adapting to stress management interventions including life style changes and relaxation techniques for a better mode of life with the disabilities could improve the QOL [32].

Despite the age and gender, *"SPKD"* scores were significantly affected towards advanced stages of CKDu implying a major symptom burden in the latter stages of the disease (Table 2, 4). Patients undergo a barrage of symptoms including fatigue and pain which are contributing factors for reduced QOL even at the early disease stages (Table 2). Our findings are in accordance with previous studies on symptom burden of CKD/CKDu patients, where they demonstrated that excessive tiredness, sleep disturbance and pain in the bones or joints were reported more commonly among patients not requiring renal replacement therapy [21, 22, 33]. Moreover, in the study done to assess the symptom burden of patients with renal disease in the Anuradhapura district, the authors suggested that the high symptom burden of CKDu patients could be attributed to the low socio-economic conditions in the Anuradhapura district [34]. Thus, emphasis should be given to include measures on relieving symptoms associated with CKDu as a part of disease management for a better QOL.

Physical functioning has a major impact on majority of QOL aspects [35]. In the present study *"work status"* and *"physical function"* were highly affected with a substantial impairment progressing from stage 3 to stage 5 from a score of 52.78 ± 49.20 to 7.69 ± 27.73 and 60.14 ± 29.96 to 18.08 ± 19.42 respectively (Table 2). This phenomenon portrays that famers find it challenging to engage in work even from the early stages of CKDu and will eventually be unfit for employment. This leads to a decline in earning potential and inability to sufficiently provide for their families placing an economic burden on their families.

With disease progression protein energy wasting (PEW) is a common state encountered for CKD patients caused due to hyper-metabolism, uremic toxins, and inflammation. Complications associated with PEW could be significant risk factors for weakness, low quality of life, hospitalization and mortality. Creatinine and serum albumin are considered to be some of the diagnosing or modifiable bio chemical markers associated with PEW and thereby, this condition is preventable or treatable [36].

In the current patient population a significant correlation could be observed between S. Cr and U. Alb with "*physical functioning"*, and S. Cr with *"work status"* (Table 3). This association and the heavy labor of the farmers may indicate an increased risk in mortality and complications associated with PEW with disease progression. However, the findings of Allen and team demonstrated that serum creatinine was independently associated with the *"PCS*" scores [37], and this could be due to the variation in sample. Nevertheless in the systematic review done by Spiegel and colleagues, they concluded that nutritional biomarkers including creatinine and albumin had a strong correlation with the physical domains of the HRQOL in ESRD patients [38]. Therefore, it is essential to maintain the nutritional parameters and physical performance emphasizing on physical rehabilitation for an overall wellbeing of patients [39].

Males displayed overall poor HRQOL scores than the females with significant difference in *"social support"* and *"MCS"* scales (Table 4). Our findings are consistent with the study done by Senanayake et al., (2020) in Anuradhapura district, Sri Lanka where males displayed poor HRQOL than females [21]. However, majority of studies indicate that males have better CKD related health outcomes than the females [9, 13, 40]. A possible

reason for this could be due to the current study cohort residing in an agricultural setting in the North Central Province, mainly composed of male farmers with low socioeconomic status [8, 21, 22]. Since majority of the males are the breadwinner of the family they tend to work even with the disease and the physical and mental stress could accelerate the disease progression. Furthermore, literature demonstrates that stress may more directly impact HRQOL in men than females [41, 32]. This could be a partial explanation to the lower health outcomes displayed from the males compared with the females in our study.

In the present study *"sleep"* had substantially impaired scores among patients in ESRD as well as early stages of CKDu. Sleep deprivation have a profound impact on overall health and QOL of patients with kidney disease signifying morbidity and mortality burden which could be due to both physical and mental components associated with sleep [42]. Disorders including obstructive sleep apnea (OSA) are common among ESRD patients and can be improved or reversed by nasal continuous positive airway pressure (nCPAP) and slow nocturnal dialysis [43]. However, none of the patients in our study were under dialysis treatment. Therefore, evaluation on the symptoms of sleep disturbances during a clinical encounter and other remedial interventions in advance would improve QOL in patients.

A less impaired *"social support"* profile could be due to the Sri Lankan culture and hospitality, revealing CKDu patients in our study population has the ability to maintain strong family and social bonds to a favorable extent. However, impairment of *"social interaction"* and *"social function"* could be seen from the early stages of the disease **(**Table 2**)**. The patient's attitudes and interaction with the family members, certain personality traits such as extraversion and neuroticism and also affectionate social support could be a partial justification for this occurrence [44, 45]. Therefore, attention should be given when planning interventions to improve patient health outcomes.

Strong correlations observed in S.Cr, eGFR, and U.Alb with a majority of the KDQOL™-36 dimensions clearly indicate the impairments of biological parameters towards disease progression that affect adversely with QOL **(**Table 3**).** This could be useful in predicting the QOL of CKDu patients. The study done by Hallan et al., (2009) demonstrated that albuminuria correlates with the risk of adverse outcomes and progression to ESRD independently of eGFR, signifying albumin to be a good marker for QOL [46]. In the current study ACR did not present a significant correlation with the KDQOL™-36 scales. A similar observation could be seen in the research done by Peng et al., (2017) where they examined clinical features and HRQOL in Chinese patients with stage 3 CKD [47]. Accordingly since majority of the patients in our study are in stage 3, ACR might not be a good marker to assess QOL in early stages of disease. Moreover, since creatinine and albumin are routinely used biomarkers in CKDu screening and follow up, it should be noteworthy that creatinine levels have a strong correlation with muscle mass and therefore would mis-classify individuals, especially the farmers who are involved in extensive muscle labor [26, 48]

In the present study age correlated negatively with the KDQOL™-36 dimensions except *"sexual function", "role limitations-emotional"* and *"social function"*, however a substantial correlation wasn't observed **(**Table 3**).** Whereas previous studies on CKD demonstrate that age has a significant impact on disease burden [9, 13, 20], a significant variance in KDQOL™-36 scores wasn't observed between the younger and older populations **(**Table 4**)**. Thereby, portraying that through the course of the disease, CKDu patients in every age category

experience a substantial disease burden. Hence, giving a priority on clinimetrics to minimize the symptom burden by integrating symptom assessment into clinical management could be a way out to address the issue of reduced QOL from earlier stages of CKDu [33].

Overall, the *"SPKD"*, *"EKD"*, *"BKD"*, mental and physical components of KDQOL™-36 were significantly impaired and in general it follows the pattern of impairment observed in previous studies on CKD patients [9, 13, 18–22]. The poor HRQOL in the earlier stages might be a contributing factor for the rate of progression to the ESRD. Therefore, it is important to identify these high risk patients to consider treatment for CKDu from early stages as a patient centered approach rather than the disease alone to modify these factors may lead to active and healthy life. Considering the occupation of these patients, they find it challenging to work, leading to reduced earning potential and a mental burden. However, given the fact that CKDu is non-curable and worsened with disease progression, patients feel no further relief can be obtained by conventional treatment. Therefore, they tend to go for other native treatments as some of them have claimed to cure or control the disease. Hence, it is important to implement accurate palliative care, hospice, and nephrology services to enhance QOL in patients affected with CKDu in a developing nation like Sri Lanka. Moreover, predicting the QOL need to be further assed with a larger cohort studies considering other associated factors and with other novel bio markers discovered recently including Asymmetric Dimethylarginine (ADMA), Symmetric Dimethylarginine (SDMA), Uromodulin, Kidney Injury Molecule-1 (KIM-1), Neutrophil Gelatinase-Associated Lipocalin (NGAL) and other proteomic and metabolomic biomarkers [49].

Conclusion

Our findings highlight that CKDu patients in any stage of the disease despite their age and gender have a significant physical and mental health burden, and this burden is alarmingly high in advanced stages. Therefore, it is crucial to monitor the patient's QOL with standard tools regularly and directing for relevant medical subspecialties and social support groups other than their routine medical treatment for renal failure alone.

Nutritional biomarkers including albumin and creatinine impact both physical and mental domains of the KDQOL™-36 in CKDu patients. These markers are potentially modifiable and could also be mediated with both pharmacologic and non-pharmacologic therapies. Furthermore, QOL among each stage of the disease and prediction of QOL using S.Cr, eGFR and U.Alb should be further assessed with a larger cohort, since these variations could be attributed to differences in socioeconomic and education status, management approaches between the countries, and sample size between studies.

Limitations Of The Study

Study participants were relatively old with a mean age of 57.56 ± 10.90 years, and it is unclear whether our findings can be extrapolated to young, as this disease is observed from 30–60 years of age. Therefore, it would be interesting to compare these results with a relatively younger sample in the future.

We did not investigate a range of other potential determinants of HRQOL including educational background, current employment status, occupation, family income status and disease duration, as well as biomarkers

including anemia markers which are demonstrated to be predictors of worsened QOL.

Since Sri Lanka is a multicultural, multi linguistic and multi religious country with varying education levels, our cohort may also not be fully representative of QOL of CKDu in Sri Lanka as a whole. Therefore, further larger community-based studies reflecting a variety of parameters including age, educational background and geographical groups would be worth paying attention to in the future.

Abbreviations

Asymmetric Dimethyl arginine (ADMA), Burden of kidney disease (BKD), Chronic kidney disease (CKD), Chronic kidney disease of unknown etiology (CKDu), Effects of kidney disease (EKD), End stage renal disease (ESRD), Energy/fatigue (VT), Estimated glomerular filtration rate (eGFR), General health perceptions (GH), Health related quality of life (HRQOL), Kidney Disease Quality of Life Short-Form survey (KDQOL™-36), Mental component summary (MCS), Mental health/emotional well-being (MH), Modification of Diet in Renal Disease (MDRD), Neutrophil Gelatinase-Associated Lipocalin (NGAL). North Central Province (NCP), pain (BP), Physical component summary (PCS), physical function (PF), protein energy wasting (PEW), quality of life (QOL), role limitations caused by emotional problems (RE), role limitations caused by physical problems (RP), serum creatinine (S.Cr), social function (SF), Symmetric Dimethylarginine (SDMA), symptoms and problems of kidney disease (SPKD), Urine albumin to creatinine ratio (ACR), urine albumin (U.Alb), Kidney Injury Molecule-1 (KIM-1), World Health Organization (WHO)

Declarations

Ethics approval and consent to participate

The ethical approval was obtained from Institute of Biology, Sri Lanka where the analysis of patient results was given approval. The consent forms were given to patients involved in the study where they signed reading to all conditions of the research. The patients had the right to leave the study at any time willingly if they needed to.

Consent for publication

All the personal involved in the research gave their consent and agreed upon publishing this article with no conflicts of interest.

Availability of data and material

The dataset is available only to the research team of CKDu-Care unit, Institute of Ayurveda and Alternative Medicine (IAAM), Sri Lanka, and will not be publicly available since this is an ongoing research and it is necessary to maintain confidentiality and privacy of patients as this disease is associated with high social stigma.

Competing Interests

None of the researchers have relationships with organizations that have interest over the manuscript data available.

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Authors Contribution

V.S. and N.K. designed the study and N.K. supervised the project. R.G. and D.G. conducted patient interviews and designed the database. T.S. analyzed and interpreted the data. C.K. and T.S. performed the lab analysis. V.S., T.S., R.G. and D.G. wrote the manuscript. N.K. edited the final manuscript. All authors discussed the results and implications and commented on the manuscript at all stages.

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