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Evaluation and comparison of quality of life and its related factors in pre-dialysis and hemodialysis patients

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ABSTRACT

Introduction: Chronic kidney disease (CKD) in advanced stages leads to some changes in lifestyle, health status, and personal functioning and consequently affects the patients' quality of life.

Objectives: Given the high prevalence of CKD in the country, this study aimed to determine quality of life and its related factors in this group of patients. Since there has been low focus on quality of life in pre-dialysis stage, this study compared the two groups of pre-dialysis and hemodialysis patients regarding quality of life.

Patients and Methods: This descriptive analytical research was conducted as a cross-sectional study. Using convenience sampling method, we selected a total of 60 kidney failure patients in pre-dialysis stage that referred to nephrology clinics in Semnan and 60 hemodialysis patients who referred to the dialysis center of Kosar hospital in Semnan. Using SF-36 questionnaire and a demographic form, the required data was collected via interviews.

Results: The results showed that the majority of patients had a moderate quality of life. Concerning demographic variables, quality of life had a significant relationship with age, gender, marital status, number of children, employment status, education level, income level, hemoglobin, underlying disease, duration of disease, and duration of dialysis. Moreover, patients in pre-dialysis stage had a better score than hemodialysis patients regarding the overall quality of life ($P \leq 0.05$).

Conclusion: This study showed, a design a framework for care services provided by medical staffs and supports provided by insurance organizations and other institutions is necessary. The framework must help to improve quality of life of patients and prevent the deterioration of quality of life in advanced stages of the disease.

Original

Implication for health policy/practice/research/medical education:
CKD has high prevalence and quality of life and its related factors are important issues in this group of patients. Since there has been low focus on quality of life in pre-dialysis stage, this study compared the two groups of pre-dialysis and hemodialysis patients in regarding quality of life. It is necessary to design a framework for care services provided by medical staffs and supports provided by insurance organizations and other institutions.

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Introduction

Chronic kidney disease (CKD) is a threat to public health throughout the world and its prevalence is increasing, especially in adults aged 60 years and older (1,2). It is estimated that more than 10% of adult population in the United States, that includes twenty million people of the total population of the US, are affected by CKD (3). In Iran there is no exact statistical data on the number of CKD patients. However, based on a national report in 2004, the incidence of CKD among the total population of the country is 700 000 and every year more than 2% of Iran's population is added as well (4,5). Patients with CKD are affected by varying degrees of the disease (zero to five) that are measured based on the level of glomerular filtration rate (GFR) declinE (6). The clinical and laboratory signs are highlighted in stage 3 and 4

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patients. In addition, stage 5 patients usually have obvious complications in daily activities, health, nutritional status, and homeostasis of water and electrolytes. Such patients finally develop uremic syndrome that leads to death if remains untreated (7). Dialysis and kidney transplant are renal replacement therapies that are applied for patients with end-stage renal disease. These methods can improve the patient's health status and protect their lives. However in advanced stages of the disease the patients are faced with many physical, psychological, and social problems (1,8-10). Clinical complications such as muscle cramps, nausea, vomiting, dizziness, anorexia, anemia, shortness of breath, sleep disturbances, fatigue, as well as dependence to others, decreased self-esteem, and loneliness are among the physical and psychological complications which reduce the patients' quality of life (8,11). Hence, today the medical care services are aimed not only to increase the life time of CKD patients but also to improve quality of life of the patients. Thus, the promotion of quality of life has become one of the main goals of the medical community and has attracted their attention (9).

According to the World Health Organization (WHO), quality of life is defined as an individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations and standards and concerns (12). According to the views of experts, quality of life is a feeling of wellbeing that is rooted in satisfaction or dissatisfaction with various important aspects of an individual's life. A sense of security, personal beliefs, emotional conflicts, objectives, and level of failures tolerance altogether determine an individual's perceptions of oneself. In fact, when someone feels happy and satisfied with its own life and does not feel discomfort at the time of illness, he/she will have more energy to take care of its own health. When a person is good in self-care, he/she will live healthier and therefore will have a better quality of life (13,14).

Studies have shown that poor quality of life is a factor effective in the development of cardiovascular diseases, recurrent hospitalizations, and mortality of the patients)15(. Evaluation of quality of life in these patients is an important criterion for determining the effectiveness of health care services that can help to plan medical and supportive care services and would be utilized as an appropriate approach to reduce the adverse effects of the disease (16). Therefore, evaluating the quality of life of patients with CKD and determining its different stages is of great importance. Several studies have investigated and determined the quality of life and its related factors in CKD patients and their results suggested low levels of quality of life, as compared with the healthy subjects (10,17,18). According to the results of these studies, among the important factors associated with quality of life we may note age, gender, occupation, marital status, income level, concurrent disease, education level, hemoglobin level, duration of dialysis therapy, and stage of CKD (8,10,19,20). However, there are conflicting results about the relationship between these factors and the levels of quality of life. For instance, some of the studies have reported that factors such as gender, being single, and low level of education are among the factors adversely affecting quality of life. However, such a finding is not consistent with the results of similar studies in other regions (21-23).

Objectives

So far, previously conducted studies have paid little attention to quality of life of patients in pre-dialysis stage. In addition, the relationship between the potential factors and quality of life of patients with CKD might have been affected by different geographical and cultural factors and types of instruments used. The present study aimed to investigate quality of life of patients with CKD in Semnan through using SF-36 questionnaire at different stages of disease (pre-dialysis, hemodialysis stage). It was also aimed to identify potential risk factors affecting quality of life of these patients to provide an appropriate ground for improving quality of life of this group of patients.

Patients and Methods

Study population and research design

This descriptive analytical study was conducted on pre-dialysis patients with CKD who referred to nephrology clinics and hemodialysis patients who referred to dialysis center of Kosar hospital in Semnan from September 2015, to March 2016. Convenience sampling method was used to select the patients in pre-dialysis stage. In addition, in order to randomly select the hemodialysis patients, we used the list of all dialysis patients who referred to Kosar hospital. The selected patients met the laboratory and clinical requirements and conditions to be allocated to one of the two groups of pre-dialysis and hemodialysis. Moreover, patients with a history of mental illness, cancer, and other severe and limiting diseases were excluded.

The eligible patients who met the inclusion criteria were informed about the goals of the study. After obtaining informed consent, the questionnaire was completed by an interview at the time of patient's admission to the clinic or dialysis center. To enroll pre-dialysis patients into the study, the list of these patients and their files were reviewed by the researcher and their records at the clinic were extracted. Some of the patients had an appointment to visit the clinic during the period of study. At the time of their visits to the clinic, the questionnaire was completed via face to face interview. However, some other patients have no appointments. They were called by phone and were invited to visit the researcher where patients desired or were more convenient for them (clinic or hospital). To collect the required data from dialysis patients, the researcher visited the dialysis center and obtained the necessary data. The questionnaire was completed for all the patients via interviews.

A researcher-made questionnaire was used to collect demographic data as well as medical profile. The questionnaire included items to collect data on demographic characteristics including gender, age, Blood type, underlying diseases, marital status, number of children, residence status, employment status, education level, duration of disease (for pre-dialysis patients), duration of dialysis (for dialysis patients), hemoglobin level, and income level. To evaluate quality of life of the studied patients we used SF36 questionnaire. This questionnaire includes 36 questions to assess the quality of life in eight domains including the followings; general health (6 items), physical functioning (10 items), role limitations due to physical health (4 items), role limitations due to emotional problems (2 items), social functioning (2 items), vital force and energy (4), bodily pain (2 items), and mental health of people (5 questions). All questions have a Likert type scale ranging from zero to five (where zero indicates the worst and five indicates the best possible state for every individual). Total scores of questions range from zero to 100. Based on the responses of the patients, their quality of life was classified as "good" (between the 75th percentile and higher), "somewhat favorable" or "moderate" (between 25th and 75th percentile), and "bad" (less than 25th percentile). The validity and reliability of this questionnaire had already been proved by various studies. In the present study, the validity of the tool was proved based on the results of other similar studies and comments by the experts. In addition, in order to test the reliability of the tool, it was run on 20 students and the Cronbach's alpha was measured (α = 0.83).

Ethical issues

The research followed the tenets of the Declaration of Helsinki. Informed consents were obtained from all patients. The study was approved by the Social Determinants of Health Research Center, Semnan University of Medical Sciences (#A-10-23-2). This paper is extracted from general practitioner thesis of Sajad Hasani, in the Department of Internal Medicine, Semnan University of Medical Sciences (Ref. No: 496).

Statistical analysis

To analyze the data, first, the collected data were entered into SPSS version 20 software. Descriptive statistics were used to describe the data. On the other hand, the relationship between the variables was studied using analytical statistics including Kolmogorov–Smirnov test (to determine normality), parametric tests including *t* test, analysis of variance (ANOVA), non-parametric test including Mann-Whitney test and Kruskal Wallis test. The significance level was set at 5%.

Results

A total of 120 patients, including 60 patients at pre-dialysis stage and 60 dialysis patients were studied. Of all the patients in both groups, 62 persons (51.7%) were male and the rest were female (n = 58, 48.3%). Among all the age group, the highest frequency of patients (n = 44, 36.7%) was observed in the age group 60 years and the lowest frequency of patients (n = 5, 4.2%) was observed in the age group 29 years and younger. Of all, 91 patients (75.8%) were married. The most frequent number of children was "three children and less" which was reported by 68 patients (56.7%). Of all the patients, 102 patients (85%) were employed. Primary education was the most frequent education level (n = 39, 32.5%) among all the patients. The majority of patients (n = 93, 77.5%) had poor or very poor income level, while 96 persons (80%) were living in urban areas and the rest (n = 24, 20%) were living in rural areas. Hemoglobin level lower than 11 was the most prevalent level of hemoglobin among the studied patients (n = 64, 53.3%). The maximum duration of the disease was more than 60 months (n = 50, 41.7%). Hypertension (n = 78, 65%) and diabetes (n = 62, 51.7%), respectively, were the most prevalent underlying diseases reported by the studied patients. The blood types O (n = 43, 36.1%) and blood type B (n = 38, 31.9%) were the most prevalent Blood types. Among dialysis patients, 40 patients (66.6%) were on dialysis for three years or less, while 14 patients (23.4%) were on dialysis for 4 to 9 years, and only 6 patients (10%) were on dialysis for 10 years and more. According to the results of our evaluation, the demographic and medical characteristics including age, gender, marital status, number of children, employment status, education level, income, place of residence, hemoglobin level, duration of illness, and Blood types were not significantly different ($P > 0.05$). Tables 1 and 2 present the distribution of demographic and medical characteristics of the studied patients by pre-dialysis and hemodialysis groups.

Mean (SD) total score of quality of life of all patients was 68.78 ± 13.39. Among all the dimensions of quality of life, the highest score was related to emotional role functioning (100 points). The two domains of general health (58 ± 17.15) in pre-dialysis patients and physical functioning (47.25 ± 24.41) in dialysis patients had the lowest scores. Pre-dialysis patients, as compared with dialysis patients, had significantly higher mean (SD) scores in the domains of total quality of life, physical functioning, social functioning, energy/fatigue, bodily pain, and general health ($P < 0.05$). However, there was no significant difference between the two groups regarding physical role functioning, emotional role functioning, and mental health ($P > 0.05$). Table 3 presents mean and standard deviation of scores obtained for total quality of life and its different domains in the two groups of pre-dialysis and dialysis patients.

We evaluated the relationship between total quality of life and the factors affecting it. The results of evaluation in pre-dialysis patients showed that several factors including age, marital status, employment status, education level,

Table 1. Distribution of demographic characteristics of patients in the two groups of pre-dialysis and hemodialysis

Variables		Pre-dialysis patients, n=60	Hemodialysis patients, n=60	P value
Age	≥ 29	0	5 (8.3%)	0.521
	30-39	9 (15%)	8 (13.3%)	
	40-49	14 (23.3%)	12 (20%)	
	50-59	15 (25%)	13 (21.7%)	
	≥ 60	22 (36.7%)	22 (36.7%)	
Being male		28 (46.7%)	34 (56.7%)	
Marital status	Single	3 (5%)	8 (13.3%)	0.652
	Married	49 (81.7%)	42 (70%)	
	Widowed	8 (13.3%)	10 (16.7%)	
Number of children	3 ≥	43 (6/71%)	40 (7/66%)	
	3 <	17 (4/28%)	20 (8/28%)	
Employment		11 (18.3%)	7 (11.7%)	0.711
Education level	Illiterate	9 (15%)	8 (13.3%)	0.541
	Primary school	18 (30%)	21 (35%)	
	High school diploma	26 (4/43%)	27 (45%)	
	Academic	7 (11.7%)	4 (6.7%)	
Income rate (Toman)	<500 thousand (very poor)	0	2 (3.3%)	0.241
	500 thousand – 1 million (poor)	44 (73.3%)	47 (78.3%)	
	1 million – 1.5 million (moderate)	16 (26.7%)	11 (18.3%)	
	> 1.5 million (good)	0	0	
Living in urban areas		43 (71.7%)	53 (88.3%)	0.340

Table 2. Distribution of medical characteristics in the two groups of pre-dialysis and dialysis patients

Variables	Pre-dialysis patients, n=60	Hemodialysis patients, n=60	*P* value
Hemoglobin level			
<11	26 (43.3%)	38 (63.3%)	0.130
≥11	34 (56.3%)	22 (7/36%)	
Duration of disease			
<12 months	13 (21.7%)	9(15%)	0.214
13–48 months	24 (40%)	19 (31.7%)	
49–60 months	1 (1.7%)	4 (6.7%)	
>60 months	22 (36.7%)	28 (46.7%)	
Underlying disease			
Hypertension	40 (66.7%)	38(63.3%)	0.315
Diabetes	35 (58.3%)	27 (45%)	
Other	6 (10%)	8 (13.3%)	
Blood group			
A	6 (10.2%)	13 (21.7%)	0.101
B	25 (42.4%)	13 (21.7%)	
AB	11 (18.6%)	8 (13.3%)	
O	17 (28.8%)	26 (43.3%)	

income level, duration of disease, underlying diseases, and hemoglobin level were significantly associated with better quality of life. Accordingly, patients aged between 30-39 years old, employed, single, with academic education, with a moderate average income, with disease duration less than 12 months, without diabetes, and with hemoglobin level of 11 and higher had obtained better quality of life scores. Nevertheless, the total score of quality of life in dialysis patients was only associated with employment status, income level, and duration of dialysis. Accordingly, patients with a job and moderate income level who had been under dialysis treatment for three years and less had better quality of life scores.

Moreover, we evaluated the relationship between different domains of quality of life and the factors affecting them. The results of our evaluation in pre-dialysis patients showed a significant relationship between gender and two domains of mental health and social functioning. Accordingly, women obtained significantly higher scores, as compared with men. There was a significant relationship between physical functioning and being 29 years or younger. In addition, married people were in better condition in terms of energy - fatigue domain. Patients with three children or less obtained better scores for the two domains of bodily pain and physical functioning while people with three children or more obtained better scores for the domain of mental health. Employed patients had better scores in the domains of energy - fatigue, mental health, social functioning, and general health. Moreover, in domains of physical functioning, energy – fatigue, mental health, and general health people with moderate income level received higher scores than those with low income levels. Patients without diabetes had higher scores in domains of physical functioning, mental health, bodily pain, and general health. People with hemoglobin level of 11 and higher had better scores in domains of physical functioning and general health. No significant relationship was observed between other domains of quality of life and other factors.

Among the dialysis patients, the patients who were married or widowed had higher scores in the domain of physical role functioning (100 points), as compared with the single patients. The dialysis patients aged between

Table 3. Mean and standard deviation of scores obtained for total quality of life and its different domains in the two groups of pre-dialysis and dialysis patients

Quality of life and its domains	Pre-dialysis patients, n=60 Mean ± SD	Hemodialysis patients, n=60 Mean ± SD	*P* value
Total quality of life	75.59 ± 9.38	61.98 ± 13.40	<0.001
Physical functioning	68.75 ± 22.08	47.25 ± 24.41	<0.001
Physical role functioning	100 ± 0.0	99.58 ± 3.22	0.319
Emotional role functioning	100 ± 0.0	100 ± 0.0	-
Fatigue/Energy	68.58 ± 12.79	58.25 ± 18.01	<0.001
Mental health	70 ± 16.45	64.60 ± 19.93	0.108
Social role functioning	86.45 ± 13.07	70.20 ± 25.53	<0.001
Bodily pain	87.20 ± 12.58	55.85 ± 31.33	<0.001
General health	58 ± 17.15	40.08 ± 22.27	<0.001

30 to 39 years old had higher scores in the two domains of physical functioning and physical role functioning. The employed dialysis patients obtained better scores in domains of physical functioning, energy - fatigue, and general health. Dialysis patients without hypertension, as compared with those with hypertension, had higher scores in two domains of bodily pain and general health. Patients with disease duration of 1 year or less had better general health scores. In addition, patients with disease duration of 1 year or less obtained higher scores in domains of physical functioning and general health. No significant relationship was observed between other domains of quality of life and other factors.

Discussion

This study aimed to determine the level of quality of life in patients with CKD and compare the two groups of pre-dialysis and hemodialysis patients in terms of the scores of quality of life and related factors. The results of this study can be utilized to provide proper education and support for nurses and other health care workers and families who provide care services for patients. Such efforts can also improve quality of life of this group of patients.

The results of analytical analysis showed that patients in pre-dialysis stage obtained better scores for total quality of life, as compared with hemodialysis patients. This finding is consistent with the results of a study by Mujais et al, which showed that quality of life of patients with CKD is associated with the stage of the disease. Accordingly, in more advanced stages of CKD, there was a more significant reduction in quality of life (24). Although end stage CKD patients on hemodialysis are saved from certain death, apparently during the disease progress they are affected by a wide range of physical, psychological, social, and economic problems which in turn will affect their quality of life (21). Based on the results of this study, with advances in stages of disease, quality of life of dialysis patients was low in the domains of physical functioning, social functioning, energy/fatigue, bodily pain, and general health. It seems that the initiation of dialysis affected these domains more than the other ones. Considering this finding, it is necessary to pay special attention to physical functioning of dialysis patients. In order to utilize an appropriate approach for reducing adverse complications, it is recommended to improve the condition of patients during dialysis and identify new ways to enhance quality of life of this group of patients. In addition, it might be also helpful to protect pre-dialysis patients against more advanced stages of disease through utilizing newer and more accurate treatment methods.

The results of this study showed that in the two domains of mental health and social functioning the scores obtained by women in pre-dialysis group were better than the scores obtained by men. However, in dialysis patients there was no significant relationship between gender and the mentioned domains. In a study by Al Wakeel et al which was conducted on quality of life in patients treated with peritoneal dialysis and hemodialysis, men had lower quality of life (25). In a study by Bayoumi et al, the researchers investigated quality of life of 100 hemodialysis patients and the same result was obtained (26). On the contrary, the study by Edalat-Nejad et al and the study of Rafiei et al showed no relationship between gender and quality of life in hemodialysis patients (27,28). Given the conflicting results of studies which investigated the relationship between gender and quality of life of CKD patients, and based on the results of this study, apparently in the more advanced stages of the disease a more important factors other than gender, such as the initiation of dialysis, which is effective in determining quality of life was existed.

According to the results of the present study, in pre-dialysis patients younger age was associated with higher scores of total quality of life and physical functioning. However, in dialysis patients older age was associated with lower scores of physical functioning domain. In three studies conducted in Saudi Arabia, China, and the United States, older age was among the negative factors affecting quality of life in dialysis patients (24,25,29). However, in a study in Tehran which investigated the quality of life of 202 CKD patients, there was no significant relationship between age and quality of life (28). Due to inconsistencies

in the results of previous studies, probably quality of life of patients with chronic disease in later stages of life is not only associated with age, but also is affected by other factors such as diseases and concurrent disabilities, social limits, psychological stress, loneliness, and lack of support. Thus, it is recommended to conduct further similar studies to determine the underlying factors affecting quality of life of older people.

Various studies have investigated the relationship between quality of life and marital status, but their results are conflicting. Some of these studies indicate that being married is associated with better quality of life while others expressed opposite results (19,21,22). The results of this study showed that lower number of children in both groups of patients was associated with better scores in domains of physical functioning and bodily pain. In pre-dialysis group, patients with more than three children had better mental health scores. It seems that families and children act as sources of support for patients with chronic disease and thus reduce depression and improve mental health (28). However having a child was not necessarily effective in improving quality of life of patients in the physical domains. Based on the results of this study, the higher education level in pre-dialysis patients was associated with more favorable quality of life, especially in the physical domains. This relationship is also confirmed in a study by Wu et al (29).

In this study, employment played an important role in improving quality of life of CKD patients and similar studies could confirm this finding. In a study by Porter et al, unemployment was associated with quality of life of patients with CKD (30). In a study by Bayoumi et al unemployment was one of the factors adversely affecting quality of life (26). However, in a study by Rafiei et al in Iran, no significant relationship between employment status and quality of life was detected (28). However, apparently with the initiation of dialysis in end-stage CKD patients, they are faced with disability in work or job loss, which can deteriorate the economic condition of this group of patients and make a direct impact on their quality of life. Since the results of this study and many other similar studies indicate a relationship between employment and quality of life, the development of support programs to improve the employment status of patients can be helpful.

Consistent with the study by Rafiei et al (28), in our study, moderate level of income was associated with better quality of life in both groups of patients. Patients who had low or very low income had lower total scores in different domains of quality of life. The medical services used for the treatment of advanced stages of CKD, such as hemodialysis and kidney transplantation and frequent hospitalizations, are expensive. Thus, insurance organizations and other institutions must provide more financial supports to improve the quality of life of this group of patients.

Concerning underlying diseases, diabetes was more effective than hypertension and other underlying diseases in reducing the quality of life of pre-dialysis patients. Previous studies have reported conflicting results on the relationship between diabetes and quality of life (24,31). In addition, no significant relationship between diabetes and quality of life in hemodialysis patients was seen. On the contrary, in this group of patients, hypertensive was significantly associated with reduced quality of life in the domains of public health and bodily pain. This finding is consistent with the results of a study by Porter et al (30). The results of this study showed that higher levels of serum hemoglobin in CKD patients was associated with better quality of life, especially in domains of physical functioning and general health. This association was significant in pre-dialysis patients. This finding is consistent with the results of a study by Perlman et al (32). In addition, the results of the study by Mujais et al, showed that anemia and low hemoglobin were among the major factors affecting quality of life in CKD patients in the final stages of the disease (24). Considering the results of this study and other similar studies, therapeutic interventions to increase and maintain hemoglobin level in patients with CKD can be useful in improving the quality of life of this group of patients. Thus, it is recommended to conduct interventional studies in this area.

In CKD patients, duration of disease was inversely related to quality of life; this relationship was observed in the domains of physical functioning, bodily pain, and general health. Moreover, the duration of dialysis in patients undergoing hemodialysis was associated with their quality of life. In other words, it had an inverse relationship with the domains of physical functioning and general health. These results are consistent with the findings of some other similar studies (25,26,31). However, in other studies that have been conducted in Iran, no significant relationship between duration of dialysis and quality of life is reported; thus their results are not consistent with our finding (27,28). Based on the results of the study, it seems that with the passage of time people become more adapted to their disease, however because of disease and treatment complications which gradually emerge, people will suffer from higher levels of disability and face more social limits, economic tensions, and mental stresses. Such conditions can lower patients' satisfaction with life and decrease their functioning and quality of life. Therefore, several measures, such as culture building for organ donation and the provision of suitable alternative treatments such as kidney transplant, can be utilized to increase the duration of the disease and help to improve the quality of life for this group of patients.

According to the results of the present study, the majority of patients (80%) were living in urban areas and there was no significant relationship between place of residence and quality of life. Although people living in rural areas have more limited access to health centers, hospitals, and amenities, they are not necessarily the determinants of

quality of life. In urban areas, there are some problems such as air pollution and low physical activity which can affect a person's quality of life. Therefore, it is recommended to conduct further similar studies on this subject.

The results of the study showed no significant relationship between blood type and quality of life. In our study, blood type O was the most common blood type in the studied patients. On the other hand, other studies did not pay much attention to this issue. Thus, it is recommended to conduct further similar studies on the relationship between blood type and quality of life. In addition, given the results of this study and other similar which indicated the effects of known factors on quality of life of CKD patients, it is suggested to conduct interventional studies to eliminate some of the factors that negatively affect the quality of life.

Conclusion

Overall, the findings of this study showed that in the majority of patients with CKD the mean score of quality of life was at a good level (between 25th to 75th percentiles). Moreover, pre-dialysis patient, as compared with patients who were on hemodialysis, had a higher quality of life. This study showed that different factors including age, marital status, employment status, education level, income level, duration of disease, underlying disease, and hemoglobin level could affect the quality of life of patients with CKD.

Limitations of the study

This study was conducted on a limited sample size and needs further confirmation by larger studies.

Authors' contribution

MRT supervised the research. EF and SH conducted the investigation. MM prepared the primary draft. MRT finalized the final manuscript. All authors read and signed the final paper.

Conflicts of interest

There were no points of conflicts to declare.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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