Research

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Quality of Life (QoL) and Depression Among Children With End Stage Renal Disease Attending Hemodialysis Units in Gaza Strip

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ABSTRACT

Aim: The aim of this study was to compare the quality of life (QoL) and depression among children with end-stage renal disease (ESRD) undergoing hemodialysis in the Gaza strip compared to the control group of children with chronic medical problems attending the same hospitals.

Methodology: The study sample consisted of children diagnosed with ESRD (N=47) and a control group of children with chronic medical problems attending the same hospitals (N=95). Data collection was performed using sociodemographic scale, medical status checklist, QoL questionnaire and the birleson depression self-rating scale (DSRS) in a face-to-face interview.

Results: The results showed that prevalence of depression reported in children with ESRD was 20.13% and for the control group was 12.63%. The study showed that the mean total QoL for end stage renal (ESR) failure in children was 48.98 relative to 52.75 SD for the control group. There were statistically significant differences in the QoL among the control group children. Physical functioning mean for ESR failure was 14.02% and for the control group was 21.24%. There were statistically significant differences in physical functioning for the group being studied. Emotional functioning for ESR failure was 14.04% and the control mean was 9.68%. There were statistically significant differences in emotional functioning in the control group. Social functioning mean in ESR failure was 9.96% and 8.32% for the control group. There were statistically significant differences in social functioning towards the ESR failure. School functioning mean in ESR failure was 11.38% and 12.77 % for the control group. There were statistically significant differences in school functioning in the control group.

Conclusion: The findings of the study showed that the ESRD have positive perceptions about their QoL (emotional, social), negative perception towards physical functioning and school, compared to the control group who have positive perception about physical functioning, school and their QoL and negative perception towards social and emotional functioning, and indicate a higher incidence of depression among ESRD relative to the control group.

KEY WORDS: Children; Depression; ESRD; QoL.

ABBREVIATIONS: QoL: Quality of Life; ESRD: End-Stage Renal Disease; DSRS: Depression self-rating scale; CKD: Chronic Kidney Disease; CRF: Chronic Renal Failure.

INTRODUCTION

According to the American Society of Nephrology, chronic kidney disease (CKD) has affected 5-10% of the world population and has become a global public health problem.[1] CKD is an important health problem for adults as well as pediatric and adolescent populations. Now-a-days, the frequent use of conventional concepts such as morbidity, mortality, and life expectancy

for the evaluation of public health, is not sufficient to assess the state of health and well-being. Replacing these concepts, the measurement of quality of life (QoL) was proposed as a more appropriate approach for the evaluation of health care services.[2] Health-related quality of life (HQoL) focuses only on the well-being of an individual, and refers to an individual's satisfaction with his/her own present health state.[3]

Comparisons of QoL and depression among end stage renal diseases (ESRD) children and non-ESRD children is an important health issue due to the higher reported rate of depression among these groups. Depression is the most common psychological problem encountered in patients with end-stage renal disease.[2]

Hemodialysis is the most common form of renal replacement therapy (RRT), with over 75% of ESRD patients being treated using this type of therapy.[4] Hemodialysis is a technique implemented to mediate the removal of waste products such as creatinine, urea and free water from the blood during renal failure. Hemodialysis is one of the three renal replacement therapies (the other two being renal transplant and peritoneal dialysis).[5,6] Stressors, including medication procedures, dietary constraints, fear of death, and dependency upon treatment, may affect the QoL and exacerbate the feeling of a loss of control.[7] Depression is widely believed to be the most common mental health problem among patients with ESRD.[8]

The prevalence of major depression in the general population is approximately 1.1-15% for men and 1.8-23% for women.[9] However, the prevalence of major depression among ESRD patients is approximately 20-30%, and it may be as high as 47%.[10] Some studies have indicated that moderate depressive syndromes are common in approximately 25% of ESRD patients, and that major depression is common in 5-22% of ESRD patients.[11]

The aims of this study were 1) To compare the QoL and prevalence rate of depression among children with ESRD undergoing hemodialysis compare to the control group, 2) To examine the relationship between QoL and depression among ESRD children and non-ESRD children (control group) in relation to socio-demographic variables such as (age, gender, family income, place of residence, etc.) in the Gaza Strip hospitals.

METHOD

Participants

The study sample include all children (N=47) aged between 6-18 years, attending 4 hemodialysis centers in Gaza Strip, who have a medical record and are registered in the hospital of Ministry of Health as ESRD patients to receive regular hemodialysis sessions during the study. The sample consisted of 28 boys

(19.7%) and 19 girls (13.4%). The control group included children (N=95) admitted at the time of the study and were selected randomly from the other departments in the 4 hospitals. Their age group was between 6-18 years. There were 47 boys (33.1%) and 48 girls (33.8%) at the time of the study.

Measures

Socio-Demographic Information: Variables including age, sex, educational level, living area and family income.

Medical History

Additional information on medical history was obtained, including primary diagnosis, treatment status with respect to dialysis.

The Pediatric QoL Inventory Scale (version 4.0) Arabic Versions[12]

It is a brief, 23-item multidimensional instrument designed by Varni for measuring pediatric health-related QoL.[13] The pediatric QoL inventory (PQLI) consists of 4 generic core scales: (1) Physical functioning, (2) Emotional functioning, (3) Social functioning, and (4) School functioning. For this study, the parent proxy-report format was used. The instructions assess how much of a problem each item has posed over the past month. The response scale uses a 5-point Likert-type format, ranging from 0 (never a problem) to 4 (almost always a problem). The raw score for each item is reverse-scored and transformed to a scale from 0 to 100 (0-100, 1-75, 2-50, 3-25, and 4-0), with higher scores indicating better health-related QoL to create the total scale score, the mean is computed as the sum of the items divided by the number of items answered on all scales. To determine the psychosocial health summary (PHS) score, the sum of items divided by the number of items answered on the social, emotional, and school functioning scales is computed.[13] The Arabic version was used in the Gaza strip and showed high reliability.[14,15]

The parent was asked about how much of a problem a specific function has been for their child in the past 4 weeks. The response to each item is based on a 5-point Likert category, ranging from "never", "almost never", "sometimes", "often", and "almost always" having a problem. As per the user's guidelines, the subject's missing item value of a specific domain using a mean score of the rest of items was included, which do not contain missing values. If more than 50% of the items in the domain are missing, the domain scores of that subject were not computed. We calculated the domain score by adding the item scores of the corresponding domain, dividing the summated item score by the number of items used in the domain. Then, we linearly transformed the domain scores to a 0-100 scale. We referred 0 as the lowest HRQoL and 100 as the highest HRQoL.[14,15] The reliability of QoL (Arabic version) scale in this study was N=0.65.

Birleson Depression Self-Rating Scale (DSRS)[16]

Depression self-rating scale (DSRS) for children: The DSRS for children was developed to assess the degree of depression in children and the youth. The scale comprises 18 items, and is scored on a 3-point scale: Mostly, sometimes, and never, with eight items reversed. The total score ranges from 0 to 36. The clinical cutoff score for depression has been set to ≥15 (Birleson, Hudson, Buchanan, Wolff, 1987).[16] The DSRS has been reported to have good internal consistency.[16] The reliability of our Arabic version of the depression scale in this study was N=0.89; split half was 0.81. This scale had been used in previous studies in the Gaza strip and showed high reliability.[17]

STUDY PROCEDURE

Inclusion and Exclusion Criteria ESRD Patients

Participants were all children (N=47) aged between 6-18 years who have a medical record and are registered in hospitals of Ministry of Health as ESRD, attending 4 hemodialysis centers in Gaza strip receiving regular hemodialysis sessions during the study. The age of the children ranged from 6 to 18 years with a mean age of 12.31 years.

Controls

The control group consisted of (N=95) children matched in sex- and age, admitted with chronic diseases to the same hospitals. The age of the children ranged from 6 to 18 years with a mean age of 11.7 years.

Children and their parents in both groups were told about the aims of the study and they had the right not to participate in the study. Every subject and his parent in the study received an explanatory letter about the study; the researcher explained to all the participants that the information will be kept exclusively for the research purpose. Informed consent to take part in the study was obtained from the patient and their parents. An official letter of approval to conduct the research was obtained from Helsinki Ethical Committee Gaza Strip (HECGS) and an official letter of approval to conduct the study has been obtained from the Human Resource Development Department in Ministry of Health (HRDDMH), which allowed the researcher to carry out the study. Another official letter was obtained from the general administration of hospitals in order to conduct the study in Government hospitals and facilitate the process of data collection. Data collection was done in a face-to-face interview with all the children and inside the hospitals. The time of the interview was 15-20 minutes. The data collection was done on March 2015.

Statistical Analysis

We analyzed our dataset of 350 subjects using the SPSS 20 Software (Statistical Package for the Social Sciences). We used means and percentages to describe the characteristics of the study sample. In addition to estimating the overall QoL and prevalence of depression, we calculated the prevalence on the basis of the type of participants (cases and control). Independent t-test and analysis of variance (ANOVA) were performed to examine differences in both ESRD children and the control groups with respect to QoL, depression and socioeconomic status. For analyzing the association between depression and QoL, Pearson correlation coefficient test was done. Two group MANOVA (e.g., Hotelling's t-squared was done) in which case/control were entered as independent variable and depression and QoL as dependent variables. Statistical significance was assumed at $p<0.05$.

RESULTS

Sociodemographic Characteristics of the Study Sample

Out of 142 children, 47 children were suffering from ESRD and undergoing kidney dialysis, of which 28 children were male (19.7%) and 19 were females (13.4%). While 47 participants of the control group were boys (33.1%) and 48 were girls (33.8%). The age of 15.5% of the participants with ESRD ranged from 6-12 years, the age of 11.3% of the participants ranged from 13-15 years, and the age of 6.3% of the participants ranged from 16-18 years. While the age of 43.7% of the participants in the control group ranged from 6-12 years, age of 14.1% of the participants ranged from 13-15 years, and the age of 9.2% of the participants ranged from 16-18 years. The mean age for ESRD was 12.31 (SD=2.15) and the mean age for control was 11.7 (SD=3.20). According to the place of residence, 11.3% of the control and 7.1% of the ESR failure patients were from north Gaza, 41.1% of control and 11.3% of ESR failure were patients from Gaza, 7.1% of the control were patients from the middle area and 3.5% of the patients were from the middle area, 5% of the control and 8.5% of ESR failure patients were from Khan Younis, and 2.1% of the control and 2.8% of the ESR failure patients were from Rafah. On the basis of family monthly income, 20.4% of the ESR failure patients had a family income of $300 and less, 4.2% had a family income in the range $301-500, 5.6% had a family income in the range $501-750, and 2.8% had a family income in the range $751 and more. While, 29.6% of the control patients had family income less than $300, 23.2% of the control patients had $301-500, 7.2% of the control patients had $501-750, and 6.3% of the control patients had $751 and more (Table 1).

Medical Characteristics of the Kidney Dialysis End Stage Renal Failure

As shown in Table 2, the analysis of the medical characteristics of end stage renal disease, showed that 59.6% of the children had consanguineous relationship between parents, while, 40.4% had no consanguinity. Also, 95.7% of the children had ESRD alone and 4.3% had co-morbid disease with ESRD. Regarding family history of renal disease in children with ESRD, 14.9% of

Table 1: Sociodemographic Characteristics of the Study Sample.

	Case (ESRD) (n= 47)		Control (n= 95)	
	Mean=12.31 (SD=3.25)		Mean=11.17 (SD=3.20)	
Age	N	%	N	%
6-12 years	22	15.5	62	43.7
13-15 years	16	11.3	20	14.1
16-18 years	9	6.3	13	9.2
Sex				
Male	28	19.7	47	33.1
Female	19	13.4	48	33.8
Place of residence				
North Gaza	10	7.1	16	11.3
Gaza	16	11.3	59	41.5
Middle area	5	3.5	10	7.1
Khan Younis	12	8.5	7	5
Rafah	4	2.8	3	2.1
Family monthly income				
$300 and less	29	20.4	42	29.6
$301-500	6	4.2	33	
$501-750	8	5.6	11	7.7
$751 and more	4	2.8	9	6.3

ESRD: End-stage renal disease; SD: Standard deviation.

children reported a family history of renal disease. According to the number of dialysis sessions, 42.6% of the children took dialysis for less than three sessions per week and 57.4% of the children took dialysis for less than five sessions per week (Table 2).

Means and Standard Deviation of Depression between Two Groups

In order to find the differences in the mean of depression between the two groups, independent *t*-test was conducted. The results showed that the mean depression scores in children with ESRD was 20.13 (SD=7.67) and mean depression scores in control groups was 12.63 (SD=6.16). There were statistically significant differences in depression scores between the two groups among children with ESRD ($t(140)=7.50$, $p<0.001$) (Table 3).

Prevalence of Depression Disorder

Using the clinical cut-off score for depression which had been set to ≥15 by Birleson[16] and used in the previous studies conducted in Gaza strip.[17] The result showed that (N=37/47) children with ESRD had depression (78.7%) compared to (N=28/95) of control group children who had depression (29.5%). There were statistically significant differences in depression among children with ESRD ($\chi2=29.81$, df=1, $p=0.001$) (Table 4).

QoL of Study Sample Means and Standard deviation of QoL and subscale

As shown in Table 4, the study showed that the mean total QoL

in children with ESRD was 48.98 (SD=10.88) compared to the mean scores of 52.75 (SD=10.15) in the control group. There were statistically significant differences in the total QoL between the children in the control group ($t(140)=2.03$, $p<0.04$). The mean physical functioning scores for children with ESRD was 14.02 (SD=5.98) and for the control group was 21.24 (SD=5.77). There were statistically significant difference in physical functioning among children in the control group ($t(140)=6.94$, $p<0.001$). Emotional functioning for ESRD mean was 14.04 (SD=4.32), and the control group children mean scores were recorded at 9.68 (SD=4.21). There were statistically significant differences in emotional functioning for children with ESRD ($t(140)=6.94$, $p<0.001$). The social functioning mean in ESRD children was 9.96 (SD=3.93) and 8.32 in control group (SD=3.69). There were statistically significant differences in social functioning for children with ESRD ($t(140)=2.44$, $p<0.02$). School functioning mean in children with ESRD was 11.38 (SD=3.61) and control group children was 12.77 (SD=2.68). There were statistically significant differences in school functioning among children in the control group ($t(140)=2.56$, $p<0.01$) (Table 5).

Relationship between Depression and QoL of the Children with End Stage Renal Failure

The Pearson correlation test shows that there is a statistically significant positive relationship between total depression and emotional functioning ($r(140)=0.53$, $p<0.001$) and a negative relationship with school functioning ($r(140)=-0.36$, $p<0.001$). For the control group, there was a statistically significant positive relationship between total depression and social functioning ($r(140)=0.27$, $p<0.001$) and negative relationship with physical

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Table 2: Medical Characteristic of ESRD Children undergoing Dialysis.

	N	%
Consanguinity of parents		
Consanguineous	28	59.6
No Consanguinity	19	40.4
Current diseases		
Renal Failure	45	95.7
Renal Failure & other disease	2	4.3
Previous family history of renal failure		
No	40	85.1
Yes	7	14.9
Number of other diseases in family		
Less than 2 diseases	15	31.9
Less than 4 diseases	3	6.4
None	29	61.7
Other diseases in family		
Handicapped	1	2.1
Thalassemia	1	2.1
Diabetes	2	4.2
Cancer	1	2.1
Neurological	1	2.1
Liver cirrhosis	1	2.1
Gastric problems	1	2.1
Renal failure	4	8.5
Kidney Stone	1	2.1
Nothing	34	72.3
Weekly dialysis		
Less than 3 times	20	42.6
Less than 5 times	27	57.4
Dialysis Hours		
Less than 3 Hours	5	10.6
Less than 5 hours	42	89.4
Place of dialysis		
Shifa Hospital	14	29.8
Rantisi Hospital	25	53.2
Al Aqsa Hospital	4	8.5
Naser Hospital	4	8.5
Total	47	100.0

ESRD: End-stage renal disease.

Table 3: Depression of Cases and Control Group.

	N	Mean	SD	SE	MD	t	p	95% Confidence interval of the difference	
								Lower	Upper
ESRD	47	20.13	7.67	1.12	-6.28	-7.50	0.001	-9.86	-5.14
Control	95	12.63	6.16	0.63					

ESRD: End-stage renal disease; SD: Standard deviation; SE: Standard error; MD: Mean deviation.

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Table 4: Differences in Prevalence of Depression Between Children with ESRD and Control Group.

		ESRD	Control	χ^2 (df=1)	p
No depression	N	10	67		
	%	21.3	70.5	29.81	0.001
Depression	N	37	28		
	%	78.7	29.5		

ESRD: End-stage renal disease.

Table 5: Means and Standard Deviation of Quality of Life and Subscales.

	Group	Mean	SD	SE	t	p	95% Confidence Interval of the Difference	
							Lower	Upper
Quality of life	Control	52.75	10.15	1.04	2.03	0.04	0.10	7.43
	ESRD	48.98	10.88	1.59				
Physical functioning	Control	21.24	5.77	0.59	6.94	0.001	5.16	9.28
	ESRD	14.02	5.98	0.87				
Emotional functioning	Control	9.68	4.21	0.43	-5.76	0.001		
	ESRD	14.04	4.32	0.63			-5.85	-2.86
Social functioning	Control	8.32	3.69	0.38	-2.44	0.02		
	ESRD	9.96	3.93	0.57				
School functioning	Control	12.77	2.68	0.28	2.57	0.01	-2.97	-.31-
	ESRD	11.38	3.61	0.53				

ESRD: End-stage renal disease; SD: Standard deviation; SE: Standard error.

functioning (r(140)=-0.29, p<0.001) (Table 6).

Differences in Depression and QoL in the Children with ESRD and Control Group

Cohen's d[18] was selected as the measure of effect size, because of its widespread use in the literature. To calculate d, the difference in means between ESRD children with depression compared to control group children was as follows:

Input data provided:

For ESRD children, Mean 1: 20.13 (SD 1: 7.67).

For control group children, Mean 2: 12.63 (SD 2: 6.16).

Cohen's d was: (d=1.085).

Such findings showed high effect size (effect sizes as small (d=0.2), medium (d=0.5), and large (d=0.8) based on the benchmarks suggested by Cohen (1988).[18]

In order to find the effect size between the children with ESRD and the control group with respect to the QoL, Cohen's d[18] was selected as the measure of effect size, because of its widespread use in the literature. To calculate d, the difference in means between children with ESRD with respect to QoL was

Table 6: Pearson Correlation Coefficient Test of the Study Variables in Children with ESRD and Control Group.

	Depression	
	Cases	Control
1. Depression	-	-
2. QoL	0.07	-0.07-
3. Physical functioning	-0.21-	-0.29-**
4. Emotional unctioning	0.53**	0.20
5. Social functioning	0.34*	0.27**
6. School functioning	-0.36-*	-0.04-

ESRD: End-stage renal disease;

Table 7: Multivariate Test of Total Depression and QoL According to Case/Control.

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected model total QoL	Depression	1766.85a	1	1766.85	39.45	0.001
		446.58b	1	446.58	4.13	0.04

df: Degrees of freedom; QoL: Quality of life.

compared with the control group children as follows:

Input data provided:

For ESRD children, Mean 1: 52.75 (SD 1: 10.15).

For control group children Mean 2: 48.98 (SD 2: 10.88).

Cohen's d was: (d=0.35). Such finding showed small effect size (effect sizes as small (d=0.2), medium (d=0.5), and large (d=0.8) based on the benchmarks suggested by Cohen.[18]

Partial eta squared can be computed with SPSS (e.g. using "effect size" under Analyze, General Linear Model) to compare the QoL and depression between children with ESRD relative to the control group.

In order to find the differences in total depression and QoL between the two groups, Hotelling's T, MANOVA analogue of the two group *t*-test situation; was done in which one dichotomous independent variable was ESRD and control group, and multiple dependent variables were depression and QoL. The results showed that there was a statistically significant interaction effect between case/control on the combined dependent variables (depression and QoL), $F (2,139)=21.36$, $p=0.001$; Hotelling's Trace=0.307 (Table 7).

DISCUSSION

This study was conducted to determine the prevalence of depression and the QoL among children with ESRD attending hemodialysis sessions in Gaza strip compared to the children who were admitted to the hospital. This study showed that the prevalence of depression in children with ESRD and under dialysis was 21.1% compared to 12% among children in the control groups. Our study showed that the mean total QoL in children with ESRD was 48.98 as compared to the mean scores of QoL 52.75 in the control group. There were statistically significant differences in the total QoL with the children in the control group. Our study rate of depression was higher than found by Bakr et al[19] in a study of 19 children with pre-dialysis chronic renal failure (CRF) and 19 children with end stage renal disease undergoing regular hemodialysis. The prevalence rate of psychiatric disorders in all the studied patients was 52.6%. Adjustment disorders were the most common disorders (18.4%), followed by depression (10.3%) and neurocognitive disorders (7.7%). Anxiety and

elimination disorders were reported in 5.1% and 2.6%, of the children respectively. The disorders were more prevalent in dialysis (68.4%) than in pre-dialysis patients (36.8%).[19]

Similarly, in a study to assess depression, anxiety, and QoL in a cohort of children and adolescents with ESRD, were compared with healthy controls. Thirty-two children and adolescents 8-18 years of age were enrolled in the study. There was a significant difference in mean depression score, which was significantly higher for the ESRD patients. The mean anxiety score was significantly lower for ESRD patients than for the control group. Regarding QoL score, there were significant differences between the ESRD patients and control groups for both child-rated and parent-rated QoL scores, which were significantly lower for ESRD patients.[20] Similarly, clinical data were collected from 28 children and adolescents with pre-dialysis CKD and 28 healthy sex- and age-matched controls. The results showed that, of the 56 children enrolled in the study, the CKD patients were referred to mental health professionals more frequently than the controls. Patients exhibited higher scores for separation anxiety and a higher frequency of clinically significant depressive symptoms. They also had lower overall QoL scores, as well as poorer scores for the psychological, educational and psychosocial subdomains of QoL instruments. There was a negative correlation between anxiety and depressive symptoms and all domains of QoL.[21] Our results were consistent with who undertook a study to determine the incidence of depressive symptomatology and to evaluate the QoL among 64. Sudanese children on hemodialysis and 6 on continuous ambulatory dialysis. Almost half of the patients were having depressive symptomatology (47.1%) with a variable degree of severity. Depression symptoms were found to be common among patients undertaking hemodialysis (44.3%) and were associated with school absentees, low adequacy of dialysis, female gender and adolescent age. One third of the patients on chronic dialysis had impaired QoL, another third had poor QoL and the rest had average QoL.[22] Similarly, Kul et al[23] in a study aimed to compare the QoL of children and adolescents in various stages of their CKD, who were managed with different treatment modalities to that of children and adolescents without any chronic disease. The study included 18 renal transplant and 21 dialysis patients (8 on hemodialysis, 13 on peritoneal dialysis) and 16 patients who did not yet require renal replacement therapy. The control group consisted of 37 children without any chronic disease. CKD patients had lower scores in all scales of pediatric QoL inventory (PQLI) than the control group. There were no differences in self-reported scores on the

pediatric QoL scale scores between treatment groups; however, parents of the transplant patients had reported higher (more favorable) physical health summary scores than those of the dialysis patients. Our study showed that physical, school functioning were more in control group children. While, emotional functioning and social functioning were more in children with ESRD. Such findings were consistent with the study of Varni and co-workers who reported that children with ESRD exhibited better emotional scores of HRQoL than children with other chronic diseases, including diabetes, asthma, cerebral palsy and cardiac and rheumatologic diseases.[24]

CONCLUSION

This study showed that the prevalence of depression in children with renal failure and under dialysis was double the prevalence rate among other control groups. Also, total QoL for ESR failure was lower than the control group. There were statistically significant positive relationships between total depression and emotional functioning, and negative relationship and school functioning. These findings suggest that there are very strong risk factors associated with depression, which increase emotional functioning and decrease school functioning of children with ESR failure.

CLINICAL IMPLANTATIONS

The results of the present study might help in developing a deep understanding of the issues that may influence the overall health of the subjects affecting their QoL leading to depression. Moreover, due to a significant decrease in the QoL domains among ESRD patients undergoing HD in Gaza, and a significant increase in the rate of depression among ESRD patients, we emphasized on increasing the efforts to avoid negative impacts on QoL and depression by establishing a psychosocial support program to decrease the level of depression and enhance the QoL, to coordinate between the Ministry of Health and non-governmental organization to apply for a psychological support program. The training of the team needs to be conducted to deal with ESRD to provide support to the patient and their families, encourage communication between healthcare givers and ESRD patients. The educational program should be designed and counseling team set up, to work with the patients to be able to cope with the new condition. Psychological programs should be designed for families dealing with their children to decrease the level of depression and promote their QoL.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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