

# WHOQOL-BREF survey of quality of life among dialyzed end-stage renal disease patients

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## Abstract

**Introduction:** Hemodialysis (HD) improves health and prolongs the life of end-stage renal disease patients, but simultaneously leads to emotional disturbances and impairs the quality of life (QOL). The study was conducted to evaluate the QOL of HD patients. The study was approved by the Regional Bioethical Committee (K.B.Cz.-0014/2017).

**Material and methods:** The World Health Organization Questionnaire of QOL (WHOQOL-BREF) was used in this study with the formal agreement of the WHO. The associations between each patient-related and dialysis-related factor and WHOQOL-BREF domains and questions were computed. The variables were compared by the Student *t*-test.

**Results:** Data were collected in August 2017 in a single access center. Sixty-nine patients, including 23 (33.3%) women, were evaluated. The factors lowering the scores for particular questions and domains of WHOQOL-BREF were senility, marriage, wrist and arm AVF, not-tunneled CVCs (vs. tunneled), and unwillingness to have a kidney graft. The factors that increased scores for particular questions and domains of WHOQOL-BREF were short dialysis, tunneled CVCs (vs. not-tunneled), and higher URR. The relations between domains and questions of WHOQOL-BREF and sex, education, months on dialysis, kidney graft in the past, fulfillment of medical recommendations, Kt/V and UF were not significant.

**Conclusions:** Although a kidney graft is the best kidney replacement therapy, there is a large group of patients who do not want to receive this treatment. This group should be given special attention. The medical professionals in HD units should remember that patients may not feel comfortable with their disease and satisfied with their body image affected by therapy.

**Key words:** quality of life, World Health Organization Questionnaire of Quality of Life, hemodialysis, end-stage renal disease, chronic kidney disease, vascular access.

## Introduction

The growing population of end-stage renal disease (ESRD) patients require hemodialysis (HD), which is the most common renal replacement therapy. The HD improves health and prolongs life, but simultaneously

leads to emotional disturbances and reflects the quality of life (QOL) [1, 2]. All patients with chronic illnesses are reported to have impaired QOL [3], but ESRD patients on HD have considerably poorer QOL compared to healthy individuals, the general population and even to patients with other chronic diseases and to renal transplant patients [4–6]. The QOL is an important indicator of effective HD, a measure of patient outcome and an important variable assessing HD patients [1, 4, 7–9].

Due to the lack of measures assessing QOL, the World Health Organization (WHO) has developed its own instrument named the World Health Organization Questionnaire of Quality of Life (WHOQOL). The long version is the WHOQOL-100 containing 6 domains and 100 questions. The abbreviated questionnaire, WHOQOL-BREF, consists of 26 questions. According to the WHO definition, health is “a state of physical, mental and social well-being, not merely the absence of disease and infirmity”. Thus both WHOQOL-100 and WHOQOL-BREF are focused on self-perceived QOL [10–13]. These questionnaires can be applied in broad-ranging ways, irrespectively of diseases, disabilities and symptoms [10–12, 14].

The aim of this study was to evaluate the QOL of ESRD patients undergoing HD with the WHOQOL-BREF questionnaire. The inclusion criteria were ESRD and HD, regardless of HD modality. The only exclusion criterion was lack of consent for participation. The patients received questionnaires at the dialysis session and were asked to complete them on the following day. The questionnaires were collected at the succeeding dialysis by medical staff.

The study was approved by the Bioethical Committee of the Regional Chambers of Physicians and Dentists (K.B.Cz.-0014/2017) and conducted in the Department of General and Vascular Surgery and the Dialysis Unit in the Regional Specialist Hospital in Częstochowa, Poland.

## Material and methods

Data were collected in August 2017. At that time 135 patients were dialyzed in the Dialysis Unit in the Regional Specialist Hospital in Częstochowa, Poland. Each patient received information on a survey and was invited to participate. They received a questionnaire including demographic questions (age, gender, education, marital status), followed by medical history data (months on HD, modality of vascular access, kidney grafts, fulfillment of medical recommendations). Sixty-nine patients agreed to participate, gave formal consent in accordance with the requirements of the Bioethical Committee and were enrolled for further evaluation. Received data were supplemented with clinical information including Kt/V, urea

reduction ratio (URR), ultrafiltration (UF), and duration of a single HD (Tables I–III). Finally, participants completed WHOQOL-BREF questionnaires. The association between each factor and each WHOQOL-BREF domain and separate question was computed and presented in Tables I–III.

Upon the formal agreement of the WHO, the WHOQOL-BREF questionnaire was chosen for the study. The WHO provided the WHOQOL-BREF instrument along with a Code book. WHOQOL-BREF includes four domains (Physical health, Psychological, Social relationships and Environment, consisting of 7, 6, 3 and 8 questions, respectively) along with two separately scored questions about overall self-perception of QOL (question 1) and overall self-perception of health (question 2) [10–12]. The Physical health domain assesses activities of daily living, dependence on medicinal substances and medical aids, energy and fatigue, mobility, pain and discomfort, work capacity, sleep and rest. The Psychological domain covers: bodily image and appearance, negative and positive feelings, self-esteem, spirituality, religion and personal beliefs, thinking, learning, memory and concentration. The Social relationship domain includes: personal relationships, social support and sexual activity. The Environment domain assesses: financial resources; freedom, physical safety and security; accessibility and quality of health care and social care; home environment; opportunities for acquiring new information and skills; physical environment; participation in and opportunities for recreation and leisure activities [11, 12]. If in any of these domains more than 20% or at least 3 answers are missing, the whole domain assessment needs to be discarded. The Social relationship domain is an exception. Here only 1 missing answer is permissible. If one or two questions in a single domain are not answered, they may be substituted by the mean of the others in the same domain. In each domain the score is scaled positively, which means that a higher score corresponds to a higher QOL. Mean raw scores were transformed to a 0–100 scale according to the scoring procedures by multiplying by four [11, 12, 15].

The factors which may affect the WHOQOL-BREF score were analyzed. The demographic variables were: age, gender, marital status and education (Table I). The patient-related variables were: months on HD, vascular access, fulfillment of medical recommendations, kidney graft in the past or a desire to be a kidney graft recipient in the future (Table II). The dialysis-related variables were: duration of a single HD, Kt/V, URR and UF (Table III). The significance of association between each demographic, patient-related and dialysis-related factor and WHOQOL-BREF domains and two independent questions was evaluated.

Table I. Demographic factors affecting WHOQOL-BREF questions and domains

Demographic factors	Participants		WHOQOL Questions		WHOQOL Domains			
			1. How do you rate your quality of life?	2. How satisfied are you with your health?	Physical health	Psychological	Social relationships	Environment
	N (%)	M [range] (SD) [years]	Sample vs. population/sample (p)	Sample vs. population/sample (p)	Sample vs. population/sample (p)	Sample vs. population/sample (p)	Sample vs. population/sample (p)	Sample vs. population/sample (p)
Gender:	69	62.6 [28–84] (12.2)						
Male	46 (66.7)	62.7 [28–84] (12.6)	N/S	N/S	N/S	N/S	N/S	N/S
Female	23 (33.3)	62.5 [37–80] (11.4)	N/S	N/S	N/S	N/S	N/S	N/S
Age [years]:								
< 60	24 (34.8)	49.7 [28–59] (9.3)	N/S	↑ < 0.05 (vs. ≥ 70 y)	↑ < 0.02 (vs. ≥ 70 y)	N/S	N/S	N/S
60–69	25 (36.2)	64.2 [60–69] (2.4)	N/S	↑ < 0.02 (vs. ≥ 70 y)	↑ < 0.03 (vs. ≥ 70 y)	N/S	N/S	N/S
≥ 70	20 (29.0)	76.2 [70–84] (4.2)	N/S	↓ < 0.01 (vs. population) (vs. population) ↓ < 0.05 (vs. < 60 y) ↓ < 0.02 (vs. < 60 y) ↓ < 0.02 (vs. 60–69 y) ↓ < 0.03 (vs. 60–69 y)	↓ < 0.02 (vs. population) (vs. population) ↓ < 0.02 (vs. < 60 y) ↓ < 0.03 (vs. 60–69 y)	N/S	N/S	N/S
Marital status:								
Married	48 (70.6)		N/S	↓ < 0.01 (vs. population)	N/S	N/S	N/S	N/S
Not married	20 (29.4)		N/S	N/S	N/S	N/S	N/S	N/S
Education:								
Elementary school	16 (23.6)		N/S	N/S	N/S	N/S	N/S	N/S
Middle school	21 (30.9)		N/S	N/S	N/S	N/S	N/S	N/S
High school	19 (27.9)		N/S	N/S	N/S	N/S	N/S	N/S
University	12 (17.6)		N/S	N/S	N/S	N/S	N/S	N/S

Table II. Patient-related factors affecting WHOQOL-BREF questions and domains

Patient-related factors	Participants		WHOQOL Questions		WHOQOL Domains			
			1. How do you rate your quality of life?	2. How satisfied are you with your health?	Physical health	Psychological	Social relationships	Environment
	N (%)	M [range] (SD)	Sample vs. population/sample (p)	Sample vs. population/sample (p)	Sample vs. population/sample (p)	Sample vs. population/sample (p)	Sample vs. population/sample (p)	Sample vs. population/sample (p)
Months on dialysis:								
		46.6 [1–317] (61.1)						
< 24	30 (46.2)	9.8 [1–20] (5.4)	N/S	N/S	N/S	N/S	N/S	N/S
24–60	20 (30.8)	39.7 [24–60] (12.7)	N/S	N/S	N/S	N/S	N/S	N/S
> 60	15 (23.1)	129.3 [63–317] (79.3)	N/S	N/S	N/S	N/S	N/S	N/S
Vascular access:								
AVF:								
	59 (88.1)		N/S	N/S	N/S	N/S	N/S	N/S
Wrist	32 (47.8)		N/S	↓ < 0.04 (vs. population)	N/S	N/S	N/S	N/S
Forearm	15 (22.4)		N/S	N/S	N/S	N/S	N/S	N/S
Elbow	10 (14.9)		N/S	N/S	N/S	N/S	N/S	N/S
Arm	2 (3.0)		N/S	N/S	↓ < 0.05 (vs. population)	N/S	N/S	N/S
CVC:								
	8 (11.9)		N/S	N/S	N/S	N/S	N/S	N/S
Not-tunneled CVC	3 (4.5)		↓ < 0.02 (vs. tunneled)	↓ < 0.02 (vs. tunneled)	N/S	N/S	N/S	N/S
Not-tunneled CVC	5 (7.5)		↑ < 0.02 (vs. not tunneled)	↑ < 0.02 (vs. not tunneled)	N/S	N/S	N/S	N/S
Kidney transplant in the past:								
	5 (7.2)		N/S	N/S	N/S	N/S	N/S	N/S
No	64 (92.8)		N/S	N/S	N/S	N/S	N/S	N/S
Willingness for kidney transplant:								
	35 (53.0)		N/S	N/S	↑ < 0.03 (vs. “no”)	↑ < 0.03 (vs. population) ↑ < 0.03 (vs. “no”)	N/S	N/S
No	31 (47.0)		N/S	N/S	↓ < 0.01 (vs. population) ↓ < 0.03 (vs. “yes”)	↓ < 0.03 (vs. population) ↓ < 0.03 (vs. “yes”)	N/S	N/S
Fulfillment of medical recommendations:								
	43 (68.3)		N/S	N/S	N/S	N/S	N/S	N/S
No	20 (31.7)		N/S	N/S	N/S	N/S	N/S	N/S

AVF – arteriovenous fistulas, CVC – central venous catheters.

Table III. Dialysis-related factors affecting WHOQOL-BREF questions and domains

Dialysis-related factors	Participants		WHOQOL Questions			WHOQOL Domains			
			1. How do you rate your quality of life?	2. How satisfied are you with your health?		Physical health	Psychological	Social relationships	Environment
	N (%)	M [range] (SD)	Sample vs. population/sample (p)	Sample vs. population/sample (p)	Sample vs. population/sample (p)	Sample vs. population/sample (p)	Sample vs. population/sample (p)	Sample vs. population/sample (p)	Sample vs. population/sample (p)
Dialysis duration [h]:		3.9 [3–5] (0.34)							
< 4	18 (26.9)	3.5 [3–3.75] (0.14)	N/S	N/S	N/S	N/S	N/S	↑ < 0.05 (vs. population) ↑ < 0.04 (vs. “4”)	N/S
4	38 (56.7)	4 [4] (0)	N/S	N/S	N/S	N/S	N/S	↓ < 0.04 (vs. “<4”)	N/S
> 4	11 (16.4)	4.5 [4.15–5] (0.28)	N/S	N/S	N/S	N/S	N/S	N/S	N/S
Kt/V:		1.30 [0.81–3.1] (0.33)							
< 1.2	26 (38.8)	1.04 [0.81–1.19] (0.11)	N/S	N/S	N/S	N/S	N/S	N/S	N/S
1.2–1.4	23 (34.3)	1.30 [1.20–1.39] (0.06)	N/S	↓ < 0.04 (vs. “> 1.4”)	↓ < 0.03 (vs. “> 1.4”)	N/S	N/S	N/S	N/S
> 1.4	18 (26.9)	1.67 [1.41–3.11] (0.38)	N/S	↑ < 0.04 (vs. “1.2–1.4”)	↑ < 0.03 (vs. “1.2–1.4”)	N/S	N/S	N/S	N/S
URRL:		0.66 [0.51–0.90] (0.07)							
< 0.65	28 (41.8)	0.59 [0.51–0.65] (0.04)	N/S	N/S	N/S	N/S	N/S	N/S	N/S
0.65–0.70	22 (32.8)	0.68 [0.65–0.70] (0.01)	↓ < 0.04 (vs. „ > 0.70”)	N/S	↓ < 0.05 (vs. “> 0.70”)	N/S	N/S	N/S	N/S
> 0.70	17 (25.4)	0.75 [0.71–0.90] (0.05)	↑ < 0.02 (vs. population) ↑ < 0.04 (vs. “0.65–0.70”)	N/S	↑ < 0.03 (vs. population) ↑ < 0.05 (vs. “0.65–0.70”)	N/S	N/S	N/S	N/S
UF [ml]:		2282 [300–4200] (907)							
≤ 1500	15 (22.4)	973 [300–1500] (417)	N/S	N/S	N/S	N/S	N/S	N/S	N/S
1501–2599	27 (40.3)	2181 [1600–2500] (312)	N/S	N/S	N/S	N/S	N/S	N/S	N/S
≥ 2600	25 (37.3)	3176 [2600–4200] (398)	N/S	N/S	N/S	N/S	N/S	N/S	N/S

URR – urea reduction ratio, UF – ultrafiltration.

## Statistical analysis

Statistical analysis was performed with StatPac software, version 4.0. Mean, range and standard derivation (SD) were calculated for continuous variables: age, gender, months on HD, dialysis duration, Kt/V, URR and UF. The variables were compared by the Student *t*-test. Means of three or more groups were compared with the ANOVA test. A *p*-value of less than 0.05 was considered to be statistically significant.

## Results

Participants, including 23 (33.3%) women and 46 (66.7%) men, ranged in age from 28 to 84, with a mean age of  $62.6 \pm 12.2$  (Table I).

No statistically significant relations were found between any of the WHOQOL-BREF domains or questions and the following demographic and patient-related factors: gender, education, months on HD, kidney graft in the past and fulfillment of medical recommendations (Tables I, II).

Despite a lack of age-related differences in the rating of the first question, in the Psychological, Social relationship and Environment domains, the eldest group (over 70 years old) rated significantly lower both the satisfaction with health ( $p < 0.01$ ) and Physical health domain ( $p < 0.02$ ) (Table I).

Married HD patients rated their satisfaction with health (question 2) significantly lower ( $p < 0.01$ ). However, marital status did not reflect the rating of overall QOL (question 1) or any of the four WHOQOL-BREF domains (Table I).

HD patients with wrist arteriovenous fistulas (AVFs) were less satisfied with their health (question 2) ( $p < 0.04$ ), while those with arm AVFs rated the Physical health domain significantly lower ( $p < 0.05$ ). Among HD patients with central venous catheters (CVCs) those with tunneled CVCs rated both their QOL (question 1) and satisfaction with their health (question 2) higher, with  $p < 0.02$  and  $p < 0.02$ , respectively (Table II). Other significant differences in answering the questions or rating the domains related to vascular access were excluded. Additionally, there were no significant differences between "AVF" and "CVC" patients (Table II).

Although history of kidney graft did not influence the rating of any WHOQOL-BREF questions or domains, those who do not want to receive a kidney graft in the future rate both the Physical health and the Psychological domains lower, with  $p < 0.01$  and  $p < 0.03$ , respectively (Table II).

Patients whose HD duration does not exceed 4 h rated the Social relationship domain significantly higher ( $p < 0.05$ ). Influence of HD duration on two independent questions and Physical health, Psychological or Environment domains was excluded (Table III).

Kt/V higher than 1.4 compared with 1.2–1.4 was associated with higher rating of overall satisfaction with health (question 2) and the Physical health domain ( $p < 0.04$  and  $p < 0.03$ , respectively). URR higher than 0.70 was associated with higher rating of both overall QOL (question 1) and the Physical health domain ( $p < 0.02$  and  $p < 0.03$ , respectively). The HD-related factors including Kt/V, URR and UF did not influence any other domains or questions (Table III).

## Discussion

A growing group of ESRD patients require adequate management, including adequate HD, in order to prolong their life. However, these patients consider HD as a time-consuming procedure, which needs to be repeated three times a week. Additionally, HD may cause QOL impairments [1, 2, 16, 17]. The ESRD patients, regardless of the treatment modality, have to manage many adversities: cognitive impairment, physical symptoms, fluid and dietary restriction, and changed body image [3, 5, 6, 15, 18, 19]. They may have many risk factors of reduced QOL such as diabetes, hypertension, dyslipidemia, hypoxemia, proinflammatory state, as well as fluid, osmolar and uremic toxin variations [6]. Additionally, they feel a significant lack of sufficient control over the whole treatment [3, 6, 15]. These factors affect the whole life of ESRD patients, including their physical and social relations. Patients need to reconsider their personal, social and professional goals when living with a chronic illness such as ESRD and undergoing HD [3, 15, 20].

WHOQOL-BREF is a self reported QOL inventory [11] (Tables I–III). It was administered to 69 ESRD patients undergoing HD recruited from one hospital-based dialysis unit. They were asked to answer demographic questions, fill in the medical history data along with 26 questions included in WHOQOL-BREF, taking into account the last 2 weeks. Those who had problems filling out the forms could get help from the staff or their families.

The recovery period after a HD session affects QOL. Just after the HD session patients may feel tired and in need of rest or sleep [21]. For this reason our patients were asked to fill in the questionnaire during the day after HD, when their cognitive functions were optimal.

The first question was focused on rating patients' overall QOL. The patients whose URR exceeded 0.70 rated the QOL significantly higher ( $p < 0.02$ ) (Table III). Additionally, patients with tunneled CVCs rated both the overall QOL (question 1) and satisfaction with health (question 2) significantly higher than those with not-tunneled CVCs ( $p < 0.02$ ,  $p < 0.02$ , respectively) (Table II). However, no significant difference was observed



between “CVC” and “AVF” groups (Table II). Patients with an acute vascular access such as not-tunneled CVC may not accept the new chronic disease and a time-consuming HD procedure, spending a long time three times a week in the HD unit and being tired for a long time after the HD session [3, 6, 15, 21]. These factors may explain the reduced overall rating of both the QOL and the satisfaction with health (Table II).

The satisfaction with health was rated in the second question significantly lower by the eldest patients aged over 70 years ( $p < 0.01$ ), married ( $p < 0.01$ ) and those with wrist AVF ( $p < 0.05$ ) (Tables I, II). Additionally, the eldest patients rated the Physical health domain significantly lower ( $p < 0.02$ ) (Table I). For the eldest patients the reduced satisfaction with overall health and the Physical health domain may be associated not only with ESRD and HD *per se*, but also with their age and age-related impairments and weakness [4–6]. In the case of married patients, ESRD and HD affect not only their own life, but also the life of a spouse and therefore may lower satisfaction with overall health (Table I) [6]. Wrist AVF is obviously the best vascular access. However, anastomosis located on the wrist, the scar and the dilated vein easy for others to see may cause discomfort and embarrassment (Table II) [4, 5].

According to the WHO definition health can be considered in a physical, mental and social dimension [1]. The Physical health domain of the WHOQOL-BREF assesses activities of daily living, dependence on medicinal substances and medical aids, energy and fatigue, mobility, pain and discomfort, work capacity, sleep and rest [11, 12]. The Physical health domain was rated significantly lower not only by the eldest patients ( $p < 0.02$ ), but also by those with arm AVFs ( $p < 0.05$ ) and those who do not want to receive a kidney graft ( $p < 0.01$ ) (Tables I, II). Patients who do not want to be a recipient of a kidney graft rated both Physical health ( $p < 0.01$ ) and Psychological ( $p < 0.03$ ) domains lower (Table II). The Physical health domain was rated significantly higher by those with URR over 0.70 ( $p < 0.03$ ) (Table III). The AVF location at the arm level may follow more distal previous AVFs which failed or be a consequence of peripheral vascular difficulties caused by e.g. diabetes [4, 5]. This may affect many aspects of the patient's life, including the physical dimension [6, 16]. Unwillingness to be a recipient of a kidney graft, which is the best kidney replacement therapy, may be a result of a lack of energy and mobility necessary to go through the graft procedure as well as a desire to avoid greater dependence on medical staff and medical aids following the graft [3, 15]. The HD patients besides the dialysis *per se* need to manage the physical

symptoms and dietary regimes and accept changes in the overall body image. They have a higher rate of suicide and more depressive symptoms [3, 22]. Depression may be caused by HD modality, when patients have to be continually connected to the HD machine and experience significant restrictions in independent living [3]. The HD patients report insufficient availability of health services, difficulties in transportation, finances and opportunities for recreation, and acquiring skills and knowledge [15]. Authors have drawn attention to psychosocial problems of HD patients including the influence of HD on their careers, visits three times a week to the dialysis center and a long time spent on HD [3, 23].

The Psychological domain covers: bodily image and appearance, negative and positive feelings, self-esteem, spirituality, religion and personal beliefs, thinking, learning, memory and concentration [8, 11, 12]. This domain was rated significantly lower by those who do not want to receive a kidney graft ( $p < 0.03$ ), while those who want a kidney graft rated this domain significantly higher ( $p < 0.03$ ) (Table II). Patients who are not satisfied with their body image experience more negative feelings. This may result in unwillingness to receive a transplant and go through a variety of intense post-procedure treatments [3, 8].

The Social relationship domain assesses: personal relationships, social support and sexual activity [11, 12]. Patients whose HD took less than 4 h rated the Social relationship domain significantly higher ( $p < 0.05$ ) (Table III). Duration of a single HD is the only factor significantly influencing the Social relationship domain. Authors point out that long HD impedes social relationships. HD patients report experiencing less support from their community. It may be associated with the restrictions on their lives and being dependent on the HD procedure, which may cause social isolation [15, 24]. The HD treatment is a continuous and stressful condition. The treatment is received in the centre three times a week and the waiting time in the HD unit is relatively long [3, 15]. When the HD is prolonged, patients spend a longer time in the HD unit three times a week. This may affect patients' careers and cause psychosocial problems. For this reason it is noted that patients may feel that the social support is not sufficient enough [3, 17, 24].

The Environment domain covers: financial resources; freedom, physical safety and security; accessibility and quality of health care and social care; home environment; opportunities for acquiring new information and skills; opportunities for recreation, leisure activities; physical environment such as pollution, noise, traffic, climate, transport [11, 12]. The demographic, patient-related and di-

alysis-related factors had no significant impact on the Environment domain scoring (Tables I–III).

The study has some obvious limitations. The first one is the limited population of a single HD unit. The population of ESRD patients is getting old. Also the percentage of coexisting diseases including diabetes is high. This could cause difficulty in completing the questionnaires and may explain why 49.9% of patients did not participate in the survey. Patients completed the questionnaires at their homes to limit the influence of the researcher.

In conclusion, the factors lowering the scores for particular questions and domains of the WHOQOL-BREF questionnaire were: senility, marriage, wrist and arm AVF, not-tunneled CVC (vs. tunneled), and unwillingness to have a kidney graft.

The factors that increased the scores for particular questions and domains of the WHOQOL-BREF questionnaire were: short HD, tunneled CVC (vs. not-tunneled), and higher URR.

This is a cross-sectional study of the population of a single hospital-based HD unit and the results cannot be generalized. However, the data suggest that the group of HD patients, especially the eldest of them, should be given special attention. It indicates that despite an awareness and a necessity of a kidney graft as the best kidney replacement therapy, there is a large group among the HD patients who do not want to receive this treatment. The medical professionals in HD units should remember that patients may not feel comfortable with their disease and satisfied with their body image affected by disease and therapy and may not accept even a treatment which is recommended.

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## Conflict of interest

The authors declare no conflict of interest.

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