ORIGINAL ARTICLE

The effect of renal transplantation on quality of sleep in former dialysis patients

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SUMMARY

Data on sleep quality in renal transplanted (RTX) patients are scarce, and longitudinal studies are lacking. The purpose of this study was to assess the prevalence of sleep complaints in RTX patients and identify variables associated with improvement in sleep quality. In a longitudinal study, 301 dialysis patients were followed for up to 5.5 years, during which time 142 were transplanted. Out of the transplanted patients, a total of 110 were eligible for inclusion. Sleep quality and depression were assessed with the validated questionnaires Pittsburgh Sleep Quality Index (PSQI) and Beck Depression Inventory (BDI), and data were collected during dialysis and after RTX. Based on PSQI scores, 59% were characterized as poor sleepers after RTX compared to 75% when in dialysis ($P = 0.016$). A total of 46% experienced a clinical relevant improvement in overall sleep quality, while 21% experienced a clinical relevant deterioration. In multivariable analyses, clinical meaningful change in sleep quality was not associated with either depressive symptoms assessed with BDI or other clinical variables. Sleep quality improved after RTX in nearly half of the patients, but poor sleep quality was prevalent in RTX patients. Therefore, sleep quality should routinely be assessed in RTX patients.

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Key words
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Introduction

Sleep complaints are common in all stages of chronic kidney disease (CKD) and include among other symptoms of sleep apnoea, insomnia and excessive daytime sleepiness [1]. Disorders such as restless legs syndrome and periodic limb movement disorder (PLMD) are frequent in patients with end-stage renal disease (ESRD) and often lead to sleep deprivation and reduced quality of sleep [2]. Sleep complaints are among the most disturbing symptoms experienced by the patients in chronic dialysis treatment [3], and are associated with reduced health-related quality of life (HRQoL) and depression [4]. Furthermore, it has been shown that poor sleep quality is an independent predictor of mortality in patients with ESRD [5,6].

Studies have shown that HRQoL and sleep complaints worsen with advancing stages of CKD, with the worst self-perceived HRQoL and quality of sleep seen in dialysis patients [7]. HRQoL and quality of sleep are less explored in renal transplanted (RTX) patients. In cross-sectional studies, the quality of sleep seems better in RTX patients compared to dialysis patients [8,9]. To our knowledge, only one longitudinal study has assessed sleep with polysomnography in renal patients in the transition from dialysis to transplantation [10], while there is no study

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exploring self-perceived quality of sleep. Cross-sectional studies have shown that patients who have received a renal graft have less sleep apnoea [11] and reduced PLMD [12]. Kidney transplantation is regarded as the optimal treatment option for patients with ESRD, as transplantation alleviates the problems associated with uraemia and prolongs survival. Furthermore, we have recently shown in a longitudinal study that HRQoL improved from dialysis to RTX [13]. Our hypothesis is thus that also quality of sleep would improve after RTX. The aims of this study were therefore first to assess the prevalence of sleep complaints and associated symptoms in the transition from dialysis to transplantation, and second to explore variables associated with change in quality of sleep after transplantation.

Patients and methods

The recruitment of patients and study design has been described elsewhere and is only briefly delineated below [4,13]. Patients were recruited and consecutively included between August 2005 and February 2007. Patients in dialysis units from ten different hospitals providing renal health care to about two million inhabitants, about half of the Norwegian population at that time, were approached and considered for eligibility. All adult patients (i.e. ≥18 years) receiving haemodialysis (HD) or peritoneal dialysis (PD) were screened for study participation and could be included if they had been in dialysis for >2 months and were able to understand and write Norwegian. Severely disturbed cognitive function based on clinical judgement, psychosis, drug abuse and hospitalization during the investigation period led to exclusion. However, patients could be included 4 weeks or more after hospital discharge if they were in stable clinical condition. Both oral and written information about the study were given to the patients, and signed informed consent was required before enrolment. Self-administered questionnaires were answered 30 min into a regular midweek HD session for HD patients or after a scheduled midweek control at the outpatient clinic for PD patients. All questionnaires had to be returned before the patients left the renal ward. Clinical information was obtained from patient records.

Between July 2010 and September 2012, all patients that were enrolled at baseline were approached and invited to participate in the follow-up study. The same exclusion criteria were applied in the follow-up study. Both oral and written information about the follow-up study were given to the patients, and signed informed consent was required before enrolment. The same self-reported questionnaires were answered after a scheduled control at the outpatient clinic, and information on comorbidities was obtained from patient records.

The Regional committees for medical and health research ethics in Norway approved the study protocol, and concession to file patient information was obtained from the Norwegian Data Protection Authority. The study was carried out in accordance with the Helsinki Declaration.

Instruments

The Pittsburgh Sleep Quality Index (PSQI) questionnaire [14] assesses subjective sleep quality in the preceding month and contains 19 questions for the patient to answer (http://www.psychiatry.pitt.edu/node/8240). These 19 items are summarized into seven components (ranging from 0, i.e. no difficulties, to 3, i.e. severe difficulties): subjective sleep quality, sleep onset latency, sleep duration, sleep efficiency, sleep disturbance, use of hypnotic medication and daytime dysfunction. These seven components provide a sum (0–21) defined as the global PSQI score, with higher scores reflecting lower sleep quality. Patients scoring >5 were characterized as poor sleepers. Missing data led to exclusion of the whole questionnaire.

The Beck Depression Inventory (BDI) was used to assess depressive symptoms. It consists of 21 items, each answered on a scale from 0 to 3, which gives a total score ranging from 0 to 63 where a higher score reflects a more pronounced depressive state. It has been used in both the general and CKD population [15,16]. In the literature, different cut-off values have been used to characterize clinical significant depressive symptoms. Based on a sensitivity analysis by Preljevic *et al.* [17] from our group, BDI value >16 was chosen as cut-off value for clinical significant depressive symptoms.

To assess comorbidity, the Charlson Comorbidity Index (CCI) [18] was used. It provides a weighted score for 17 predefined comorbid conditions: coronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, mild liver disease and diabetes are given one point. Hemiplegia, moderate or severe renal disease, diabetes with end-organ damage and any tumour, leukaemia or lymphoma are given two points. Moderate or severe liver disease is given three points. Metastatic solid tumours and AIDS are given six points. In the original version, each decade >40 years of age was given one point, but as age was entered as an independent variable

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in the regression analyses, age was not calculated into the total CCI score. We used the modified CCI as previously described by Beddhu *et al.* [19].

Statistics

Data are presented as mean ± standard deviation (SD) or as median with interquartile range (IQR) if the data distribution was skewed. Patients were characterized as poor (PSQI >5) or good (PSQI ≤5) sleepers based on the global PSQI score. The change in PSQI score (Δ PSQI) was calculated as the pre-transplantation PSQI score subtracted from the post-transplantation PSQI score (i.e. positive Δ PSQI scores were considered as a worsening of sleep quality). A change equivalent to half of the SD in the baseline PSQI score was considered as a clinically relevant change [20]. Pre- and post-transplantation comparisons were carried out using paired Student's *t*-test for normally distributed continuous data, Wilcoxon signed-rank test for skewed data and McNemar's test for categorical data. For comparisons between good and poor sleepers, independent Student's *t*-test was used for normally distributed data and Mann–Whitney *U*-test for skewed data and chi-square test for dichotomized data. Correlation coefficients were calculated using Spearman's rho. To assess possible determinants for improved sleep quality after RTX, multivariable logistic regression models were built. The Δ PSQI was dichotomized into a clinically relevant positive improvement (i.e. lower PSQI scores after RTX) versus no change/deterioration and set as the dependent variable. The independent sociodemographic and clinical variables that were considered are presented in Table 1, and variables for the logistic regression model were identified based on clinical assessments and reports by others. The independent variables that were identified were age, gender, CCI, dialysis vintage and BDI. They were entered into a logistic multivariable regression analysis. Skewed variables were dichotomized. All independent variables were pre-transplantation values. The assumptions for all statistical analyses were checked and adequately met.

The statistical analyses were carried out using IBM SPSS statistical software (IBM SPSS Inc. Chicago, IL, USA; v. 22.0). A significance level of 0.05 was chosen for all analyses.

Results

A total of 301 dialysis patients was enrolled in the original study. Out of these patients, 142 died during the observation period and 31 did not meet the inclusion criteria for the follow-up. A total of 142 patients were transplanted, and out of these, 110 (mean age 57 ± 15 years, males 66%) could be included in this study (Fig. 1). They answered the questionnaires 7 (3–15) months after initiation of dialysis and were transplanted after 22 (15–36) months in dialysis. The 110 patients were then re-examined 42 (34–50) months after the RTX. Basic characteristics of the study population are given in Table 1.

Poor sleepers had more depressive symptoms than good sleepers [BDI score 8 (3–12) vs. 4 (1–8), $P = 0.04$]. No difference could be observed between poor and good sleepers after RTX with regard to total dialysis vintage or dialysis modality, time from RTX or CCI score (data not shown). Neither did the use of immunosuppressants or diuretics, GFR, BMI or gender differ between poor and good sleepers (data not shown).

The PSQI score was significantly reduced after RTX, indicating improved quality of sleep (Table 1). The median change in the PSQI score was −1.0 (IQR −6.5 to 2.0). Patients that were classified as poor sleepers in dialysis showed greater improvement in quality of sleep than those classified as good sleepers (Δ PSQI score −3.5 ± 5.2 vs. 1.8 ± 3.2, $P < 0.001$). After RTX, a total of 58% ($n = 45$) had a lower PSQI score indicating better quality of sleep, 9% ($n = 7$) had the same, and 33% ($n = 25$) had a higher PSQI score, signifying reduced quality of sleep.

The threshold for a clinical relevant change was 2.2, half of the SD of the baseline PSQI score. Thus, a change in PSQI score ≥2.2 was considered a clinically relevant change. A total of 46% ($n = 35$) experienced a clinical relevant improvement in sleep quality, while 21% ($n = 16$) a clinical relevant worsening. There were observed less depressive symptoms after RTX, but the proportion of patients characterized as depressed did not change (Table 1).

Changes in different aspects of quality of sleep in the transition from dialysis to transplantation are presented in Fig. 2. In patients that experienced a clinical relevant improvement of overall sleep quality, significant improvement was observed in all components except for sleep disturbance, while patients that experienced a clinical relevant deterioration of overall sleep quality, significant improvement were observed in sleep onset latency and sleep disturbance only (data not shown).

The change in PSQI scores was associated with pre-RTX BDI scores ($\rho = -0.26$, $P = 0.037$). Clinically relevant change in PSQI scores was not associated with any

Table 1. Characteristics of former dialysis patients (n = 110) before and after renal transplantation.

	Dialysis	After transplantation	*n*	*P*-value
Clinical and sociodemographic variables				
Age (years)	51.3 ± 14.8	56.7 ± 14.7	110	<0.001
Male, *n* (%)		73 (66.4)	110	
Dialysis vintage (months)*	22 (15–36)		109	
Haemodialysis, *n* (%)	83 (76)		110	
Time since transplantation (months)*		42 (34–50)	109	
Systolic blood pressure (mmHg)	141.5 ± 21.1	135.8 ± 14.8	93	0.029
Diastolic blood pressure (mmHg)	79.7 ± 12.0	77.2 ± 9.7	92	0.095
Haemoglobin (g/dl)	12.2 ± 1.6	13.4 ± 1.8	108	<0.001
Albumin (g/l)	39.3 ± 4.3	42.8 ± 3.5	105	<0.001
Parathyroid hormone (pmol/l)*	26 (15–45)	12 (8–21)	83	<0.001†
Glomerular filtration rate (ml/min/1.73 m^2)*	6 (5–8)	54 (45–72)	109	<0.001†
Body mass index (kg/m^2)	25.9 ± 4.3	26.8 ± 5.3	96	0.012
Coronary artery disease, *n* (%)	14 (12.7)	22 (20.0)	110	0.021‡
Peripheral vascular disease, *n* (%)	5 (4.5)	13 (11.8)	110	0.021‡
Chronic pulmonary disease, *n* (%)	12 (10.9)	14 (12.7)	110	0.727‡
Diabetes mellitus, *n* (%)	19 (17.3)	25 (22.7)	110	0.109‡
Charlson comorbidity index	3.0 ± 1.5	3.4 ± 1.7	108	0.001
Use of sleep medication, *n* (%)	22 (20.0)	8 (7.3)	109	0.004‡
Use of immunosuppressants, *n* (%)		109 (100.0)	109	
Prednisolone, *n* (%)		104 (98.1)	106	
Cyclosporin, *n* (%)		61 (56.0)	109	
Tacrolimus, *n* (%)		38 (34.9)	109	
Mycophenolate mofetil, *n* (%)		102 (93.6)	109	
Everolimus, *n* (%)		15 (13.8)	109	
Azathioprine, *n* (%)		2 (1.8)	109	
Quality of sleep and depression				
Global Pittsburgh Sleep Quality Index (PSQI) score	8.8 ± 4.6	6.6 ± 3.9	77	0.001
Poor sleepers (i.e. PSQI score >5), *n* (%)	72 (75)	51 (59)	77	0.016‡
Beck depression inventory (BDI)*	8 (5–15)	5 (2–10)	71	0.004†
Depressed (i.e. BDI score >16), *n* (%)	11 (15.5)	10 (14.1)	71	1.000‡

Charlson comorbidity index is calculated without age after Beddhu *et al.* [19]. *P*-values are calculated with Student's paired samples *t*-test unless otherwise stated.

*Data given as median with interquartile range.

†*P*-value calculated with Wilcoxon signed ranks test. Data are given as mean ± standard deviation unless otherwise stated.

‡*P*-value calculated with McNemar's test.

clinical or sociodemographic variables in multivariable analyses, details in Table 2.

Discussion

To the best of our knowledge, this is the first longitudinal study that has assessed self-perceived quality of sleep in dialysis patients in the transition from dialysis to RTX. We observed that nearly half of the patients experienced a clinical relevant improvement in sleep quality, yet still close to 60% were characterized as poor sleepers after RTX. It is surprising that the prevalence of poor sleepers remained so high after transplantation. However, our longitudinal study corroborated previous cross-sectional studies in transplanted patients, which have found a prevalence of poor sleepers between 52% and 62% [21–23]. These observations are consistent with estimates from other solid organ transplantation populations [24,25], but still higher than in the general population [21]. It has been hypothesized that the higher frequency of poor sleepers seen in RTX patients compared to the general population might be secondary to comorbidities [21,22]. This could be true, although patients were reported with more comorbidity after RTX in the present study. A plausible explanation for that may be that patients are thoroughly investigated

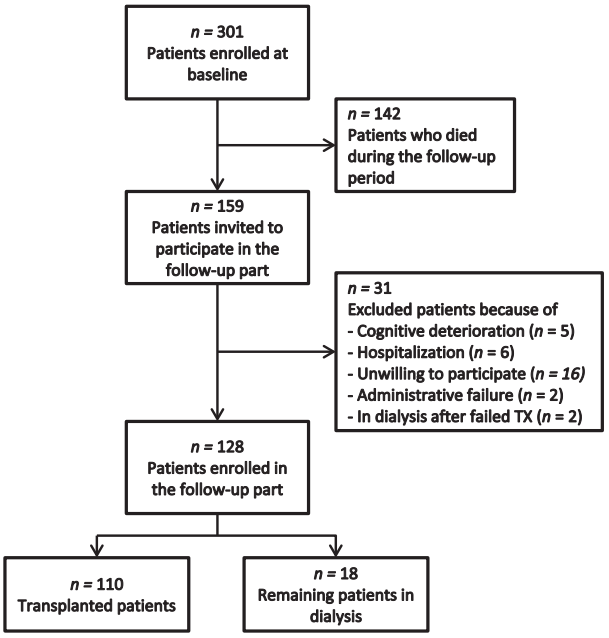

Figure 1 Flowchart of the recruitment process.

prior to transplantation, and conditions that were not known in dialysis may be revealed.

Immunosuppressive drugs, especially corticosteroids and calcineurin inhibitors, may affect sleep [26,27]. In the present study, all transplanted patients except two were treated with corticosteroids and the majority with calcineurin inhibitors. Furthermore, only 7% of the current transplanted patients used hypnotic medication, fewer than what has been observed in dialysis and actually less than in the general population [28]. The low number of users of hypnotic drugs after transplantation is noteworthy. Combined, the treatment with immunosuppressants and the restricted use of hypnotics may contribute to the poor sleep quality experienced by a number of the RTX patients and may perhaps explain the clinically relevant deterioration in sleep quality seen in some of the patients. The reduced use of sleep medication after RTX could be due to fear of interactions with other drugs or that sleep disturbances had not been given any consideration from either the patients or

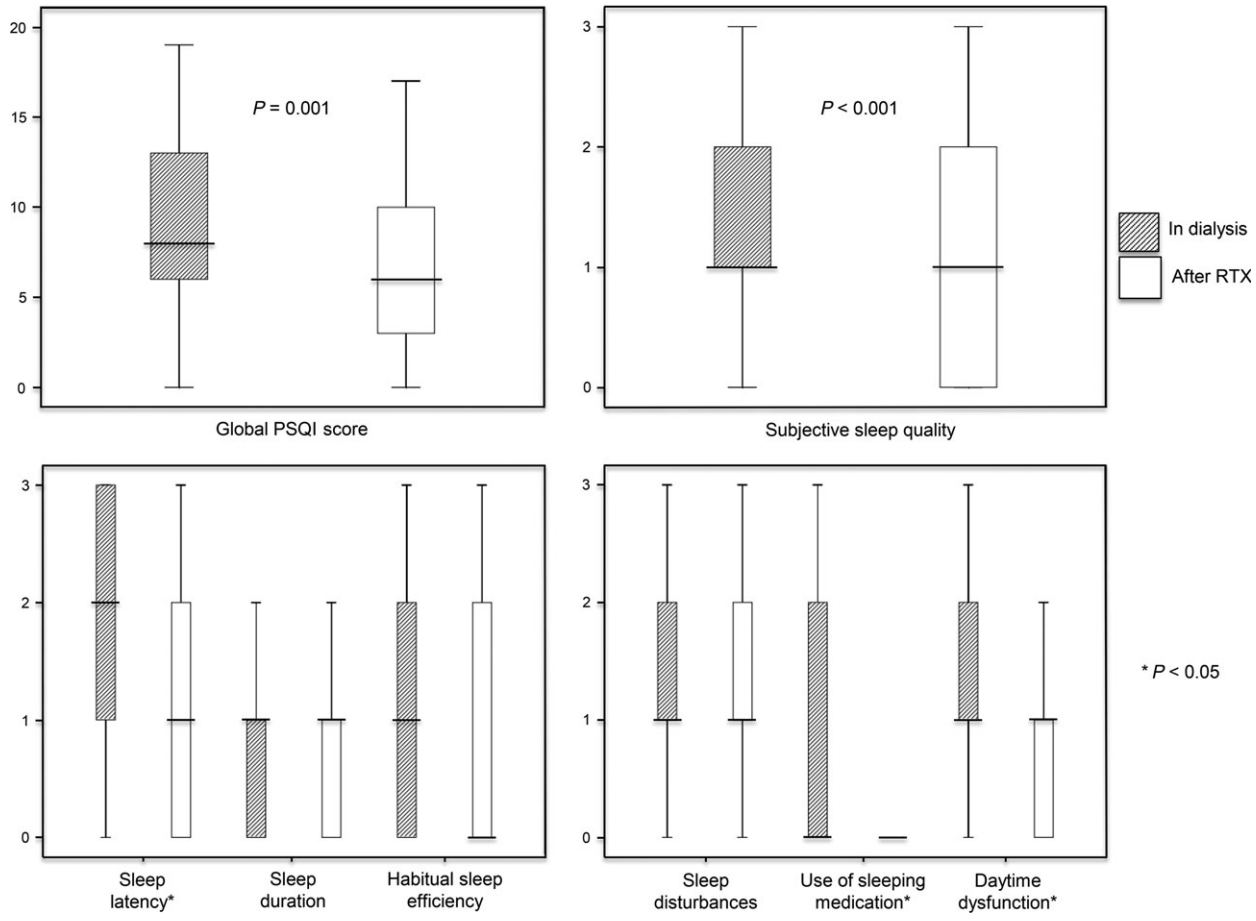

Figure 2 Comparison of Pittsburgh Sleep Quality Index scores from before and after transplantation.

Table 2. Multivariable regression model with the clinical significant improvement (n = 28) versus no improvement (n = 33) in sleep quality as the dependent variable.

	Crude odds ratio (OR) with 95% confidence interval (CI)	Adjusted OR with 95% CI	*P*-value
Age (per 10 years)	0.85 (0.62–1.16)	0.80 (0.55–1.19)	0.27
Gender (female versus male)	0.65 (0.25–1.69)	0.81 (0.23–2.90)	0.75
Charlson comorbidity index (CCI)	1.25 (0.94–1.66)	1.41 (0.99–2.01)	0.06
Dialysis vintage (>22 months vs. <22 months)	0.34 (0.13–0.86)	0.52 (0.16–1.65)	0.27
Beck depression inventory (score >16 vs. <16)	1.03 (0.25–4.29)	0.76 (0.16–3.67)	0.74

The ΔPSQI score was calculated as the pretransplantation score subtracted from the post-transplantation score and dichotomized into a clinically significant positive change (i.e. ≥3) versus no/negative change. Variables were identified based on clinical assessment or reports by others. The variables were entered into a multivariate logistic regression model as presented here. The Beck Depression Inventory score was dichotomized into >16 (i.e. clinically significant depressive symptoms), and dialysis vintage was dichotomized into >22 months based on median dialysis vintage. CCI was calculated without age after Beddhu *et al.* [19].

the physicians. Also, all patients reported less sleep onset latency after RTX, signifying that the need of hypnotics might be lower than in dialysis.

Depressive symptoms are common in dialysis patients and related to both poor sleep quality and poor HRQoL [17]. Less depressive symptoms were seen after RTX in the present study. This is in accordance with cross-sectional studies [29–31]. However, the proportion of patients classified as clinically significant depressed did not change from dialysis to RTX in our prospective cohort study. The prevalence of physician-diagnosed depression in RTX and dialysis patients did not differ according to a recent meta-analysis [32]. An apparent shortcoming in these studies is the cross-sectional design, which inhibits causative conclusions to be made. In the present study, depressive symptoms were not associated with change in sleep quality from dialysis to transplantation. However, interpreting associations between quality of sleep and depression in the present study would have required another design as well as more extensive diagnostic work-up with regard to depression.

The change in PSQI scores from dialysis to transplantation was not associated with age, gender, comorbidity, dialysis vintage or depression in a multivariable analysis. The improved quality of sleep after RTX could simply be explained by absence of uremic symptoms and actual relief of being freed from tiresome dialysis treatment. That some patients experienced worsened sleep quality was surprising and could not be explained by depression. However, other factors such as fear of graft loss, worries of drug-related side effects or perhaps overestimated expectation of how life would be after RTX may have contributed to the increased sleep disturbances.

There are some limitations that should be mentioned. Polysomnography would have been desirable, but at the time of the first study, ambulatory polysomnography had just been introduced in Norway and was not an available option. The alternative was to hospitalize patients overnight, but too few were willing. Nearly all patients were Caucasian. This may limit the applicability to other transplant populations. Sleep complaints may show seasonal variation with most sleep problems during winter time when daylight is limited [33]. Our study was not designed to detect possible seasonal variations. On the other hand, the strengths of this study were the longitudinal design, that is in the transition from dialysis to transplantation. When assessing patient-reported outcome measures, differences that are statistically significant might not be perceived as important for the patient. This has been adjusted for by only considering changes that are clinically relevant. Several methods are available, but pragmatically, we have chosen a distribution-based method [34,35], which also has been used in other study populations [36,37]. This method also takes possible regression to the mean into account. Regression to the mean is a statistical phenomenon that states that extreme variables tend to lie closer to the observed mean on later measurements [38]. The study population comprised almost one-third of the total Norwegian dialysis patients at the outset of the first study and age, gender, cause of renal failure,

prevalence of diabetes and cardiovascular disease were comparable to the total Norwegian dialysis population. Also, the catchment area for the ten hospitals included comprised about two million inhabitants, close to half of the Norwegian population at that time. A large proportion of the transplanted patients that were eligible participated in the follow-up study and none was lost to follow-up.

In summary, although transplantation may improve quality of sleep in close to half of the patients, a high number of patients still suffered from sleep disturbances after RTX. We conclude that all patients should be assessed for possible sleep complaints after RTX and that chronic sleep problems should be routinely assessed in the clinical setting. For RTX patients with poor quality of sleep, a treatment plan should be discussed. Improved sleep hygiene should certainly be advised, and in some instances, cognitive behavioural therapy, hypnotics and other medication should be considered. Also, more research is warranted to identify why poor sleep quality was maintained even after RTX, and why some patients experienced worsened quality of sleep after RTX.

Authorship

FBB: has participated in the cleaning of the data, conducted the statistical analyses and drafted the manuscript. BW-G: has supervised the statistical analyses and contributed in the discussions. NvdL: has contributed in the discussions of the manuscript. IO: has planned the study, collected data and supervised the study, and contributed in the discussions. All authors have critically reviewed the manuscript for important intellectual content.

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Conflict of interest

The authors declare no conflicts of interests.

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