Patient-relevant outcomes after kidney transplantation

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Chapter 4

Mapping health-related quality of life after kidney transplantation by group comparisons: a systematic review

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Abstract

Background: Health-related quality of life (HRQOL) is becoming an increasingly important outcome in kidney transplantation. To describe HRQOL in kidney transplant recipients (KTRs), this systematic review summarizes literature that compared HRQOL between KTRs to other relevant populations (i.e. patients receiving dialysis, patients on the waiting list for kidney transplantation, patients with chronic kidney disease [CKD] not receiving renal replacement therapy (RRT), the general population, and healthy controls) and themselves before kidney transplantation.

Methods: The literature search was conducted in PubMed, EMBASE, Web of Science, and COCHRANE Library. Eligible studies published between January 2000 and October 2020 were included.

Results: 44 studies comprising 6929 KTRs were included in this systematic review. Despite the study heterogeneity, KTRs reported a higher HRQOL after kidney transplantation compared with pre-transplantation and compared with patients receiving dialysis with or without being on the waiting list, especially in disease-specific domains (i.e. burden and effects of kidney disease). Additionally, KTRs had similar to marginally higher HRQOL compared with patients with CKD stage 3-5 not receiving RRT. When compared with healthy controls or the general population, KTRs reported similar HRQOL in the first one or two years after kidney transplantation, and lower physical HRQOL and lower to comparable mental HRQOL in studies with longer post-transplant time.

Conclusions: The available evidence suggests that HRQOL improves after kidney transplantation and can be restored to but not always maintained at pre-CKD HRQOL levels. Future studies investigating intervention targets to improve or maintain post-transplant HRQOL are needed.

Introduction

Kidney transplantation is a preferred and cost-effective treatment for patients with end-stage kidney disease (ESKD) compared to long-term dialysis[1, 2]. Over the past decades, post-transplant graft and patient survival have improved considerably due to the availability of upgraded surgical techniques and innovative immunosuppressants[3]. The reported 5-year graft and patient survival rate of kidney transplant recipients (KTRs) exceeded 80% across different countries[3, 4]. However, KTRs often experience a considerable number of potential side effects (e.g. cardiovascular disease, osteoporosis, neurotoxicity, infections and weight gain) due to the chronic immunosuppressive treatment required to maintain normal graft function[5]. Such treatment-related side effects, along with the underlying kidney disease and other comorbidities, are believed to negatively influence post-transplant health-related quality of life (HRQOL)[6]. In recent years, different international workgroups have recognized HRQOL as a valuable patient-centered outcome to assess treatment effects and healthcare quality in kidney transplantation[7-9].

Therefore, knowledge of HRQOL after kidney transplantation in comparison to other related conditions (e.g. dialysis) is also necessary to inform shared decision-making between patients with ESKD and healthcare professionals. The most recent systematic review fulfilling this purpose compared HRQOL across different renal replacement therapies (RRT; i.e. kidney transplantation, hemodialysis and peritoneal dialysis) and showed better HRQOL in KTRs[10]. However, it only included articles published before 2005 and compared generic HRQOL measured by the 36-item Short-Form Health Survey (SF-36). With the considerable improvements in nephrology care and the exponential increase in studies focusing on HRQOL (and other related patient-reported outcomes), an updated overview of the current literature is urgently needed. Moreover, to gain a comprehensive picture of HRQOL in KTRs, it is necessary to shed light on disease-specific HRQOL and HRQOL measured with other (non-SF-36) questionnaires and to include relevant comparison groups such as the general population and healthy controls to better understand the extent to which HRQOL can be restored to a "pre-chronic kidney disease (CKD)" level.

In this systematic review, we will describe and summarize the published literature to date that compares HRQOL after kidney transplantation with that of all other relevant populations (i.e. patients receiving dialysis, patients on the waiting list for kidney transplantation, patients with CKD not receiving RRT, the general population and healthy controls) and themselves before kidney transplantation.

Methods

This systematic review was conducted and reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline[11]. The protocol for this systematic review is registered on PROSPERO (registration number CRD42021223864).

Eligibility criteria

The eligibility criteria for inclusion in this review included: 1) KTRs above 18 years old at the time of transplantation with a single organ kidney transplantation; 2) HRQOL as one of the outcomes; 3) HRQOL in KTRs compared to that in the same cohort before kidney transplantation, patients receiving dialysis, patients on the waiting list for kidney transplantation, patients with CKD not receiving RRT, the general population and healthy controls via observational studies or randomized control trials; 4) Original articles published between January 1st, 2000 and October 19th, 2020 in the English language.

Information sources and searching strategy

The literature research was conducted on October 19th, 2020 using the MESH keywords for "kidney transplantation" and "HRQOL"(**Table S1**) on PubMed (MEDLINE) to identify relevant studies, followed by a manual search in EMBASE, Web of Science, and COCHRANE Library. Bibliographies of the included articles were also screened for studies missed by the searching strategy (**Figure 1**).

Selection of articles

The screening of titles and abstracts for relevant articles was conducted by one researcher (YW). Next, full-texts of potentially relevant studies were screened by the main reviewer (YW) in collaboration with a nephrologist (JDS) and a medical psychologist (YM). During the selection process, each article was marked as "inclusion", "exclusion", or "not sure" based on prespecified inclusion criteria. Any article marked "not sure" was discussed among the reviewers to achieve consensus based on the prespecified criteria. Articles not meeting the aforementioned eligibility criteria were excluded. Articles with poor accuracy of the outcome measurement (i.e. HRQOL scores higher than the maximum possible value, total HRQOL scores from a questionnaire that does not support such total score calculation, and a higher HRQOL score as an indication for a worse HRQOL while the scoring-algorithm hints the opposite [i.e. better HRQOL]) and unavailable full-text versions were excluded (**Figure 1**).

Extracted data items

Data extraction of prespecified items was conducted by YW and checked for accuracy by YM. Extracted data included: 1) demographic and clinical characteristics of the study population: age, sex, time after transplantation for KTRs, and percentage of living donor kidney transplantation in KTRs; 2) characteristics of the study: the country where a study was conducted, study design, sample size, patient type (i.e. incident and prevalent), follow-up period, loss to follow-up rate, response rate, and statistical methods; 3) characteristics of the outcome: the questionnaire used to measure HRQOL, HRQOL scores and the statistical significance of the results.

Study quality assessment and data synthesis

Following the PRISMA guideline, the quality of the included studies was assessed using the National Institutes of Health (NIH) Quality Assessment Tools for Observational Cohort and Cross-sectional Studies and Before-After Studies With No Control Group[12]. Studies were not excluded based on the quality assessment. A meta-analysis was not conducted due to the heterogeneity in the study population (i.e. prevalent and incident), questionnaires used to measure HRQOL, scoring algorithms to calculate HRQOL with the same questionnaire, and inconsistent reporting of domain scores and summary scores. Therefore, data were summarized narratively without pooled estimates for the outcome of interest.

Result

Searching result

We identified 1454 unique records with the prespecified searching strategy, of which 86 full-text articles were screened. Finally, 44 original studies were selected for this review (**Figure 1**)[13-56]. The sample sizes of KTRs in the included studies ranged from 15 to 1658, and the studies were conducted in 23 different countries, with Europe (45%) being the most common continent on which included studies were conducted. The characteristics of each study are presented in **Table 1**.

KTRs studied

The mean age of KTRs at the time of HRQOL-measurement ranged from 29 to 72 years old, and only two studies were conducted in an elderly cohort older than 60 years (n=43). The majority of studies (93%) reported a higher percentage of male KTRs (median 62%; range 43% - 86%; n=43). The average time of HRQOL-measurements after kidney transplantation ranged from 1 to 234 months after the operation (median 12 months; n=35). Twenty-three studies

reported donor type for kidney transplantation, and the percentages of living donor kidney transplantation varied from 3.3% to 100% (median 100%). Data on comorbidities, dialysis vintage and primary kidney disease were infrequently reported and could therefore not be systematically collected within this review. All characteristics of KTRs are presented in **Table 2-4**.

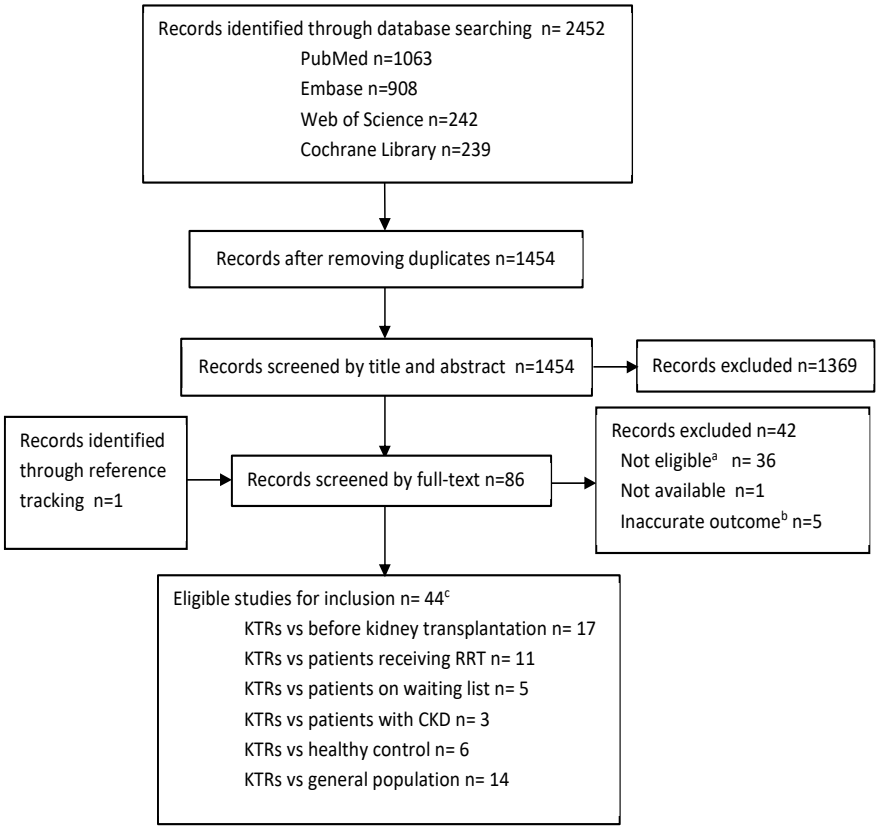

Figure 1. Study inclusion and exclusion flowchart

[a]Inclusion criteria for full-text screening: 1) subjects received single-organ transplantation in adults; 2) disease-specific and/or generic HRQOL was measured post-transplantation; and 3) post-transplant HRQOL was compared to that of other populations, including the general population, healthy controls, patients with CKD not receiving RRT, patients on the waiting list and patients receiving dialysis.
[b]Inaccurate outcome: HRQOL scores higher than the maximum possible value, total HRQOL scores from a questionnaire that does not support such total score calculation, and a higher HRQOL score as an indication for a worse HRQOL while the scoring-algorithm hints the opposite (i.e. better HRQOL).
[c]Ten studies conducted more than one comparison.

Tabel 1. Characteristics of the included studies (n=44)

Reference	Year	Country	Study type	KTR (n)	Comparison group	N	LOF (%)	RR (%)	Questionnaire	
									Disease-specific	Generic
Griva et al.[13]	2012	U.K.	R	60	Before KT	-	-	98	-	SF-36
Das et al.[14]	2014	India	C (S)	20	Before KT	-	0	100	-	WHOQOL
Junchotikul et al.[15]	2015	Thailand	R (S)	232	Before KT	-	0	-	-	WHOQOL
Shrestha et al.[16]	2010	U.K	C (S)	58	Before KT	-	-	77	KTQ	SF-36
					HC	38		32		
Lopes et al.[17]	2013	Portugal	P	35	Before KT	-	-	-	-	SF-36
Mendonca et al.[18]	2014	Brazil	P (S)	63	Before KT	-	0	-	-	WHOQOL
Virzi et al.[19]	2007	Italy	P	48	Before KT	-	-	100	-	SF-36
Balaska et al. [20]	2006	Grace	R (S)	85	Before KT	-	0	100	-	SF-36
Russcher et al.[21]	2015	Netherlands	P (S)	23	Before KT	-	18	-	-	SF-36
Painter et al. [22]	2012	U.S	p	20	Before KT		31	-	KDQOL	SF-36
Mousavi-Roknabadi et al. [23]	2019	Iran	P (S)	120	Before KT	-	0	-	-	SF-36
Gil et al.[24]	2020	Brazil	P (S)	40	Before KT	-	7.5	-	KDQOL	-
Purnajo et al.[25]	2019	U.S	R	831	Before KT	-	-	-	-	SF-36
Mitsui et al.[26]	2020	Japan	R (S)	32	Before KT	-	13	-	-	SF-36
Von der Lippe et al.[27]	2014	Norway	p	110	Before KT	-	0	-	KDQOL	-
					Norwegian GP	5903				
Lonning et al.[28]	2018	Norway	P (S)	120	Before KT	-	1	87-90	KDQOL	-
					Norwegian GP	-				
Lumsdaine et al. [29]	2005	U.K	P (S)	35	Before KT	-	-	72	-	WHOQOL
					U.K. GP	-				
Ranabhat et al.[30]	2020	Nepal	C	92	HD (WL?)	69	-	89	-	WHOQOL
Tomasz et al.[31]	2003	Poland	C	83	HD (WL?)	61	-	36	-	WHOQOL
Fujisawa et al.[32]	2000	Japan	C (S)	117	HD & WL	49	-	96	-	SF-36
					HD not on WL	65				
Sayin et al.[33]	2007	Turkey	C	20	HD (WL?)	75	-	100	-	SF-36
					PD (WL?)	41				
Tamura et al.[34]	2018	Japan	C (S)	68	HD (WL?)	165	-	-	-	SF36
Rambod et al.[35]	2011	Iran	C	200	HD (WL?)	200	-	100	-	QLI-DT
Sapkota et al.[36]	2013	Nepal	C	57	HD (WL?)	62	-	-	-	WHOQOL
Czyzewski et al.[37]	2014	Poland	P	120	HD (WL?)	50	-	-	KDQOL	SF-36
					PD (WL?)	30				
Zheng et al.[38]	2014	China	C (S)	124	HD (WL?)	100	-	73	-	SF-36
Rosenberger et al.[41]	2010	Slovak	P	87	WL	93	1	69-89	-	SF-36

Kovacs et al.[42]	2011	Hungary	C	888	WL	187	-	84	KDQOL	-
Franke et al.[43]	2000	Germany	R (S)	149	WL	149	-	80-90	-	MLDL
					HC	149	-			
Neipp et al.[44]	2006	U.S	R (S)	139	WL	57	-			
					U.S GP	-	-	81	KTQ	SF-36
Karine et al.[39]	2020	France	C	1658	CKD 3b	1487	-	84-100	-	SF-36
					CKD 4	1206	-			
					HD & PD (WL?)	1251	-			
					French GP	20574	-			
Iqbal et al.[40]	2020	Bangladesh	C (S)	15	CKD patients	28			KDQOL	-
					HD (WL?)	20	-			
					HC	40				
Stomer et al.[48]	2013	Norway	C (S)	38	CKD patients	30	-	59	-	SF-36; VAS
					Norwegian GP	-	-			
Ay et al.[45]	2015	Turkey	P (S)	47	HC	47	0	100	-	SF-36
Taskintuna et al.[46]	2009	Turkey	C	69	HC	45	-	-	-	SF-36
Yagil et al.[47]	2018	Israel	C (S)	45	HC	45	-	98	-	SF-12
Zhao et al.[49]	2018	China	C (S)	253	Chinese GP	-	-	-	-	SF-36
Cornella et al.[50]	2008	Italy	C (S)	52	Italian GP	52	-	91	-	SF-36
Aasebo et al.[51]	2009	Norway	C	131	Norwegian GP	-	-	47	-	SF-36
Karam et al.[52]	2003	France	C	229	French GP	487	-	85	-	NIDDK-QOL
Liu et al.[53]	2015	China	C	204	Chinese GP	-	-	100	-	SF-36
Esposito et al.[54]	2017	U.S	C	132	U.S GP	-	-	80	-	SF-36
Wei et al.[55]	2013	Taiwan	C (S)	88	Taiwanese GP	-	-	63	-	SF-36
Costa et al.[56]	2017	Spain	P (S)	124	Spanish GP	-	-	68-85	KDQOL	-

"WL?" indicates unknown waiting list status. "-" indicates not applicable or not reported. Abbreviations: C, cross-sectional study; GP, general population; HC, healthy controls; HD, hemodialysis; PD, peritoneal dialysis; KDQOL, kidney disease quality of life questionnaire; KTQ, kidney transplant questionnaire; LOF, loss to follow-up; MLDL, Munich life quality dimension list; NIDDK-QOL, national institute of diabetes and digestive and kidney diseases liver transplant database quality of life questionnaire; P, prospective study; QLI-DT, quality and life index questionnaire-dialysis and transplantation; R, retrospective study; RR, response rate; S, single-center; SF-12, 12-item short-form health survey; SF-36, 36-item short-form health survey; VAS, visual analog scale; WHOQOL, world health organization quality of life questionnaire; WL, waiting list.

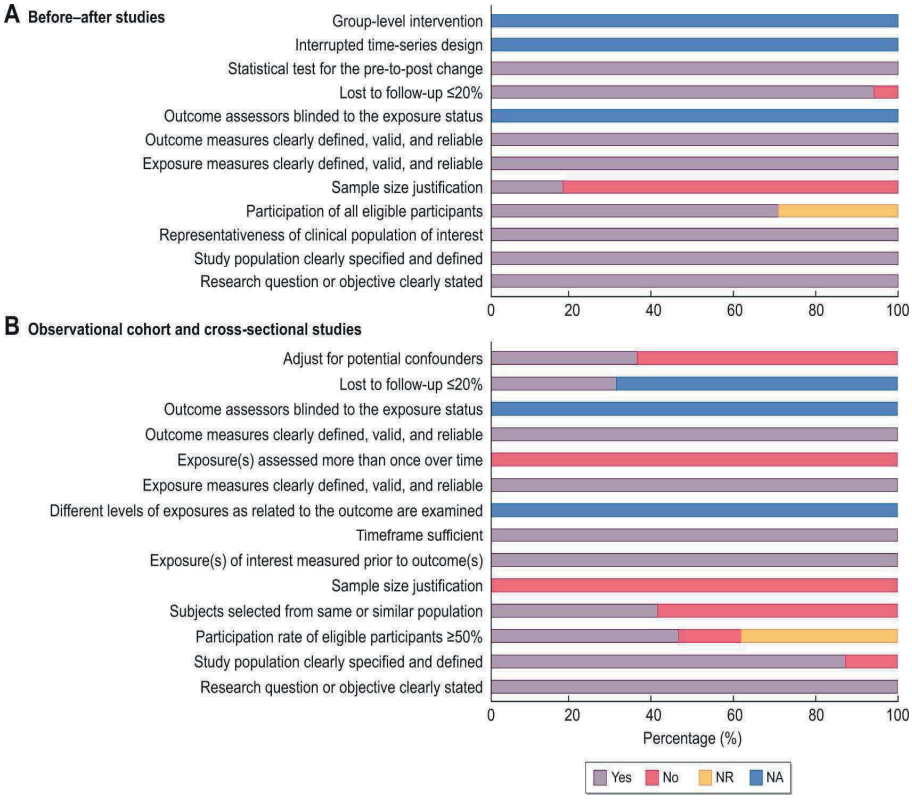

Figure 2. Quality assessment for included studies via the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-sectional Studies and Before-After Studies With No Control Group.

For studies conducted more than one comparison, the quality assessment was conducted per comparison. Figure 2A and 2B show the assessment for before-after studies (n=17) and observational cohort and cross-sectional studies (n=39), respectively. Abbreviations: NA, not applicable; NR, not reported.

Study quality assessment

A great clinical and methodological heterogeneity was observed across the included studies. Among the studies, there were no randomized controlled trials; 50% had a cross-sectional design; 32% had a prospective and 18% had a retrospective design; and 55% of the studies were single-center studies. Different validated questionnaires were used to measure HRQOL (**Table S2**). The most frequently used HRQOL questionnaire was the SF-36 (61%), followed by the Kidney Disease Quality of Life questionnaire (KDQOL; 18%) and the World Health Organization Quality of Life (WHOQOL; 16%). The quality of the included studies was assessed for before-after studies and observational cohort and cross-sectional studies (**Figure 2**). For studies with more than one comparison, the quality appraisal was conducted separately for different comparisons. Therefore, the quality appraisal was conducted for 56 records in total. Among the other observational cohort and cross-sectional studies (n=39), 36% adjusted for

demographical or/and clinical variables for the comparison. **Table S3** shows the assessment for all included studies.

HRQOL before and after kidney transplantation

Seventeen studies compared pre-transplant and post-transplant HRQOL (**Table 2**)[13-29]. Multiple measurements of HRQOL were collected for the same patients before and after kidney transplantation: pre-transplant HRQOL was measured at the transplantation, 2 weeks before transplantation, or at study inclusion of the cohort study; post-transplant measurements were, on average, conducted at 1.5 to 46 months after kidney transplantation. Eight studies reported the RRT before kidney transplantation: the percentages of patients on dialysis ranged from 36% to 100%, with hemodialysis being the most common dialysis modality[13, 18-21, 26-28].

Within the first year after kidney transplantation, studies using the SF-36 and the KDQOL reported consistently better post-transplant HRQOL in the physical HRQOL domain *general health* and mental HRQOL domain *vitality,* as well as in the disease-specific HRQOL domain *effect of kidney disease* in both young[13, 17, 19-26] and elderly KTRs[28]. Two studies using the WHOQOL also showed improvement in physical HRQOL during the first year after kidney transplantation[14, 29]. In KTRs with a post-transplant time of 46 months, Shresth and colleagues found an increase in all mental, physical and disease-specific HRQOL domains compared to preoperative HRQOL[16]. This improvement in disease-specific HRQOL was also found by Lippe et al. in KTRs with a similar post-transplant time[27].

HRQOL of KTRs and patients receiving maintenance dialysis

Eleven studies compared HRQOL between KTRs and patients receiving dialysis (**Table 3**)[30-40]. The average time of HRQOL-measurements after kidney transplantation varied from 3 to 126 months. In a prospective study, Czyzewski et al. showed better physical HRQOL in the domain *physical functioning* and better disease-specific HRQOL in the domain *burden of kidney disease* in KTRs at 3 and 12 months post-transplantation compared to patients receiving dialysis and found similar mental HRQOL in the two groups[37]. The other studies in prevalent KTRs detected a significantly better HRQOL in various physical and/or mental domains[30-36, 38-40]. Notably, only one study specified the waiting list status of its dialysis population, and this study showed better physical (i.e. the domains *role physical* and *bodily pain*) and mental (i.e. the domain *social function*) HRQOL in KTRs 10 years after kidney transplantation compared to patients receiving dialysis for 8 years without awaiting kidney transplantation[32].

HRQOL of KTRs and patients on the waiting list for kidney transplantation

Five studies compared the HRQOL of KTRs with that of patients on the waiting list (**Table 3**)[32, 41-44]. The average time of HRQOL-measurements after kidney transplantation varied from 12 to 234 months. All patients on the waiting list received either hemodialysis or peritoneal dialysis treatment. In a prospective study, Rosenberger et al. reported comparable mental and physical HRQOL between KTR and patients on the waiting list after matching for age, gender, and comorbidity at 3 and 12 months after kidney transplantation[41]. However, in a retrospective study, Franke et al. reported better global HRQOL in KTRs on an average of 5 years after transplantation compared to age- and sex-matched patients on the waiting list[43]. Kovacs et al. found higher scores in the physical HRQOL domain *general health* and disease-specific HRQOL domains (i.e. *burden of kidney disease* and *effect of kidney disease*) in prevalent KTRs with a mean post-transplant time of 5 years after adjusting for demographic and clinical variables[42]. Fujisawa et al. compared KTRs and patients awaiting kidney transplantation on other RRTs for 10 years and detected better physical HRQOL in the domain *general health* in KTRs[32]. Finally, in a cross-sectional study, long survivors (mean post-transplant time: 20 years) after kidney transplantation reported better HRQOL scores in the domains *physical symptom experience*, *fatigue*, *fear* and *emotions* but a lower score in the domain *appearance*[44].

HRQOL of KTRs and patients with CKD not receiving RRT

Three studies compared HRQOL between KTRs and patients with CKD stage 3-5 before RRT (**Table 3**)[39, 40, 48]. Stomer et al. reported comparable physical and mental HRQOL between age-, gender-, and estimated glomerular filtration rate (eGFR)- matched KTRs and CKD patients when measured by the SF-36. When HRQOL was measured using a visual analog scale (VAS), a better HROQL was found in CKD patients compared to KTRs[48]. Karine and colleagues reported marginally better physical and mental HRQOL in KTRs compared to patients with CKD stage 3-5 after adjusting for age, sex, education and diabetes[39]. Finally, Iqbal et al. described higher mean scores in all physical and mental HRQOL domains in KTRs (mean eGFR: 49) compared to patients with CKD stage 3-5 (mean eGFR: 36)[40].

HRQOL of KTRs and healthy controls

Six studies compared HRQOL between KTRs and healthy controls (**Table 4**)[16, 40, 43, 45-47]. The average post-transplant time in these studies varied from 3 to 66 months. The healthy controls were often potential donors, staff from the same research institute or recruited by social media. Ay et al. reported comparable summary scores for physical and

Tabel 2. HRQOL before and after kidney transplantation (n=17).

Reference	Patient characteristics					Effect measure	HRQOL using SF-36 and KDQOL													HRQOL using WHOQOL				
							Physical					Mental					Disease-specific							
	Mean age	Male (%)	LDKT (%)	RRT before KT (%)	Time after KT (m)		PCS	PF	RP	BP	GH	MCS	VT	SF	RE	MH	S	EKD	BKD	PHY	PSY	SOC	ENV	Total
Mousavi-Roknabadi et al.[23]	39	65	37	-	3	Mean rank (after/before)		**55/50**[e]	**40/27**[e]	**48/47**[e]	**65/13**[e]		**56/24**[e]	**49/54**[e]	**47/26**[e]	**54/30**[e]								
Russcher et al.[21]	51	64	100	36	3	Mean change		6	**24**[b]	0	**15**[b]		**18**[b]	**16**[b]	10	2								
Gil et al. [24]	36	65	100	-	3	Mean (after/before)	**52/43**[b]	**93/75**[b]	**81/35**[b]	92/85	**78/60**[b]	**56/46**[b]	**74/58**[b]	**92/64**[b]	**93/58**[b]	**86/70**[b]	-	**78/41**[b]	-					
					6		**51/43**[b]	**94/75**[b]	**70/35**[b]	80/82	**70/60**[b]	**53/46**[b]	**76/58**[b]	**80/64**[b]	**79/58**[b]	**85/70**[b]								
Virzi et al.[19]	41[a]	58	100	92	6	Mean (after/before)		77/72	**58/38**[e]	**21/32**[c]	**78/70**[c]		**63/56**[c]	**62/49**[c]	-	**77/60**[c]	-	**74/41**[b]	-					
Griva et al.[13]	43	54	3	100	6	Cohen's d	**1.3**	**1.2**	**0.5**	**0.5**	**1.6**	**0.8**	**0.7**	**1.0**	**0.6**	**0.7**								
Painter et al.[22]	44	85	100	-	6	Mean change	**7**[b]	**7**[b]	**11**[b]	**3**[b]	**5**[b]	2	**7**[b]	**15**[b]	3	0	**9**[b]	**19**[b]	**24**[b]					
Lopes et al.[17]	37[a]	63	100	-	12	Median (after/before)		**100/7**[b]	**100/2**[b]	**100/7**[b]	**72/40**[b]		**80/55**[b]	**100/6**[b]	**100/100**[b]	**84/68**[b]								
Mitsui et al.[26]	44[a]	86	100	38	3	% > MCID (PEKT/non-PEKT)	40/40	40/45	**80/60**	20/35	**70/60**	**55/60**	**55/70**	**70/65**	35/30	**60/60**								
					12		**50**/33	33/**50**	33/25	25/25	**83/92**	**58/75**	**67/83**	**67/58**	33/33	50/42								
Balaska et al.[20]	44[a]	52	54	100	12	Mean (after/before)		77/56	**62/10**	90/46	**84/34**		**83/26**	78/31	**83/40**	68/23								
Purnajo et al.[25]	48	67	34	-	12	% > MCID		37	**58**	39	39		42	41	44	23								
Lonning et al.[28]	72	71	21	90	2	Mean difference (SD)		<0.5	<0.5	<0.5	**>0.5**		**>0.5**	<0.5	<0.5	<0.5	<0.5	**>0.5**	<0.5					
					6			<0.5	<0.5	<0.5	**>0.5**		**>0.5**	<0.5	<0.5	<0.5	**>0.5**	**>0.5**	<0.5					
					12			<0.5	**>0.5**	<0.5	**>0.5**		**>0.5**	<0.5	<0.5	<0.5	**>0.5**	**>0.5**	<0.5					
Lippe et al.[27]	57	66	-	100	40	Mean difference[b]		<0.5	<0.5	<0.5	<0.5		<0.5	<0.5	<0.5	**>0.5**	<0.5	**>0.5**	**>0.5**					

Tabel 2 (continued).

Shrestha et al.[16]	39[a]	53	100	-	46	Mean (after/before)	**65/35[c]**	**71/48[c]**	**65/17[c]**	72/59	**54/22[c]**	**69/39[c]**	**63/30[c]**	**77/43[c]**	**76/44[c]**	**79/59[c]**					
Das et al. [14]	60%: 30-45[g]	80	100	-	6	Mean (after/before)											**76/47[c]**	**84/47[c]**	**77/62[c]**	**74/55[c]**	
Lumsdaine et al. [29]	37[a]	51	100	-	1.5	Mean (after/before)											**15/11[f]**	16/15	16/16	17/16	
					12												**16/11[f]**	16/15	16/16	16/16	
Junchotikul et al.[15]	88%: 33-60[g]	62	-	-	-	Mean difference											-	-	-	-	**29[c]**
Mendonca et al.[18]	39	62	-	97	-	Mean (after/before)											**17/10[c]**	**18/13[c]**	**17/13[c]**	**14/12[c]**	**18/9[c]**

Continuous variables are presented as mean if not otherwise indicated. HRQOL results are presented in bold if they were reportedly significant according to statistical testing ($p < 0.05$) or a threshold for mean difference (difference>0.5SD or Cohen's d>0), or the percentages of patients reported an improvement larger than MCID > 50%. "-" indicates not reported. Abbreviations: BKD, burden of kidney disease; BP, bodily pain; EKD, effect of kidney disease; ENV, environmental; GH, general health; HRQOL, health-related quality of life; KDQOL, the kidney disease quality of life questionnaire; KT, kidney transplantation; LDKT, living donor kidney transplantation; MCID, minimal clinically important difference; MCS, mental component summary; MH, mental health; PCS, physical component summary; PEKT, preemptive kidney transplantation; PF, physical functioning; PHY, physical; PSY, psychological; RE, role emotional; RP, role physical; RRT, renal replacement therapy; S, symptom; SD, standard deviation; SF, social functioning; SF-36, 36-item short-form health survey; SOC, social; VT, vitality; WHOQOL, world health organization quality of life questionnaire.

[a]values presented as median; [b]$p<0.05$; [c]$p<0.01$; [d]$p<0.001$; [e]$p<0.0001$; [f]statistical test only conducted for comparison at three timepoints (before KT, 1.5 and 12 months after KT) and the $p<0.05$; [g]percentage within the indicated range.

Table 3. HRQOL of KTRs compared to patients on dialysis (n=11), patients on the waiting list (n=5), and patients with CKD not receiving RRT (n=3).

Reference	Patient characteristics								Effect measure	HRQOL using SF-36 and KDQOL												HRQOL using WHOQOL or QLI-DT				
	KTRs				Patients on dialysis/ with CKD					Physical					Mental					Disease-specific							
	Mean age	Male (%)	LDKT (%)	Time after KT (m)	Mean age	Male (%)	RRT	Time on D		PCS	PF	RP	BP	GH	MCS	VT	SF	RE	MH	S	EKD	BKD	PHY	PSY	SOC	ENV/FAM	Total
KTRs vs patients on dialysis																											
Czyzewski et al.[37]	-	55	-	3	-	58	HD	78	Mean (KT/D)	**45/35**[b]	**72/50**[b]	42/30	78/46	45/28	45/44	58/49	70/59	65/47	64/61	**85/66**[b]	**76/54**[b]	**48/30**[b]					
					-	50	PD	40		**45/38**[b]	**72/52**[b]	42/36	78/66	45/42	45/50	58/68	70/74	65/74	64/50	**85/74**[b]	**77/65**[b]	**48/54**[b]					
				12	-	58	HD	78		**46/35**[b]	**76/50**[b]	50/30	67/46	**44/28**[b]	44/44	**56/49**[b]	70/59	65/48	63/61	**83/66**[b]	**78/54**[b]	**56/30**[b]					
					-	50	PD	40		**46/38**[b]	**76/52**[b]	50/36	67/66	44/42	44/50	56/68	70/74	65/74	63/50	83/74	79/65	**53/54**[b]					
Sayin et al. [33]	33	65	70	41	47	72	HD	46	Mean		69/56	43/41	64/63	50/40		**68/56**[g]	58/63	46/30	66/58								
					46	61	PD	35	(KT/D)		69/56	43/39	64/66	50/41		**68/52**[g]	58/56	46/46	66/61								
Zheng et al.[38]	34	78	100	39[a]	-	-	HD	>3	Mean (KT/D)		**80/68**[d]	**74/35**[d]	**72/62**[d]	**67/40**[d]		**64/46**[d]	**75/55**[d]	**77/42**[d]	**72/59**[d]								
Tamura et al.[34]	52	60	100	47[a]	53	48	HD	-	Mean (KT/D)		**47/23**[c]	**46/20**[c]	**49/43**[c]	**45/40**[c]		**51/41**[c]	**49/38**[c]	**48/35**[c]	**52/49**[c]								
Fujisawa et al.[32]	44	43	74	126	46	69	HD	92	Mean (KT/D)		86/82	**78/64**[b]	**80/67**[b]	56/52		63/58	**82/74**[b]	78/70	70/69								
Karine et al.[39]	55	61	-	-	69	65	D	>12	Mean (KT/D)	**45/35**[d]					**46/40**[d]												
Iqbal et al.[40]	39	-	-	>6	43	-	HD	>3	Mean (KT/D)		91/37[f]	30/0[f]	69/30[f]	48/21[f]		66/40[f]	70/24[f]	33/0[f]	56/41[f]								
Ranabhat et al.[30]	39	75	-	>6	44	75	HD	>3	Mean (KT/D)														**13/11**[d]	**14/11**[d]	**14/13**[b]	**12/11**[c]	**13/11**[d]
Sapkota et al.[36]	41	70	-	72%: 3-24[h]	46	68	HD	76%: 3-24[h]	Mean (KT/D)														**70/49**[d]	**69/52**[d]	**69/58**[d]	**60/56**[d]	**267/215**[d]
Tomasz et al.[31]	43	52	-	35	58	61	HD	41	Mean (KT/D)														**14/12**[e]	14/13	**14/13**[e]	13/13	**14/12**[e]
Rambod et al.[35]	51	56	-	>3	50	48	HD	>3	Mean (KT/D)														**21/19**[d]	18/21	19/18	**24/25**[b]	21/20[b]

Table 3. (Continued).

KTRs vs patients on dialysis and on the waiting list																										
Rosenberger et al.[41]	47	56	-	3	49	58	D	42	Mean (KT/WL)	52/48							60/57									
				12						54/50							63/62									
Kovacs et al.[42]	49	58	-	54	49	60	D	36	Beta-coeeficient		0.01	-	-	**0.16**[d]			0.03	-	-	-0.001	0.04	**0.22**[d]	**0.18**[c]			
Fujisawa et al.[32]	44	43	74	126	46	76	HD	120	Mean (KT/WL)		86/82	78/74	80/74	**56/50**[b]			63/61	82/75	78/80	70/68						
Franke et al.[43]	48	62	-	56	48	62	D	65	Mean (KT/WL)															**7/5**[b]	**6/5**[b]	**7/6**[b]	7/6	**7/6**[b]
Neipp et al.	55	63	-	234	43[a]	72	-	-	Mean (KT/WL)															**6/5**[f]	**5/4**[f]	**5/4**[f]	6/6	5/5
KTRs vs patients with CKD not receiving RRT																												
Iqbal et al.[40]	39	-	-	>6	49	-	CKD	3-5	Mean (KT/WL)		91/69[f]	30/13[f]	49/44[f]	48/31[f]			66/51[f]	70/61[f]	33/16[f]	56/46[f]								
Karine et al.[39]	55	61	-	-	66	68	CKD	3b	Mean (KT/WL)	45/43[f]							46/48[f]											
					68	63	CKD	4-5		45/40[f]							46/47[f]											
Stomer et al.[48]	56	61	-	169	57	61	CKD	3b-4	Mean (KT/CKD)	43/43							50/52											

Continuous variables are presented as mean if not otherwise indicated. HRQOL results are presented in bold if they were reportedly significant according to statistical testing ($p < 0.05$). "-" indicates not reported. Abbreviations: BKD, burden of kidney disease; BP, bodily pain; D, dialysis; EKD, effect of kidney disease; ENV, environmental; GH, general health; HD, hemodialysis; HRQOL, health-related quality of life; KDQOL, the kidney disease quality of life questionnaire; KT, kidney transplantation; LDKT, living donor kidney transplantation; MCS, mental component summary; MH, mental health; PCS, physical component summary; PD, peritoneal dialysis; PF, physical functioning; PHY, physical; PSY, psychological; QLI-DT, the quality and life index questionnaire-dialysis and transplantation; RE, role emotional; RP, role physical; RRT, renal replacement therapy; S, symptom; SD, standard deviation; SF, social functioning; SF-36, the 36-item short form of health survey; SOC, social; VT, vitality; WHOQOL, the world health organization quality of life questionnaire. [a]values presented as median; [b]$p<0.05$; [c]$p<0.01$; [d]$p<0.001$; [e]$p<0.0001$; [f]p value not reported; [g]Statistical test only conducted for comparison across more than two groups (KTRs, HD and PD) and the $p<0.05$; [h]percentage within the indicated range.

Table 4. HRQOL of KTRs compared heathy controls (n=6) and the general population (n=14).

Reference	Patient characteristics						Effect measure	HRQOL using SF-36										HRQOL using WHOQOL				
	KTRs				HC and the GP			Physical					Mental									
	Mean age	Male (%)	LDKT (%)	Time after KT (m)	Mean age	Male (%)		PCS	PF	RP	BP	GH	MCS	VT	SF	RE	MH	PHY	PSY	SOC	ENV	Total
KTRs vs healthy controls																						
Ay et al.[45]		60	100	3	38	51	Mean (KT/HC)	46/48	**72/80**[b]	**52/74**[c]	68/67	57/62	44/45	63/64	**66/70**[b]	50/66	64/64					
				9				46/48	78/80	**51/74**[c]	70/67	58/62	44/45	61/64	67/70	56/66	63/64					
Shrestha et al.[16]	39[a]	53	100	46[a]	55[a]	34	Mean (KT/HC)	**65/81**[d]	**71/84**[b]	**65/92**[d]	**72/84**[b]	**54/73**[d]	69/78	63/69	77/81	76/90	79/77					
Taskintuna et al.[46]	33	74	100	39	Matched	80	Mean (KT/HC)		**73/92**[b]	**54/84**[d]	**69/82**[c]	**53/67**[c]		63/56	70/69	51/67	64/60					
Yagil et al.[47]	53	62	-	64	Matched	Matched	Mean (KT/HC)		**52/88**[b]	**45/82**[b]	**60/80**[b]	**54/68**[b]		**44/62**[b]	**69/83**[b]	**55/90**[b]	**61/74**[b]					
Iqbal et al.[40]	39	-	-	>6	34	-	Mean (KT/HC)		91/100	30/100	69/94	48/85		66/91	70/99	33/100	56/94					
Franke et al.[43]	48	62	-	56	Matched	Matched	Mean (KT/HC)											7/7	7/6	6/6	7/7	7/7
KTRs vs general population from the same country or region																						
Costa et al.[56]	53	68	19	1	-	-	Mean difference	**>0.5**	**>0.5**	**>0.5**	**>0.5**	<0.5	<0.5	**>0.5**	**>0.5**	<0.5	<0.5					
				6/12/18			(SD)	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5					
				24				**>0.5**	<0.5	<0.5	**>0.5**	**>0.5**	<0.5	<0.5	<0.5	<0.5	<0.5					
Lonning et al.[28]	72	71	21	12	Matched	Male	Mean difference		<0.5	<0.5	<0.5	<0.5		<0.5	**>0.5**	<0.5	<0.5					
						Female	(SD)		<0.5	<0.5	<0.5	<0.5		<0.5	<0.5	<0.5	<0.5					
Zhao et al.[49]	77%: 18-44[g]	72	-	62%: 6-12[g]	-	-	Mean (KT/GP)		**82/91**[e]	**46/80**[e]	**68/86**[e]	**59/70**[e]		**64/70**[e]	**87/87**[e]	**51/76**[e]	**62/73**[e]					
Liu et al.[53]	43	62	15	39	-	-	Mean (KT/GP)		**80/91**[e]	**63/80**[e]	**71/86**[e]	**52/70**[e]		**66/70**[e]	**71/87**[e]	**72/76**[e]	73/73					

Table 4. (continued).

von der Lippe et al.[27]	57	66	-	40	Matched	Matched	Mean (KT/GP)	**44/50**[d]	**73/82**[d]	**52/75**[d]	71/73	**57/74**[d]	**48/53**[b]	**54/61**[d]	**81/88**[b]	**71/85**[d]	78/82			
Cornella et al.50]	67	64	-	41	Matched	Male	Mean (KT/GP)		82/84	-	**18/74**[b]	**37/62**[b]		**50/68**[b]	**47/78**[b]	76/74	65/69			
						Female			63/64	-	**22/59**[b]	**40/49**[b]		47/52	**42/71**[b]	74/68	59/57			
Aasebo et al.[51]	29	44	66	59[a]	-	-	Mean (KT/GP)	**49/53**[d]	**87/94**[d]	**74/90**[d]	76/80	**60/81**[d]	**49/52**[d]	**56/61**[d]	**80/89**[d]	**76/90**[d]	**77/80**[c]			
Esposito et al.[54]	52	59	-	6	-	-	Mean (KT/GP)	**41/50**[b]					49/50							
				7-60				**46/50**[b]					49/50							
				>60				**44/50**[b]					52/50							
Stomer et al.[48]	56	61	-	169	-	-	Mean (KT/GP)	**43/50**[d]					**50/50**[d]							
Neipp et al.[44]	55	63	-	234	-	-	Mean (KT/GP)		**66/84**[f]	81/81	**60/75**[f]	**52/72**[f]		**51/61**[f]	79/83	87/81	69/75			
Wei et al.[39]	49	46	4	173	-	-	Mean (KT/GP)		**80/92**[c]	**68/84**[c]	83/85	**59/69**[c]		**61/68**[c]	**77/87**[c]	**70/79**[b]	**68/73**[b]			
Karine et al.[35]	55	61	-	-	45	47	Mean (KT/GP)	**45/50**[d]					**46/47**[d]							
Lumsdaine et al.[29]	37	51	100	1.5	-	-	Mean (KT/GP)											15/16	**16/15**[c]	17/15 17/15
				12														16/16	**16/15**[c]	17./15 16/15
Karam et al.[52]	53	53	-	>120	-	-	Mean (KT/GP)	For the HRQOL results of HRQOL using the NIDDK-QOL, see notes below the table.												

Karam et al. reported significantly lower personal function (median 1 vs 4[d]) and general health (median 6 vs 7[c]), more physical symptom (median 10 vs 8[d]) and more burden caused by physical (median 23 vs 15[d]) and mental symptoms (median 6 vs 5[b]). Continuous variables are presented as mean if not otherwise indicated. HRQOL results are presented in bold if they were reportedly significant according to statistical testing ($p < 0.05$). "-" indicates not reported. Abbreviations: BP, bodily pain; D, dialysis; ENV, environmental; GH, general health; GP, general population; HC, healthy controls; HD, hemodialysis; HRQOL, health-related quality of life; KDQOL, the kidney disease quality of life questionnaire; KT, kidney transplantation; LDKT, living donor kidney transplantation; MCS, mental component summary; MH, mental health; NIDDK-QOL, the national institute of diabetes and digestive and kidney diseases liver transplant database quality of life questionnaire; PCS, physical component summary; PD, peritoneal dialysis; PF, physical functioning; PHY, physical; PSY, psychological; RE, role emotional; RP, role physical; RRT, renal replacement therapy; SD, standard deviation; SF, social functioning; SF-36, the 36-item Short Form of Health Survey; SOC, social; VT, vitality; WHOQOL, the world health organization quality of life questionnaire. [a]values presented as median; [b]$p<0.05$; [c]$p<0.01$; [d]$p<0.001$; [e]$p<0.0001$; [f]p value not reported; [g]percentage within the indicated range.

mental HRQOL in incident KTRs at 3 and 9 months after kidney transplantation to healthy controls, while a consistently lower score in the physical HRQOL domain *role physical*[45]. Three cross-sectional studies in KTRs, with a mean time of 3 years after kidney transplantation, showed comparable mental HRQOL to healthy controls, and two studies reported lower physical HRQOL in the KTRs[16, 43, 46]. In KTRs on an average of 5 years after kidney transplantation, Yagil et al. detected lower physical and mental HRQOL in KTRs compared to age-, sex-, marriage status-, and education level- matched healthy controls[47]. Finally, Iqbal et al. described lower mean scores in physical (i.e. *role physical* and *general health*) and mental (i.e. *vitality*, *role emotional* and *mental health*) HRQOL domains in KTRs with unreported post-transplant time compared to healthy controls[40].

HRQOL of KTRs and the general population

Fourteen studies compared HROQL in KTRs with the general population from the same country or region (**Table 4**)[27-29, 39, 44, 48-56]. The average post-transplant time in KTRs varied from 1 to 234 months. When compared to the general population, three prospective studies reported comparable physical and mental HRQOL in both young and elderly KTRs at 1 year after kidney transplantation, among which one study by Costa et al. reported significantly lower physical HRQOL at 1 month after kidney transplantation[28, 29, 56]. Eight studies in KTRs with an average of 3 to 15 years after kidney transplantation, showed generally lower physical HRQOL and lower to comparable mental HRQOL compared to the general population[27, 48, 50-55]. One of these studies was conducted in elderly KTRs and reported similar HRQOL in the physical HRQOL domain *physical functioning* and the mental HRQOL domains *role emotional* and *mental health* to the general population, but lower HRQOL in the physical HRQOL domains *bodily pain* and *general health*, and the mental HRQOL domains *vitality* and *social functioning*[50]. In KTRs with an average of 20 years after kidney transplantation, Neipp et al. reported lower HRQOL among KTRs in three out of the four physical HRQOL domains (i.e. *physical functioning*, *bodily pain* and *general health*) and one out of the four mental domains (i.e. *vitality*)[44]. Two other studies without reported post-transplant time, reported lower mental and physical HRQOL in KTRs, with the exception of the mental HRQOL domain *social functioning* in one study[39, 49].

Discussion

HRQOL is a valuable outcome for KTRs and nephrology care. This systematic review summarized the published literature in recent decades that compared HRQOL in KTRs, measured with different validated HRQOL questionnaires, with that of all relevant populations (i.e. patients receiving dialysis, patients on the waiting list for kidney transplantation, patients with CKD not receiving RRT, the general population and healthy

controls) and themselves before kidney transplantation. Despite the heterogeneity of included studies, the results of this systematic review suggest a better HRQOL after kidney transplantation compared to the same individuals preoperatively and compared to patients receiving dialysis with or without being on the waiting list for kidney transplantation. KTRs also seem to experience similar or marginally higher HRQOL compared to patients with CKD stage 3-5not receiving RRT. Finally, when compared with healthy controls and the general population, KTRs appear to have comparable HRQOL shortly after kidney transplantation but a lower physical HRQOL and a lower to comparable mental HRQOL in the long term, hereby suggesting that HRQOL of KTRs may be restored to, but is not always maintained at "pre-CDK" HRQOL levels.

HRQOL in KTRs compared to patients with ESKD

The results of this review suggest consistently better HRQOL in KTRs, including elderly KTRs when compared to patients with ESKD (i.e. the same cohort pre-transplantation [consisting of patients receiving dialysis or patients not receiving RRT with preemptive kidney transplantation] and patients receiving dialysis with or without being on the waiting list)[14-22, 27, 28, 57, 58]. Our findings are in line with the previous systematic review conducted by Liem and colleagues in 2007, showing higher HRQOL in physical (i.e. physical functioning, role physical, bodily pain and general health) and mental (i.e. role emotional) SF-36 domains in KTRs compared to patients on either hemodialysis or peritoneal dialysis after adjusting for age and diabetes[10].

There are several possible explanations for our findings that KTRs experience a higher HRQOL compared to patients with ESKD regardless of dialysis initiation and being on the waiting list or not. First, after an immediate decrease in self-reported physical activity due to the operation, KTRs report a 30% higher physical activity level than the pre-transplant level and this increase in physical activity persists until 5 years after successful kidney transplantation[59]. This finding is also supported by a study with physical activity being objectively measured using an accelerometer, showing a higher proportion of physically active KTRs compared to patients receiving dialysis (65% vs. 20%)[60]. Nana et al. have indeed found an association between a higher physical activity level measured objectively and subjectively and better HRQOL[61]. Second, kidney transplantation can reduce the high symptom burden and treatment burden in ESKD patients and consequently improve HRQOL. Compared to ESKD patients, KTRs report less fatigue[44, 62, 63], decreased frequency of depressive symptom[19, 62], better sleep quality[21, 64, 65], less pain and immobility[63]. Third, kidney transplantation can have a positive impact on social functioning – an important component of HRQOL. In a Swiss transplant cohort study, approximately 80% of patients with

ESKD maintained their employment after kidney transplantation, and around 20% of unemployed patients with ESKD restarted working after their kidney transplantation[66]. Social participation in leisure and religious activities was also significantly improved in KTRs compared to patients on hemodialysis[67]. The increased social functioning can be a result of the reduced treatment burden following RRT modalities change from dialysis to kidney transplantation. A commonly seen regime of in-center hemodialysis requires patients to visit the dialysis clinics 3 times a week and to be tied to a dialysis machine for around 4 hours each time[68]. The negative impact of such treatment burden on social activities is foreseeable. Finally, KTRs appear to have more favourable illness perceptions (i.e. stronger positive beliefs about the seriousness and controllability of their condition) compared to themselves before the transplantation, and such beliefs could also positively influence patient outcomes such as HRQOL[57, 69].

HRQOL in KTRs compared to CKD patients, healthy controls and the general populations

Our results showed that KTRs had similar or marginally better HRQOL in comparison to patients with CKD stage 3-5 before dialysis initiation[39, 40, 48]. Despite the restored renal function in KTRs, the commonly occurring side effects of immunosuppressants and a longer duration of underlying kidney disease might explain that their HRQOL was not significantly different from that of patients with CKD.

When comparing KTRs with healthy controls or the general population, eligible studies suggested comparable physical and mental HRQOL in a short period after kidney transplantation (<2 years)[28, 29, 45, 56]. However, KTRs with a longer post-transplant time reported consistently lower physical HRQOL and lower to comparable mental HRQOL when compared to healthy controls or the general population. The comparable HRQOL in KTRs in the short term after kidney transplantation could be a result of improved clinical health status[1], dramatically decreased treatment burden (especially for dialysis patients)[68], happiness and relief in the early post-transplant phase[70], and a potential response shift effect[71]. The response shift, in this specific context, refers to a phenomenon where part of the perceived improvement of HRQOL is due to patients' adaption to the post-transplant health condition[71]. In a study comparing coping strategies between KTRs and the general population, successfully transplanted KTRs did have relatively more optimistic, self-reliant and supportive coping[72], which are considered effective in handling a chronic condition such as kidney disease. A more obvious example is the study conducted by Lumsdaine et al., which has detected better psychological health in KTRs than that in the general population[29]. For patients with a longer post-transplant time, the comparatively lower

HRQOL might be contributed to treatment-related side effects and complications, a longer duration of pre-existing comorbidities or underlying kidney disease, and the progressive decline of kidney function due to different causes (e.g. toxicity of immunosuppressants, progression of donor-derived lesions and recurrence of primary kidney disease). According to a large registry study in Australia and New Zealand, up to 10% of the KTRs experienced a more than 30% decrease in their kidney function between the first and third year after transplantation[73].

Clinical implications

The results of this systematic review reinforce the benefits of kidney transplantation among patients with ESKD in terms of HRQOL and, at the same time, suggest that there is room for improvement. HRQOL after successful kidney transplantation is dynamic and is influenced by many factors. Previous studies showed a wide range of factors to be associated with suboptimal post-transplant HRQOL, including socio-demographic characteristics (e.g. older age, female gender, low education and income, unemployment, and living alone), clinical characteristics (e.g. disability, high serum creatinine, comorbidities, and side effects from treatment and hospitalization), lifestyle characteristics (e.g. insufficient physical activity) and psychosocial characteristics (i.e. depression, negative illness perceptions, and a lack of esteem or social support)[74-76]. Therefore, personalized treatment approaches addressing individual (modifiable) factors driving poor outcomes are needed to optimize HRQOL in kidney transplant care. Previous studies have investigated the effects of lifestyle, psychoeducational and self-management interventions to improve post-transplant HRQOL in addition to interventions for biochemical markers. A meta-analysis, including six randomized trials, showed that supervised exercise training could significantly improve HRQOL in KTRs[77]. Cognitive-behavioral therapy also positively influenced HRQOL in this population[78]. Ongoing trials and research suggest the possibility of improving HRQOL by means of combined lifestyle interventions (exercise and diet) and web-based self-management[79, 80].

Our results also showed that post-transplant HRQOL could reach the levels reported by the general population or healthy controls shortly after kidney transplantation but seemed to be lower in the long term. However, most studies that compared HRQOL between KTRs and the general population or healthy controls are cross-sectional, and the relatively small sample size and short follow-up time of the included longitudinal studies suggest a need for studies with a sufficiently large sample of incident KTRs to map the evolution of HRQOL over time. Renal registries that routinely collect HRQOL-data in clinical practice may fill this gap and provide insight into “real world” HRQOL of KTRs longitudinally. Finally, our systematic review

suggested a need for more research on HRQOL in elderly KTRs, especially with the aging population.

Strengths and limitations

The strengths of this up-to-date systematic review include a thorough literature search, the inclusion of all validated questionnaires to measure generic HRQOL as well as disease-specific HRQOL, and the inclusion of all relevant comparison groups to provide a comprehensive picture of HRQOL after kidney transplantation. This systematic review also has its limitations. First, due to the inability to calculate pooled estimates and to adjust for potential variables, the strength of our conclusion greatly depends on the quality of individual studies. Unfortunately, some studies only performed an unadjusted comparison between the comparison groups, and some studies were conducted in prevalent patients, which are prone to selection bias, with the latter potentially being more evident in cross-sectional studies of long survivors. Second, it might be worth noting that most included studies commented on HRQOL differences being a statistically significant difference or change, but few of the studies commented on whether the difference or change could also be considered a clinically relevant difference or change in HRQOL – with the former not necessarily implying the latter[81]. Future studies addressing the clinically relevant HRQOL differences and changes in the field of nephrology are necessary to facilitate the interpretation of HRQOL scores in literature and in clinical practice. Finally, we only included publications written in the English language, hereby limiting the generalizations of our results.

Conclusion

Patients report a higher HRQOL after successful kidney transplantation than before the transplantation and compared to patients receiving dialysis. KTRs also experience similar to a slightly better HRQOL compared to non-dialysis dependent patients with CKD stage 3-5. When compared to healthy controls and the general population, HRQOL appeared to be restored to a “pre-CKD” level shortly after successful kidney transplantation, but these higher HRQOL levels did not last in the long term. Future studies investigating interventions on modifiable risk factors for impaired HRQOL, such as immunosuppressive strategies, are needed to maximize the long-term benefit of kidney transplantation.

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Supplementary files

Supplementary Table S1. Systematic searching strategy for literature about health-related quality of life in kidney transplant recipients.

Supplementary Table S2. HRQOL questionnaires used in selected studies and their domain coverage.

Supplementary Table S3. Quality appraisal of included studies using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-sectional Studies and Before-After Studies With No Control Group.

Table S1. Systematic searching strategy for literature about health-related quality of life in kidney transplant recipients.

Searching strategy	(("Kidney Transplantation"[majr] OR "Kidney Transplantation"[ti] OR "Kidney Transplant"[ti] OR "Kidney Transplants"[ti] OR "Renal Transplantation"[ti] OR "Renal Transplant"[ti] OR "Renal Transplants"[ti] OR "Kidney Grafting"[ti] OR "Kidney Graft"[ti] OR "Kidney Grafts"[ti] OR "Renal Grafting"[ti] OR "Renal Graft"[ti] OR "Renal Grafts"[ti] OR (("Kidney"[ti] OR Kidney*[ti] OR "Renal"[ti] OR Renal*[ti]) AND ("Transplantation"[ti] OR "Transplant"[ti] OR "Transplants"[ti] OR transplant*[ti] OR "Grafting"[ti] OR "Graft"[ti] OR "Grafts"[ti] OR Graft*[ti]))) **AND** ("health related quality of life"[tw] OR "HRQOL"[tw] OR "Quality of Life"[mesh] OR "quality of life"[tw] OR "QOL"[tw] OR "life quality"[tw] OR "HRQL"[tw]) **AND** ("2000/01/01"[PDAT] : "3000/12/31"[PDAT]) **AND** english[la] **NOT** (("Child"[mesh] OR "Infant"[mesh] OR "Adolescent"[mesh]) NOT "Adult"[mesh]) **NOT** ("Animals"[mesh] NOT "Humans"[mesh]) **NOT** (("case reports"[ptyp] OR "case report"[ti] OR "Review"[ptyp] OR "review"[ti]) NOT ("Clinical Study"[ptyp] OR "trial"[ti] OR "RCT"[ti]))

Table S2. HRQOL questionnaires used in selected studies and their domain coverage.

Type of the questionnaire	Questionnaire	HRQOL domains
Generic questionnaire	SF-36	Physical Component Summary (PCS; containing four domains: physical functioning (PF), role physical (RP), bodily pain (BP) and general health (GH))
		Mental Component Summary (MCS; containing four domains: vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH))
	SF-12	PCS (containing four domains: PF, RP, BP, and GH) MCS (containing four domains: VT, SF, RE, and MH)
	WHOQOL	Physical health Psychological health Social relationships Environment health
	MLDL	Physical Status Psychological Status Social Situation Daily Life
Kidney disease-specific questionnaire	QLI-DT	Health/functioning Socioeconomic Psychological/spiritual Familial
	KDQOL	SF-12/36 Burden of kidney disease Symptom Effect of disease
	KTQ	Physical symptoms Fatigue Uncertainty/fear Appearance Emotions
	NIDDK-QOL	Measures of disease (physical and mental symptoms and corresponding distress) Psychologic status Personal function Social and role function General health perception

Abbreviations: KDQOL, kidney disease quality of life questionnaire; KTQ, kidney transplant questionnaire; MLDL, Munich life quality dimension list; NIDDK-QOL, national institute of diabetes and digestive and kidney diseases liver transplant database quality of life questionnaire; QLI-DT, quality and life index questionnaire-dialysis and transplantation; SF-12, 12-item short-form health survey; SF-36, 36-item short-form health survey; WHOQOL, world health organization quality of life questionnaire.

Table S3. Quality appraisal of included studies using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-sectional Studies and Before-After Studies With No Control Group.

	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14
Razieh 2012	YES	YES	YES	YES	YES	YES	YES	NA	YES	YES	NA	NA	-	-
Ana 2020	YES	YES	YES	YES	YES	YES	YES	NA	YES	YES	NA	NA	-	-
Intan 2020	YES	YES	YES	YES	NO	YES	YES	NA	YES	YES	NA	NA	-	-
Yosuke 2020	YES	YES	YES	YES	NO	YES	YES	NA	YES	YES	NA	NA	-	-
Griva 2012	YES	YES	YES	YES	NO	YES	YES	NA	YES	YES	NA	NA	-	-
Das 2014	YES	YES	YES	YES	NO	YES	YES	NA	YES	YES	NA	NA	-	-
Junchotikul 2015	YES	YES	YES	YES	NO	YES	YES	NA	YES	YES	NA	NA	-	-
Shrestha 2010[a]	YES	YES	YES	YES	NO	YES	YES	NA	YES	YES	NA	NA	-	-
Shrestha 2010[f]	YES	YES	YES	NO	NO	YES	YES	NA	YES	NO	YES	NA	YES	NO
Lopes 2013	YES	YES	YES	NR	NO	YES	YES	NA	YES	YES	NA	NA	-	-
Mendonca 2014	YES	YES	YES	NR	NO	YES	YES	NA	YES	YES	NA	NA	-	-
Virzi 2007	YES	YES	YES	NR	NO	YES	YES	NA	YES	YES	NA	NA	-	-
Balaska 2006	YES	YES	YES	NR	NO	YES	YES	NA	YES	YES	NA	NA	-	-
Russcher 2015	YES	YES	YES	YES	YES	YES	YES	NA	YES	YES	NA	NA	-	-
Painter 2012	YES	YES	YES	YES	NO	YES	YES	NA	NO	YES	NA	NA	-	-
Lippe 2014[a]	YES	YES	YES	YES	NO	YES	YES	NA	YES	YES	NA	NA	-	-
Lippe 2014[c]	YES	YES	NR	NO	NO	YES	YES	NA	YES	NO	YES	NA	YES	YES
Lumsdaine 2005[a]	YES	YES	YES	NR	NO	YES	YES	NA	YES	YES	NA	NA	-	-
Lumsdaine 2005[c]	YES	YES	NR	NO	NO	YES	YES	NA	YES	NO	YES	NA	YES	NO
Lonning 2018[a]	YES	YES	YES	YES	NO	YES	YES	NA	YES	YES	NA	NA	-	-
Lonning 2018[c]	YES	YES	YES	NO	NO	YES	YES	NA	YES	NO	YES	NA	YES	YES
Czyzewski 2014	YES	YES	NR	YES	NO	YES	YES	NA	YES	NO	YES	NA	YES	NO
Rosenberger 2010	YES	YES	NR	YES	NO	YES	YES	NA	YES	NO	YES	NA	YES	YES
Franke 2000[e]	YES	NO	YES	YES	NO	YES	YES	NA	YES	NO	YES	NA	YES	YES
Franke 2000[f]	YES	NO	YES	NO	NO	YES	YES	NA	YES	NO	YES	NA	YES	YES
Neipp 2006[e]	YES	YES	YES	NO	NO	YES	YES	NA	YES	NO	YES	NA	YES	NO
Neipp 2006[f]	YES	YES	YES	NO	NO	YES	YES	NA	YES	NO	YES	NA	YES	NO
Karine 2020[b]	YES	YES	NO	YES	NO	YES	YES	NA	YES	NO	YES	NA	NA	YES
Karine 2020[c]	YES	YES	NO	NO	NO	YES	YES	NA	YES	NO	YES	NA	NA	YES
Karine 2020[d]	YES	YES	NO	NO	NO	YES	YES	NA	YES	NO	YES	NA	NA	YES
Iqbal 2020[b]	YES	NO	NR	YES	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO
Iqbal 2020[d]	YES	NO	NR	NO	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO
Iqbal 2020[f]	YES	NO	NR	NO	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO
Ranabhat 2020	YES	YES	NR	YES	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO
Tomasz 2003	YES	YES	NO	YES	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO
Fujisawa 2000[b]	YES	YES	NR	YES	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO
Fujisawa 2000[e]	YES	YES	NR	YES	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO
Sayin 2007	YES	YES	YES	YES	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO
Tamura 2018	YES	YES	NR	YES	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO
Rambod 2011	YES	YES	NR	YES	NO	YES	YES	NA	YES	NO	YES	NA	NA	YES
Sapkota 2013	YES	YES	YES	YES	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO
Zheng 2014	YES	YES	YES	YES	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO

Table S3 (continued).

	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14
Kovacs 2011	YES	YES	YES	YES	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO
Stomer 2013[d]	YES	YES	YES	YES	NO	YES	YES	NA	YES	NO	YES	NA	NA	YES
Stomer 2013[c]	YES	YES	YES	NO	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO
Ay 2015	YES	YES	NR	NO	NO	YES	YES	NA	YES	NO	YES	NA	YES	NO
Taskintuna 2009	YES	YES	NR	NO	NO	YES	YES	NA	YES	NO	YES	NA	NA	YES
Yagil 2018	YES	YES	NR	NO	NO	YES	YES	NA	YES	NO	YES	NA	NA	YES
Zhao 2018	YES	YES	YES	NO	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO
Cornella 2008	YES	YES	YES	NO	NO	YES	YES	NA	YES	NO	YES	NA	NA	YES
Aasebo 2009	YES	YES	NO	NO	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO
Karam 2003	YES	YES	YES	NO	NO	YES	YES	NA	YES	NO	YES	NA	NA	YES
Liu 2015	YES	YES	NO	NO	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO
Esposito 2017	YES	YES	YES	NO	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO
Wei 2013	YES	YES	YES	NO	NO	YES	YES	NA	YES	NO	YES	NA	NA	NO
Costa 2017	YES	YES	YES	NO	NO	YES	YES	NA	YES	NO	YES	NA	YES	NO

The assessment tool for before-after studies with no control group comprises 12 items: 1. research question or objective clearly stated; 2. study population clearly specified and defined; 3. representativeness of clinical population of interest; 4. participation of all eligible participants; 5. sample size justification; 6. exposure measures clearly defined; valid; and reliable; 7. outcome measures clearly defined; valid; and reliable; 8. outcome assessors blinded to the exposure status; 9. lost to follow-up≤20%; 10. statistical test for the pre-to-post change; 11. interrupted time-series design; and 12. group-level intervention.

The assessment tool for observational cohort and cross-sectional study comprises 14 items: 1. research question or objective clearly stated; 2. study population clearly specified and defined; 3. participation rate of eligible participants≥50%; 4. subjects selected from the same or similar population; 5. sample size justification; 6. exposure(s) of interest measured prior to outcome(s); 7. timeframe sufficient; 8. different levels of exposures as related to the outcome are examined; 9. exposure measures clearly defined; valid; and reliable; 10. exposure(s) assessed more than once over time; 11. outcome measures clearly defined; valid; and reliable; 12. outcome assessors blinded to the exposure status; 13. lost to follow-up ≤20%; and 14. adjust for potential confounders.

For studies conducted more than one comparison, the quality appraisal was conducted per comparison. [a]before-after; [b]kidney transplant recipients (KTRs)-dialysis patients; [c]KTRs-general population; [d]KTRs-patient with CKD not receiving dialysis; [e]KTRs-patients on the waiting list; [f]KTRs-healthy control. Abbreviations: NA, not applicable; NR, not reported.