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ORIGINAL ARTICLE

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Worse Health-Related Quality of Life at long-term follow-up in patients with Cushing's disease than patients with cortisol producing adenoma. Data from the ERCUSYN

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Summary

Objective: Hypercortisolism in Cushing's syndrome (CS) is associated with impaired health-related quality of life (HRQoL), which may persist despite remission. We used

*See Appendix 1.

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the data entered into the European Registry on Cushing's syndrome (ERCUSYN) to evaluate if patients with CS of pituitary origin (PIT-CS) have worse HRQoL, both before and after treatment than patients with adrenal causes (ADR-CS).

Methods: Data from 595 patients (492 women; 83%) who completed the CushingQoL and/or EQ-5D questionnaires at baseline and/or following treatment were analysed.

Results: At baseline, HRQoL did not differ between PIT-CS (n = 293) and ADR-CS (n = 120) on both EuroQoL and CushingQoL. Total CushingQoL score in PIT-CS and ADR-CS was 41 ± 18 and 44 ± 20, respectively ($P = .7$). At long-time follow-up (>1 year after treatment) total CushingQoL score was however lower in PIT-CS than ADR-CS (56 ± 20 vs 62 ± 23; $P = .045$). In a regression analysis, after adjustment for baseline age, gender, remission status, duration of active CS, glucocorticoid dependency and follow-up time, no association was observed between aetiology and HRQoL. Remission was associated with better total CushingQoL score ($P < .001$), and older age at diagnosis with worse total score ($P = .01$). Depression at diagnosis was associated with worse total CushingQoL score at the last follow-up ($P < .001$).

Conclusion: PIT-CS patients had poorer HRQoL than ADR-CS at long-term follow-up, despite similar baseline scoring. After adjusting for remission status, no interaetiology differences in HRQoL scoring were found. Age and presence of depression at diagnosis of CS may be potential predictors of worse HRQoL regardless of CS aetiology.

KEYWORDS
Cushing's syndrome, ERCUSYN, health-related quality of life

1 | INTRODUCTION

Chronic excessive cortisol exposure in patients with Cushing's syndrome (CS) determines severe physical morbidity and psychological dysfunctions, which invariably impair healthrRelated quality of life (HRQoL).[1-3] In fact, CS patients have worse HRQoL when compared with both healthy subjects and patients with other pituitary diseases.[4-6]

Although HRQoL improves after successful treatment of hypercortisolism, it does not completely normalise.[5,7-15] This is likely due to the persistence, to various degrees, of several features associated with previous cortisol excess, including cardiovascular morbidity, myopathy-related fatigability, bone fragility, affective alterations and cognitive dysfunctions.[6,16,17] All these factors, along with negative illness perception, affect well-being of CS patients, even years after remission[2,18]; (Figure 1).

HealthrRelated quality of life at diagnosis is similar in patients with active CS of pituitary origin (PIT-CS) and in those with adrenal causes (ADR-CS).[2,19] However, data on HRQoL in PIT-CS and ADR-CS after remission are somewhat conflicting.[2,3,9,20] While one report indicated that "cured" PIT-CS patients, but not ADR-CS, had poorer HRQoL than controls,[9] two other studies comparing CS patients in remission of either aetiology did not document any different HRQoL scoring.[20,21] A recent study in patients with hypothalamic-pituitary-adrenal (HPA) axis dysregulation reported worse outcome on the generic questionnaires SF-36 in patients with PIT-CS as compared with ADR-CS, both during active hypercortisolism and postoperatively.[3] Of note, these studies evaluated HRQoL using generic questionnaires and/or the total score of the disease-generated CushingQoL questionnaire.[2] It has been recently suggested that, in addition to the global score, the CushingQoL questionnaire may also provide useful information on specific issues of patient's well-being, including physical, psychological and social dimensions.[22]

The European Registry on Cushing's syndrome (ERCUSYN) is the largest prospective database existing to date, which collects information on diagnosis, management, HRQoL, and long-term follow-up in CS. In this study we used data from ERCUSYN to 1) determine if HRQoL, as measured using both the generic questionnaire EuroQoL and the disease-specific questionnaire CushingQoL, was different in PIT-CS patients in comparison with patients with cortisol producing adenomas, at three time-points: baseline, at first postoperative visit and last follow-up visit; 2) identify potential predictive factors influencing HRQoL in patients with CS of both etiologies.

2 | PATIENTS AND METHODS

2.1 | Description of the database

At the time of the analysis, the ERCUSYN database included 1566 CS patients entered between 1 January 2000 and 31 January 2017,

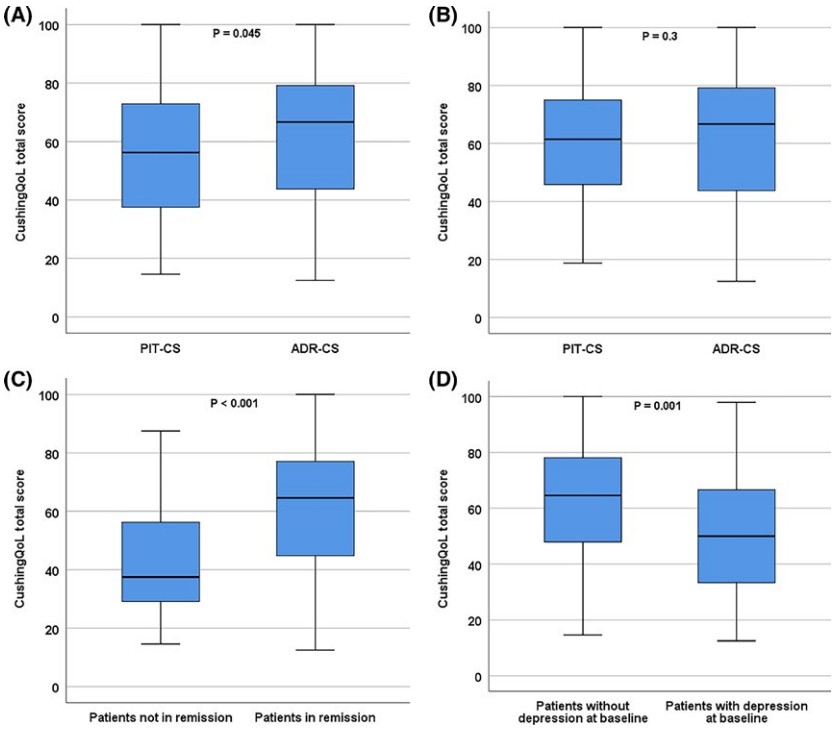

FIGURE 1 CushingQoL total score at long-time follow-up (>365 days) in a) patients with pituitary-dependent Cushing's syndrome (PIT-CS) and adrenal-dependent Cushing's syndrome (ADR-CS) (56 ± 20 vs 62 ± 23; *P* = .045), b) PIT-CS and ADR-CS in remission (61 ± 19 vs 43 ± 19; *P* < .001), c) patients in remission or not in remission (60 ± 19 vs 63 ± 23; *P* = 0.3) and d) patients with and without depression at baseline (52 ± 21 vs 63 ± 20; P = 0.001) [Colour figure can be viewed at wileyonlinelibrary.com]

from 57 centres in 26 European countries. For this study, we analysed data from 1045 (67%) patients with PIT-CS and 386 (26%) with ADR-CS.

A detailed description of the database layout has been provided previously.[19,23] This study has interrogated data entered in the "Diagnosis," "Therapy" and "Follow-up visit" sections of the register, to obtain information on HRQoL and its potential predictors at baseline, first postoperative visit (within 7-365 days since surgery) and last follow-up (after more than 1 year since surgery).

Patients were classified as being "in remission" when their cortisol values, at first postoperative visit, were either "low/undetectable" or "within the normal range," according to the criteria used in each centre.

The ERCSUYN database contains space for entering results of both the EuroQoL and CushingQoL questionnaires at all the visits included by participating centres.

2.2 | Questionnaires

EuroQoL is a self-completion, generic questionnaire that is divided into two parts. EuroQoL-5D profile evaluates five health dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) through a single item with three possible answers (having no problems, having some or moderate problems and being unable to do/having extreme problems). Scores are expressed on a 1-3 scale per dimension, with a higher score indicating worse QoL. The EuroQoL-VAS is a visual analogue scale that measures the self-perception of current health, ranging from 0 (worst possible) to 100 (best possible QoL).[24]

CushingQoL is a disease-generated questionnaire, which consists of 12 items referring to problems relevant to CS patients. Each item has five categories of response related to frequency and degree of agreement with the sentence. Answers are rated on a scale of 1-5; "1" corresponds to "Always" or "Very much" and 5 to "Never" or "Not at all". A lower score indicates poorer HRQoL. The score is the sum of all the item responses and ranges from 12 (worst HRQoL) to 60 points (best HRQoL), which is standardised on a scale from 0 (worst HRQoL) to 100 (best HRQoL), through a formula described elsewhere.[21]

2.3 | Ethics

The ERCUSYN study was approved by the ethics committee (CEIC) of the Hospital Sant Pau, Barcelona, Spain, which is the coordinating centre. In addition, the local ethics committee approval was obtained in each participating institution and all patients gave their written or verbal informed consent, depending on national legal requirements. All the data reported into the system were carefully monitored for inconsistencies, queried when necessary and validated before statistical analysis.

2.4 | Statistical methods

Statistical analyses were performed with IBM® SPSS® Statistics, version 25. Continuous variables are presented as mean ± SD or median (25-75 percentiles). Categorical variables are presented as number (n) and percentage (%). For comparison between two groups, we used unpaired *t* test for normally distributed data and Mann-Whitney *U*-test for non-normally distributed data. For comparisons within a group, a paired *t* test was used for normally distributed data and a Wilcoxon signed rank tests for non-normally distributed data. For proportions, Pearson chi-square or Fisher's exact test were used.

The influence of gender, age at diagnosis, aetiology (pituitary or adrenal), duration of active hypercortisolism, remission status (in remission vs not in remission), follow-up time and glucocorticoid dependency, on QoL at the most recent clinical visit was analysed by multiple linear or logistic regression models with backward elimination (Model 1). In model 2, the influence of hypertension, diabetes mellitus, muscle weakness and depression at diagnosis, on HRQoL at long-term follow-up, was analysed after adjustment for the variables that were associated with HRQoL in model 1 (remission status and age at diagnosis). In model 3, the influence of hypopituitarism, radiotherapy and relapse (yes/no) on HRQoL in PIT-CS patients was studied with the same adjustments as in model 2. Variables that were not normally distributed (duration of symptoms before diagnosis and follow-up time) were log transformed before they were used in the regression analyses. In the logistic regression analysis for EQ-5D, the results were divided into a) no influence or b) some/severe influence. The results from the multiple regression analyses are presented as unstandardised coefficients (B) with 95% confidence interval (CI) and results from the logistic regression analyses as odds ratio with 95% CI.

A *P*-value of < .05 was considered statistically significant.

TABLE 1 Baseline characteristics and health-related quality of life scores in ERCUSYN patients with pituitary-dependent (PIT-CS) or adrenal-dependent (ADR-CS) Cushing's syndrome (CS)

	All (n = 410)	PIT (n = 294)	ADR (n = 116)	*P*
Women, n (%)	339 (83)	243 (83)	96 (83)	1.0
Age at diagnosis (y)	43.0 ± 13.3	42.3 ± 13.3	44.7 ± 13.4	.10
Years with active CS	2.0 (1.0-4.0)	2.0 (1.0-4.0)	2.0 (1.0-3.0)	.2
Education	(n = 329)	(n = 240)	(n = 89)	.7
Elementary school	36 (11)	24 (10)	12 (13)	
Upper secondary education	197 (60)	146 (61)	51 (57)	
University education	96 (29)	70 (29)	26 (29)	
EuroQoL-5D	(n = 343)	(n = 245)	(n = 98)	
Mobility	1.6 ± 0.5	1.6 ± 0.5	1.6 ± 0.5	.5
Self-care	1.3 ± 0.5	1.3 ± 0.5	1.3 ± 0.5	.5
Usual activities	1.7 ± 0.6	1.8 ± 0.6	1.7 ± 0.6	.6
Pain/Discomfort	1.9 ± 0.6	1.9 ± 0.6	1.8 ± 0.6	.8
Anxiety/Depression	1.9 ± 0.6	1.9 ± 0.6	2.0 ± 0.6	.3
VAS	54 ± 20	54 ± 21	53 ± 19	.7
CushingQoL	(n = 358)	(n = 261)	(n = 97)	
Sleep	2.6 ± 1.2	2.6 ± 1.2	2.6 ± 1.3	.6
Pain	3.1 ± 1.3	3.1 ± 1.3	3.2 ± 1.3	.8
Wound healing	2.9 ± 1.3	2.9 ± 1.3	3.0 ± 1.3	.4
Easy bruising	2.3 ± 1.2	2.3 ± 1.2	2.3 ± 1.1	.5
Irritability	2.7 ± 1.1	2.7 ± 1.1	2.5 ± 1.1	.08
Self confidence	2.8 ± 1.1	2.9 ± 1.1	2.7 ± 1.1	.2
Physical appearance	2.0 ± 1.2	2.0 ± 1.1	2.1 ± 1.4	.7
Leisure time	2.7 ± 1.2	2.6 ± 1.2	2.7 ± 1.1	.7
Social activities	3.0 ± 1.3	2.9 ± 1.3	3.1 ± 1.4	.3
Everyday activities	2.6 ± 1.3	2.6 ± 1.3	2.8 ± 1.3	.08
Memory	3.0 ± 1.1	3.0 ± 1.1	3.1 ± 1.2	.4
Worries on future health	2.1 ± 1.1	2.1 ± 1.0	2.1 ± 1.2	.6
Total score	41 ± 18	41 ± 18	42 ± 20	.7

Data are presented as mean ± standard deviation or median (interquartile range).
VAS, visual analogue scale; QoL, quality of life.

3 | RESULTS

In total, 595 patients (492 women; 83%) completed the CushingQoL and/or EQ-5D questionnaires at baseline (n = 410), at the first postoperative visit (7-365 days postoperatively; n = 224) and/or at long-term follow-up (>365 days postoperatively; n = 230), 414 had PIT-CS and 179 ADR-CS. The mean age at diagnosis in the whole cohort was 44.0 ± 13.6 years.

3.1 | Baseline

Of 410 patients with HRQoL assessment available at baseline, 293 (71%) had PIT-CS and 120 (29%) ADR-CS (Table 1). HRQoL did not differ between PIT-CS and ADR-CS on either EuroQoL or CushingQoL questionnaires. The total CushingQoL score in PIT-CS and ADR-CS was 41 ± 18 and 44 ± 20, respectively (P = .7).

3.2 | First postoperative visit (7-365 days postoperatively)

HRQoL at the first postoperative visit was evaluated in 224 patients (Table 2). All patients with PIT-CS had undergone pituitary surgery and all patients with ADR-CS had been treated by unilateral adrenalectomy. Of 218 PIT-CS patients with information on postsurgical remission status, 203 (93%) were in remission. All ADR-CS patients were in remission. HRQoL was significantly worse in PIT-CS as compared with ADR-CS for 3 of the 12 items of CushingQoL; pain, wound healing and physical appearance (P < .05). HRQoL was worse in ADR-CS than PIT-CS for 1 of the 5 items of EuroQoL (anxiety/depression; P = .04). Total CushingQoL score in remitted PIT-CS and ADR-CS did not differ.

3.3 | Long-term follow-up (>365 days)

Information on either CushingQoL and/or EuroQoL at the last postoperative clinical visit was available in 230 patients, 153 (67%)

TABLE 2 Health-related quality of life scores in ERCUSYN patients with pituitary-dependent (PIT-CS) or adrenal dependent (ADR-CS) Cushing's syndrome (CS) at first postoperative visit (7-365 days postoperatively)

	All (n = 224)	PIT (n = 151)	ADR (n = 73)	*P*
Women, n (%)	186 (83)	123 (81)	63 (86)	.4
Age at diagnosis (y)	44.0 ± 12.8	43.0 ± 13.0	46.1 ± 12.2	**.01**
Days from first treatment	105 (55-194)	102 (52-169)	109 (81-212)	.2
GC dependency, n (%)	109 (87)	81 (86)	28 (90)	.5
EuroQoL-5D	(n = 190)	(n = 130)	(n = 60)	
Mobility	1.5 ± 0.5	1.5 ± 0.5	1.5 ± 0.5	.6
Self-care	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.4	.7
Usual activities	1.6 ± 0.6	1.6 ± 0.6	1.7 ± 0.6	.4
Pain/Discomfort	1.8 ± 0.6	1.8 ± 0.6	1.6 ± 0.6	.5
Anxiety/Depression	1.6 ± 0.6	1.6 ± 0.6	1.8 ± 0.6	**.04**
VAS	64 ± 19	66 ± 19	58 ± 22	.06
Cushing QoL	(n = 199)	(n = 136)	(n = 63)	
Sleep	3.1 ± 1.2	3.0 ± 1.3	3.1 ± 1.1	.7
Pain	3.6 ± 1.2	3.2 ± 1.3	3.6 ± 1.2	**.049**
Wound healing	3.8 ± 1.2	3.7 ± 1.2	3.9 ± 1.3	**.047**
Easy bruising	3.2 ± 1.4	3.3 ± 1.2	3.4 ± 1.4	.5
Irritability	3.3 ± 1.1	3.3 ± 1.0	3.3 ± 1.1	.8
Self confidence	3.5 ± 1.1	3.4 ± 1.1	3.4 ± 1.0	.9
Physical appearance	3.3 ± 1.4	2.8 ± 1.4	3.3 ± 1.5	**.030**
Leisure time	3.5 ± 1.2	3.3 ± 1.1	3.5 ± 1.3	.3
Social activities	3.6 ± 1.3	3.4 ± 1.3	3.4 ± 1.3	1.0
Everyday activities	3.2 ± 1.3	3.0 ± 1.3	3.2 ± 1.4	.4
Memory	3.2 ± 1.1	3.3 ± 1.1	3.3 ± 1.1	.7
Worries on future health	2.5 ± 1.1	2.4 ± 1.1	2.6 ± 1.2	.3
Total score	56 ± 21	54 ± 20	58 ± 22	.2

Data are presented as mean ± standard deviation or median (interquartile range). Significance is reported in bold.
GC, glucocorticoid; VAS, visual analogue scale; QoL, Quality of Life.

PIT-CS and 77 (33%) ADR-CS (Table 3). Of 153 PIT-CS patients with information on postsurgical remission status, 107 were in remission (70%). All PIT-CS patients primarily underwent pituitary surgery except for two who were operated on with bilateral adrenalectomy. Thirteen (8.5%) patients with PIT-CS had received additional treatment with pituitary radiotherapy. All patients with ADR-CS were treated with unilateral adrenalectomy and were in remission. The median (IQR) time from the first surgery was 38 (20-65) months with no difference between PIT-CS and ADR-CS ($P = .9$). One-hundred and eighty (82%) patients were receiving glucocorticoid replacement therapy.

Total CushingQoL score was lower in PIT-CS compared to ADR-CS (56 ± 20 vs 62 ± 23; $P = .045$) (Figure 1a). PIT-CS patients scored worse than those with ADR-CS on 4 of 12 CushingQoL items (leisure time, everyday activities, memory, worries on future health; $P < .05$) (Table 3 and Figure 1c). In contrast, no item of EuroQoL differed between PIT-CS and ADR-CS. In comparison with patients in remission, patients not in remission scored worse on all items of both EuroQoL and CushingQoL (Table 3 and Figure 1c). Analysing only patients in remission, HRQoL did not differ between PIT-CS and ADR-CS on either EuroQoL or CushingQoL (Table 4 and Figure 1b). Patients with depression at baseline had lower total CushingQol score than those without (52 ± 21 vs. 63 ± 20; P=0.001) (Figure 1d).

3.4 | Potential determinants of HRQoL at long-term follow-up

In a regression analysis, after adjustment for age at diagnosis, gender, remission status, duration of active CS, glucocorticoid dependency and follow-up time, no association was observed between aetiology (PIT-CS and ADR-CS) and HRQoL (Model 1). Remission was associated with better total CushingQoL score [B 18 (95% CI 10 to 27); $P < .001$], and older age at diagnosis with worse total score [B −0.32/additional years (95% CI −0.56 to −0.08); $P = .01$]. Gender, duration of active CS, glucocorticoid dependency, glucocorticoid dose and follow-up time were not associated with HRQoL.

TABLE 3 Health-related quality of life scores in ERCUSYN patients with pituitary-dependent (PIT-CS) or adrenal dependent (ADR-CS) Cushing's syndrome (CS) at last follow-up visit (>365 days postoperatively)

	All (n = 230)	PIT (n = 153)	ADR (n = 77)	P	Patients in remission (n = 179)	Patients not in remission (n = 41)	P
Women, n (%)	198 (86)	132 (86)	66 (86)	.9	153 (85)	37 (90)	.4
Age at diagnosis (y)	43.9 ± 14.1	43.1 ± 13.7	45.6 ± 14.7	.2	44.2 ± 16.3	43.7 ± 13.6	.8
Months from first treatment	38 (20-65)	38 (24-69)	37 (19-60)	.9	29 (35-61)	47 (33-87)	**.03**
GC dependency, n (%)	180 (82)	119 (78)	61 (79)	.4	147 (83)	24 (59)	**.001**
EQ-5D	(n = 192)	(n = 129)	(n = 63)		(n = 148)	(n = 36)	
Mobility	1.4 ± 0.5	1.4 ± 0.5	1.4 ± 0.5	.7	1.3 ± 0.5	1.7 ± 0.6	**.001**
Self-care	1.2 ± 0.4	1.2 ± 0.4	1.1 ± 0.3	.3	1.1 ± 0.3	1.4 ± 0.6	**.003**
Usual activities	1.5 ± 0.6	1.6 ± 0.6	1.5 ± 0.6	.3	1.4 ± 0.5	2.0 ± 0.6	**<.001**
Pain/Discomfort	1.7 ± 0.6	1.7 ± 0.6	1.6 ± 0.6	.2	1.6 ± 0.6	1.9 ± 0.6	**.005**
Anxiety/Depression	1.6 ± 0.6	1.6 ± 0.6	1.6 ± 0.7	.8	1.6 ± 0.6	1.9 ± 0.6	**.003**
VAS	67 ± 22	66 ± 21	71 ± 24	.3	70 ± 20	50 ± 16	**.006**
Cushing QoL	(n = 213)	(n = 144)	(n = 69)		(n = 163)	(n = 41)	
Sleep	3.1 ± 1.2	3.0 ± 1.2	3.4 ± 1.2	.053	3.3 ± 1.2	2.7 ± 1.0	**.002**
Pain	3.6 ± 1.2	3.5 ± 1.2	3.7 ± 1.3	.17	3.7 ± 1.2	3.2 ± 1.3	**.014**
Wound healing	3.8 ± 1.2	3.8 ± 1.2	3.9 ± 1.3	.5	4.0 ± 1.1	3.2 ± 1.3	**<.001**
Easy bruising	3.2 ± 1.4	3.1 ± 1.4	3.3 ± 1.4	.4	3.4 ± 1.3	2.4 ± 1.3	**<.001**
Irritability	3.3 ± 1.1	3.2 ± 1.1	3.5 ± 1.2	.10	3.4 ± 1.1	2.9 ± 1.1	**.007**
Self confidence	3.5 ± 1.1	3.4 ± 1.1	3.5 ± 1.2	.5	3.6 ± 1.1	2.9 ± 1.0	**<.001**
Physical appearance	3.3 ± 1.4	3.2 ± 1.4	3.6 ± 1.5	.5	3.5 ± 1.4	2.6 ± 1.3	**<.001**
Leisure time	3.5 ± 1.2	3.4 ± 1.2	3.7 ± 1.3	**.046**	3.6 ± 1.2	2.7 ± 1.2	**<.001**
Social activities	3.6 ± 1.3	3.6 ± 1.3	3.8 ± 1.3	.073	3.8 ± 1.3	3.0 ± 1.4	**.001**
Everyday activities	3.2 ± 1.3	3.1 ± 1.3	3.5 ± 1.4	.09	3.4 ± 1.3	2.6 ± 1.3	**.001**
Memory	3.2 ± 1.1	3.0 ± 1.0	3.4 ± 1.1	**.048**	3.3 ± 1.1	2.7 ± 1.0	**.001**
Worries on future health	2.5 ± 1.1	2.4 ± 1.0	2.7 ± 1.3	**.008**	2.6 ± 1.1	2.1 ± 1.0	**.014**
Total score	58 ± 21	56 ± 20	62 ± 23	**.045**	61 ± 19	43 ± 19	**<.001**

Data are presented as mean ± standard deviation or median (interquartile range). Significance is reported in bold.
GC, glucocorticoid; VAS, visual analogue scale; QoL, quality of life.

TABLE 4 Health-related quality of life scores in ERCUSYN patients with pituitary-dependent (PIT-CS) in remission or adrenal dependent (ADR-CS) Cushing's syndrome (CS) at last follow-up visit (>365 days postoperatively)

	PIT (n = 107)	ADR (n = 72)	*P*
Women, n (%)	91 (85)	62 (86)	.8
Age at diagnosis (y)	41.2 ± 13.4	45.6 ± 12.4	.062
Months from first treatment	34 (21-60)	35 (20-62)	.3
GC dependency, n (%)[a]	86 (91)	44 (96)	.4
EuroQoL-5D	(n = 89)	(n = 59)	
Mobility	1.3 ± 0.5	1.4 ± 0.5	.5
Self-care	1.1 ± 0.4	1.1 ± 0.3	.9
Usual activities	1.4 ± 0.5	1.4 ± 0.6	.9
Pain/Discomfort	1.6 ± 0.6	1.6 ± 0.7	.6
Anxiety/Depression	1.5 ± 0.6	1.6 ± 0.7	.3
VAS	69 ± 20	71 ± 24	.6
CushingQoL	(n = 98)	(n = 65)	
Sleep	3.2 ± 1.1	3.4 ± 1.2	.13
Pain	3.6 ± 1.2	3.8 ± 1.3	.3
Wound healing	4.0 ± 1.1	3.9 ± 1.3	.6
Easy bruising	3.4 ± 1.2	3.4 ± 1.4	.9
Irritability	3.3 ± 1.0	3.5 ± 1.3	.4
Self confidence	3.6 ± 1.0	3.5 ± 1.2	.8
Physical appearance	3.4 ± 1.4	3.5 ± 1.5	.5
Leisure time	3.6 ± 1.1	3.7 ± 1.3	.6
Social activities	3.8 ± 1.2	3.8 ± 1.4	.4
Everyday activities	3.3 ± 1.3	3.5 ± 1.4	.2
Memory	3.1 ± 1.0	3.5 ± 1.2	.054
Worries on future health	2.5 ± 1.0	2.7 ± 1.3	.3
Total score	60 ± 19	63 ± 23	.3

Data are presented as mean ± standard deviation or median (interquartile range).
GC, glucocorticoid; VAS, visual analogue scale; QoL, quality of life.
[a]Missing in 38 patients.

Analysing each HRQoL item (the 12 CushingQoL plus the 5 EuroQoL dimensions) separately showed that remission was associated with better outcome on 14 of 17 items, and older age at diagnosis with poorer HRQoL on 7 of 17 items (Table 5). No clear association was observed between HRQoL items and gender, duration of active CS, glucocorticoid dependency or time since first surgical treatment. By adding symptoms at diagnosis (hypertension, diabetes mellitus, depression and muscle weakness) to the regression model (Model 2), depression was associated with a worse total CushingQoL score at the last clinical visit [B −10 (95% CI −17 to −3); *P* = .004], whereas hypertension, diabetes mellitus or muscle weakness had no significant influence. Similarly, presence of depression [B −16 (95% CI −23 to −9); *P* < .001] and treatment for depression [B −14 (95% CI −22 to −6); *P* = .001] at the last visit were associated with worse total CushingQoL score at the last follow-up.

In an analysis including only patients with PIT-CS, radiation therapy, hypopituitarism and relapse were not associated with total CushingQoL score at the last visit (Model 3; data not shown).

In patients who had completed CushingQoL at both baseline and last clinical visit (n = 68), the mean total score increased from 35 ± 18 to 64 ± 20 (*P* < .001). Remission [B 28 (95% CI 14 to 44); *P* < .011] and younger age at diagnosis [B −0.7 (95% CI −1.1 to −0.3); *P* = .001] were the only predictive factors that were associated with better outcome.

4 | DISCUSSION

In this study, we evaluated HRQoL in a large cohort of patients with CS, both at diagnosis, within 1 year after surgery and at long-term follow-up (>1 year after surgery). The main purpose of the study was to investigate whether hypercortisolism of pituitary origin had a different impact on HRQoL as compared with the ADR-CS. We found that HRQoL was impaired and similar between both etiologies at baseline, whereas scores for several CushingQoL items within 1 year after surgery were worse in remitted PIT-CS as compared with treated ADR-CS patients. At long-term follow-up, PIT-CS had poorer HRQoL as compared with ADR-CS patients. However, when only patients in remission were analysed, no differences in any of the HRQoL measures were observed between PIT- CS and ADR-CS. In fact, remission was the single most important predictor of beneficial outcome for the CushingQoL questionnaire in the entire series, pointing to hypercortisolism itself as the main reason for HRQoL impairment in CS.

Some previous studies have provided conflicting results regarding the effect of the aetiology of CS on postsurgical HRQoL. Lindholm et al observed no abnormality in perceived health using the generic questionnaire SF-36 in 12 patients treated for adrenal adenoma. This was in sharp contrast with 37 PIT-CS patients, both "cured" and active, whose HRQoL, after more than 5 years following surgery, was worse than in the general population.[9] On the contrary, Webb et al[21] did not demonstrate any differences in the total CushingQoL score between PIT-CS (n = 60) and ADR-CS (n = 18) two years after treatment. Also, Wagenmakers et al[20] reported that no HRQoL dimensions of several generic questionnaires were poorer in CS patients after a mean remission time of 13 years as compared with controls. Furthermore, the total CushingQoL score was similar in 99 remitted PIT-CS patients as compared with 24 patients treated for ADR-CS, again suggesting that prior hypercortisolism *per se*, rather than aetiology, is the major cause of reduced HRQoL.[20]

Our results are in agreement with these previous findings, showing that the main factor influencing long-term HRQoL is the remission status and not aetiology. After a median time since surgery of 38 months, PIT-CS patients showed worse total CushingQoL score as well as worse scoring on several CushingQoL items (leisure time, memory, and worries on future health) as compared with ADR-CS.

TABLE 5 Regression analysis at the last follow-up—Explanatory variables that were significantly associated with the HRQoL items are shown

EuroQoL-5D items (logistic regression)	Odds ratio	95% CI	*P*
Mobility			
Age at diagnosis	1.05	1.02 to 1.08	**.002**
Self-care			
None			
Usual activities			
Not in remission	5.0	1.8 to 13.7	**.002**
Pain/Discomfort			
Not in remission	3.4	1.2 to 9.6	**.02**
Anxiety/Depression			
Not in remission	5.6	1.8 to 17.4	**.003**
CushingQoL items (linear regression)	**B**	**95% CI**	***P***
Sleep			
Age at diagnosis	−0.02	−0.03 to −0.004	**.012**
Remission	0.50	0.02 to 0.99	**.042**
Pain			
None			
Wound healing			
Remission	0.97	0.49 to 1.47	**<.001**
Easy bruising			
Remission	1.05	0.50 to 1.60	**<.001**
Female gender	−0.76	−1.40 to −0.12	**.020**
Irritability			
Remission	0.72	0.26 to 1.18	**.002**
Self confidence			
Remission	0.71	0.27 to 1.15	**.002**
Age at diagnosis	−0.02	−0.03 to −0.005	**.007**
Physical appearance			
Remission	0.86	0.48 to 1.41	**.003**
Leisure time			
Remission	0.95	0.47 to 1.43	**<.001**
Social activities			
Remission	0.81	0.29 to 1.34	**.003**
Age at diagnosis	−0.02	−0.03 to −0.001	**.04**
Everyday activities			
Age at diagnosis	−0.03	−0.04 to −0.01	**.002**
Remission	0.65	0.12 to 1.18	**.016**
Memory			
Age at diagnosis	−0.02	−0.03 to −0.005	**.006**
Remission	0.60	0.15 to 1.05	**.009**
Future health			
Remission	0.57	0.10 to 1.04	**.018**
Total CushingQoL			
Remission	18	10 to 27	**<.001**
Age at diagnosis	−0.32	−0.56 to 0.08	**.010**

QoL, quality of life; CI, confidence interval. Significance is reported in bold.

Yet, in remitted patients of both etiologies, these differences were no longer significant. In particular, the total CushingQoL score was 60 ± 19 in PIT-CS and 63 ± 23 in ADR-CS, with similar scores on all the specific items of CushingQoL. Previous studies using the CushingQoL questionnaire to evaluate HRQoL in long-term "cured" PIT-CS found a total CushingQoL score of 40 ± 10 and 50 ± 18, after 6 and 16 years of remission, respectively.[16,18]

Of note, Wagenmakers et al showed that better CushingQoL scoring is associated with longer duration of remission, consistent with previous observations reporting a gradual improvement in psychopathology after correction of cortisol excess.[4] On the contrary, and in agreement with other studies, we did not find an association between HRQoL scores and duration of remission, likely because remission had occurred a long time before in most patients.[11,21]

In our study, we demonstrate, in addition to persistent hypercortisolism, that concomitant depression or treatment for depression also play a pivotal role in affecting patients' well-being. This was found for CS of both adrenal and pituitary origin, regardless of factors which have previously been associated with HRQoL, including gender, hypopituitarism and glucocorticoid dependency.[5,11,20,21,25] Van Aken et al[11] described a significant association between anxiety and depression scores and HRQoL parameters in CD patients after 13 years in remission. Another study showed that affective alterations, mainly depressive symptoms, were the main determinant of CushingQoL score after 6 years in remission.[19] Indeed, remitted PIT-CS patients have been shown to present with depressive symptoms, peculiar psychopathology and maladaptive disorders even long-term after correction of hormone excess.[1] These features might be due to irreversible structural as well as functional impairment of cerebral regions controlling cognitive and emotional processing.[26,27] Moreover, dysregulation of the HPA axis, and emotional stress due to a chronic disease might also contribute to the occurrence and/or maintenance of depressive symptomatology in CS patients despite resolution of hypercortisolism.

Interestingly, depression at diagnosis was the only baseline feature that was associated with total CushingQoL score in our patients, further strengthening the role of depression as a main determinant of long-lasting impaired well-being. In our remitted patients, depression may either occur "ex-novo" after surgery or persist despite "cure". ERCUSYN does not allow to distinguish between both these different periods of onset.

When a shorter period of follow-up (<1 year) was considered, PIT-CS had a worse HRQoL on several CushingQoL items than ADR-CS patients, including pain, wound healing and physical appearance. Although remission status is of great importance, another possible explanation is that psychophysical status in patients with PIT-CS patients may take longer time to recover than in ADR-CS patients.[28] Indeed, in a survey on symptom resolution in adrenalectomized patients, Sippel et al identified specific time intervals for the disappearance of typical features related to hypercortisolism. In particular, most of the symptoms and signs took at least 6 to 12 months to resolve but a wide inter-patient variability was also observed, and some physical complaints took up to 4 years to recover.[29] The median time to the first postoperative evaluation of our patients was 3.5 months and, therefore, assessment of HRQoL may have been conducted too early to detect a clear improvement.

Total CushingQoL score was similar between PIT-CS and ADR-CS patients short-term after surgery. Indeed, our "cured" patients had a total score of 56 ± 20, which is in line with a previous study showing a score of 54 ± 13.4 months after surgery.[25] Patients with persistent disease had a score of 47 ± 18, similar to that of remitted patients, suggesting that the beneficial effects of biochemical remission do not become evident until later.

Recently, it has been proposed that analysing different dimensions of CushingQoL provides additional information on physical, psychological and social issues characteristic of CS, that are not reflected by the global score.[22] As a matter of fact, when specific issues were analysed early after surgery, remitted patients already presented a significant improvement of some physical characteristics along with reduced worries about changes in their physical appearance as compared with patients not in remission. Thus, scoring on a single item may "capture" subtle, early changes in some dimensions of HRQoL which might be overlooked using only the total CushingQoL score. Moreover, although in our large study both CushingQoL and the generic questionnaire EuroQoL provided similarly significant total scorings which reliably reflected the impairment of HRQoL in CS patients, the former, per definition, is more sensitive to identify specific problems encountered by them, especially in smaller samples.[21]

Worse HRQoL in PIT-CS may be due to complications of pituitary surgery, including hypopituitarism and abrupt ACTH deficiency, although we did not find any correlations between HRQoL and these parameters. Another possible factor potentially influencing poorer early postsurgical HRQoL in PIT-CS patients may be worse preoperative clinical status as compared with ADR-CS but, again, no association emerged between HRQoL measurements and baseline features from our analysis.

Concomitant hypopituitarism and radiotherapy were not related to worse HRQoL in our population, in contrast with the study by van Aken et al, but in agreement with others.[5, 11, 21] Wagenmakers et al found that patients treated for CD without hypopituitarism had better scores on several questionnaires, including the CushingQoL, than those with hormone deficiencies.[20] However, in that study, patients in remission without hormonal deficiencies had persistent impairment of HRQoL on 50% of the items analysed as compared with healthy controls. Indeed, after multiple regression analysis, HRQoL remained impaired in CS patients in long-term remission regardless of hormonal deficiencies and treatment strategies.[20] Thus, any additional impact of both hormone deficiencies and previous pituitary radiotherapy on HRQoL may be "masked" by the predominant effects of prior exposure to glucocorticoid excess. In addition, the results concerning the lack of effect of radiotherapy on HRQoL must be interpreted with caution as only thirteen patients had received such treatment.

It should be highlighted that these ERCUSYN results do not allow a longitudinal evaluation of the HRQoL parameters in all subjects

from baseline to the end of follow-up, and this is clearly a limitation of our study. However, ERCUSYN involves a careful validation process which provides, in a large cohort, a reliable clinical picture of patient's status before and after surgery throughout Europe.

Moreover, first evaluation of our patients was carried out after a median of 3.5 months and, therefore, assessment of HRQoL may have occurred too early to detect a clear improvement. It should be highlighted that ERCUSYN patients are classified in remission when their postoperative cortisol levels are either "undetectable" or "normal". Thus, we cannot exclude that some PIT-CS patients with "normal" cortisol levels were not completely "cured" at the first post-surgical assessment.[30,31]

In conclusion, we have shown that PIT-CS patients had poorer HRQoL than ADR-CS at both short-term and long-term follow-up after surgery, despite similar baseline scoring. Remission status was the single most important predictor of HRQoL improvement at long-term follow-up after treatment, indicating that the hypercortisolism itself is the major determinant for impaired HRQoL. However, depression at baseline or at last follow-up was another important determinant of poor HRQoL even after remission is achieved. Measurement of specific CushingQoL items provides useful information on patients' well-being which may not be entirely reflected by the total CushingQoL score.

CONFLICT OF INTERESTS

MR received financial support, research grants, consultant or speaker fees from Ipsen, Novartis, Pfizer. DM received consultant and speaker fees from HRA Pharma, Ipsen, Novartis, Novo-Nordisk and Pfizer. MT has received consultant and speaker fees from Novartis, Ipsen and Pfizer. AT received financial support, research grants, consultant fees from Novartis and HRA pharma. CJS has received lecture fees, consultancy remuneration or research support from HRA Pharma, Novartis and Strongbridge. SMW received financial support, research grants, consultant or speaker fees from Ipsen, Novartis, Pfizer, HRA and Strongbridge. The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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APPENDIX 1

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