Economic and Health-Related Quality of Life Burden in Endogenous Cushing's Syndrome: A Systematic Literature Review

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INTRODUCTION

- Endogenous Cushing's syndrome (CS) is a rare, debilitating disorder caused by chronic overproduction of cortisol[1,6,7]

OBJECTIVES

- To perform a systematic literature review (SLR) to summarize the latest evidence on the economic and health-related quality of life (HRQoL) burden associated with endogenous CS, its treatment, and management, and to describe differences between patients in remission and those with active disease using available data

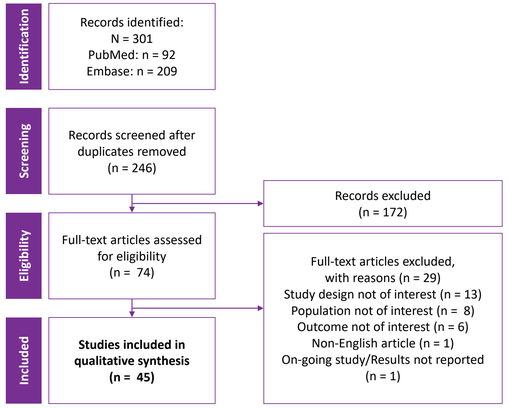
METHODS

- SLR conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[8]
- Primary studies (clinical trials, observational studies, economic analyses), or SLRs examining economic or HRQoL outcomes in patients with endogenous CS treated with any pharmacotherapy, surgery, or radiotherapy
- Searches in PubMed, MEDLINE, and Embase identified manuscripts and conference abstracts, published from 2015 to December 4th, 2020, meeting the eligibility criteria
- Duplicates across the three databases were removed using EndNote[9]
- Selected studies were screened using Covidence, a web-based software[10]
- Data from included studies were extracted in a Microsoft Excel™ grid

RESULTS

- Results of the study selection are presented in Figure 1[11-55]
- Of the 45 studies that met eligibility criteria for qualitative analysis, 37 were primary studies from which data were extracted (Tables 1A and 1B); 8 were published SLRs used for reference purposes only[11-47, 48-55]
- The majority of studies (32 of 37) reported HRQoL burden[11-13,17-23,25,27-47], four studies reported economic burden[14-16,26], and one study reported both[24]
- Nine studies reported pre-/post treatment burden using general or symptom specific patient reported outcome (PRO) measures [17,18,21, 36,37,41,42,46,47]

FIGURE 1. PRISMA FLOW DIAGRAM OF STUDY SELECTION



RESULTS

TABLE 1A. STUDY CHARACTERISTICS

Geographical Region	Number of studies (n)
Europe	21
North America	14
South America	1
Asia	1
Study Types	**Number of studies (n)**
Prospective studies	11
Cross-sectional Studies	10
Retrospective Studies	13
RCTs	3
Studies reporting prior interventions (including transsphenoidal surgery, adrenalectomy, radiotherapy, hormone replacement therapy, and pharmacotherapy)	37
Studies reporting comorbidities associated with endogenous CS (e.g., diabetes, hypertension, osteoporosis, and obesity)	9

Abbreviations: RCT: Randomized controlled trial

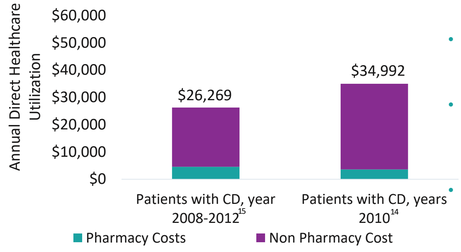
TABLE 1B. PATIENT CHARACTERISTICS

Patient Characteristics (n=number of studies)	Ranges Reported in Studies
Mean age (n=26)	13-55 years
Median age (n=3)	42-53 years
Proportion of female patients (n=29)	18-100%
Number of patients with endogenous CS (n=37)	6-1852 patients

Abbreviations: CS: Cushing's Syndrome

ECONOMIC BURDEN

FIGURE 2. ANNUAL DIRECT HEALTHCARE COSTS AS REPORTED IN TWO STUDIES



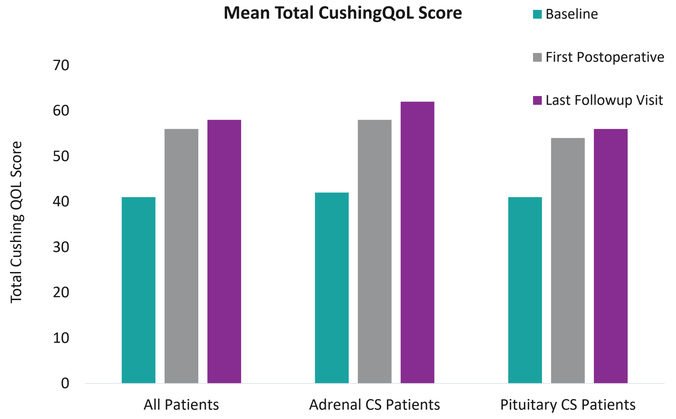
- Five studies reported on economic burden including 3 studies which only reported direct economic burden
- Of the 5 studies, n = 3 used claims data for analysis, n = 1 included a budget impact model and n = 1 was a cross-sectional study
- Non-pharmacy costs included costs related to inpatient stays, emergency rooms, and outpatient visits[14,15]

References: 14, 15 **Abbreviations:** CD: Cushing's Disease

PRE- AND POST-TREATMENT BURDEN OF CS

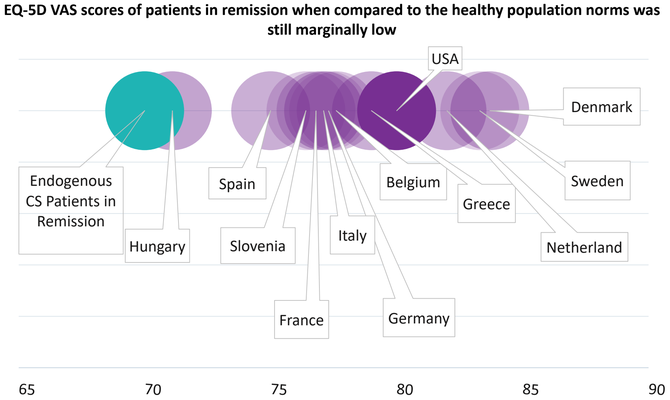
- SF-36 was the most utilized (12 of 37) PRO measure to report general HRQoL[17,18, 27, 29, 32, 34, 37, 38, 43, 44, 46, 47]
- Comparison of EQ-5D VAS scores of patients with CS versus healthy population norms are presented in Figure 4
- Of the 9 studies reporting pre- and post-treatment outcomes, 8 studies reported pre and post surgery outcomes with 50% of studies having longitudinal ≥ 1 year post surgical outcome data [17,18, 36,37,41,42,46,47]
- Post-surgery, patients demonstrated improved mean total CushingQoL score irrespective of subtype of CS; however, the difference did not reach statistical significance[17,18,35,36,41,42,47,46]
- Another study found no statistically significant differences in HRQoL, measured using CushingQOL between patients treated with 1-4 pituitary surgeries[36]

FIGURE 3. MEAN TOTAL CUSHING QOL SCORE FOLLOWING SURGERY



Note: Figure includes data from a selected study that best illustrates patient burden using the CushingQoL instrument[41]
Note: The CushingQoL total scores ranged from 0 (worst QoL) to 100 (best QoL)

FIGURE 4. COMPARISON BETWEEN EQ-5D VAS SCORES OF PATIENTS IN REMISSION POST SURGERY AND HEALTHY POPULATION NORMS FROM EUROPE AND THE UNITED STATES OF AMERICA (USA)



EQ-5D VAS is a generic measure of HRQoL, and its scores range from 0 to 100 with higher scores corresponding to better HRQoL

Note: EQ-5D VAS scores for Endogenous CS patients in remission are from a study conducted among European patients and included in this SLR[36, 42, 57]

SYMPTOM SPECIFIC POST-SURGERY HRQOL

- Statistically significant decreases in HRQoL in domains, including depression, anxiety, and fear were reported following surgery in three studies[37, 38, 47]
- Mean role-physical/physical role functioning[§] and bodily pain improved 8-12 months following surgery in two studies utilizing the SF-36[46,47] (Table 2)
- Post-operative SF-36 scores were collected ~8-12 months following surgery[46,47]

TABLE 2. SF-36 SCORES PRE AND POST SURGERY

Author, Year	Outcome	Treatment Arm (n)	Scores
Zarino, 2019[47]	Physical Functioning*	Cushing's Disease pre-op (10)	80.5 ± 19.64
		Cushing's Disease 12 mo. post-op (10)	57 ± 12.07
	Role-Physical*§	Cushing's Disease pre-op (10)	52.2 ± 38.64
		Cushing's Disease 12 mo. post-op (10)	63.5 ± 28.29
	Bodily Pain*	Cushing's Disease pre-op (10)	59.2 ± 24.97
		Cushing's Disease 12 mo. post-op (10)	60.7 ± 16.04
Ye VC, 2017[46]	Physical Functioning	Peri-op (42)	41.26 ± 33.30
		Second Post-Op (11)	61.87 ± 37.22
	Physical Role Functioning§	Peri-op (42)	21.34 ± 36.47
		Second Post-Op (11)	52.27 ± 48.03
	Bodily Pain	Peri-op (42)	44.55 ± 28.11
		Second Post-Op (11)	58.45 ±23.58

Abbreviations: Peri-op: Peri-operative; Pre-op: Pre-operative; Post-op: Post-operative; n: Sample size
Notes:
1. *Statistically significant differences at p-value=0.05
2. Figure includes data for selected studies that best illustrate patient burden using the SF-36 instrument
3. §The role physical or physical role functioning subscale is defined as role limitations due to physical health[57]
4. SF-36 total scores range from 0 (maximum disability) to 100 (no disability)

DISCUSSION AND CONCLUSION

- Patients with endogenous CS experience a substantial, complex, and multi-symptomatic HRQoL burden
- Despite surgical interventions, endogenous CS patients continue to have worse HRQol scores compared to healthy individuals, suggestive of long-term effects of CS
- Patient wellbeing is impacted by a high HRQoL burden, which persists in key domains despite current treatment interventions, including surgery
- Lack of significant improvement suggests additional interventions may be needed to restore normal HRQoL for patients even after treatment of endogenous CS
- Few studies address the economic burden of CS; however, the available data indicate patients experience a high direct economic burden
- Further research is needed to better characterize economic burden of endogenous CS

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