Volumen 12, número 3 de 2025
https://doi.org/10.53853/encr.12.3.950

REVISTA COLOMBIANA de Endocrinología Diabetes & Metabolismo

Residents' Notes

Review

Global landscape of Cushing's syndrome registries: A systematic mapping study of design, coverage, and outcomes

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How to cite this article: Rivera-Martínez WA, Ramírez-Castaño MJ, Román-González A, Gutiérrez-Restrepo J, Builes-Montaño CE. Global landscape of Cushing's syndrome registries: A systematic mapping study of design, coverage, and outcomes. Rev Colomb Endocrinol Diabet Metab. 2025;12(3):e950. https://doi.org/10.53853/encr.12.3.950

Submitted: 15/April/2025 **Accepted:** 08/September/2025 **Published:** 26/September/2025

Abstract

Context: Cushing's syndrome (CS) is a rare endocrine disorder associated with high morbidity and mortality. Its low prevalence and clinical heterogeneity challenge large-scale population studies, highlighting the role of patient registries as key sources of information for epidemiological surveillance, clinical research, and public health decision-making.

Objective: To describe and analyze the clinical, therapeutic, and outcome characteristics of population-based registries of Cushing's syndrome worldwide.

Methodology: A systematic literature review was conducted in PubMed up to December 2024. Articles in English and Spanish reporting population-based registries of adult patients with Cushing's syndrome were included. The search was complemented by manual reference screening.

Results: Fifteen articles corresponding to twelve registries were identified. Most registries originated in Europe, notably the multinational ERCUSYN registry. Only one study from Argentina represented Latin America. Significant heterogeneity was found in diagnostic criteria, treatment approaches, and remission definitions. The most frequent comorbidities were hypertension and type 2 diabetes. Reported mortality ranged from 0% to 26.5%, depending on follow-up duration.

Highlights

- Twelve population-based registries of Cushing's syndrome were identified worldwide, mostly from Europe. Latin America is underrepresented in Cushing's syndrome registry initiatives.
- High heterogeneity exists in diagnostic definitions, outcomes, and therapeutic approaches across registries.
- Registries are essential tools to improve Cushing's syndrome's clinical and epidemiological understanding.

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E-ISSN: 2805-5853 | L-ISSN: 2389-9786

Conclusions: Population-based registries are essential tools to improve clinical and epidemiological understanding of Cushing's syndrome. However, their geographic coverage remains limited, and methodological standardization is insufficient. There is a pressing need to develop registries in underrepresented regions such as Latin America.

Keywords: Registries, review, Cushing syndrome, rare diseases, translational research, biomedical, comorbidity, diagnosis, treatment outcome, clinical decision-making

Panorama global de los registros de síndrome de Cushing: un estudio de mapeo sistemático sobre su diseño, cobertura y desenlaces

Resumen

Contexto: el síndrome de Cushing (SC) es una enfermedad endocrina rara, asociada a una alta carga de morbilidad y mortalidad. Su baja prevalencia y la heterogeneidad clínica dificultan su estudio en poblaciones amplias, lo que resalta la importancia de los registros poblacionales como fuente de información para la vigilancia epidemiológica, el análisis clínico y la toma de decisiones en salud pública.

Objetivo: describir y analizar las características clínicas, terapéuticas y de desenlaces de los registros poblacionales de síndrome de Cushing disponibles a nivel mundial.

Metodología: se realizó una revisión de la literatura disponible en PubMed hasta diciembre de 2024. Se incluyeron artículos en inglés y español que describieran registros poblacionales con pacientes adultos con diagnóstico de síndrome de Cushing. La búsqueda fue complementada con una revisión manual de referencias relevantes.

Resultados: se identificaron 15 artículos correspondientes a 12 registros poblacionales. La mayoría provino de Europa, destacándose el registro multinacional ERCUSYN. América Latina estuvo representada únicamente por un estudio en Argentina. Se evidenció alta heterogeneidad en los criterios diagnósticos, los tratamientos empleados y las definiciones de remisión. Las comorbilidades más frecuentes fueron hipertensión arterial y diabetes tipo 2. La mortalidad varió entre 0 % y 26.5 %, dependiendo del tiempo de seguimiento.

Conclusiones: los registros poblacionales son herramientas fundamentales para mejorar el conocimiento clínico y epidemiológico del síndrome de Cushing. Sin embargo, su cobertura geográfica es limitada y su estandarización metodológica insuficiente. Es necesario promover el desarrollo de registros en regiones subrepresentadas como América Latina.

Palabras clave: registros, revisión, síndrome de Cushing, enfermedades raras, investigación biomédica traslacional, comorbilidad, diagnóstico, resultado del tratamiento, toma de decisiones clínicas.

Destacados

- Se identificaron 12 registros poblacionales de síndrome de Cushing en el mundo, con predominio europeo. América Latina está subrepresentada en estos registros.
- Existe alta heterogeneidad en las definiciones diagnósticas, desenlaces y modalidades terapéuticas entre los registros.
- Los registros son herramientas fundamentales para mejorar la comprensión clínica y epidemiológica del síndrome de Cushing.

Introduction

Cushing's syndrome (CS) is a rare endocrine disorder caused by prolonged exposure to supraphysiologic levels of glucocorticoids (GCs), either of endogenous or exogenous origin (1–3). Endogenous CS is classified into two categories: adrenocorticotropic hormone (ACTH)-dependent, which accounts for 80–85% of cases, and ACTH-independent. Among ACTH-dependent forms, Cushing's disease (CD), due to a pituitary adenoma secreting ACTH, is the most common cause,

followed by ectopic ACTH-producing tumors and, rarely, corticotropin-releasing hormone (CRH)-secreting tumors (3).

The clinical presentation is heterogeneous and depends on the severity and duration of hypercortisolism (4). Patients may develop central obesity, facial plethora, proximal muscle weakness, and violaceous striae (5,6). Because these features are often nonspecific, diagnosis is frequently delayed (7). The diagnostic approach includes exclusion of exogenous GC exposure, biochemical testing such as 24-hour urinary free cortisol (UFC), late-night salivary cortisol (LNSC), and the low-dose dexamethasone suppression test (DST), followed by ACTH measurement, imaging, and, in selected cases, bilateral inferior petrosal sinus sampling (BIPSS) (8). Surgery remains the first-line treatment. In cases of persistent or recurrent disease, or when surgery is not feasible, medical and radiotherapeutic options are available (9). Pharmacologic agents include steroidogenesis inhibitors, such as ketoconazole (10,11), osilodrostat (12,13), and metyrapone (14), dopamine agonists (e.g., cabergoline) (15), somatostatin analogs (e.g., pasireotide) (16), and glucocorticoid receptor antagonists (e.g., mifepristone) (17).

Although rare, with an estimated incidence of 3.2 cases per million individuals per year (18), CS carries significant morbidity (19), and mortality may be up to three times higher than in the general population (20). Even after achieving remission, many patients experience persistent complications and reduced quality of life. Although significant advances have been made in the diagnosis and treatment of CS, there remains a substantial knowledge gap regarding its true epidemiology, natural history, and long-term outcomes—particularly in resource-limited settings (2,3). In countries like Colombia, epidemiological information on CS remains scarce and fragmented (21-24). These figures underscore the urgent need for timely diagnosis, effective treatments, long-term follow-up, and context-specific public health strategies.

Patient registries represent a critical tool for characterizing rare conditions such as CS. They enable the collection of homogeneous and systematic clinical data across defined populations, which is essential for understanding disease progression, assessing treatment effectiveness, and establishing quality indicators in healthcare (25). In the context of orphan diseases, marked by low prevalence and high clinical heterogeneity, registries are especially valuable. They help overcome the sample size limitations of clinical trials, facilitate the identification of clinical patterns and prognostic factors, and support the evaluation of therapeutic responses. In addition, they promote collaboration across centers and regions, enhancing the scientific and clinical utility of collected data (26,27). Most registries allow the epidemiological characterization of the disease, the evaluation of medical care, and a better understanding of the natural history; however, they also present challenges related to the design, management, and sustainability of rare disease registries (27).

Given the clinical relevance of CS and the lack of structured data, it is essential to analyze existing population-based registries worldwide. This systematic mapping study aims to identify, describe, and synthesize available information on CS-focused registries, including both dedicated and broader registry systems. The review seeks to highlight their strengths, limitations, and areas for improvement, while also promoting the development of regional registries in Latin America to help close the current knowledge gap. Registries enable comparative assessment of treatment strategies (both surgical and pharmacologic), facilitate clinical outcome monitoring, foster collaborative networks among healthcare centers, and generate evidence to guide clinical and policy decision-making. Additionally, they serve as essential tools for epidemiological surveillance, allowing the identification of prognostic factors and supporting the continuous improvement of care delivery.

In health systems such as Colombia's—characterized by structural heterogeneity and barriers to access—a national CS registry could provide valuable insights into clinical presentation, therapeutic approaches, short- and long-term outcomes, and health disparities. Furthermore, it could support the identification of optimal clinical practices and the implementation of evidence-based quality improvement strategies tailored to the local context.

Methods

Literature search strategy

A systematic literature search was conducted using the MedLine database via PubMed. The search strategy included Medical Subject Headings (MeSH) combined with Boolean operators, specifically using the following formula:

(((Cushing syndrome / all fields topic) AND (Diagnosis / all fields) AND (Registries / all fields))).

The search aimed to identify articles reporting on registries that included adult patients (≥18 years) diagnosed with Cushing's syndrome. Only articles published in English or Spanish between 2000 and December 31, 2024, were considered for inclusion.

Selection criteria

Studies were included if they met the following criteria:

- Reported on registries specifically designed for Cushing's syndrome or broader registries with specific CS-related data.
- Included adult populations (≥18 years).
- Provided descriptive or analytical data relevant to diagnosis, clinical features, outcomes, or registry design.
- Published in peer-reviewed journals in English or Spanish.

Exclusion criteria were:

- Case reports, narrative reviews without registry data, or studies focused exclusively on pediatric populations.
- Conference abstracts or unpublished data.

Data collection and manual search

In addition to the database search, a manual review of the reference lists from the selected articles was performed to identify additional relevant publications. Articles identified through this method were subject to the same inclusion and exclusion criteria.

Results

Characteristics and geographic distribution of Cushing's syndrome registries

The initial literature search yielded 58 results. After screening, two studies involving patients under 18 years of age were excluded, along with two duplicate reports. An additional 29 studies were excluded for not meeting the definition of a registry focused on Cushing's syndrome. Ultimately, 15 articles were selected for inclusion (28-42) corresponding to 12 distinct population-based registries.

Of these, one was a multinational European registry (ERCUSYN) (42), six were national registries (31-37,39,41), and five were local or single-center initiatives (28-30,38,40). Figure 1 illustrates the geographic distribution of these registries.

Unfortunately, Latin American representation in these initiatives has been limited to a single study conducted in Argentina (29). Orphanet—one of the leading international directories for rare disease registries—lists only two Cushing's syndrome-specific registries: the German CUSTODES registry (33,35-37) and the European ERCUSYN registry (42). Notably, no Latin American registries are currently included in this database.

The registries reviewed reported key information such as geographic coverage, demographic characteristics of the enrolled populations, and treatment modalities employed, including surgical, pharmacologic, or alternative interventions.

Figure 1. Geographic distribution of Cushing's syndrome registries worldwide
Source: Own elaboration.

Table 1 summarizes the characteristics of each registry, including the total number of patients, treatment approaches used, and outcomes reported during follow-up.

Table 1. Characteristics and geographic distribution of Cushing's syndrome registries

Continent/ Country/ Region/City	Year	Num-ber of patients	F (%)	Age at diag-nosis	OS (years)	FU (years)	MA (%)	DC (%)	ACTH-indepen-dent CS (%)	EAS (%)	Ref.
Padua/Italy	2009	45	51.1	-	-	7.7	-	0	100	0	(28)
Buenos Aires/ Argentina	2010	153	82	35.7	-	-	13	100	0	0	(29)
Birmingham/ United Kingdom	2012	72	79.2	40	-	10.9	-	100	0	0	(30)
Denmark	2013	343	74.9	43.8	-	12.1	-	61.5	38.5	0	(31)
Iran	2017	27	77.8	36.5	-	-	17.2	100	0	0	(32)
Germany	2017	196	64	-	-	-	-	65.3	24.5	10.2	(33)
Sweden	2019	502	77	43	-	13	-	100	0	0	(34)

Germany	2019	99	79.8	–	–	1	14.1	100	0	0	(35)
Germany	2020	205	75.6	42.2	–	7.4	–	62.4	37.6	0	(36)
Germany	2020	88	78	49	–	4	–	55.7	38.6	5.7	(37)
Massachusetts/ United States	2020	260	83.3	–	–	5.2	27.8	100	0	0	(38)
Swiss	2020	10	100	41	–	5.7	30	100	0	0	(39)
Vienna/Austria	2021	213	22.5	45.6	3	4.1	–	47.4	46.5	6.1	(40)
Thailand	2023	49	89.8	–	1.4	3.5	29.3	100	0	0	(41)
Europe	2023	1791	88	44.7	2.9	15	45.2	69	25	6	(42)

Note. F: female; OS: onset of symptoms; FU: follow-up time; MA: macroadenoma; CD: Cushing's disease; ACTH-independent CS: adrenal Cushing's syndrome; EAS: ectopic ACTH syndrome.
Source: Own elaboration.

Most of the included studies originated from European populations, comprising one multinational registry, four national registries, and three local initiatives. Additionally, two national studies were identified from Asia and one local study from Latin America. Collectively, these registries account for more than 4,000 patients with Cushing's syndrome (CS). Five of the studies were based on single-center data, while the largest registry—ERCUSYN—enrolled patients from 57 centers across 26 European countries.

CS was most frequently diagnosed between the fourth and fifth decades of life, with a reported delay of 1.4 to 2.9 years from symptom onset to diagnosis. Follow-up duration reached up to 15 years in the ERCUSYN registry, and the female-to-male ratio across studies was approximately 4.4:1. Pituitary tumors were predominantly microadenomas, with prevalence ranging from 13% in the Argentinian study to 45.2% in the European registry.

The studies from Argentina (29), the United Kingdom (30), Iran (32), Sweden (34), one German sub-analysis (35), the United States (38), Switzerland (39), and Thailand (41) included only patients with ACTH-dependent hypercortisolism of pituitary origin. The Italian study from Padua focused on patients with ACTH-independent adrenal CS. In contrast, ectopic ACTH syndrome (EAS) was reported in a small subset of patients—ranging from 2% to 6%—in one German sub-analysis, the Austrian study, and the ERCUSYN registry.

Comorbidities

The most frequently reported comorbidities were hypertension and type 2 diabetes mellitus, with wide variability in prevalence across populations—ranging from 29% to 94% for hypertension (28-31,33-36,38,40-42) and from 13% to 31% for type 2 diabetes (28,30,31,34,35,40,41). Less commonly reported conditions included dyslipidemia, overweight or obesity, osteoporosis, and fragility fractures (28-30,38,40,42). A history of cardiovascular events was noted in 6% of patients in the UK registry (30) and 14.6% in the Austrian registry (40) (Table 2).

Table 2. Comorbidities in populations with Cushing's syndrome

Continent/ Country/ Region/City	Year	Number of patients	F (%)	HT	T2 DM	Dys	OW/ Ob	CVD	Fx	Ost	Ref.
Padua/Italy	2009	45	51.1	73.3	31.1	33.3	26.7	–	–	24.4	(28)
Buenos Aires/ Argentina	2010	153	82	31	–	–	46	–	–	–	(29)
Birmingham/ United Kingdom	2012	72	79.2	78	31	12	68	6	–	33	(30)
Denmark	2013	343	74.9	25.4	13.1	–	–	–	–	–	(31)
Iran	2017	27	77.8	–	–	–	–	–	–	–	(32)
Germany	2017	196	64	91.2	–	–	–	–	–	–	(33)
Sweden	2019	502	77	41	15	–	–	–	–	–	(34)
Germany	2019	99	79.8	94	29	–	–	–	–	–	(35)
Germany	2020	205	75.6	61.9	–	–	–	–	–	–	(36)
Germany	2020	88	78	–	–	–	–	–	–	–	(37)
Massachusetts/ United States	2020	260	83.3	66.6	–	–	79.6	–	24.1	58.9	(38)
Swiss	2020	10	100	–	–	–	–	–	–	–	(39)
Vienna/Austria	2021	213	22.5	86.9	31	74.6	30.5	14.6	–	–	(40)
Thailand	2023	49	89.8	29.3	17.1	–	–	–	–	–	(41)
Europe	2023	1791	88	69.2	29.6	–	–	–	14.2	–	(42)

Note. F: female; HT: hypertension; T2DM: type 2 diabetes mellitus; Dys: dyslipidemia; OW/Ob: overweight/obesity; CVD: cardiovascular disease; Fx: fragility fracture; Ost: osteoporosis.

Source: Own elaboration.

Type of treatment

Among the registries that included only patients with Cushing's disease (CD), transsphenoidal resection was the treatment of choice in nearly all cases: 92.6% in the Iranian cohort (32), 94.1% in Argentina (29), 98.9% in Thailand (41), and 100% in the United Kingdom (30), United States (38), Switzerland (39), and a German sub-analysis (36).

Regarding adrenalectomy, it was not performed in the Iranian (32) or Swiss (39) studies and was reported in only 2.6% of patients in Argentina (29) and 25% in the UK cohort (30). None of these studies provided information on the use of medical therapy. Radiotherapy was employed in up to 22% of cases in the Argentinian, British, and Thai studies (29,30,41). Treatment modalities are summarized in Table 3.

In the study from Padua, Italy, which included patients with ACTH-independent adrenal CS, medical therapy was selected as first-line management in 48.9% of cases. However, 62.2% of patients ultimately underwent adrenal surgery, including those initially assigned to surgery and those requiring it following failure of medical management (28).

Among the registries that included patients with ectopic ACTH syndrome (EAS), only the ERCUSYN registry reported ectopic tumor resection, performed in 4% of all cases (42). In studies reporting on mixed populations with CD and adrenal CS, the proportion of patients undergoing pituitary surgery ranged from 46.9% in Vienna, Austria (40) to 89.9% in a German sub-registry (35). The highest reported use of radiotherapy was observed in the Swedish registry, at 26% (34).

Table 3. Treatment modalities received by patients with Cushing's syndrome

Continent/Country/ Region/City	Year	Number of patients	F (%)	NS (%)	Adx (%)	MT (%)	RT (%)	1L-MT (%)	Ref.
Padua/Italy	2009	45	51.1	0	62.2	48.9	0	48.9	(28)
Buenos Aires/ Argentina	2010	153	82	94.1	2.6	-	1.3	-	(29)
Birmingham/United Kingdom	2012	72	79.2	100	25	-	22.2	-	(30)
Denmark	2013	343	74.9	61.5	34.5	-	-	-	(31)
Iran	2017	27	77.8	92.6	0	0	0	0	(32)
Germany	2017	196	64	-	76	0	0	0	(33)
Sweden	2019	502	77	73	20	-	26	-	(34)
Germany	2019	99	79.8	89.9	-	-	-	-	(35)
Germany	2020	205	75.6	100	-	-	-	-	(36)
Germany	2020	88	78	55.7	38.6	-	-	-	(37)
Massachusetts/United States	2020	260	83.3	100	-	-	-	-	(38)
Swiss	2020	10	100	100	0	0	0	0	(39)
Vienna/Austria	2021	213	22.5	46.9	45.5	-	-	-	(40)
Thailand	2023	49	89.8	98.9	-	-	12.2	-	(41)
Europe	2023	1791	88	87.7	12.3	28.2	11.1	28.2	(42)

Note. F: female; NS: neurosurgery; Adx: adrenal surgery; MT: medical therapy; RT: radiotherapy; 1L-MT: first-line medical therapy.

Source: Own elaboration.

Outcomes following treatment

No deaths were reported in the German sub-registries (33,35-37), the Italian study (28), or the Thai registry (41). Among other cohorts, mortality ranged from 0.8% in the United States (25) to 21.6% in Denmark (31) and 26.5% in Sweden (34), the latter two being the national registries with the longest follow-up periods (12.1 and 13 years, respectively). Treatment outcomes are summarized in Table 4.

Postoperative clinical and biochemical remission was reported in eight registries (29,30,32,38,39,41,42), although definitions varied substantially. The Argentinian registry defined remission as postoperative serum and/or urinary cortisol levels within the subnormal range, with a reported rate of 69.4% (29). In the UK registry, initial remission was defined as a postoperative morning cortisol level <1.8 µg/dL (50 nmol/L) measured between day 4 and week 6, achieved in 83% of patients (30). The Iranian registry defined biochemical remission in CD as a morning serum cortisol level <5 µg/dL within 7 days of tumor resection or ongoing GC dependency beyond six months after surgery; remission was achieved in 88.9% (32). The U.S. registry defined remission as postoperative hypocortisolism or eucortisolism, which occurred in 77.7% of cases (38). The Swiss registry considered remission as normalization or suppression of late-night salivary cortisol and basal serum cortisol levels, reported in 90% of patients (39). The Austrian registry defined remission as successful surgical removal of the cortisol source, bilateral adrenalectomy for ACTH-dependent CS, or medical therapy leading to cortisol/UFC normalization, achieved in 91.5% (40). In Thailand, postoperative cure was reported in 31.25% of patients, although no specific criteria were described; the low rate was attributed to the procedures being performed by non-expert surgeons (41). The ERCUSYN registry did not detail remission criteria but reported an overall rate of 64.3%, which was significantly lower in patients aged >65 years compared to younger individuals [37/71 (52%) vs. 636/979 (65%); p = 0.03] (42).

Long-term clinical and biochemical remission was described as "prolonged remission" in seven studies (33-38,42) and as "cure" in two (30,31). The UK registry defined cure as the sustained absence of hypercortisolism at the last follow-up, achieved in 72% of patients at 10.9 years (30). The Danish registry defined cure as (1) patients who underwent adrenalectomy or (2) patients who underwent pituitary surgery and were diagnosed with hypopituitarism within 6 months postoperatively, with a resulting cure rate of 54.2% (31).

In the German sub-registry by Berr et al. (33), prolonged remission was defined as either (a) sustained adrenal insufficiency requiring hydrocortisone replacement therapy for at least 2 years or (b) normal results on biochemical testing (UFC, LNSC, and DST), and was achieved in 82% of patients. The Swedish registry defined prolonged remission based on resolution of clinical features, normalization of UFC, late-night salivary or serum cortisol, and cortisol suppression following DST, as well as adrenal insufficiency and/or bilateral adrenalectomy; this was achieved in 83.5% of patients (34). The sub-registry by Stieg et al. (35) defined stable disease control as biochemical and clinical remission at 1 year, observed in 70.3% of patients. The study by Müller et al. (36) reported prolonged remission at follow-up in 56.3% of patients with CD and 44.2% with adrenal CS. Vogel et al. (37) included only patients with prolonged biochemical remission at 4 years.

In the U.S. registry, prolonged remission was defined as the need for GC replacement or sustained clinical and biochemical eucortisolism for ≥1 year post-surgery, reported in 45.8% of cases (38). The ERCUSYN registry did not specify remission criteria but reported long-term remission rates of 48%, 51%, 51%, and 51% at 1, 5, 10, and 15 years, respectively, for patients aged >65 years, compared to 60%, 65.5%, 66.3%, and 66.3% for younger patients at the same time points (42).

Table 4. Postoperative outcomes in patients with Cushing's syndrome according to the subtype

Continent/Country/ Region/City	Year	Number of patients	F (%)	FU (years)	Mo (%)	IR (%)	PR (%)	Cur (%)	Ref.
Cushing's disease only									
Buenos Aires/Argentina	2010	153	82	–	–	69.4	–	–	(29)
Birmingham/United Kingdom	2012	72	79.2	10.9	16.3	83	–	72	(30)
Iran	2017	27	77.8	–	7.4	88.9	–	–	(32)
Sweden	2019	502	77	13	26.5	–	83.5	–	(34)
Germany	2019	99	79.8	1	0	–	70.3	–	(35)
Massachusetts/United States	2020	260	83.3	5.2	0.8	77.7	45.8	–	(38)
Swiss	2020	10	100	5.7	–	90	–	–	(39)
Thailand	2023	49	89.8	3.5	0	31.25	–	–	(41)
Adrenal Cushing's syndrome only									
Padua/Italy	2009	45	51.1	7.7	0	–	–	–	(28)
Studies with at least two subtypes									
Denmark	2013	343	74.9	12.1	21.6	–	–	54.2	(31)
Germany	2017	196	64	–	0	–	82	–	(33)
Germany	2020	205	75.6	7.4	0	–	51.7	–	(36)
Germany	2020	88	78	4	0	–	100	–	(37)
Vienna/Austria	2021	213	22.5	4.1	2.8	91.5	–	–	(40)
Europe	2023	1791	88	15	3.7	64.3	64.8	–	(42)

Note. In the group of studies that only included DC, surgery consisted of transsphenoidal resection. For ACTH-independent CS, adrenalectomy was the sole surgical approach, and in studies that included two or three subtypes, transsphenoidal resection predominated for CD in most cases, followed by adrenalectomy for ACTH-independent CS. In one German sub-analysis, the Austrian study, and the ERCUSYN registry, in patients with EAS, the procedure was resection of the ectopic tumor.

F: female; FU: follow-up; Mo: mortality; IR: initial remission; PR: prolonged remission; Cur: cure.

Source: Own elaboration.

Discussion

This review identified and analyzed existing population-based registries of Cushing's syndrome (CS) worldwide. Despite the significant impact of CS on both individual health and healthcare systems, critical gaps remain in the generation of structured population-level data

that would enable a global understanding of this rare disease.

Findings from this review reveal a marked geographic concentration of available registries. Europe leads data collection efforts, particularly through the ERCUSYN registry (42), which has enabled for characterization of case distribution, clinical profiles, and long-term outcomes in patients with CS across multiple European countries. However, limited representation from regions such as Latin America, Africa, and much of Asia hinders accurate global estimates of incidence, prevalence, and disease burden. This geographic bias restricts the extrapolation of findings to settings with different demographic, socioeconomic, and healthcare profiles.

The reviewed registries have been instrumental in describing common phenotypic features of CS, diagnostic approaches, treatment strategies, and clinical outcomes. Data from these registries and other studies highlight important variations in clinical presentation and therapeutic practices, including differences in age at diagnosis, rates of ACTH-producing adenomas, and preferred surgical modalities (43). As previously reported, comorbidities such as diabetes mellitus, hypertension, and osteoporosis are highly prevalent among patients with CS (44,45). Treatment outcomes also vary across regions, with surgical remission rates ranging from 60% to 90% in Europe (42), Iran (29), the United States (38), and Argentina (29), but remaining considerably lower in countries like Thailand (41). These findings underscore the need for multicenter, comparative registries to identify practice variations and generate context-specific evidence.

Registry data have also revealed substantial diagnostic delays in CS; however, only three registries explicitly reported the interval from symptom onset to diagnosis, which ranged from 1.4 to 3 years (40-42). This limited reporting highlights a critical gap in the systematic assessment of diagnostic timelines. Delays in recognition and confirmation of CS contribute to the progression of chronic complications and deterioration of patients' quality of life (20,31,34,40,44,45). Furthermore, the intraindividual variability and differences across analytical methods, as well as the disparities in the definitions of biochemical remission both between and within countries, underscore the need for standardized international protocols to guide diagnosis and long-term follow-up.

Population-based registries play a strategic role in the surveillance of rare diseases such as CS. Their ability to identify patterns of morbidity, assess care quality, monitor treatment access, and support cost-effectiveness studies is essential for evidence-based health planning (27). However, this review shows that existing registries often face structural limitations, including inconsistent data collection methods, ambiguous variable definitions, and limited inclusion of social determinants of health. These elements are critical to understanding disparities in access to care and treatment outcomes, particularly in vulnerable populations.

A key contribution of this review is the identification of an urgent need to develop and strengthen national and international population-based CS registries. The creation of interoperable platforms that integrate clinical, sociodemographic, economic, and quality-of-life data would enable a more comprehensive characterization of the disease, with implications for both individual patient care and public policy.

Major limitations identified among the reviewed registries include the underrepresentation of low- and middle-income countries, limited longitudinal follow-up in many systems, and the absence of systematic mechanisms for external data validation. These limitations must be addressed in future collaborative efforts aimed at improving registry coverage and data quality. The review also revealed significant discrepancies in the analytical methods used (immunoassay vs. LC-MS/MS), hormonal confirmation methods, and remission thresholds, all of which complicate inter-study comparisons. These differences are likely influenced by access to diagnostic technology, physician training, and the clinical guidelines adopted in each setting. Methodological standardization and international consensus on operational definitions of CS are essential steps to improve the reliability and comparability of registry data.

Finally, this review highlights the value of registries as tools to advance translational research and inform health policy. Systematic data collection enables the generation of real-world evidence, the optimization of resource allocation, and the evaluation of healthcare interventions. In rare diseases such as CS, where clinical trials are limited, population-based registries represent a critical source of information to support clinical decision-making and healthcare management.

Conclusion

Population-based registries of Cushing's syndrome are essential for understanding disease burden, evaluating the effectiveness of interventions, and informing public health policy. However, their limited availability, methodological heterogeneity, and restricted geographic coverage pose critical challenges. This review provides an integrated overview of existing registries, identifies key knowledge gaps, and offers recommendations to support the development of more robust, equitable, and outcome-oriented information systems aimed at improving the care of patients with Cushing's syndrome.

Authors' contributions

Wilfredo Antonio Rivera Martínez: Conceptualization, research, methodology, writing (original draft); Johana Ramírez: conceptualization, writing (original draft); Alejandro Román González: conceptualization, writing (referring and editing corrections); Johnayro Gutierrez Restrepo: conceptualization, writing (referring and editing corrections); Carlos Esteban Builes Montaño: Conceptualization, research, methodology, writing (original draft). All authors critically reviewed and contributed to the final version of the manuscript.

Ethical implications

This work was a systematic review, so no specific ethical considerations were identified. The study did not directly involve patients, human participants, or animals and was based exclusively on a review of scientific literature and contributions from the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare the following conflicts of interest: CEBM has received consulting and speaking fees from Sanofi, Novo Nordisk, Novartis, Recordati Rare Diseases, Janssen, Chiesi, Abbott, and Boehringer Ingelheim and is a shareholder from Festina Lente. ARG has received consulting and speaking fees from Roche, Novo Nordisk, Knightx, PTC Therapeutics, Bayer, Amryt. The remaining authors report no conflicts of interest.

Acknowledgements

The authors assume full responsibility for the content and conclusions expressed in this manuscript.

Data statement

No data was collected in the development of this manuscript.

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