# Diagnostic challenges in cyclic Cushing's syndrome: a systematic review

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**Cyclic Cushing's syndrome is a subentity of Cushing's syndrome in which phases of biochemical hypercortisolism (peaks) are followed by spontaneous periods of physiological or even hypocortisolaemic cortisol secretion (troughs). To identify common features of cyclic Cushing's syndrome, we systematically reviewed single case reports and case series in MEDLINE from database inception to Oct 10, 2022, and identified 707 articles, of which 149 articles were assessed for eligibility and 118 articles (covering 212 cases) were included in the analysis. Pituitary tumours accounted for 67% of cases of cyclic Cushing's syndrome (n=143), ectopic tumours for 17% (n=36), and adrenal tumours for 11% (n=23). Occult tumours accounted for 2% of cases (n=4), and 3% of cases were unclassified (n=6). We compared the clinical symptoms and comorbidities of patients with cyclic Cushing's syndrome with those of patients with non-cyclic Cushing's syndrome and observed no major difference. In adrenocorticotropic hormone (ACTH)-dependent cyclic Cushing's syndrome, bilateral inferior petrosal sinus sampling had a positive (ie, true pituitary) and negative (ie, true ectopic) predictive value of 100% when performed during periods of hypercortisolism, versus a positive predictive value of 73% and a negative predictive value of 86% when performed, irrespective of cortisolaemic status. Overall, 6% of patients (n=12) with cyclic Cushing's syndrome had unnecessary surgery due to misclassification. Remission rates were significantly lower and the time to remission significantly longer in patients with cyclic Cushing's syndrome compared with patients with non-cyclic Cushing's syndrome (p<0·001). Variations in biochemical test results due to unpredictable cycle duration and frequency might cause diagnostic challenges resulting in misdiagnoses and missed diagnoses.**

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## Introduction

Cyclic Cushing's syndrome is considered a rare subentity of Cushing's syndrome. This syndrome describes a condition in which phases of biochemical hypercortisolism (peaks) are followed by periods of physiological or even hypocortisolaemic cortisol concentrations (troughs). These phases can be of variable length, ranging from a few days to many years.[1,2] The most impressive presentations of cyclic Cushing's syndrome consist of case reports in which the cyclicity of cortisol hypersecretion follows a pseudorhythm with multiple episodes of identical length,[3] or in which several years might pass between cycles.[4–10]

Several alternative terms and definitions of cyclicity have been proposed and are used indiscriminately to describe variations in adrenocorticotropic hormone (ACTH) and cortisol secretion in patients with Cushing's syndrome. Common alternative terms include intermittent,[6–8,11–20] variable,[3,21] periodic,[22–30] and episodic[31,32] hypercortisolism, with episodic usually referring to episodic pulsatility observed during a 24-h period. All terms are descriptive rather than mechanistic. Some studies suggested use of the term mild or episodic hypercortisolism on the basis of at least one physiological 24-h urinary free cortisol (UFC) measurement during repeated testing.[33,34] Notably, episodic excessive cortisol secretion and a high degree of day-to-day variability are general characteristics of endogenous hypercortisolism reported in Cushing's disease.[35,36]

The cyclic nature of the condition interferes with the outcome of diagnostic procedures, resulting in both missed diagnoses and misdiagnoses. Patients with cyclic Cushing's syndrome might be turned away from physicians when presenting during a trough phase (and hence with physiological cortisol concentrations). Likewise, misleading biochemical test results in patients with cyclic ectopic Cushing's syndrome could lead to unnecessary pituitary surgeries.[37–41] Interestingly, according to some references, overall outcome does not seem to differ significantly among patients with non-cyclic versus cyclic Cushing's disease.[1,42] However, to the best of our knowledge, no systematic review of the literature has been performed, holistically investigating all aspects relevant to cyclic Cushing's disease, cyclic adrenal Cushing's syndrome, and cyclic ectopic Cushing's syndrome.

We conducted the first systematic literature search to produce a comprehensive assessment of the common clinical and biochemical features of cortisol cyclicity, to identify avoidable pitfalls in the diagnosis of cyclic Cushing's syndrome, and to detect differences in treatment outcomes.

## Methods

### Search strategy and selection criteria

Between Oct 3 and 10, 2022, we searched MEDLINE (via PubMed) from database inception to Oct 10, 2022, for single case reports and case series of patients with cyclic Cushing's syndrome. We first used the term "Cushing's syndrome AND cyclic" and identified 320 articles. We then extended the search with the term ("Pituitary ACTH Hypersecretion" [MeSH] OR "cushing syndrome" [MeSH] OR hypercortisolism [tiab]) AND (cyclic* [tiab] OR intermitt* [tiab] OR periodic* [tiab] OR episodic* [tiab]), identifying 387 articles. Thus, 707 articles were

See Online for appendix

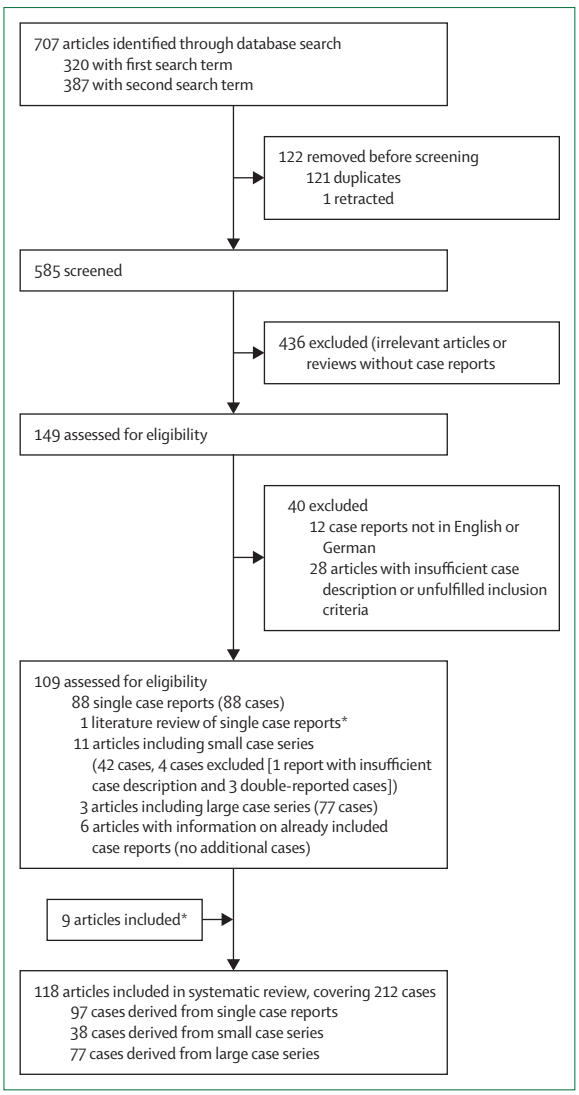


***Figure:*** **Flow diagram of article selection**
*An additional nine single case reports[43–51] were not identified using the PubMed search strategy, but were selected from a literature review.[2]

identified by the combination of search terms (figure).[52,53] We included single case reports and case series that described confirmed cases of Cushing's syndrome with at least two clinical and biochemical hypercortisolaemic peaks separated by a spontaneous eucortisolaemic or hypocortisolaemic trough. We excluded articles not focusing on cyclic Cushing's syndrome, reviews without case reports, articles in languages other than English and German, and case reports on drug-induced cyclic Cushing's syndrome[54] or periodic steroidogenesis due to food-dependent Cushing's syndrome.[55] We also excluded case reports that provided insufficient data (eg, age and tumour origin were not described), and where the authors were unsure about the true cyclicity of the case.[33–35,56–63] We excluded articles describing cyclic subclinical hypercortisolism referring to biochemically confirmed variable hypercortisolism in the absence of Cushing-typical symptoms.[58,64–67] A full list of inclusion and exclusion criteria is available (appendix p 3). The removal of duplicates was performed manually. When multiple articles referred to the same case, data were primarily extracted from the source that provided the most detailed description and complemented with information from the other sources. Studies were screened and selected independently by EN and MR, who maintained frequent communication during the selection process. In uncertain cases, articles were discussed between the authors and included or excluded on the basis of mutual agreement.

In addition to the PubMed search, we manually searched references cited in one key identified article—the largest previously reported non-systematic review on cyclic Cushing's syndrome published by Meinardi and colleagues in 2007,[2] which reviewed 65 cases published in 56 articles. Nine additional single case reports, which had non been identified by the two search terms, were included from this literature review. To ensure that further relevant articles were not overlooked, we screened two additional databases (Cochrane Library and Embase) with our first search term. No relevant articles were identified in the Cochrane Library. Relevant articles found on Embase were already included in the results of our MEDLINE search. We found 14 cases of cyclic Cushing's syndrome reported in conference abstracts on Embase. We decided not to include these cases in our analysis due to the absence of peer review.

### Case definition of cyclic Cushing's syndrome

Although no uniform definition exists, we identified two widely accepted definitions of cyclic Cushing's syndrome in the literature. Whereas earlier studies suggested the requirement of at least three peaks and two troughs in cortisol concentration,[2,30] and differentiated between regular and irregular cycles with and without corresponding clinical symptoms,[3] more recent articles from the last 14 years proposed the definition of cyclicity as the presence of at least two peaks and one trough in cortisol concentration.[1] We used this wider definition as the primary definition of cyclic Cushing's syndrome in our systematic review. An exception was the calculation of the prevalence of cyclic Cushing's syndrome, where both definitions were used (table 1).

### Data extraction and analysis

Data collection and extraction into a predefined extraction spreadsheet were performed by EN and MR. Close consultation was maintained between the authors and consensus was obtained in uncertain cases. The variables included were clinical, biochemical, and radiological findings, tumour origin, cycle characterisation, intervention and treatment, remission status, time to remission, comorbidities, diagnostic errors, and time of follow-up. Missing data were displayed and dealt with

| | Time period | Number of patients with Cushing's syndrome | Definition of cyclicity | Number of patients with cyclic Cushing's syndrome | Main biomarker |
|---|---|---|---|---|---|
| McCane et al (1993)[68] | 1977–1990 retrospective | 41 | .. | 7 (17%, 7–32) | UFC |
| Streeten et al (1997)[13] | .. | 33 | .. | 7 (21%, 9–39) | UFC or DST |
| Powel et al (2008)[69] | 1969–2006 retrospective | 34 | .. | 9 (26%, 13–44) | UFC |
| Alexandraki et al (2009)[1] | 1946–2007 retrospective | 201 | Two peaks of cortisol and one trough, clinical and biochemical or biochemical alone | 30 (15%, 10–21) | 5-point serum cortisol day curves |
| Jahandideh et al (2018)[42] | 2007–2018 retrospective | 205 | Three peaks of cortisol and two troughs, only biochemical | 17 (8%, 5–13) | LNSC or UFC |
| Jahandideh et al (2018)[42] | 2007–2018 retrospective | 205 | Two peaks of cortisol and one trough, only biochemical | 38 (19%,14–25) | LNSC or UFC |
| Total | 1946–2018 | 514 | .. | 70 (14%, 11–17) to 91 (18%, 15–21) | .. |

Data are N or n (%, 95% CI). DST=dexamethasone suppression test. LNSC=late-night salivary cortisol. UFC=urinary free cortisol.

***Table 1:*** **Proportion of patients with cyclic Cushing's syndrome in cohorts of patients with Cushing's syndrome**

according to the *Cochrane Handbook for Systematic Reviews of Interventions* and either imputed from the available information or reported as missing.[70,71] Data obtained from three case series that compared patients with cyclic Cushing's syndrome with patients with non-cyclic Cushing's syndrome in their respective cohorts were analysed and displayed separately to ensure the highest possible transparency. To distinguish these data from the single case report and small case series data, they are referred to as larger case series. Biochemical results were converted into standardised SI units. When biochemical data were depicted only in graphs or information was not precisely available, estimations were made by the authors on the basis of the available data when appropriate. To ensure extraction of treatment-naive data only, and to provide a realistic representation of the variations in steroid secretion, the first rather than the highest documented biochemical data were chosen for analysis. On the basis of the biochemical information given in the case reports, we grouped results from bilateral inferior petrosal sinus sampling (BIPSS) into those conducted during periods of confirmed biochemical hypercortisolism and those conducted during periods of eucortisolism or an unclear cortisolaemic state. The criteria used to determine hypercortisolism in the literature-derived cases were based on the diagnostic reference values used in the respective institutions, referring to local laboratory references. If no reference value was given, we referred to the internationally accepted reference values of morning (0900 h) serum cortisol concentrations greater than 25 µg/dL and morning serum cortisol concentrations after 1 mg dexamethasone suppression tests greater than 1·8 µg/dL. Therapy-induced remission was defined as successful tumour surgery or radiation, or both, or bilateral adrenalectomy followed by the normalisation of clinical features and documentation of biochemical hypocortisolism or eucortisolism. Spontaneous remission was defined as the normalisation of biochemical and clinical features unforced by treatment and referred to patients who were in remission by the time the case report was published. Time to remission was defined in months from the first documented contact with the physician until remission. Time of follow-up was defined as the time from the first to the last documented contact with the physician. Data extraction procedures and definitions of common terms and outcomes are summarised in the protocol (appendix pp 4–7).

### Reference population of patients with non-cyclic Cushing's syndrome

Several outcome variables required a reference standard. We therefore screened the references used in this systematic review for additional cohorts of patients with non-cyclic Cushing's syndrome. Three case series that compared retrospectively enrolled patients with cyclic Cushing's syndrome with patients with non-cyclic Cushing's syndrome were identified and displayed separately.[1,42,69] However, since these case series did not provide sufficient information for all the relevant outcomes, we included our longitudinal cohort from the Department of Internal Medicine IV, LMU University Hospital, LMU Munich, Munich, Germany, as part of the German Cushing's registry. The structure and general characteristics of this registry have previously been described in detail.[72–75] The cohort consisted of 139 treatment-naive patients with clinically and biochemically confirmed overt Cushing's syndrome who had a thorough, standardised clinical examination and biochemical screening at baseline. Evaluation of Cushing's syndrome at the LMU Munich is in line with the *Endocrine Society Clinical Practice Guideline*,[76] which usually include two elevated UFC measurements (>85 µg/24 h). Patients with cyclic Cushing's syndrome and mild autonomous cortisol secretion were excluded from this cohort.

| | Cyclic Cushing's syndrome | | | | | Non-cyclic Cushing's syndrome | | | | | p value (cyclic *vs* non-cyclic Cushing's syndrome) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Jahandideh et al (2018)[42] | Alexandraki et al (2009)[1] | Powel et al (2008)[69] | Single case reports and small case series[2–10,12–30,32,37–41,43,44,46–50,79–145] | Total | Jahandideh et al (2018)[42] | Alexandraki et al (2009)[1] | Powel et al (2008)[69] | LMU Munich longitudinal cohort* | Total | |
| Number of patients | 38 | 30 | 9 | 135 | 212 | 167 | 171 | 25 | 139 | 502 | .. |
| Pituitary tumour | 38 (100%, 91–100) | 30 (100%, 88–100) | .. | 75 (56%, 47–64) | 143 (67%, 61–74) | 167 (100%, 98–100) | 171 (100%, 98–100) | .. | 88 (63%, 55–71) | 426 (85%, 81–88) | <0·0001 |
| Adrenal tumour | .. | .. | 9 (100%, 66–100) | 14 (10%, 6–17) | 23 (11%, 7–16) | .. | .. | 25 (100%, 86–100) | 41 (30%, 22–38) | 66 (13%, 10–16) | 0·4574 |
| Ectopic tumour† | .. | .. | .. | 36 (27%, 19–35) | 36 (17%, 12–23) | .. | .. | .. | 10 (7%, 4–13) | 10 (2%, 1–4) | <0·0001 |
| Occult tumour‡ | .. | .. | .. | 11 (8%, 4–14) | 11 (5%, 3–9) | .. | .. | .. | 0 (0%, 0–3) | 0 (0%, 0–1) | .. |
| Unclassified | .. | .. | .. | 6 (4%, 2–9) | 6 (3%, 1–6) | .. | .. | .. | 0 (0%, 0–3) | 0 (0%, 0–1) | .. |

Data are n, N, or n (%, 95% CI). *Patients treated at the LMU Munich hospital between 2012 and 2022. †A full list of ectopic cases is in the appendix pp 10–11. ‡Patients with tumours of unknown origin.

***Table 2:*** **Tumour origin in patients with cyclic and non-cyclic Cushing's syndrome**

### Critical appraisal

The JBI critical appraisal checklist for case reports and case series was used for risk of bias assessment to account for the reporting biases of each case report from which data were derived.[77,78] Following JBI guidance, critical appraisal of the 118 papers selected for inclusion was performed by two authors (EN and MR).

### Statistical analysis

We performed statistical analyses to compare outcomes in patients with cyclic Cushing's syndrome with patients with non-cyclic Cushing's syndrome. Statistical analysis was conducted with GraphPad Prism, version 9.4.1. Fisher's exact test was used for binary variables, with cyclic Cushing's syndrome and non-cyclic Cushing's syndrome being defined as independent variables and the respective outcomes defined as dependent variables. For analysis of BIPSS results, the true origin of the tumour was defined as the independent variable, and the test result was defined as the dependent variable. Welch's *t* test or the Mann–Whitney U test were used for parametric or non-parametric variables, as appropriate. Percentages were reported alongside the number of individuals, with 95% CIs calculated following the Clopper-Pearson method. p values less than 0·05 were considered statistically significant. p values were not adjusted for potential confounding.

## Results

### Prevalence of cyclic Cushing's syndrome

707 articles were identified through two independent search strategies, of which 121 were overlapping. After excluding publications that did not meet our criteria, we identified 118 articles, covering 97 single case reports (of which nine were obtained through the manual reference search), 11 small case series reporting 38 cases (n=2–7 cases), and three larger case series reporting 77 cases (n=9–38 cases), resulting in a total number of 212 included cases (figure). The first identified case was documented in 1966, with a continuously increasing number of cases reported every decade since (appendix p 8). Cyclic Cushing's syndrome could account for 7–21% of patients with Cushing's disease [1,13,42,68] and up to 26% of patients with micronodular adrenal hyperplasia.[69] Depending on the criteria used, there was an overall proportion of cyclicity of 14% (three peaks and two troughs) to 18% (two peaks and one trough; table 1).

### Patient age, sex, ethnicity, and origin of cyclic Cushing's syndrome

Most patients with cyclic Cushing's syndrome were female (169 of 212 [80%, 95% CI 74–85] *vs* 393 of 502 patients with non-cyclic Cushing's syndrome [78%, 95% CI 74–82; p=0·6904; appendix p 9). Race and ethnicity were only reported in 61 cases of cyclic Cushing's syndrome (51 White patients, seven Asian patients, two Black patients, and one patient reported as other). In the adult population, patients with cyclic Cushing's syndrome had a mean age of 44·9 years (SD 15·5, range 18–78) compared with 44·1 years (SD 14·7, 19–78) for patients with non-cyclic Cushing's syndrome (p=0·5871). 23 of the 203 patients with relevant age data (11%, 95% CI 7–17) were children with a mean age of 10·4 years (SD 4·4, range 0–17), with more girls being affected by cyclic Cushing's syndrome than boys.

Pituitary tumours accounted for most cases of cyclic Cushing's syndrome (143 of 212 patients; 67%, 95% CI 61–74; table 2), followed by ectopic tumours (36 of 212; 17%, 12–23), and adrenal causes (23 of 212; 11%, 7–16). Most adrenal causes were due to micronodular adrenal hyperplasia or primary pigmented nodular adrenocortical disease (19 of 23 patients; 83%, 61–95). We did not find case reports of cyclic Cushing's syndrome in patients with primary bilateral macronodular adrenal hyperplasia. Within the group of patients with ectopic tumours, pulmonary neuroendocrine tumours were the most frequent (11 of 36; 31%, 16–48), followed by thymic neuroendocrine tumours (nine of 36; 25%, 12–42; appendix pp 10–11). 11 cases of cyclic Cushing's syndrome were of occult origin, of which seven were probably ectopic in origin. In line with Meinardi and colleagues,[2] we categorised six cases as unclassified referring to undescribed cases, possible cases of hypothalamic disorders, and cases of empty sella syndrome.[8,16,18,43,44,79]

### Clinical presentation and comorbidities of cyclic Cushing's syndrome

Documentation of clinical characteristics in the literature-derived case reports was often imprecise and incomplete. Due to the large number of undocumented features we decided against statistical analyses and displayed the available data as percentages (appendix pp 12–17). In cases with very long trough phases, clinical symptoms occurred with peaks of hypercortisolism and ceased with troughs.[4,6,10] In patients with more rapid cycling, clinical symptoms did not always resolve completely between peaks.[13,17,25,26,28,30,32,46–49,80–88] Weight gain (84 of 165 patients; 51%, 95% CI 43–59), moon face (69 of 135; 51%, 42–60), muscle weakness (75 of 165; 45%, 38–53), bruising (58 of 165; 35%, 28–43), and oedema (53 of 165; 32%, 25–40) were frequently reported during hypercortisolaemic peaks. Hirsutism was described in 61 (48%, 95% CI 39–57), and menstrual irregularities in 36 (28%, 21–37) of the 127 affected women. In the paediatric population, growth retardation was reported in seven of 23 patients (30%, 95% CI 13–53). Overall, there was no distinct cyclic phenotype and Cushing-typical symptoms were present to varying extents.

Likewise, patients with cyclic Cushing's syndrome presented with typical metabolic complications of Cushing's syndrome (appendix pp 18–19), such as hypertension (121 of 203; 60%, 95% CI 53–66), obesity (114 of 203; 56%, 49–63), diabetes (53 of 173; 31%, 24–38), and osteoporosis (28 of 203; 14%, 9–19). Depression and emotional lability were also common in patients with cyclic Cushing's syndrome (77 of 203; 38%, 31–45). Headache was reported in 28 of 165 patients (17%, 12–24) and insomnia in 12 of 165 patients (7%, 4–12). Thromboembolic complications were reported in seven (three deep vein thromboses,[89–91] two pulmonary embolisms,[16,45] one stroke,[79] and one transient ischaemic attack)[80] of 135 patients with cyclic Cushing's syndrome (5%, 2–10) of which two complications occurred before diagnosis and treatment and five complications after diagnosis and treatment. Infections were described in 27 of 165 patients with cyclic Cushing's syndrome (16%, 95% CI 11–23), of which seven were opportunistic (pneumocystis pneumonia, cryptococcal pneumonia, necrotising *Aspergillus* bronchopneumonia, tuberculous peritonitis, and oral candidiasis).

### Biochemical findings in cyclic Cushing's syndrome

Median plasma cortisol concentrations were significantly higher in patients with cyclic Cushing's disease (25·0 µg/dL, range 2·7–290·0, IQR 18·5–34·9) compared with patients with non-cyclic Cushing's disease (21·0 µg/dL, 5·1–67·1, 15·7–27·3; p=0·0339). They were also significantly higher in patients with adrenal cyclic Cushing's syndrome (27·1 µg/dL, 15·0–54·0, 18·8–42·9) compared with patients with non-cyclic adrenal Cushing's syndrome (17·0 µg/dL, 3·2–32·0, 9·8–22·8; p=0·0027; appendix p 20). Median UFC measurements were significantly lower in patients with cyclic Cushing's disease (278·1 µg/24 h, range 4·7–4240·0, IQR 87·5–705·5) compared with patients with non-cyclic Cushing's disease (426·0 µg/24 h, 29·0–10 824·0, 269–827; p=0·0187). There were no significant differences in ACTH between the two groups (cyclic Cushing's disease 70·4 pg/mL, range 5·1–378·3, IQR 37·7–125·1 *vs* non-cyclic Cushing's disease 54·5 pg/mL, 10·0–142·0, 37·0–83·0; p=0·0755) or in late-night salivary cortisol (LNSC) concentrations between the groups (cyclic Cushing's disease 7·6 ng/mL, range 0·3–30·8, IQR 0·957–10·9375 *vs* non-cyclic Cushing's disease 8·3 ng/mL, 0·3–306·1, 4·2–12·3; p=0·4265), but a trend of higher median plasma ACTH was observed in patients with cyclic Cushing's disease. Both groups showed large interindividual differences. Salivary cortisol samples were only reported in 58 of 212 cases of cyclic Cushing's syndrome (27%, 95% CI 22–34), with absolute numbers available for 13 patients derived from single case reports and small case series. Data on hair cortisol concentrations were available for five patients with cyclic Cushing's syndrome and corresponded with the presence and absence of clinical symptoms.[39] Hypokalaemia was reported in 46 of 212 cases of cyclic Cushing's syndrome (22%, 95% CI 16–28).

### Imaging studies in cyclic Cushing's syndrome

Imaging studies were reported in 142 cases of cyclic Cushing's syndrome, of which 91 (64%, 95% CI 56–72) were helpful or diagnostic. A pituitary lesion was found in 60 of the 88 patients with cyclic Cushing's disease who received imaging (68%, 57–78; appendix pp 21–22). Imaging was suggestive in six of 14 patients with adrenal tumours (43%, 18–71), and in 25 of 32 patients with ectopic tumours and documented imaging (78%, 60–91).

| | PPV (ie, a true central source of ACTH) | NPV (ie, a true ectopic source of ACTH) | Sensitivity | Specificity |
|---|---|---|---|---|
| Hypercortisolism biochemically confirmed (n=27) | 14/14 (100%, 77–100) | 13/13 (100%, 75–100) | 14/14 (100%, 77–100) | 13/13 (100%, 75–100) |
| Hypercortisolism not biochemically confirmed (n=27) | 5/12 (42%, 15–72) | 11/15 (73%, 45–92) | 5/9 (56%, 21–86) | 11/18 (61%, 36–83) |
| Total (N=54) | 19/26 (73%, 52–88) | 24/28 (86%, 67–96) | 19/23 (83%, 61–95) | 24/31 (77%, 59–90) |

Data are n/N (%, 95% CI). 54 BIPSS procedures performed in 42 patients with ACTH-dependent cyclic Cushing's syndrome (performed twice in eight patients, and performed three times in two patients). 27 BIPSS procedures performed in 25 patients during hypercortisolism (performed twice in two patients). 27 BIPSS procedures performed in 24 patients during trough phases or unclear cortisolaemic states (performed twice in three patients). ACTH=adrenocorticotropic hormone. BIPPS=bilateral inferior petrosal sinus sampling. NPV=negative predictive value. PPV=positive predictive value.

*Table 3:* **The predictive value of BIPSS in patients with cyclic Cushing's syndrome**

Three patients with occult tumours and five patients with tumours of unclassified origin received imaging studies, which were negative. For the 58 cases that described adrenal morphology, radiological bilateral enlargement was reported in 27 (47%, 33–60). Of these patients, 14 had ectopic cyclic Cushing's syndrome, eight had cyclic Cushing's disease, three had adrenal cyclic Cushing's syndrome, one had occult cyclic Cushing's syndrome, and one had unclassified cyclic Cushing's syndrome.

### BIPSS in cyclic Cushing's syndrome

In patients with ACTH-dependent hypercortisolism, BIPSS is used to distinguish between central (ie, pituitary) and non-central (ie, ectopic) tumour origins.[146] This procedure is particularly useful when a central tumour source is suspected but MRI does not detect a pituitary adenoma.[147] Our systematic review revealed 57 BIPSS performed in 44 patients. As two of these procedures were performed in one patient with an unclassified tumour, and one was performed in a patient with an adrenal tumour, the remaining 54 BIPSS, which were performed in 42 patients with biochemically proven ACTH-dependent cyclic Cushing's syndrome, were chosen for further analysis. When analysed irrespective of whether BIPSS was performed during a peak or a trough phase, the positive predictive value (PPV) was 73% (19 of 26, 95% CI 52–88) meaning that BIPSS correctly identified a pituitary tumour origin. The negative predictive value (NPV), and hence the correct identification of an ectopic source of ACTH, was 86% (24 of 28, 95% CI 67–96; sensitivity 83% [19 of 23], 95% CI 61–95; specificity 77% [24 of 31], 95% CI 59–90; table 3; appendix p 23). When performed during periods of hypercortisolism (27 BIPSS performed in 25 patients), BIPSS had both a PPV and NPV of 100% (14 of 14 [95% CI 77–100] and 13 of 13 [75–100], respectively; sensitivity 100% [14 of 14], 95% CI 77–100; specificity 100% [13 of 13], 95% CI 75–100). The remaining 27 BIPSS were conducted in 24 patients during a trough phase or unclear biochemical activity. This timing resulted in a low PPV (ie, true pituitary origin) of 42% (five of 12, 95% CI 15–72) and a NPV (ie, true ectopic) of 73% (11 of 15, 95% CI 45–92; sensitivity 56% [five of nine], 95% CI 21–86; specificity 61% [11 of 18], 95% CI 36–83). Analysis of stimulatory conditions revealed that corticotropin-releasing hormone was used in 24 of 42 patients (57%, 95% CI 41–72) and desmopressin in five of 42 patients with cyclic Cushing's syndrome (12%, 4–26). The remaining 13 of 42 cases (31%, 18–47) either did not specify or only reported baseline gradients without stimulation. When performed during periods of hypercortisolism, all stimulatory conditions resulted in 100% correct identification of tumour origin. When performed during a trough phase or unclear cortisolaemic state, only stimulation with desmopressin still resulted in 100% correct identification; however, as this finding was only reported in one patient, the results are not representative (appendix pp 24–26).

### Cycle characterisation in cyclic Cushing's syndrome

Cycles varied in length—from a few days,[20,29,30,43–45,47,49,80–84,87,88,92–98] to weeks, to months.[3,5,9,14,16,18,19,24,25,28,37–39,48,79,85,99–113] Irregular intervals were more frequently reported (25 of 212 cases; 12%, 95% CI 8–17)[5,6,9,10,14,16,18,20,25,40,80,99,106,107,109–111,114–121] than regular intervals (13 of 212; 6%, 3–10).[29,30,44,83–85,93,98,102,105,112,113,122] The longest trough phases in between two hypercortisolaemic peaks were 3 years,[4,123] 3·5 years,[6] 4 years,[10] and 3–5 years,[124] during which the patients had repeatedly physiological biochemical findings. Spontaneous phases of hypocortisolism were described in seven of the 212 cases (3%, 95% CI 1–7%).[4,5,24,50,91,115,121] Due to the absence of a uniform definition of a cycle, imprecise reporting of cases with challenges in clinical and biochemical follow-up, and the frequent use of adrenostatic therapy, a reliable analysis of cycle length and characterisation that included all studies was not feasible. Jahandideh and colleagues[42] described a median number of 2 peaks (range 1–3) according to UFC results and 3 peaks (1–10) according to LNSC results in their cohort of patients with cyclic Cushing's disease (n=38), with a median time interval of 199 days (range 15–1725) according to UFC results and 94 days (4–792) according to LNSC results, and a significantly higher sensitivity for the LNSC results.[42] Alexandraki and colleagues observed a median number of 2 cycles (range 1–4) with a mean cycle length of 3·8 years (SD 0·6; n=30).[1]

### Treatment and outcome in cyclic Cushing's syndrome

Differences in treatment and outcome for patients with cyclic and non-cyclic Cushing's syndrome are displayed in table 4. 114 of 143 patients with cyclic Cushing's disease (80%, 95% CI 72–86) had pituitary surgery, which was initially reported as successful in 79 patients (69%, 60–78). However, there was a higher recurrence rate among patients with cyclic Cushing's disease (24 of 79; 30%, 21–42) than among patients with non-cyclic Cushing's disease (54 of 275; 20%, 95% CI 15–25; p=0·0465) during an overall mean follow-up time of 7·2 years (SD 7·0) for patients with cyclic Cushing's syndrome compared with 9·2 years (8·9) for patients with non-cyclic Cushing's syndrome (p=0·0113). 17 of 143 patients with cyclic Cushing's disease (12%, 95% CI 7–18) received pituitary radiation. 31 of the 188 patients with ACTH-dependent cyclic Cushing's syndrome (16%, 12–23) had a bilateral adrenalectomy. Overall, therapy-induced remission was reported in 94 of 165 patients with cyclic Cushing's syndrome (57%, 49–65): 59 of 105 patients with cyclic Cushing's disease (56%, 46–66), 13 of 14 patients with adrenal cyclic Cushing's syndrome (93%, 66–100), and 21 of 36 patients with ectopic cyclic Cushing's syndrome (58%, 41–75). There were significantly fewer cases of therapy-induced remission in patients with cyclic Cushing's syndrome (94 of 165; 57%, 49–65) than in patients with non-cyclic Cushing's syndrome (226 of 310; 73%, 95% CI 68–78; p=0·0007). There was a significantly higher usage of medical or adrenostatic therapy in patients with cyclic Cushing's syndrome (75 of 203; 37%, 30–44) than in patients with non-cyclic Cushing's syndrome (77 of 477; 16%, 13–20; p<0·0001) with an increasing trend over time; appendix p 27). Consequently, overall control rates were similar in patients with cyclic Cushing's disease (103 of 143; 72%, 64–79) and patients with non-cyclic Cushing's disease (337 of 426; 79%, 75–83; p=0·0844) and in patients with adrenal cyclic Cushing's syndrome (22 of 23; 96%, 78–100) and patients with non-cyclic adrenal Cushing's syndrome (59 of 66; 89%, 79–96; p=0·6745). In patients with cyclic ectopic Cushing's syndrome, control rates were slightly lower (24 of 36; 67%, 49–81) than in patients with non-cyclic ectopic Cushing's syndrome (10 of 10; 100%, 69–100; p=0·0439), but due to the small sample size this difference in rates should be interpreted with caution. Patients with cyclic Cushing's syndrome had significantly more unnecessary surgeries (12 of 135 [eight pituitary surgeries performed in seven patients, two pulmonary surgeries, two unilateral adrenalectomies, and one thymectomy]; 9%, 5–15) than patients with non-cyclic Cushing's syndrome (two of 139; 1%, 0–5; p=0·0055). Overall, time to remission was significantly longer for patients with cyclic Cushing's syndrome (19 months, range 0·3–252·0) than for the reference cohort of patients with non-cyclic Cushing's syndrome derived from the LMU Munich hospital (2·1 months, 0·03–123·6; p<0·0001).

### Suggested pathophysiological mechanisms underlying cyclicity in Cushing's syndrome

The possible causes and suggested mechanisms underlying cyclic Cushing's syndrome described in the case reports are summarised alongside a list of counter-arguments (appendix pp 28–29).

## Discussion

Although cyclic Cushing's syndrome is widely considered to be a rare form of Cushing's syndrome, our literature search revealed an overall frequency of cyclicity of 14–18%. Some sources suggested cyclic Cushing's disease to be discovered particularly frequently after pituitary surgery with a postoperative prevalence of 7–18%.[13,68] However, this prevalence might also be related to more regular postoperative biochemical testing for adrenal insufficiency. In primary pigmented nodular adrenocortical disease, cyclic Cushing's syndrome could even account for one in four patients.[69]

Patients with cyclic Cushing's syndrome presented with typical clinical symptoms and comorbidities of Cushing's syndrome, with varying extent and intensity. On the basis of poor data availability, a distinct cyclic phenotype could not be distinguished. We suggest documenting any clinical findings photographically to capture possible changes over time. Likewise, patients with cyclic Cushing's syndrome should receive the same comorbidity screening and appropriate treatment as patients with non-cyclic Cushing's syndrome.

Our analysis revealed that cyclic Cushing's syndrome occurs in patients with both ACTH-dependent and ACTH-independent Cushing's syndrome. The Endocrine Society practice guidelines suggest UFC and LNSC measurements rather than dexamethasone suppression tests in patients suspected of having cyclic Cushing's syndrome.[76] Although UFC was measured and reported in almost all cases, data on LNSC were scarce. This difference could be due to the less frequent use of LNSC in earlier studies. There is evidence that LNSC can reliably identify short-term variations in cortisol concentrations[42,148] and enables long-distance surveillance because samples can easily be sent by mail. Our analysis confirmed the great diagnostic value of BIPSS in differentiating between pituitary and ectopic origin, when performed during periods of hypercortisolism. Close monitoring of hypercortisolism is therefore paramount to avoid misleading results, as recommended in the 2021 consensus update of the Pituitary Society.[149] When investigated during a trough phase or undetermined cortisolaemic state, ACTH secretion from healthy pituitary corticotroph cells might not be fully suppressed. In a patient with ectopic Cushing's syndrome, unsuppressed physiological ACTH could lead to a high central-to-peripheral ACTH gradient, falsely indicating

| | Cyclic Cushing's syndrome | | | | | Non-cyclic Cushing's syndrome | | | | | p-value (cyclic *vs* non-cyclic Cushing's syndrome) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Jahandideh et al (2018)[42] | Alexandraki et al (2009)[1] | Powel et al (2008)[69] | Single case reports and small case series[2–10,12–30,32,37–41,43,44,46–50,79–145] | Total | Jahandideh et al (2018)[42] | Alexandraki et al (2009)[1] | Powel et al (2008)[69] | LMU Munich longitudinal cohort* | Total | |
| Number of patients | 38 | 30 | 9 | 135 | | 167 | 171 | 25 | 139 | 502 | .. |
| Pituitary surgery in Cushing's disease | 38/38 (100%, 91–100) | 19/30 (63%, 44–80) | .. | 57/75 (76%, 65–85) | 114/143 (80%, 72–86) | 167/167 (100%, 98–100) | 127/171 (74%, 67–81) | .. | 79/88 (90%, 82–95) | 373/426 (88%, 84–91) | 0·0272 |
| Successful pituitary surgery in Cushing's disease | 31/38 (82%, 66–92) | 10/19 (53%, 29–76)† | .. | 38/57 (67%, 53–79) | 79/114 (69%, 60–78) | 136/167 (81%, 75–87) | 79/127 (62%, 53–71)‡ | | 60/79 (76%, 65–85) | 275/373 (74%, 69–78) | 0·4005 |
| Relapse after successful pituitary surgery in Cushing's disease | 10/31 (32%, 17–51) | 4/10 (40%, 12–74) | .. | 10/38 (26%, 13–43) | 24/79 (30%, 21–42) | 36/136 (26%, 19–35) | 12/79 (15%, 8–25) | .. | 6/60 (10%, 4–21) | 54/275 (20%, 15–25) | 0·0465 |
| Pituitary radiation in Cushing's disease | 4/38 (11%, 3–25) | 1/30 (3%, 0–17) | .. | 12/75 (16%, 9–26) | 17/143 (12%, 7–18) | 27/167 (16%, 11–23) | .. | .. | 5/88 (6%, 2–13) | 32/255 (13%, 9–17) | 1·0000 |
| BADX in ACTH-dependent Cushing's syndrome | 4/38 (11%, 3–25) | 8/30 (27%, 12–46) | .. | 19/120 (16%, 10–24) | 31/188 (16%, 12–23) | 5/167 (3%, 1–7) | 47/171 (27%, 21–35) | .. | 10/98 (10%, 5–18) | 62/436 (14%, 11–18) | 0·4645 |
| Medical or adrenostatic treatment (ever) | 14/38 (37%, 22–54) | 2/30 (7%, 1–22) | ..§ | 59/135 (44%, 35–53) | 75/203 (37%, 30–44) | 48/167 (29%, 22–36) | 0/171 (0%, 0–2) | ..§ | 29/139 (21%, 14–29) | 77/477 (16%, 13–20) | <0·0001 |
| Patients receiving unnecessary pituitary surgeries | 0/38 (0%, 0–9) | 0/19 (10%, 0–18) | .. | 7/65 (11%, 4–21)¶ | 7/122 (6%, 2–12) | 0/167 (0%, 0–2) | 0/127 (0%, 0–3) | .. | 2/81 (2%, 0–9) | 2/375 (1%, 0–2) | 0·0011 |
| Patients receiving unnecessary surgeries | .. | .. | .. | 12/135 (9%, 5–15) | 12/135 (9%, 5–15) | .. | .. | .. | 2/139 (1%, 0–5) | 2/139 (1%, 0–5) | 0·0055 |
| Therapy-induced remission irrespective of tumour origin | .. | 14/30(47%, 28–66)‖ | ..§ | 80/135 (59%, 51–68) | 94/165 (57%, 49–65) | .. | 114/171 (67%, 59–74)** | ..§ | 112/139 (80%, 73–87) | 226/310 (73%, 68–78) | 0·0007 |
| Therapy-induced remission in Cushing's disease | .. | 14/30(47%, 28–66)‖ | .. | 45/75 (60%, 48–71) | 59/105 (56%, 46–66) | .. | 114/171 (67%, 59–74)** | .. | 69/88 (78%, 68–87) | 183/259 (71%, 65–76) | 0·0100 |
| Therapy-induced remission in adrenal Cushing's syndrome | .. | .. | ..§ | 13/14 (93%, 66–100) | 13/14 (93%, 66–100) | .. | .. | ..§ | 34/41 (83%, 68–93) | 34/41 (83%, 68–93) | 0·6639 |
| Therapy-induced remission in ectopic Cushing's syndrome | .. | .. | .. | 21/36 (58%, 41–75) | 21/36 (58%, 41–75) | .. | .. | .. | 9/10 (90%, 56–100) | 9/10 (90%, 56–100) | 0·1302 |
| Therapy-induced remission or controlled irrespective of tumour origin | 31/38 (82%, 66–92) | 16/30 (53%, 34–72)†† | 9/9 (100%, 66–100)§ | 99/135 (73%, 65–81)‡‡ | 155/212 (73%, 67–79) | 148/167 (89%, 83–93) | 114/171 (67%, 59–74)** | 25/25 (100%, 86–100)§ | 119/139 (86%, 79–91) | 406/502 (81%, 77–84) | 0·0278 |
| Therapy-induced remission or controlled in Cushing's disease | 31/38 (82%, 66–92) | 16/30 (53%, 34–72)†† | .. | 56/75 (75%, 63–84) | 103/143 (72%, 64–79) | 148/167 (89%, 83–93) | 114/171 (67%, 59–74)** | .. | 75/88 (85%, 76–92) | 337/426 (79%, 75–83) | 0·0844 |
| Therapy-induced remission or controlled in adrenal Cushing's syndrome | .. | .. | .. | 13/14 (93%, 66–100) | 22/23 (96%, 78–100) | .. | .. | 25/25 (100%, 86–100)§ | 34/41 (83%, 68–93) | 59/66 (89%, 79–96) | 0·6745 |
| Therapy-induced remission or controlled in ectopic Cushing's syndrome | .. | .. | .. | 24/36 (67%, 49–81) | 24/36 (67%, 49–81) | .. | .. | .. | 10/10 (100%, 69–100) | 10/10 (100%, 69–100) | 0·0439 |
| Mean time to therapy induced remission, months | .. | .. | .. | 39·8 (SD 48·2, 0·3–252·0)§§ | 39·8 (SD 48·2, 0·3–252·0)§§ | .. | .. | .. | 5·6 (SD 14·2, 0·03–123·6)¶¶ | 5·6 (SD 14·2, 0·03–123·6)¶¶ | <0·0001 |
| Median time to therapy-induced remission, months | .. | .. | .. | 19·0 (0·3–252·0, 8·85–48·0)§§ | 19·0 (0·3–252·0, 8·85–48·0)§§ | .. | .. | .. | 2·1 (0·03 –123·6, 1·2–3·2) | 2·1 (0·03–123·6, 1·2–3·2) | <0·0001 |
| Total median time of follow-up, months | 43·7 (2–128·2) | .. | .. | 44·8 (0·3–252·0, 22·75–252·0)‖‖ | .. | | .. | .. | 37·6 (0–120·2, 7·23–63·47) | .. | .. |

(Table 4 continued on next page)

| | Cyclic Cushing's syndrome | | | | | Non-cyclic Cushing's syndrome | | | | p-value (cyclic vs non-cyclic Cushing's syndrome) |
|---|---|---|---|---|---|---|---|---|---|---|
| | Jahandideh et al (2018)[42] | Alexandraki et al (2009)[1] | Powel et al (2008)[69] | Single case reports and small case series[2–10,12–30,32,37–41,43,44,46–50,79–145] | Total | Jahandideh et al (2018)[42] | Alexandraki et al (2009)[1] | Powel et al (2008)[69] | LMU Munich longitudinal cohort* | Total | |
| (Continued from previous page) | | | | | | | | | | | |
| Total mean time of follow-up, years | .. | 14·8 (8·8, *** 0–30) | .. | 5·0 (4·50–1·0)\|\|\|\| | 7·2 (7·0) | .. | 14·0 (10·5, *** 0–52) | .. | 3·3 (2·8, 0·0–10·0) | 9·2 (8·9) | 0·0113 |

Data are N, n/N (%, 95% CI), mean (SD, range), or median (range, IQR). Cushing's disease was confirmed in patients with pathological ACTH-dependent hypercortisolism on the basis of histopathological diagnosis of a corticotroph tumour, positive immunostaining for ACTH, a well defined sellar lesion on imaging, clinical and biochemical remission following pituitary surgery, biochemical confirmation of ACTH-dependent Cushing's syndrome with a central gradient on BIPSS, or a combination of these indicators. ACTH=adrenocorticotropic hormone. BADX=bilateral adrenalectomy. *Patients treated at the LMU Munich hospital between 2012 and 2022. †Six patients with cyclic Cushing's syndrome were cured and four patients had recurrence after pituitary surgery, indicating an initial remission of ten patients.[1] ‡67 patients with non-cyclic Cushing's syndrome were cured and 12 had recurrence after pituitary surgery, indicating an initial remission of 79 patients.[1] §Five patients of unknown phenotype (ie, whether the patients had cyclic or non-cyclic Cushing's syndrome was not indicated) received adrenostatic therapy, and 32 of 34 patients of unknown phenotype were in remission.[69] ¶Eight unnecessary pituitary surgeries were performed in seven patients. ‖Six patients were cured after pituitary surgery and eight patients had BADX, indicating a total of 14 patients with cyclic Cushing's syndrome in remission.[1] **67 patients were cured after pituitary surgery and 47 patients had BADX, indicating a total of 114 patients with non-cyclic Cushing's syndrome in remission.[1] ††Two patients received block-and-replace therapy, indicating a total of 16 patients with controlled cyclic Cushing's syndrome or cyclic Cushing's syndrome in remission. ‡‡Including five patients with cyclic Cushing's syndrome who underwent spontaneous remission (two pituitary tumours, one ectopic tumour, one occult tumour, and one unclassified tumour). §§n=53. ¶¶n=112. ‖‖n=106. ***SD imputed from SE of the mean.

***Table 4:*** **Differences in treatment and outcome between patients with cyclic and non-cyclic Cushing's syndrome**

a pituitary source of ACTH hypersecretion. After Cushing's syndrome is confirmed by standardised screening, we suggest that the morning serum cortisol concentration on the day of the BIPSS procedure should ideally lie within the range of previously measured cortisol excess to indicate hypercortisolism. However, as cases with a rapid drop of steroid secretion have been described, even a high morning serum cortisol concentration cannot entirely ensure a reliable result. In these cases, serum cortisol and ACTH values obtained during and after BIPSS performance can provide further evidence. Some cases reported on variations in cortisol concentrations in hair in accordance with symptomatic periods in cyclic Cushing's syndrome.[39] Used as an additional diagnostic tool hair offers the potential for earlier diagnosis and treatment.[39,150–152] Variations in cortisol concentrations in hair could be useful in patients who have long biochemical troughs, are oligosymptomatic, or both. However, hair cortisol concentrations are not routinely measured, and standardised reference ranges are missing. In general, we suggest repeated, standardised biochemical screening in patients with strong clinical suspicion of Cushing's syndrome, but with incongruous or negative biochemical findings.

Imaging was described as helpful in correctly identifying the tumour origin in 64% of patients with cyclic Cushing's syndrome, most often in patients with ectopic cyclic Cushing's syndrome, followed by patients with cyclic Cushing's disease. However, identification of the origin was not always successful at the patient's first visit and repeated imaging was often necessary to detect suspicious lesions. When compared with patients with non-cyclic Cushing's syndrome, imaging was similarly useful in identifying tumour origins in patients with Cushing's disease and ectopic Cushing's syndrome, but less useful than in patients with adrenal Cushing's syndrome. This difference is probably due to higher rates of bilateral hyperplasia and unilateral adenoma in patients with non-cyclic Cushing's syndrome.

We found a significantly higher use of medical or adrenostatic therapy in patients with cyclic Cushing's syndrome. This therapy might be of particular use in treating occult or ectopic cyclic Cushing's syndrome, as the time to tumour identification might be longer. In cases with more rapid cycling or when regular control visits are not feasible, we suggest a block-and-replace approach to avoid adrenal insufficiency due to unpredictable cycle intensity and the possibility of spontaneous hypocortisolism. We observed a barely significantly higher (p=0·0465) postoperative recurrence rate in patients with cyclic versus non-cyclic Cushing's disease. There is no evidence that a surgical procedure could trigger cyclicity, and the findings might be biased by more frequent postoperative testing and by the heterogeneity of the different cohorts. Cushing's disease was also not histologically confirmed in all patients. In general, treatment approaches should be in line with

non-cyclic Cushing's syndrome, and all patients should receive a close postoperative follow-up. We advise that patients suspected of having cyclic Cushing's syndrome be referred to specialised departments to avoid unnecessary surgical procedures and delayed diagnoses due to challenges in diagnostic tests.

The absence of a uniform definition for cyclic Cushing's syndrome and the common use of alternative terms impede precise reporting of cases and leave room for interpretation and potentially misinterpretation of results. The two most widely accepted definitions of cyclic Cushing's syndrome are based on either three hypercortisolaemic peaks in cortisol concentrations interspersed by two eucortisolaemic troughs[2] or on two peaks separated by one trough,[1] of which the latter also requires the resolution of clinical symptoms during eucortisolaemic phases.[1] In contrast, Sandouk and colleagues[35] proposed to distinguish between variable hypercortisolism with non-variable clinical symptoms and "true" cyclic Cushing's syndrome with variable symptoms. Our literature search showed that a substantial number of patients do not have complete remission of clinical symptoms between hypercortisolaemic peaks.[13,17,25,26,28,30,32,46–49,80–88] Also, although the term cyclic might suggest regular periods of activity, we found more cases that reported irregular intervals of steroid secretion. The heterogeneity of the affected population makes the creation of a uniform definition difficult. However, due to the complexity and probably under-reported presence of cyclic Cushing's syndrome, a uniform and comprehensible definition is essential to identify affected patients. Two, rather than three, peaks in cortisol concentrations seem reasonable to identify patients with true cyclicity, while avoiding long-term phases of observation.

Our systematic review, although subject to the reporting biases of each case report from which data were derived, is to our knowledge, the most comprehensive review on patients with cyclic Cushing's syndrome published to date. A major limitation of the study is the large number of undocumented clinical and biochemical features derived from the literature. By indicating that these features were not reported, we tried to reduce overestimation of single outcomes. As three large case series[1,42,69] accounted for 77 (36%) of the total 212 included cases of cyclic Cushing's syndrome, there might have been considerable reporting bias. To ensure the highest possible transparency, we analysed and displayed the data derived from these articles separately. Our longitudinal cohort from the LMU Munich hospital had the advantage of a nearly complete dataset, but the disadvantages of being a single-centre cohort studied during a narrow time period. We are aware that some of the significantly different outcomes between patients with cyclic Cushing's syndrome and non-cyclic Cushing's syndrome, such as time to remission, were partly due to the large heterogeneity from the literature-derived cases reported over a long period versus the well described cohort with a high pre-test probability of patients with Cushing's syndrome seen in our specialised outpatient department. These differences might therefore not reflect true differences in the outcomes. However, in line with our findings, Jahandideh and colleagues[42] observed a significantly longer interval between initial presentation and pituitary surgery in patients with cyclic Cushing's disease compared with patients with non-cyclic Cushing's disease. Prospective multicentre studies are necessary to investigate the true prevalence of cyclic Cushing's syndrome and differences in outcome between patients with cyclic and non-cyclic Cushing's syndrome. The fact that nine cases of cyclic Cushing's syndrome were not originally obtained by our search terms, but were identified by one non-systematic review on cyclic Cushing's syndrome,[2] suggests the possibility that further cases might have been overlooked. The search terms were chosen to the best of our knowledge and aimed at detecting all cases of cyclic Cushing's syndrome that met our inclusion criteria. Likewise, as not all case reports provided a precise description of how their diagnoses were established, there remains a risk of erroneous inclusion of cases without true cyclicity. We aimed to reduce this chance by only including peer reviewed case reports.

The pathophysiological mechanisms underlying the cyclic nature of cyclic Cushing's syndrome remain to be elucidated. Possible mechanisms include the influence of some neurotransmitters,[22,82,96,98,110] hypothalamic dysregulation,[97,125] and feedback mechanisms.[23,26,79,91] Cyclic Cushing's syndrome could be multifactorial, and further studies investigating tumour pathologies in patients with cyclic Cushing's syndrome are required to understand the underlying mechanisms. In addition, studies prospectively investigating steroid secretion patterns in patients with non-cyclic and cyclic Cushing's syndrome are necessary to reveal whether cyclic Cushing's syndrome is truly a distinct entity of Cushing's syndrome or whether it describes patients at one end of the spectrum for whom variability in steroid secretion is more pronounced and hence becomes more evident. Atkinson and colleagues[85,126] proposed that cyclic Cushing's syndrome might be an exaggeration of physiological cyclical variation in cortisol concentration. This theory is supported by studies reporting variations in steroid secretion in patients with non-cyclic Cushing's syndrome[35,36] and subclinical Cushing's syndrome.[64] On the other hand, the long trough phases lasting several years observed in some patients with cyclic Cushing's syndrome is an argument against the exaggeration theory.[4,6,10,123,124] Regardless, since long and possibly even permanent spontaneous remission has been described in cyclic Cushing's syndrome, further characterisation of these patients has the potential to substantially contribute to the understanding of the development and disease activity of, and even cure for, Cushing's syndrome.

**Contributors**
EN and MR designed the study and study protocol. EN and MR performed the literature search, study selection, and data extraction. EN performed the data analysis. EN and MR performed the data interpretation. EN, FV, AA, LB, GR, KR, FB, and MR recruited patients and provided medical information for this systematic review. SZ processed biosamples for patients included in this systematic review. EN wrote the initial draft of this systematic review. FV, AA, LB, GR, SZ, KR, FB, MT, and MR provided essential contributions to the systematic review. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Declaration of interests**
We declare no competing interests.

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