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**Clinical Research Article**

# Increased Mortality Persists after Treatment of Cushing's Disease: A Matched Nationwide Cohort Study

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## Abstract

**Context:** Whether biochemical remission normalizes life expectancy in Cushing's disease (CD) patients remains unclear. Previous studies evaluating mortality in CD are limited by using the expected number of deaths in the background population instead of the actual number in matched controls.

**Objective and setting:** To study mortality by time-to-event analysis in an unselected nationwide CD patient cohort.

**Design and participants:** Longitudinal data from the Swedish Pituitary Register of 371 patients diagnosed with CD from 1991 to 2018 and information from the Swedish Cause of Death Register were evaluated. Four controls per patient (n = 1484) matched at the diagnosis date by age, sex, and residential area were included.

**Main outcome measures:** Mortality and causes of death.

**Results:** The median diagnosis age was 44 years (interquartile range 32-56), and the median follow-up was 10.6 years (5.7-18.0). At the 1-, 5-, 10-, 15-, and 20-year follow-ups, the remission rates were 80%, 92%, 96%, 91%, and 97%, respectively. Overall mortality was increased in CD patients compared with matched controls [hazard ratio (HR) 2.1 (95% CI 1.5-2.8)]. The HRs were 1.5 (1.02-2.2) for patients in remission at the last follow-up (n = 303), 1.7 (1.03-2.8) for those in remission after a single pituitary surgery (n = 177), and 5.6 (2.7-11.6) for those not in remission (n = 31). Cardiovascular diseases (32/66) and infections (12/66) were overrepresented causes of death.

**Conclusions:** Mortality was increased in CD patients despite biochemical remission compared to matched controls. The study highlights the importance of careful comorbidity monitoring, regardless of remission status.

**Key Words:** Cushing, hypercortisolism, mortality, remission, hazard ratio, epidemiology

Cushing's disease (CD) is a rare disorder caused by an adrenocorticotropin-secreting pituitary tumor, and CD affects approximately 1.6 individuals per million per year with a female to male ratio of 3:1 to 5:1 [1, 2]. Due to the glucocorticoid excess, CD is associated with significantly increased cardiovascular morbidity and mortality [3-5]. First-line treatment of CD is the removal of the tumor by transsphenoidal surgery (TSS) [6], which initially results in remission in approximately 80% of patients [7]. After the initial remission following TSS, recurrence occurs in approximately one-fifth of patients [7]. Importantly, the negative effects of hypercortisolism, including vascular, cardiac, and neuropsychiatric alterations, may persist for years despite biochemical remission [8, 9]. Although several smaller studies have reported that the standardized mortality rate (SMR) is not significantly increased [10-13], a recent meta-analysis concluded that patients "cured" from CD had an increased mortality, with a pooled SMR of 2.5 (95% CI 1.4-4.2) [14].

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Subsequently, 1 large study reported increased mortality for patients in remission [3], a second smaller study did not [15], and a third study demonstrated normalized life expectancy in patients who had been in remission for 10 years after only 1 TSS [16]. Except for 1 study, which included patients with Cushing's syndrome of both adrenal and pituitary origin [17], previous studies on mortality in CD have used the expected number of deaths in the total background population as a reference and reported SMRs. Here, we investigated the influence of biochemical remission as well as other potential predictors on mortality in a large nationwide cohort of patients with verified CD and compared this cohort with a control group matched at the date of diagnosis by age, sex, and residential area. In addition, we report on causes of death at early and late stages of CD and provide longitudinal data on remission rates.

## Methods

### Study Design and Participants

The present study was a register-based matched cohort study. All patients with CD in the Swedish Pituitary Register (SPR) diagnosed from May 1991 to September 2018 were included. The end of follow-up was the date of death, the date of emigration, or December 27, 2018. The use of each patient's unique Swedish personal identification number permitted linkage to Statistics Sweden's Total Population Register and the Swedish Cause of Death Register.

The SPR is a nationwide register that includes the vast majority of Swedish patients with CD [18]. The SPR contains information on the date of diagnosis, age, sex, treatment (surgery, radiotherapy, and pharmacological treatment), hormone deficiencies, tumor size [microadenomas (<10 mm), macroadenomas (≥10 mm), or invisible tumors], and biochemical remission status evaluations. Data are collected at diagnosis, at regular follow-ups, and when surgery or radiotherapy are performed. The SPR is organized by endocrinologists, neurosurgeons, oncologists, pathologists, ophthalmologists, neuroradiologists, and endocrine nurses from all 6 healthcare regions in Sweden. Each healthcare region is linked to a university hospital (Lund, Gothenburg, Linköping, Stockholm, Uppsala, and Umeå) that also performs the pituitary surgeries.

For each patient with CD, 4 matched controls were included from Statistics Sweden's Total Population Register. Matching for sex, age, and residential area at the date of diagnosis was performed. The Total Population Register was also used to identify emigration of the participants. Six (2%) CD patients and 35 (2%) controls emigrated during the study time and were censored at the date of emigration. For time-to-event analyses, both CD patients and controls were followed from the date of diagnosis to the date of death or censoring.

The Swedish Cause of Death Register contains data on all deceased persons who at the time of death were Swedish residents. The recorded variables include the underlying cause of death, the contributing causes of death, the nature of injuries associated with death, and the basis for the statement of the cause of death. The diagnoses are coded according to the International Statistical Classification of Diseases and Related Health Problems (ICD), and coverage is excellent [19].

The study was approved by the Ethics Review Board of Linköping (approval no. 2017/60-31 and No. 2018/130-32). The SPR is approved by the Ethics Review Board, Karolinska Institute, Stockholm, Sweden (no. 2003/515/03 and no. 2012/915-32).

### CD Diagnostic and Remission status Evaluations

The diagnosis was made according to the local routine at each hospital and included clinical evaluations for typical symptoms of Cushing's syndrome; late-night salivary cortisol, overnight dexamethasone suppression, and 24-hour urinary free cortisol analyses; and petrosal sinus sampling and histopathological analysis. At every follow-up visit, the remission status was evaluated by the treating physician. Biochemical remission was defined as normal late-night salivary cortisol levels and/or s-cortisol < 50 nmol/L in an overnight dexamethasone suppression test and/or 24-hour urinary free cortisol below the upper limit of normal or hypocortisolism after pituitary surgery, radiotherapy, or bilateral adrenalectomy.

### Statistical Analysis

Continuous variables are presented as the median and interquartile range (IQR) and were compared by using the Mann-Whitney U test. Proportions were compared with Pearson's chi-squared test or Fisher's exact test. Remission rates were based on the proportions of patients in remission among the total number of patients with data on remission status. Univariable logistic regression was used to calculate odds ratios for age, sex, and tumor size at diagnosis as potential predictors of remission. A multivariable logistic regression model including age, sex, and tumor size was employed at the 1-year follow-up. The Kaplan-Meier survival function was employed to produce survival tables and graphs. Cox regression was used for time-to-event analyses. Univariable hazard ratios (HRs) for comparisons between groups (CD patients vs controls) and comparisons within the CD group (remission status, age, sex, treatment modalities, and hormone deficiencies) were also calculated. Mortality time trends were analyzed by comparing 2 groups according to the year of diagnosis (1991-1999 and 2000-2008), and setting the maximum follow-up to 10 years after the date of diagnosis for both groups. Multivariable Cox regression was used for comparisons within the CD group in models including age, sex, and remission status. The proportional hazard assumptions were assessed graphically, and robust standard error estimation was used. The results are presented as odds ratios and HRs with corresponding 95% CIs. Statistical analyses were performed with Stata (StataCorp. 2017. Stata Statistical Software: Release 15.1. College Station, TX, USA: StataCorp LLC.). Differences for which the *P*-values were <0.05 were considered significant.

## Results

### Study Cohort and Patient Characteristics

In total, 371 patients with CD (females n = 281, 76%) and 1484 matched controls were included. The median age at diagnosis was 44 years (range 11-91, IQR 32-56), and the median follow-up time of patients with CD was 10.6 years (range 0.02-28, IQR 5.7-18). Patient characteristics in relation to remission status at the last follow-up are given in Table 1. The median number of CD patients included from each of the 6 health care regions was 67 (range 37-82).

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**Table 1. Characteristics of 371 patients with Cushing's disease diagnosed between 1991 and 2018**

| | All CD patients | CD patients in remission[a] | CD patients not in remission[a] | CD patients with missing data on remission | CD patients with no follow-up visit | *P*-value[b] remission vs not in remission |
|---|---|---|---|---|---|---|
| Total, n | 371 | 303 | 31 | 16 | 21 | |
| Years in study, median (IQR) | 10.6 (5.7-18.2) | 11.4 (7.1-19.3) | 4.4 (2.2-15.0) | 8.7 (3.4-20.3) | 1.1 (0.4-2.5) | < 0.01 |
| Women, n (%) | 281 (76) | 232 (77) | 26 (84) | 10 (63) | 13 (62) | 0.5 |
| Age at diagnosis, median (IQR) | | | | | | |
| All patients | 44 (32-56) | 42 (31-54) | 53 (40-63) | 49 (37-65) | 60 (13-80) | 0.01 |
| Men | 44 (30-58) | 42 (29-53) | 53 (50-54) | 40 (29-65) | 62.5 (44-72.5) | 0.11 |
| Women | 43 (33-56) | 41.5 (31-54) | 52.5 (38-66) | 52.5 (44-64) | 59 (54-70) | 0.04 |
| Tumor size at diagnosis, n | | | | | | 0.026 |
| Microadenoma[c] | 197 | 171 | 13 | 6 | 7 | |
| Macroadenoma[d] | 79 | 60 | 10 | 5 | 4 | |
| No visible tumor | 17 | 11 | 4 | — | 2 | |
| Missing data | 78 | 61 | 4 | 5 | 8 | |
| Treatment combinations, n | | | | | | 0.03 |
| 1 S | 205 | 177 | 9 | 10 | 9 | |
| ≥2 S | 28 | 23 | 4 | 1 | — | |
| R | 3 | 1 | 1 | 1 | — | |
| M | 1 | — | 1 | — | — | |
| S + A | 7 | 7 | — | — | — | |
| S + R | 41 | 36 | 3 | 1 | 1 | |
| S + M | 45 | 33 | 7 | 1 | 4 | |
| R + M | 2 | 2 | — | — | — | |
| S + A + R | 9 | 8 | 1 | — | — | |
| S + A + M | 2 | 2 | — | — | — | |
| S + R + M | 8 | 6 | 2 | — | — | |
| S + A + R + M | 2 | 1 | — | 1 | — | |
| No treatment reported | 18 | 7 | 3 | 1 | 7 | |
| ACTH deficiency at last follow-up[e] | | | | | | <0.01 |
| Yes | 115 | 109 | 2 | 4 | — | |
| No | 213 | 184 | 28 | 1 | — | |
| Inconclusive | 2 | 1 | — | 1 | — | |
| Missing data | 20 | 9 | 1 | 10 | 21 | |
| GH deficiency at last follow-up[e] | | | | | | 1 |
| Yes | 74 | 66 | 6 | 2 | — | |
| No | 231 | 206 | 21 | 4 | — | |
| Inconclusive | 6 | 6 | — | — | — | |
| Missing data | 39 | 25 | 4 | 10 | 21 | |



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**Table 1. Continued**

| | All CD patients | CD patients in remission[a] | CD patients not in remission[a] | CD patients with missing data on remission | CD patients with no follow-up visit | *P*-value[b] remission vs not in remission |
|---|---|---|---|---|---|---|
| TSH deficiency at last follow-up[e] | | | | | | 1 |
| Yes | 98 | 86 | 8 | 4 | — | |
| No | 226 | 204 | 20 | 2 | — | |
| Inconclusive | 4 | 3 | 1 | — | — | |
| Missing data | 22 | 10 | 2 | 10 | 21 | |
| LH/FSH deficiency at last follow-up[e] | | | | | | 0.47 |
| Yes | 76 | 64 | 8 | 4 | — | |
| No | 228 | 208 | 18 | 2 | — | |
| Inconclusive | 10 | 7 | 3 | — | — | |
| Missing data | 36 | 24 | 2 | 10 | 21 | |
| ADH deficiency at last follow-up[e] | | | | | | 0.27 |
| Yes | 25 | 21 | 4 | — | — | |
| No | 294 | 262 | 25 | 7 | — | |
| Inconclusive | 1 | 1 | — | — | — | |
| Missing data | 30 | 19 | 2 | 9 | 21 | |

Abbreviations: A, bilateral adrenalectomy; ACTH, adrenocorticotropin; ADH, antidiuretic hormone; CD, Cushing's disease; GH, growth hormone; IQR, interquartile range; LH/FSH, luteinizing hormone/follicle-stimulating hormone; M, medical treatment; R, radiotherapy; S, pituitary surgery; THS, thyroid-stimulating hormone.
[a]Remission status at last follow-up.
[b]*P*-values according to the Mann-Whitney U test for continuous variables, Pearson's chi-square for comparisons of frequencies across groups of tumor size and treatment combinations, and Fisher's exact test for hormone deficiencies yes vs no.
[c]<10 mm.
[d]≥10 mm.
[e]21 patients with no follow-up visits.



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### Remission Rates and Predictive Factors

Biochemical remission was evaluated at 1 year [n = 321, median time of follow-up 1.3 years (IQR 1.0-1.6 years)], 5 years [n = 287, 5.1 (4.6-6.0)], 10 years [n = 199, 10.0 (9.3-10.7)], 15 years [n = 112, 15.3 (14.6-16.3)], and 20 years [n = 62, 20.9 (19.2-22.7)] after diagnosis. The remission rates are outlined in Table 2. At each follow-up (1, 5, 10, 15, and 20 years), age and sex did not predict remission status. At the 1-year follow-up, no significant association was found between tumor size at diagnosis (microadenomas, macroadenomas, or invisible tumors) and patients in remission.

### Survival Analysis and Predictive Factors

#### Comparisons of CD patients with matched controls

Sixty-six (18%) CD patients died during the study period, compared to 139 (9%) matched controls [HR 2.1 (95% CI 1.5-2.8)]. Mortality was increased in both male and female CD patients. HRs were increased for cardiovascular diseases and infections but not for cancer (Table 3). The estimated 5- and 10-year survival rates in patients with CD were 0.92 (95% CI 0.89-0.95) and 0.86 (0.81-0.89), respectively, compared to 0.98 (0.97-0.99) and 0.94 (0.93-0.96) in controls (Table 4). Figure 1 shows Kaplan-Meier survival curves in CD patients vs controls. The HRs were 1.5 (1.02-2.2) for patients in remission at the last follow-up (n = 303), 5.6 (2.7-11.6) for those not in remission (n = 31), and 3.3 (1.3-8.5) for those with unknown remission status (n = 16). Patients who achieved remission after a single pituitary surgery (n = 177) had an HR of 1.7 (1.03-2.8) compared to their corresponding controls. Patients with no follow-up in the SPR (n = 21) had an increased HR [4.1 (1.6-10.3)]. This group of patients was older at diagnosis (median age 60 vs 43 years, $P < 0.01$), but the sex distribution did not differ.

When the participants were divided into 2 groups according to the date of diagnosis and maximum follow-up was set to 10 years, HR for CD vs controls did not differ between the 2 time periods [HR 3.2 (1.6-6.2) for 1991-1999 (CD n = 114, controls n = 456) and HR 2.9 (1.6-5.1) for 2000-2008 (CD n = 124, controls n = 496)].

#### Comparisons within the CD group

The results from Cox regression analyses within the CD group are outlined in Table 5. Older age at diagnosis and not being in remission at the last follow-up were predictors of mortality. When adjusted for age and remission status (Model 3), male sex was associated with higher mortality. Treatment modalities (pituitary surgery only, surgery and radiotherapy, surgery and pharmacological treatment, and other combinations) were not associated with mortality. Radiotherapy per se was not associated with mortality in a model adjusted for age and remission status.

When patients in remission at the last follow-up were divided according to treatment with a single TSS (n = 177) and additional treatments (n = 119; repeat TSS, radiotherapy, adrenalectomy, medical treatment, or combinations of these treatments), survival did not differ. Adrenocorticotropin deficiency, present in 109 of 303 (36%) patients in remission at the last follow-up, was not associated with mortality. Deficiencies of growth hormone, thyroid-stimulating hormone, luteinizing hormone/follicle-stimulating hormone, and antidiuretic hormone were less common (Table 1) and not associated with mortality.

The period of diagnosis [1991-1999 n = 114 (reference group) and 2000-2008, n = 124] was not associated with mortality in the first 10 years after diagnosis [age- and sex-adjusted HR 1.25 (0.64-2.43), $P = 0.52$ for being diagnosed in the later period].

### Causes of Death During Short- and Long-term Follow-up

Out of 66 deaths, 32 (48%) were attributable to cardiovascular diseases, most commonly ischemic heart disease (n = 18) and cerebrovascular disease (n = 9) (Figure 2). Two patients died from pulmonary embolism—one 52 days after surgery and the other 2.8 years after diagnosis. Cardiovascular deaths occurred throughout the whole study period, and 17 of the 32 deceased patients were in remission at the last follow-up. Infections were the second most common cause of death. Ten out of 12 (83%) fatal infections occurred within 6 years after diagnosis. Six of the patients who died from infections were in remission at the last follow-up. There were no significant differences in the age at diagnosis, age at death, or time from diagnosis to death between patients with cardiovascular and infectious causes of death.

## Discussion

To our knowledge, this is the first study that investigated mortality in an unselected cohort of patients treated for CD and followed up in comparison to mortality in matched controls. The mortality rate was more than doubled in patients with CD, and not being in remission was a strong predictor of premature death. The study also supports findings that mortality continues to be increased despite biochemically successful treatment of hypercortisolism [HR 1.5 (95% CI 1.02-2.2)]. Cardiovascular diseases have been determined to be a main reason for a shorter life span in both active and "cured" CD [3, 5, 10, 15, 16, 20-22], which was confirmed in our study. Out of 66 deaths, 32 (48%) were due to cardiovascular diseases, including 2 fatal

**Table 2. Remission status in patients with Cushing's disease at each follow-up**

| Time of follow-up | In remission, n (%)* | Not in remission, n (%)* | Missing data, n |
|---|---|---|---|
| 1 year | 250 (80) | 63 (20) | 8 |
| 5 years | 249 (92) | 23 (8) | 15 |
| 10 years | 179(96) | 8 (4) | 12 |
| 15 years | 97 (91) | 10 (9) | 5 |
| 20 years | 60 (97) | 2 (3) | 0 |

Percentages are the proportions of patients with valid data on remission status. Patients with missing data are shown as absolute numbers.

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**Table 3. Hazard ratios for patients with Cushing's disease compared to matched controls: Cox regression analyses with corresponding 95% CIs**

| | CD, deaths/total n participants (%) | Controls, deaths/total n participants (%) | HR (95% CI) | *P*-value |
|---|---|---|---|---|
| Overall mortality | 66/371 (18) | 139/1484 (9) | 2.1 (1.5-2.8) | <0.01 |
| Males | 20/90 (22) | 40/360 (11) | 2.2 (1.3-3.8) | <0.01 |
| Females | 46/281 (16) | 99/1124 (9) | 2.0 (1.4-2.9) | <0.01 |
| Age at diagnosis ≤ 44 years | 9/191 (5) | 10/766 (1) | 3.6 (1.5-8.9) | 0.01 |
| Age at diagnosis > 44 years | 57/180 (32) | 129/718 (18) | 2.2 (1.6-2.9) | <0.01 |
| In remission at last follow-up | 35/303 (12) | 97/1212 (8) | 1.5 (1.02-2.2) | 0.04 |
| Not in remission last follow-up | 15/31 (48) | 15/124 (12) | 5.6 (2.7-11.6) | <0.01 |
| Remission status unknown at last follow-up | 7/16 (44) | 11/64 (17) | 3.3 (1.3-8.5) | 0.01 |
| No follow-up | 9/21 (43) | 16/84 (19) | 4.1 (1.6-10.3) | <0.01 |
| In remission after 1 pituitary surgery only | 21/177 (12) | 52/708 (7) | 1.7 (1.03-2.8) | 0.04 |
| Disease-specific causes of death | | | | |
| Cardiovascular disease | 32/371 (9) | 48/1484 (3) | 2.9 (1.9-4.5) | <0.01 |
| Infections | 12/371 (3) | 12/1484 (1) | 4.3 (1.9-9.5) | <0.01 |
| Cancer | 9/371 (2) | 44/1484 (3) | 0.9 (0.4-1.9) | 0.79 |

Abbreviations: CD, Cushing's disease; HR, hazard ratio.

**Table 4. Kaplan-Meier survival probability estimates (95% CI) for patients with Cushing disease and matched controls**

| Time of follow-up | Patients with CD | Controls |
|---|---|---|
| All participants | | |
| 5 year | 0.92 (0.89-0.95) | 0.98 (0.97-0.99) |
| 10 year | 0.86 (0.81-0.89) | 0.94 (0.93-0.96) |
| 15 year | 0.81 (0.76-0.85) | 0.90 (0.88-0.92) |
| 20 year | 0.74 (0.67-0.79) | 0.85 (0.83-0.88) |
| Females | | |
| 5 year | 0.93(0.90-0.96) | 0.98 (0.97-0.99) |
| 10 year | 0.87 (0.82-0.91) | 0.95 (0.93-0.96) |
| 15 year | 0.83 (0.78-0.88) | 0.90 (0.88-0.92) |
| 20 year | 0.74 (0.66-0.81) | 0.86 (0.82-0.88) |
| Males | | |
| 5 year | 0.88 (0.80-0.94) | 0.97 (0.95-0.99) |
| 10 year | 0.81 (0.70-0.88) | 0.93(0.89-0.95) |
| 15 year | 0.75 (0.62-0.84) | 0.88 (0.84-0.92) |
| 20 year | 0.71 (0.58-0.81) | 0.85 (0.79-0.89) |
| Participants in remission | | |
| 5 year | 0.98 (0.96-0.99) | 0.98 (0.97-0.99) |
| 10 year | 0.92 (0.87-0.95) | 0.96 (0.94-0.97) |
| 15 year | 0.87 (0.81-0.91) | 0.92(0.90-0.94) |
| 20 year | 0.82 (0.74-0.87) | 0.87 (0.84-0.90) |
| Participants not in remission | | |
| 5 year | 0.64 (0.44-0.78) | 0.99 (0.94-1.00) |
| 10 year | 0.64 (0.44-0.78) | 0.91 (0.82-0.96) |
| 15 year | 0.57 (0.36-0.74) | 0.81 (0.69-0.89) |
| 20 year | 0.31 (0.10-0.55) | 0.79(0.65-0.87) |

Abbreviation: CD, Cushing's disease.

pulmonary embolisms. Cardiovascular causes of death were prevalent throughout the study period, and more than half of the patients were in remission at the last follow-up. This finding is in line with persisting negative effects on the cardiovascular system despite biochemical control [8, 9] and underscores the need for aggressive treatment of comorbidities such as diabetes, hypertension, and hyperlipidemia [6, 23]. Failure to restore a normal hypothalamic-pituitary-adrenal axis and circadian rhythm after apparent successful treatment of CD might also have an impact on the cardiovascular risk profile [24].Treatment protocols, including management of comorbidities, have possibly improved during the 27-year study period. However, in the present study the period of diagnosis was not associated with mortality. In contrast to cardiovascular diseases, death due to infections seemed to occur mostly during the first years after the diagnosis of CD and was uncommon more than 6 years after diagnosis among our patients. These findings support data from the European Register on Cushing Syndrome, including 1045 patients with CD, in which infections were the leading cause of death during the first years after diagnosis [25], as well as the study by Clayton et al [16], where infections were uncommon causes of death in CD patients who had been in remission for 10 years or more. Severe hypercortisolism impairs the immune system and increases the risk of viral, bacterial, and fungal infections [17, 26-28]. Current Endocrine

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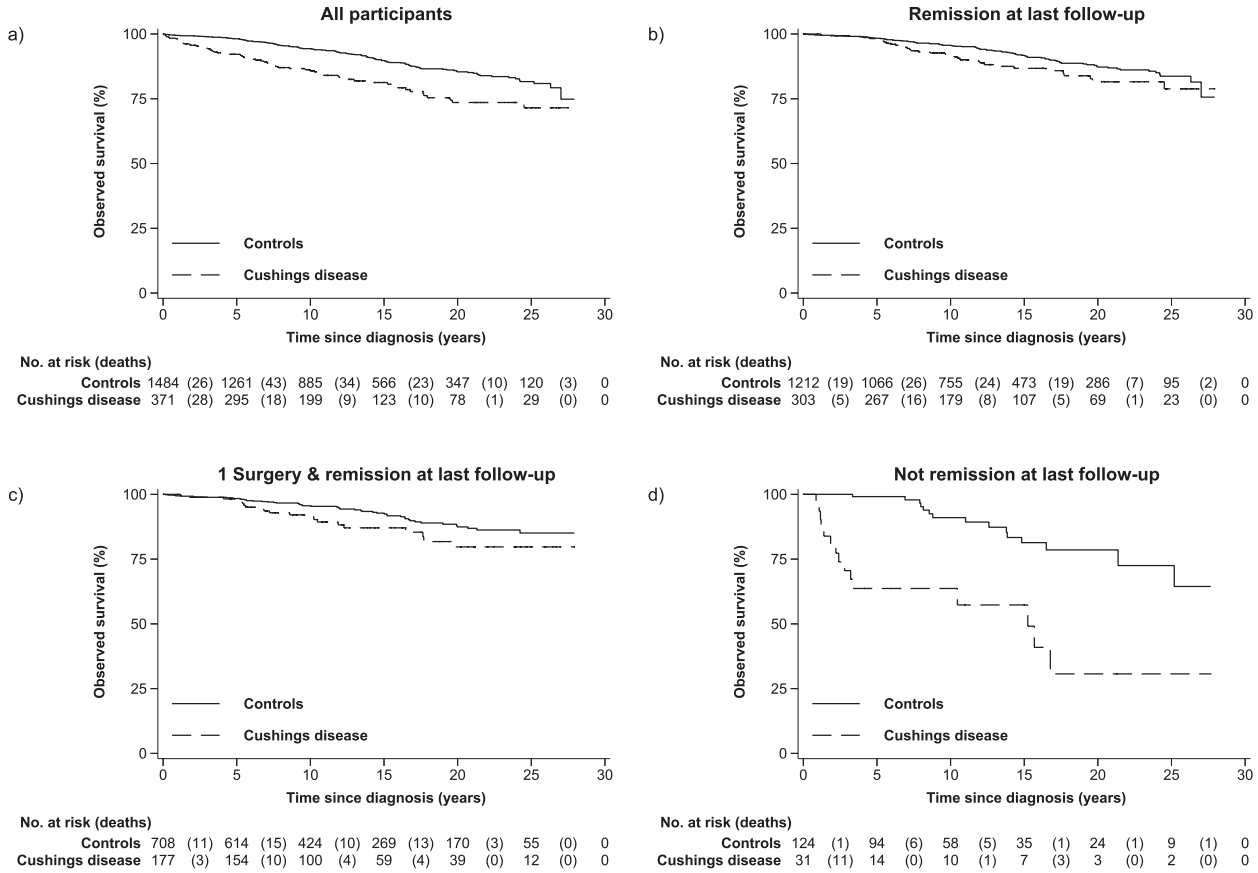


**Figure 1.** Kaplan-Meier survival curves in patients with Cushing's disease vs matched controls. (A) All participants. (B) Patients in remission. (C) Patients in remission after a single transsphenoidal surgery. (D) Patients not in remission.

Society guidelines [6] recommend the consideration of vaccinations against pneumonia, influenza, and herpes zoster in patients with Cushing's syndrome, while others have proposed prophylactic treatment of opportunistic infections such as pneumocystis pneumonia in selected patients [26]. Since infections were the second most common cause of death in our study, with a more than 4-fold HR compared to that of controls, we suggest increased attention to this issue. In addition, careful dosing of hydrocortisone in patients with hypocortisolism is mandatory [29]. Equally important is patient education on dose adjustments during intercurrent diseases since adrenal crises in response to acute stress, such as infections, are a major cause of premature death in patients with hypopituitarism [30, 31].

The overall duration of hypercortisolism might be an important explanation for persisting morbidity and increased mortality in CD. In a report by Lambert et al [32], mortality was associated with the duration of glucocorticoid excess (defined as the time from the first symptom of CD to the time of established remission). Notably, in the subgroup of patients in remission, no association was found [32]. Ragnarsson et al analyzed the time from diagnosis to remission and found no relation to mortality; however, the duration of hypercortisolism before diagnosis was not evaluated [3]. Although the delay of diagnosis was not possible to evaluate in the present study, the increased mortality of patients in remission indicates an impact of prior hypercortisolism.

Whether rapid and sustained remission after diagnosis normalizes life expectancy remains controversial. A number of small publications found mortality not to be significantly higher in "cured" patients [10-13, 15], whereas other larger studies did [3, 14, 21]. Clayton et al investigated mortality in CD patients after 10 years of remission and found a significantly increased SMR (1.6) [16]. However, they noted that patients achieving remission after a single pituitary surgery had a life expectancy comparable to that of the background population (SMR 0.95, ns). Although survival bias must be considered since they did not take into account deaths that occurred prior to 10 years, their findings indicate that early biochemical control increases the chance of survival. In the present study, the life expectancy of patients achieving remission after a single TSS (n = 177) was significantly shorter than that of controls (HR 1.7).

Coexisting diabetes mellitus, which possibly increases the risk of both cardiovascular and infectious diseases, was a risk factor for premature death in CD patients in some previous studies [15, 22, 33] but not in others [3, 32]. Hypertension [20, 22], depression at diagnosis [32], bilateral adrenalectomy [3, 33], male sex [11, 32] glucocorticoid replacement therapy [3], and the number of treatments to achieve remission [16] have also been linked to mortality in patients with CD in some studies. In our study, older age at diagnosis was associated with higher mortality, in line with most previous studies [3, 12, 20, 22, 32, 33]. It should be noted that patients younger

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**Table 5. Predictive factors of mortality in patients with Cushing's disease: Cox regression analyses with corresponding 95% CIs**

| | Deaths/total n participants (%) | HR (95% CI) | *P*-value |
|---|---|---|---|
| Age at diagnosis, years | | 1.10 (1.08-1.12) | <0.001 |
| Sex | | | |
| Female | 46/281 (16) | 1 (reference) | |
| Male | 20/90 (22) | 1.4 (0.8-2.3) | 0.27 |
| Remission status at last follow-up (n = 350) | | | |
| In remission | 35/303 (12) | 1 (reference) | |
| Not in remission | 15/31 (48) | 7.1 (3.8-13.4) | <0.01 |
| Remission status unknown | 7/16 (44) | 4.3(1.8-10.1) | <0.01 |
| Treatment combinations | | | |
| Pituitary surgery only | 34/233 (15) | 1 (reference) | |
| Surgery and radiotherapy | 9/41 (22) | 1.2 (0.6-2.5) | 0.55 |
| Surgery and medical | 5/45 (11) | 0.9 (0.3-2.2) | 0.76 |
| Other combinations | 8/34 (24) | 1.6 (0.8-3.4) | 0.18 |
| No treatment reported | 10/18 (56) | 5.2 (2.1-13.0) | <0.01 |
| Model 1 (n = 371) | | | |
| Age | | 1.10 (1.08-1.12) | <0.01 |
| Female sex | | 1 (reference) | |
| Male sex | | 1.74 (0.98-3.11) | 0.06 |
| Model 2 (n = 334) | | | |
| Age | | 1.09 (1.07-1.12) | <0.01 |
| In remission | | 1 (reference) | |
| Not in remission | | 5.1 (2.6-10.1) | <0.01 |
| Model 3 (n = 334) | | | |
| Age | | 1.10 (1.07-1.12) | <0.01 |
| Female sex | | 1 (reference) | |
| Male sex | | 2.7 (1.4-5.4) | <0.01 |
| In remission | | 1 (reference) | |
| Not in remission | | 6.7 (3.2-13.8) | <0.01 |

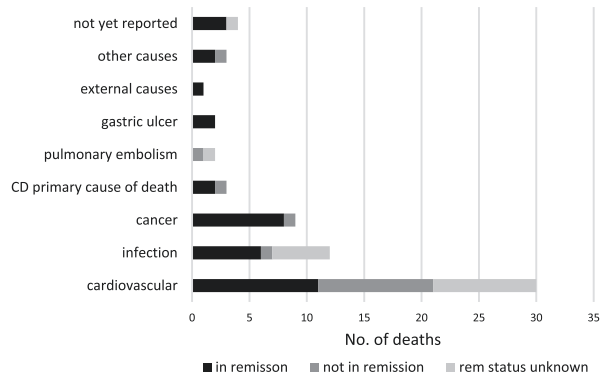


**Figure 2.** Sixty-six causes of death of 371 patients with CD. In remission n = 303, not in remission n = 31, and remission status unknown n = 37. Infection: pneumonia n = 6, *Staphylococcus* sepsis n = 1, diverticulitis and sepsis n = 1, and unspecified sepsis/infection n = 4; cardiovascular: ischemic heart disease n = 18, cerebrovascular disease n = 9, ruptured aortic aneurysm n = 2, and myocarditis n = 1; other causes: neurodegenerative disease n = 1, unspecified chock n = 1, and colon perforation n = 1; and not yet reported: cause of death not reported at time of study end.

than 40 years at diagnosis also had an elevated HR compared to controls. Men and women had a comparable increased HR in comparison to matched controls (2.2 vs 2.0).

Mortality in Swedish CD patients was investigated in 1 previous study that used ICD coding in the National Patient Registers to identify patients with CD diagnosed from years before 1987 to 2013 and found an overall SMR of 2.5 [3]. The present study investigated an unselected CD cohort, diagnosed from 1991 to 2018, in relation to a matched control group. Instead of calculating SMRs, in which standardized categories of age, sex, and calendar year are used to calculate expected deaths (deaths per person-years in the background population), we used a control group matched for age, sex, and residential area at the date of CD diagnosis. This design enabled a specific starting point of the study for both patients and controls. Another strength of the current study is that the diagnosis of CD was verified via the SPR since reliable identification of CD by using ICD coding has been questioned [2]. The SPR has a very high coverage [18] and has the advantage of including longitudinal data on remission status, treatments, tumor size, and hormone deficiencies. One previous study on mortality in patients with Cushing's syndrome of both adrenal and pituitary origin used matched controls [17]. The included CD patients (n = 211) were selected by diagnostic codes of hospital visits consistent with CD and concomitant pituitary surgery. The overall HR for CD vs controls was 2.3 (95% CI 1.7-3.0; ie, comparable to our results); the influence of remission status was not investigated in the subgroup of CD

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patients. Cox regression assumes that the hazard is equal across the whole observation time. For the patients in remission in the present study, the hazard increased after a follow-up of 5 years and then tended to decrease again after 15 to 20 years; hence, the assumption was not met. This might imply that a subgroup of "cured" patients approached a normal life expectancy, given that they survived in the first 10 to 15 years of follow-up, which would be in line with the findings by Clayton et al [16]. However, the censoring of patients with short follow-up resulted in a small number of participants at the longest follow-ups, making such conclusions uncertain. In cases such as this, where the proportional hazard assumption is not met, the HRs can be considered an average hazard during the whole study time, and survival estimates at different time points can complement the interpretation [34]. For that reason, we reported both Kaplan-Meier survival estimates with CIs and the overall HRs from Cox regression.

The limitations of the present study are mainly the lack of data on comorbidities, including hypertension and diabetes mellitus. The patients in remission (n = 303) achieved biochemical remission by different treatment modalities including medical treatment at some point (Table 1), and the data were not sufficient to identify patients with ongoing medical treatment. However, the patients in remission after a single TSS (n = 177) represent patients with normal or low cortisol levels after surgery and no previous or ongoing medical treatment. In some analyses, especially the multivariable analyses of risk factors, a small number of events might compromise the results. Nevertheless, the large and nationwide cohort of CD patients, together with the matched control group and linkage to the virtually complete Swedish Cause of Death Register, enabled robust measures of mortality. The study also provides an up-to-date evaluation of mortality, with data through 2018.

In summary, the findings of the present study confirm and complement previous findings of increased overall mortality in CD patients, who have a more than doubled HR for death compared to matched controls. Most important, an increased HR persisted among patients who had been successfully treated and reached a CD biochemical cure. Cardiovascular diseases and infections were the main causes of death, highlighting the importance of the careful follow-up of CD patients and the treatment of comorbidities.

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## Disclosures

The authors have nothing to disclose

## Data Availability

Some or all data generated or analyzed during this study are included in this published article or in the data repositories listed in the references.

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