

# High mortality within 90 days of diagnosis in patients with Cushing's syndrome: results from the ERCUSYN registry

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## Abstract

**Objective:** Patients with Cushing's syndrome (CS) have increased mortality. The aim of this study was to evaluate the causes and time of death in a large cohort of patients with CS and to establish factors associated with increased mortality.

**Methods:** In this cohort study, we analyzed 1564 patients included in the European Registry on CS (ERCUSYN); 1045 (67%) had pituitary-dependent CS, 385 (25%) adrenal-dependent CS, 89 (5%) had an ectopic source and 45 (3%) other causes. The median (IQR) overall follow-up time in ERCUSYN was 2.7 (1.2–5.5) years.

**Results:** Forty-nine patients had died at the time of the analysis; 23 (47%) with pituitary-dependent CS, 6 (12%) with adrenal-dependent CS, 18 (37%) with ectopic CS and two (4%) with CS due to other causes. Of 42 patients whose cause of death was known, 15 (36%) died due to progression of the underlying disease, 13 (31%) due to infections, 7 (17%) due to cardiovascular or cerebrovascular disease and 2 due to pulmonary embolism. The commonest cause of death in patients with pituitary-dependent CS and adrenal-dependent CS were infectious diseases ( $n = 8$ ) and progression of the underlying tumor ( $n = 10$ ) in patients with ectopic CS. Patients who had died were older and more often males, and had more frequently muscle weakness, diabetes mellitus and ectopic CS, compared to survivors. Of 49 deceased patients, 22 (45%) died within 90 days from start of treatment and 5 (10%) before any treatment was given. The commonest cause of deaths in these 27 patients were infections ( $n = 10$ ; 37%). In a regression analysis, age, ectopic CS and active disease were independently associated with overall death before and within 90 days from the start of treatment.

**Conclusion:** Mortality rate was highest in patients with ectopic CS. Infectious diseases were the commonest cause of death soon after diagnosis, emphasizing the need for careful clinical vigilance at that time, especially in patients presenting with concomitant diabetes mellitus.

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## Introduction

Patients with Cushing's syndrome (CS) have increased mortality (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14). This applies both to patients with CS of pituitary (pituitary-dependent CS) and adrenal origin (adrenal-dependent CS) (1, 2), as well as patients with ectopic CS (ectopic CS) who have the worst prognosis (1, 2, 15).

Although standardized mortality rate (SMR) is lower in patients who have been treated for CS as compared with untreated patients, an increased risk is still observed, especially in patients who are not in biochemical remission after treatment (1, 2, 5, 6, 7, 8, 10, 14).

Vascular disease is the main cause of death in CS patients (2, 4, 8, 12, 14). Indeed, the risk of cardiovascular and cerebrovascular events is greater in patients with active CS as compared with the general population and persists during long-term follow-up, even after remission has been achieved (7, 14).

Determinants of mortality have been sparsely studied in patients with CS. Older age at diagnosis (2, 3, 8, 12, 13), preoperative ACTH concentrations (11), duration of active hypercortisolism (11), number of treatments received (9), coexistence of diabetes mellitus (8, 9) and hypertension (8) have been associated with increased long-term mortality. Also, male gender, depression at diagnosis, bilateral adrenalectomy and glucocorticoid replacement predicted long-term mortality in pituitary-dependent CS patients in remission (11). Notwithstanding, rate and predictors of perioperative mortality have not been extensively studied thus far.

The aim of this study was to evaluate the cause of death in the large cohort of CS patients included in the European Registry on Cushing's Syndrome (ERCUSYN) and to establish the factors associated with mortality, both perioperatively and during long-term follow-up.

## Subjects and methods

At the time of the analysis, the ERCUSYN database included 1564 CS patients entered between January 1, 2000 and January 31, 2017, from 57 centers in 26 European countries (16). For this study, we analyzed data from 1045 (67%) patients with pituitary-dependent CS, 385 (25%) with adrenal-dependent CS, and 89 (5%) with ectopic CS. Of thirty-seven (42%) ectopic CS patients who had histology report available, 27% had bronchial carcinoid, 14% small-cell lung carcinoma, and 5% pancreatic neuroendocrine tumor. We also analyzed data from 45 (3%) patients with

other causes (CS due to other causes), most of whom with undetermined source of cortisol excess (44%). Diagnosis of adrenal carcinoma was an exclusion criterion. The median (IQR) overall follow-up time in ERCUSYN was 2.7 (1.2–5.5) years.

A detailed description of the database layout has been provided previously (17). This study interrogated data entered in the 'Death', 'Diagnosis', 'Therapy' and 'Follow-up visit' sections of the register, in order to obtain information on mortality and its potential determinants at baseline, before and within 90 days of treatment and at long-term follow-up.

The remission status was based on information included in the 'Follow-up visit' section of the database. This section contains several biochemical testing, including morning serum cortisol, 24-h urinary free cortisol and overnight 1-mg dexamethasone suppression test (DST). Centers are asked to provide information on both the value of hormone measurement and its diagnostic interpretation, that is, 'low', 'normal', 'high', according to whether the value is below, within or above the normal range of the assay used in each center. Participants are also asked to indicate if a given patient is in 'remission' or still has active hypercortisolism.

## Statistical methods

Statistical analyses were performed with IBM® SPSS® Statistics, version 25. Categorical variables are presented as number (*n*) and percentage (%). Normally distributed continuous variables are presented as mean ± s.d. and non-normally distributed as median (25–75 percentiles or range). For comparison between two groups we used unpaired *t*-test or Mann–Whitney *U* test as appropriate. For proportions, Pearson chi-square or Fishers exact test was used.

The influence of gender, age at diagnosis, remission status and duration of active hypercortisolism on mortality (total mortality as well as mortality before and within 90 days from treatment) in patients with pituitary and adrenal-dependent CS was analyzed by Cox regression with backward elimination (model 1). Since duration of symptoms before diagnosis was not normally distributed, this variable was log transformed before it was used in the regression analyses. In model 2, the influence of diabetes mellitus and muscle weakness at diagnosis on mortality was analyzed after adjustment for age at diagnosis and remission status. The results from the regression analysis are presented as hazard ratios (HR) with 95% confidence

intervals (CIs). Kaplan–Meier plot was used to illustrate survival in patients with pituitary-dependent CS, adrenal-dependent CS and ectopic CS. The mean cumulative survival rate at 1 and 5 years was based on Kaplan–Meier estimates with 95% CI.

Patients were classified as being ‘in remission’ when their cortisol values were either ‘low/undetectable’ or ‘within the normal range’, according to the criteria used in each center. Because information on early postoperative remission status was not available for all patients, the remission status at last follow-up visit was used in the regression analysis, although this may determine a potential immortality bias.

A *P* value of <0.05 was considered statistically significant.

## Results

Forty-nine ERCUSYN patients (3%) had died at the time of the analysis; 23 (47%) with pituitary-dependent CS, 6 (12%) with adrenal-dependent CS, 18 (37%) with ectopic CS and two (4%) with CS due to other causes, both with unknown source of the hypercortisolism (Table 1). Patients who died were more often males, were older, had more often ectopic CS, and had shorter duration of active CS as compared to the remaining cohort (Tables 2 and 3).

Overall, death occurred in 2.2% of pituitary-dependent CS, 1.5% of adrenal-dependent CS, 20% of ectopic CS, and 4.5% of patients with other/unknown causes of hypercortisolism. The estimated 1-year cumulative survival rate was 0.42 (95% CI 0.27–0.56) for patients with ectopic CS, 0.96 (95% CI 0.93–0.99) for patients with pituitary-dependent CS, and 0.92 (95% CI 0.87–0.99) for patients with adrenal-dependent CS. The estimated 5-year cumulative survival rate was 2.9 (95% CI 2.4–3.5) for patients with ectopic CS, 4.8 (95% CI 4.7–4.9) for patients with pituitary-dependent CS, and 4.8 (95% CI 4.7–4.9) for patients with adrenal-dependent CS (Fig. 1).

Of 42 patients whose cause of death was described, 15 (36%) died due to progression of the underlying disease, 13 (31%) due to infections, 7 (17%) due to cardiovascular or cerebrovascular disease and two due to pulmonary embolism (Table 2). Of 12 patients with known disease status, and who died from infection, 8 (67%) were in remission and were receiving glucocorticoid replacement, and 4 (33%) had active disease.

Etiology of infections was reported in 11 patients (85%). Five patients died due to pneumonia, two of which caused by *Staphylococcus aureus*, one by *Acinetobacter*

*baumannii*, and one by *Pseudomonas aeruginosa*. Two patients died of urinary tract infections, one of which caused by *Escherichia coli*, *Enterococcus faecalis* and *Proteus mirabilis*. Two patients died of sepsis, one of which caused by *Escherichia coli* and an unspecified gram negative bacterium and the other caused by unspecified gram negative bacterium. One patient died due to meningitis by an unspecified agent, and another died due to type A influenza.

Twenty of 23 (87%) patients with pituitary-dependent CS had a benign ACTH producing pituitary adenoma and three (13%) had an aggressive ACTH-producing pituitary tumor, defined as radiologically invasive, rapidly growing and therapy resistant tumour (18). The median time from diagnosis to death in patients with pituitary-dependent CS was 78 weeks (IQR 11–216; range 1–620). Fourteen of 22 (64%; information missing in one) patients with pituitary-dependent CS were in remission at the time of death. The commonest cause of death were infections (*n*=6 (43%)), cerebrovascular diseases (*n*=3 (21%)) and progression of an aggressive ACTH-producing pituitary tumor (*n*=3 (21%)) (Table 2).

Four of six (66%) patients with adrenal-dependent CS who died had a benign cortisol-producing adrenal adenoma, one (17%) had macronodular hyperplasia and one (17%) had primary pigmented nodular adrenocortical disease. The median time from diagnosis to death in patients with adrenal-dependent CS was 11 weeks (range 3–18). Three (50%) patients with adrenal-dependent CS died due to infections, two (33%) from cardiovascular disease, and one (17%) due to pulmonary embolism.

The median time from diagnosis to death in patients with ectopic CS was 4 (IQR 3–18; range 2–170) weeks and most of the patients (*n*=12; 67%) died due to progression of the underlying tumor.

## Comorbidities at diagnosis

Patients who died had a higher prevalence of diabetes mellitus (61 vs 35%; *P*<0.001) and were more likely to complain of muscle weakness (88 vs 68%; *P*=0.07), at diagnosis, as compared with those who survived (Tables 2 and 3). The prevalence of hypertension, skin manifestations and depression at diagnosis did not differ between those who died as compared with those who survived. In a regression analysis (model 1), including patients with pituitary and adrenal-dependent CS, age at diagnosis and active disease were independently associated with increased mortality (Table 4). Gender and duration of active CS were not associated with mortality.

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**Table 1** Baseline characteristics of the ERCUSYN cohort ( $n = 1564$ ).

	Deceased patients ( $n = 49$ )	Remaining cohort ( $n = 1515$ )	<i>P</i>
Gender			<b>0.001</b>
Female, $n$ (%)	29 (59)	1209 (80)	
Male, $n$ (%)	20 (41)	300 (20)	
Age at diagnosis, mean $\pm$ s.d. (years)	57 $\pm$ 14	44 $\pm$ 14	<b>&lt;0.001</b>
Years with active CS, median (IQR)	1 (0.5–2)	2 (1–4)	<b>0.001</b>
BMI, mean $\pm$ s.d. ( $\text{kg}/\text{m}^2$ )	28.3 $\pm$ 5.9	30.1 $\pm$ 6.6	<b>0.02</b>
Etiology			<b>&lt;0.001</b>
Pituitary-dependent CS	23 (47)	1022 (67)	
Adrenal-dependent CS	6 (12)	380 (25)	
Ectopic CS	18 (37)	71 (5)	
CS due to other causes	2 (4)	42 (3)	
Symptoms and signs at diagnosis*			
Hypertension, yes/no (%)	36/11 (77)	1060/338 (76)	0.9
Diabetes mellitus, yes/no (%)	27/17 (61)	466/885 (35)	<b>&lt;0.001</b>
Muscle weakness, yes/no (%)	37/5 (88)	847/388 (68)	<b>0.007</b>
Skin manifestation, yes/no (%)	36/10 (78)	1004/362 (74)	0.3
Depression, yes/no (%)	16/18 (47)	411/748 (36)	0.2
Remission at the last clinical visit**			<b>&lt;0.001</b>
Yes	26 (57)	888 (76)	
No	20 (43)	133 (11)	
Partial	–	149 (13)	
Glucocorticoid replacement at the last clinical visit***			0.3
Yes	25	778	
No	1	104	

\*Information on hypertension, diabetes mellitus, muscle weakness, skin manifestation and depression at diagnosis was missing in 120 (7.7%), 170 (10.9%), 288 (18.4%), 153 (9.8%) and 372 (23.8%) of the patients, respectively. \*\*Information on remission status at the last clinical visit was available for 46 patients who had died and 1170 patients alive. \*\*\*Patients in remission. Statistically significant ( $P < 0.05$ ) values are expressed in bold. CS, Cushing's syndrome.

After adjustment for age at diagnosis and remission status, neither diabetes mellitus nor muscle weakness was significantly associated with increased mortality (model 2; Table 4).

### 90-day mortality

Of 49 deceased patients, 22 (45%) died within 90 days from the start of treatment and 5 (10%) before any treatment was given. Of these, 7 (33%) had pituitary-dependent CS, 6 (24%) had adrenal-dependent CS, 12 (57%) had ectopic CS, and 2 (10%) had CS due to other causes. The commonest causes of deaths were infections ( $n=10$ ; 37%) and progression of the underlying tumor (7; 26%).

Sixty-two per cent of patients who died before or within 90 days from the start of treatment had diabetes mellitus at diagnosis, as compared to 38% in the whole ERCUSYN cohort ( $P=0.01$ ). The prevalence of hypertension, muscle weakness, skin manifestations and depression did not differ between the groups (data not shown). In a regression analysis, including patients with pituitary and adrenal-dependent CS, age was independently associated with death within 90 days from the start of treatment but

duration of active CS, active disease, diabetes mellitus, muscle weakness, and gender were not (Table 4).

### Discussion

We have demonstrated that mortality rate is around 2% after a median follow-up of 3 years in 1430 patients with either pituitary-dependent CS or adrenal-dependent CS who have been included in the ERCUSYN, during the period 2000–2017. Not surprisingly, a greater mortality rate was found in ectopic CS, mainly due to progression of the underlying tumor.

In 43% of patients with pituitary-dependent CS or adrenal-dependent CS, death occurred prior to treatment or within 3 months since the start of any treatment, mainly due to infections. In fact, infections were also the commonest cause of death during follow-up after treatment. In previous cohorts, most of which encompassing patients from a single center, mortality rate ranged from 3.7 to 27.5% in pituitary-dependent CS and from 3 to 10.8% in adrenal-dependent CS (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14) during a longer follow-up

**Table 2** Individual data on 49 patients in ERCUSYN who had died at the time of the analysis; 23 (45%) with pituitary-dependent CS, 6 (14%) with adrenal-dependent CS, 18 (35%) with ectopic CS and two (6%) with CS due to other causes.

Gender	Age at diagnosis	Etiology	Treatment	Cause of death	Time from first diagnosis to death (days)	Time from treatment to death (days)	Duration of symptoms (yrs)	BMI	Hypertension	Skin manifestations	Depression	Diabetes mellitus	Muscle weakness	Remission	Glucocorticoid replacement
F	21	PD-CS	MT	Cardiovascular	23	20			0	1		0		No	No
F	61	PD-CS	MT	Infection (pneumonia due to <i>Acinetobacter baumannii</i> )	34	34	3	26.0	1	0	1	1	1	Yes	Yes
F	65	PD-CS	MT	Unknown	65	38	0		1	0	0	0	0	No	No
F	45	PD-CS	TSS	Cerebrovascular	551	43	2	27.4	1	1	0	1	1	Yes	Yes
F	65	PD-CS	MT	Embolism	54	43	2	41.7	1	1	1	1	1	Yes	Yes
F	71	PD-CS	TSS	Infection (pneumonia due to unspecified agent)	130	89	1	26.5	1	1	0	1	1	Yes	Yes
F	71	PD-CS	MT	Infection (unknown agent)	220	219	2	24.6						No	No
F	48	PD-CS	TSS	Cerebrovascular	283	239	1	24.4	1	1	1	1	1	Unknown	No
M	57	PD-CS	TSS	Infection (meningitis due to unspecified agent)	396	247	2	22.5	1	1	1	0	1	Yes	Yes
F	79	PD-CS	RT+MT	Unknown	370	322	3		0	1		1	1	Yes	Yes
F	66	PD-CS	RT+MT	Unknown	827	515	1	37.5	1	1	0	1	1	No	No
F	72	PD-CS	MT	Infection (pneumonia due to <i>Staphylococcus aureus</i> followed by sepsis due to <i>Staphylococcus epidermidis</i> )	588	574	1	26.7	1	1			1	Yes	Yes
M	66	PD-CS	TSS+RT	Prostate cancer	808	679	1	26.1	1	1	1	0	1	No	No
F	56	PD-CS	RT+MT	Cerebrovascular	1179	1161	2	41.3	1	1	0	1	1	Yes	Yes
F	70	PD-CS	TSS	Sudden death	1377	1228	2		0			0	1	Yes	Yes
F	38	PD-CS	TSS	Neurodegenerative disease	1562	1462	3	21.9	0	0	1	0		Yes	Yes
F	72	PD-CS	TSS	Unknown	1832	1782	1	27.6	1	1		1		Yes	Yes
M	71	PD-CS	TSS+RT	Unknown	2175	2174	0	29.1	1	1		0		Yes	Yes
F	59	PD-CS	TSS	Colon cancer	4336	4129	0.5		1	1	1	1	1	Yes	Yes
F	57	PD-CS	No Tx	Infection (type A influenza)	7				1	1	1	1	1	No Tx	No
M	57	PD-CS, Aggressive	TSS	Tumor progression	728	672	6	23.5	0	0	1	1	1	No	No
M	43	PD-CS, Aggressive	TSS+RT	Tumor progression	1780	1668	3	28.9	1	1	0	0	1	No	No
M	64	PD-CS, Aggressive	TSS+RT	Tumor progression	2613	2608	2	27.8						Yes	Yes
F	29	AD-CS	UnilADX	Embolism	67	12	0.5	29.4	1	1		0	0	Yes	Yes
F	64	AD-CS	UnilADX	Cardiovascular	124	26			1	1	0	1	1	Yes	Yes
F	55	AD-CS	UnilADX	Infection (UTI due to <i>Escherichia coli</i> , <i>Enterococcus faecalis</i> and <i>Proteus mirabilis</i> )	78	56	0.5	27.9	1	1	1	0	1	Yes	Yes
M	65	AD-CS	MT	Cardiovascular	77	77	0.5	30.7	0	0	0	0	1	Unknown	Unknown
F	70	AD-CS (Macro)	BiADX	Infection (sepsis due to unspecified gram negative bacterium)	123	38	10	31.2	1	1	1	0	0	Yes	Yes
F	71	AD-CS (PPNAD)	No Tx	Infection (UTI due to unspecified agent)	20		5	1	1	1				No Tx	No

(Continued)



Table 2 Continued.

Gender	Age at diagnosis	Etiology	Treatment	Cause of death	Time from first diagnosis to death (days)	Time from first treatment to death (days)	Duration of symptoms (yrs)	BMI	Hypertension	Skin manifestations	Depression	Diabetes mellitus	Muscle weakness	Remission	Glucocorticoid replacement
F	61	E-CS	No Tx	Infection (pneumonia due to <i>Pseudomonas aeruginosa</i> )	13		0,1	25,2	0	1	0	1	1	No	No
M	60	E-CS	MT	Tumor progression	28	7	0,3	25,5	1	1	1	1	1	No	No
M	55	E-CS	MT	Tumor progression	44	12		21,4	0	1	0	0	1	No	Yes
M	47	E-CS	MT	Tumor progression	17	17	12		0	0			1	No	No
M	92	E-CS	MT	Tumor progression	27	20	0,2	23,0	1	1	1	1	1	No	No
F	33	E-CS	Primary tumor	Infection (sepsis due to <i>Escherichia coli</i> and unspecified gram negative bacterium)	34	21	0,5	21,4	1	1	0	1	1	Yes	Yes
M	62	E-CS	BiADX	Unknown	310	22	2	23,6	1	1	1	1	1	Yes	Yes
M	51	E-CS	MT	Tumor progression	70	25	4	35,9	1	0	1	1	1	No	No
M	46	E-CS	MT	Tumor progression	29	29	0,3	44,8	1	1	0	1	0	No	No
F	47	E-CS	BiADX	Infection (aspiration pneumonia due to <i>Staphylococcus aureus</i> followed by sepsis due to <i>Enterobacter cloacae</i> )	433	34		27,4	1	1	1	1	1	Yes	Yes
M	57	E-CS	BiADX	Tumor progression	59	51	1	24,6	1	1	0	0	1	Yes	Yes
M	46	E-CS	MT	Tumor progression	120	119	0	25,7	1	1	0	1	1	Yes	Yes
M	50	E-CS	MT	Tumor progression	144	129		26,6	1	0	0	1	1	No	No
F	67	E-CS	BiADX	Tumor progression	205	191	1	24,8	1	1		1	1	Yes	Yes
F	51	E-CS	BiADX	Tumor progression	773	731	0	23,6	0	1	0	0	1	Yes	Yes
M	41	E-CS	BiADX	Tumor progression	1191	1070	1	24,3	0	1	0	0	1	Yes	Yes
M	48	E-CS	Primary tumor	Renal failure	1104	1083	1,5	33,8	1	1	1	1	1	Yes	No
M	53	E-CS	No Tx	Cardiovascular	20		0,5	32,1	1	1	1	1	1	No Tx	No
F	63	Unknown	UnilADX	Infection	16	5	0	37,9	1	0		1	1	Unknown	No
F	21	Unknown	No Tx	Unknown	132		1		1	0	0	0	0	No Tx	Yes

Known causes of infection are shown in bold.

AD-CS, adrenal-dependent CS; BiADX, bilateral adrenalectomy; BMI, body mass index (kg/m<sup>2</sup>); CS, Cushing's syndrome; E-CS, ectopic CS; MT, medical therapy; PD-CS, pituitary-dependent CS; RT, radiotherapy; TSS, trans-sphenoidal surgery; Tx, therapy; UnilADX, unilateral adrenalectomy; UTI, urinary tract infections.

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**Table 3** Baseline characteristics of patients who died, classified by etiology (patients with OTH-CS are excluded from the table).

	<b>PIT-CS (n = 23)</b>	<b>ADR-CD (n = 6)</b>	<b>ECT-CS (n = 18)</b>	<b>P*</b>
Gender				<b>0.001</b>
Female, n (%)	17 (74)	5 (83)	5 (28)	
Male, n (%)	6 (26)	1 (17)	13 (72)	
Age at diagnosis, mean $\pm$ s.d. (years)	60 $\pm$ 13	59 $\pm$ 16	54 $\pm$ 13	0.15
Years with active CS, median (IQR)	2 (1–2.8)	0.5 (0.4–6.3)	0.5 (0.2–1.5)	0.08
BMI, mean $\pm$ s.d. (kg/m <sup>2</sup> )	28.4 $\pm$ 6.0	29.8 $\pm$ 1.5	27.3 $\pm$ 6.1	0.45
Symptoms and signs at diagnosis				
Hypertension, yes/no (%)	16/5 (76)	5/1 (83)	13/5 (72)	0.67
Diabetes mellitus, yes/no (%)	12/8 (60)	1/4 (20)	13/4 (77)	0.11
Muscle weakness, yes/no (%)	16/1 (94)	3/2 (60)	17/1 (94)	0.40
Skin manifestation, yes/no (%)	16/4 (80)	5/1 (83)	15/3 (83)	0.83
Depression, yes/no (%)	7/6 (54)	2/2 (50)	7/9 (44)	0.60
Remission at the last clinical visit				0.26
Yes	14 (64)	4 (80)	9 (50)	
No	8 (36)	1 (20)	9 (50)	

P\*, PIT-CS and ADR-CS vs ectopic CS. Statistically significant ( $P < 0.05$ ) values are expressed in bold.

ADR-CS, adrenal-dependent CS; ECT-CS, CS from an ectopic source; OTH-CS, CS from other etiologies; PIT-CS, pituitary-dependent CS.

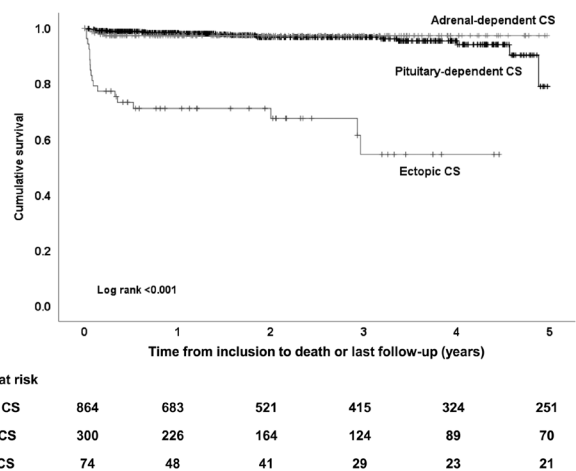
period (ranging from 7 to 15 years) as compared with that described in the present study.

Perioperative mortality has previously been reported in few studies (2, 5). Hammer *et al.* found that 4 of 29 deaths occurred within 2.5 months of transsphenoidal surgery (TSS) due to myocardial infarction and/or cardiac failure (5). Bolland *et al.* reported one death in the immediate postoperative period due to ischemic heart disease, and two before starting any treatment, due to infection and pulmonary embolism, respectively (2).

While bacterial infections were the most prevalent cause of death in CS in historical reports (19), deaths due to vascular diseases are more common in recent studies (2, 8, 9, 12).

Although mortality rate for cardiovascular disease is expected to increase in our cohort as follow-up duration is extended, our data show that infections are still a life-threatening comorbidity in these vulnerable patients and suggest that effective preventive measures should be initiated at the time of diagnosis. It is well known that hypercortisolism is related to immunosuppression and cellular immunodeficiency (20), which increases the hosts' susceptibility to common viruses, bacteria, fungal infections and opportunistic pathogens (21). Data obtained from the Danish National Registry of Patients indicated that risk for infections in CS patients is higher during the year preceding surgery as compared with the general population, and persists elevated for at least 3 months postoperatively (7). As a matter of fact, the Endocrine Society Clinical Practice Guideline on Treatment in CS recommended, as an 'ungraded best practice statement', which clinicians offer age-appropriate immunization

to patients with confirmed CS, and start prophylactic treatment for atypical infections in patients with severe CS (22). According to the World Health Organization (WHO), the burden of health care-associated infections is relevant even in high-income countries, where up to 12% of patients acquire at least one infectious disease during their hospital stay (23). This number may be even higher in patients with CS who are hospitalized and/or undergo invasive diagnostic procedures. While future studies should assess the prevalence of infections during both the pre- and postoperative setting in CS patients, and identify the most effective treatment to prevent and control



**Figure 1**

Kaplan-Meier plot showing 5-year cumulative survival in patients with pituitary-dependent CS, adrenal-dependent CS and ectopic CS. + denotes censored patients.

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**Table 4** Cox regression models analyzing the influence of age at diagnosis, gender, remission status and duration of active hypercortisolism on mortality (total and mortality within 90 days from diagnosis) in patients with pituitary-dependent CS and adrenal-dependent CS (model 1) and the influence of diabetes mellitus and muscle weakness at diagnosis on mortality, after adjustment for age at diagnosis and remission status (model 2). Duration of symptoms before diagnosis was log transformed before it was used in the regression analyses.

	Hazard ratio	95% CI	P
Total mortality (model 1)			
Age at diagnosis (years)	1.12	1.08–1.17	<b>&lt;0.001</b>
Male gender	1.2	0.5–3.5	0.6
Active disease (not in remission)	2.8	1.1–7.1	<b>0.03</b>
Duration of active CS (log)	0.7	0.6–1.4	0.7
Total mortality (model 2)			
Age at diagnosis (years)	1.10	1.06–1.15	<b>&lt;0.001</b>
Active disease (not in remission)	3.4	1.3–8.7	<b>0.01</b>
Diabetes mellitus	2.0	0.8–5.3	0.14
Muscle weakness	1.7	0.5–5.9	0.4
Mortality within 90 days (model 1)			
Age at diagnosis (years)	1.12	1.05–1.19	<b>0.001</b>
Male gender	–	–	1.0
Active disease (not in remission)	0.9	0.1–8.2	1.0
Duration of active CS (log)	1.0	0.5–2.1	1.0
Mortality within 90 days (model 2)			
Age at diagnosis (years)	1.10	1.04–1.17	<b>0.002</b>
Active disease (Not in remission)	1.7	0.3–8.6	0.5
Diabetes mellitus	1.6	0.4–6.4	0.5
Muscle weakness	0.7	0.2–2.9	0.6

Statistically significant ( $P < 0.05$ ) values are expressed in bold.

infectious disease in them, clinicians should be aware of this frequent and potentially lethal complication, and start, at the time of diagnosis, a standardized protocol of prevention, including *Pneumocystis carinii* prophylaxis, and age-appropriate immunization, especially against influenza, *Herpes zoster*, and pneumococcus (22, 24). Because active disease is an important determinant of mortality, rapid control of cortisol excess should also be achieved as soon as possible after diagnosis (8). Moreover, Sarlis *et al.* demonstrated that risk of bacterial or opportunistic infections progressively increased with more severe hypercortisolism (24). However, we could not evaluate the severity of the hypercortisolism in the ERCUSYN patients since information on the upper limit of normal range of the assays used at each center is lacking.

It has been suggested that inadequate glucocorticoid substitution may be associated with increased risk of death for infections (14), especially in remitted CS patients. We cannot exclude that Addisonian crisis, due to insufficient administration of stress-dose steroids, may also explain some of the deaths reported, especially in those patients who died from unknown reasons.

Interestingly, all patients in our cohort who died due to infection had either glucocorticoid replacement

or persistent hypercortisolism. However, glucocorticoid replacement was not more frequent in the patients who died as compared with those who survived.

Older age at diagnosis, active disease and ectopic CS independently predicted both perioperative and long-term mortality, in line with previous studies (2, 8, 9, 11, 12, 13). Although the presence of diabetes mellitus or muscle weakness at diagnosis was not a significant determinant of mortality after adjusting for age, ectopic origin and active disease, these comorbidities were more frequently reported in the patients who died. Previous studies demonstrated that coexistence of diabetes mellitus was associated with mortality in CS patients (2, 3, 8, 9). It is well known that a close link exists between diabetes and both cardiovascular disease and infections (24, 25). Nevertheless, our data showed that 58% of patients who died from infections had diabetes, especially during the perioperative period, consistent with the deleterious effect of hyperglycemia on both cell- and antibody-mediated response (25). In a recent retrospective cohort study using a large primary care database in England, the infection rate was almost twice as high among patients with type 2 diabetes compared to matched, non-diabetic population (25). Indeed, diabetes may be associated with 12% of lethal nosocomial infections, and a linear association



between the degree of postoperative hyperglycaemia and risk of surgical site infections, mainly after discharge, has also been described (25, 26). Thus, a strict control of hyperglycemia is highly recommendable in CS patients in order to reduce potentially lethal infections after surgery.

The impact of myopathy on the morbimortality in patients with CS is still to be elucidated. Skeletal muscle mass loss due to atrophy of type IIa, fast fibers, slowing muscle fiber conduction and deterioration of muscle quality have been proposed as potential mechanisms leading to myopathy in patients exposed to either exogenous or endogenous glucocorticoid excess (27, 28). Data from the ERCUSYN have previously showed that about 70% of patients with active CS complained of muscle weakness (17). Sipple *et al.* reported that resolution of weakness may occur later than many other symptoms associated with hypercortisolism, given that it may persist up to 18 months after uni- or bilateral adrenalectomy for CS (29). Berr *et al.* described greater impairment of hand-grip strength in active CS as compared with controls, which persisted or even worsened after remission (30). Coexistence of pituitary deficiencies, occurrence of glucocorticoid withdrawal syndrome, need for postoperative glucocorticoid replacement, severity and duration of hypercortisolism all may contribute to the development and maintenance of muscle weakness (31).

Low hand muscle strength has been described to predict all-cause death and cardiovascular death in a large, longitudinal population study enrolling subjects aged 35–70 years (32). Moreover, sarcopenia, defined as low muscle mass and strength, and impaired physical performance, affects mortality in several human models, including elderly people, severely ill patients, and patients who underwent general surgery or liver transplantation (33, 34, 35, 36). Future studies using objective measures of muscle function should clarify if muscle weakness at diagnosis is a clinical marker of elevated mortality risk in CS patients. Furthermore, whether muscle weakness determines mortality in CS patients or simply reflects the presence of other factors which have been associated with increased mortality such as the severity of hypercortisolism, glucocorticoid replacement and hypopituitarism, needs also to be elucidated in futures studies (31).

The main strength of this study is reporting data on perioperative mortality, a subject previously sparsely studied, and the real-life setting by using the ERCUSYN database. The study has, however, also limitations such as paucity of information on pituitary hormone function and replacement, and the relatively short median follow-up time despite some centers entered patients who

had been diagnosed almost 20 years previously. While this limitation is due to missing data on subsequent visits, inclusion and follow-up of patients with CS from countries all around Europe in the ERCUSYN is ongoing and further analysis on mortality and its relative determinants over a longer period of observation is pending. Underreporting of some deaths is also a limitation of this study, as it is not based on an exhaustive mortality registry and therefore, some ERCUSYN participants may not be aware of whether fatal outcome occurred in some of their patients. Another limitation is the lack of both quantitative data and standardized methods to evaluate both preoperative magnitude of hypercortisolism and postsurgical biochemical status. This is due to both intra- and inter-center differences in the assays used and lack of information on the normal range for each of them. Finally, information on early postoperative remission status was not available for all patients. Therefore, the remission status at the last follow-up visit was used in the regression analysis, making it possible that immortal time bias may influence the results without affecting their clinical relevance.

In conclusion, mortality was highest in patients with ectopic CS. Infectious diseases were the commonest cause of death soon after diagnosis and initiation of treatment, emphasizing the need for careful clinical vigilance at that time especially in patients with diabetes mellitus who seem to be especially vulnerable.

#### Declaration of interest

A T received financial support, research grants, and consultant fees from Novartis and HRA pharma. T B has received institutional research support from Pfizer and consultancy/lectureship fees from Novartis, Ipsen, Strongbridge and Pfizer. M R received financial support, research grants, consultant or speaker fees from Ipsen, Novartis, Pfizer. M T has received consultant and speaker fees from Novartis, Ipsen and Pfizer. S M W received financial support, research grants, consultant or speaker fees from Ipsen, Novartis, Pfizer, HRA and Strongbridge. D M received consultant and speaker fees from HRA Pharma, Ipsen, Novartis, Novo-Nordisk and Pfizer. C J S has received lecture fees, consultancy remuneration or research support from HRA Pharma, Novartis and Strongbridge. The other authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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## References

- 1 Lindholm J, Juul S, Jorgensen JO, Astrup J, Bjerre P, Feldt-Rasmussen U, Hagen C, Jorgensen J, Kosteljanetz M, Kristensen L *et al.* Incidence and late prognosis of Cushing's syndrome: a population-based study. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 117–123. (<https://doi.org/10.1210/jcem.86.1.7093>)
- 2 Bolland MJ, Holdaway IM, Berkeley JE, Lim S, Dransfield WJ, Conaglen JV, Croxson MS, Gamble GD, Hunt PJ & Toomath RJ. Mortality and morbidity in Cushing's syndrome in New Zealand. *Clinical Endocrinology* 2011 **75** 436–442. (<https://doi.org/10.1111/j.1365-2265.2011.04124.x>)
- 3 Etxabe J & Vazquez JA. Morbidity and mortality in Cushing's disease: an epidemiological approach. *Clinical Endocrinology* 1994 **40** 479–484. (<https://doi.org/10.1111/j.1365-2265.1994.tb02486.x>)
- 4 Swearingen B, Biller BM, Barker FG, 2nd, Katznelson L, Grinspoon S, Klibanski A & Zervas NT. Long-term mortality after transsphenoidal surgery for Cushing disease. *Annals of Internal Medicine* 1999 **130** 821–824. (<https://doi.org/10.7326/0003-4819-130-10-199905180-00015>)
- 5 Hammer GD, Tyrrell JB, Lamborn KR, Applebury CB, Hannegan ET, Bell S, Rahl R, Lu A & Wilson CB. Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 6348–6357. (<https://doi.org/10.1210/jc.2003-032180>)
- 6 Dekkers OM, Biermasz NR, Pereira AM, Roelfsema F, van Aken MO, Voormolen JHC & Romijn JA. Mortality in patients treated for Cushing's disease is increased, compared with patients treated

- for nonfunctioning pituitary macroadenoma. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 976–981. (<https://doi.org/10.1210/jc.2006-2112>)
- 7 Dekkers OM, Horvath-Puho E, Jorgensen JOL, Cannegieter SC, Ehrenstein V, Vandenbroucke JP, Pereira AM & Sorensen HT. Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 2277–2284. (<https://doi.org/10.1210/jc.2012-3582>)
  - 8 Clayton RN, Raskauskiene D, Reulen RC & Jones PW. Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 632–642. (<https://doi.org/10.1210/jc.2010-1942>)
  - 9 Clayton RN, Jones PW, Reulen RC, Stewart PM, Hassan-Smith ZK, Ntali G, Karavitaki N, Dekkers OM, Pereira AM, Bolland M *et al.* Mortality in patients with Cushing's disease more than 10 years after remission: a multicentre, multinational, retrospective cohort study. *Lancet Diabetes and Endocrinology* 2016 **4** 569–576. ([https://doi.org/10.1016/S2213-8587\(16\)30005-5](https://doi.org/10.1016/S2213-8587(16)30005-5))
  - 10 Hassan-Smith ZK, Sherlock M, Reulen RC, Arlt W, Ayuk J, Toogood AA, Cooper MS, Johnson AP & Stewart PM. Outcome of Cushing's disease following transsphenoidal surgery in a single center over 20 years. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 1194–1201. (<https://doi.org/10.1210/jc.2011-2957>)
  - 11 Lambert JK, Goldberg L, Fayngold S, Kostadinov J, Post KD & Geer EB. Predictors of mortality and long-term outcomes in treated Cushing's disease: a study of 346 patients. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 1022–1030. (<https://doi.org/10.1210/jc.2012-2893>)
  - 12 Yaneva M, Kalinov K & Zacharieva S. Mortality in Cushing's syndrome: data from 386 patients from a single tertiary referral center. *European Journal of Endocrinology* 2013 **169** 621–627. (<https://doi.org/10.1530/EJE-13-0320>)
  - 13 Ntali G, Asimakopoulou A, Siamatras T, Komninos J, Vassiliadi D, Tzanela M, Tsarakakis S, Grossman AB, Wass JAH & Karavitaki N. Mortality in Cushing's syndrome: systematic analysis of a large series with prolonged follow-up. *European Journal of Endocrinology* 2013 **169** 715–723. (<https://doi.org/10.1530/EJE-13-0569>)
  - 14 Ragnarsson O, Olsson DS, Papakokkinou E, Chantzichristos D, Dahlqvist P, Segerstedt E, Olsson T, Petersson M, Berinder K, Bensing S *et al.* Overall and disease-specific mortality in patients with Cushing's disease: a Swedish nationwide study. *Journal of Clinical Endocrinology and Metabolism* 2019 **104** 2375–2384. (<https://doi.org/10.1210/jc.2018-02524>)
  - 15 Ilias I, Torpy DJ, Pacak K, Mullen N, Wesley RA & Nieman LK. Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 4955–4962. (<https://doi.org/10.1210/jc.2004-2527>)
  - 16 Valassi E, Feelders R, Maiter D, Chanson P, Yaneva M, Reincke M, Krsek M, Toth M, Webb SM, Santos A *et al.* Worse Health-Related Quality of Life at long-term follow-up in patients with Cushing's disease than patients with cortisol producing adenoma. Data from the ERCUSYN. *Clinical Endocrinology* 2018 **88** 787–798. (<https://doi.org/10.1111/cen.13600>)
  - 17 Valassi E, Santos A, Yaneva M, Toth M, Strasburger CJ, Chanson P, Wass JAH, Chabre O, Pfeifer M, Feelders RA *et al.* The European Registry on Cushing's syndrome: 2-year experience. Baseline demographic and clinical characteristics. *European Journal of Endocrinology* 2011 **165** 383–392. (<https://doi.org/10.1530/EJE-11-0272>)
  - 18 Raverot G, Burman P, McCormack A, Heaney A, Petersenn S, Popovic V, Trouillas J, Dekkers OM & European Society of Endocrinology. Clinical Practice Guidelines for the management of aggressive pituitary tumours and carcinomas. *European Journal of Endocrinology* 2018 **178** G1–G24. (<https://doi.org/10.1530/EJE-17-0796>)
  - 19 Plotz CM, Knowlton AI & Ragan C. The natural history of Cushing's syndrome. *American Journal of Medicine* 1952 **13** 597–614. ([https://doi.org/10.1016/0002-9343\(52\)90027-2](https://doi.org/10.1016/0002-9343(52)90027-2))
  - 20 Dirks-Naylor AJ & Griffiths CL. Glucocorticoid-induced apoptosis and cellular mechanisms of myopathy. *Journal of Steroid Biochemistry and Molecular Biology* 2009 **117** 1–7. (<https://doi.org/10.1016/j.jsbmb.2009.05.014>)
  - 21 Aucott JN. Glucocorticoids and infection. *Endocrinology and Metabolism Clinics of North America* 1994 **23** 655–670. ([https://doi.org/10.1016/S0889-8529\(18\)30091-4](https://doi.org/10.1016/S0889-8529(18)30091-4))
  - 22 Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A & Endocrine S. Treatment of Cushing's syndrome: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 2807–2831. (<https://doi.org/10.1210/jc.2015-1818>)
  - 23 Allegranzi B, Bagheri Nejad SB, Combescurie C, Graafmans W, Attar H, Donaldson L & Pittet D. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet* 2011 **377** 228–241. ([https://doi.org/10.1016/S0140-6736\(10\)61458-4](https://doi.org/10.1016/S0140-6736(10)61458-4))
  - 24 American Diabetes Association. Cardiovascular disease and risk management: standards of medical care in diabetes-2019. *Diabetes Care* 2019 **42** S103–S123. (<https://doi.org/10.2337/dc19-S010>)
  - 25 Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ & Cook DG. Glycemic control and risk of infections among people with Type 1 or Type 2 diabetes in a large primary care cohort study. *Diabetes Care* 2018 **41** 2127–2135. (<https://doi.org/10.2337/dc18-0287>)
  - 26 Latham R, Lancaster AD, Covington JE, Pirolo JS & Thomas CS, Jr. The association of diabetes and glucose control with surgical-site infections among cardiothoracic surgery patients. *Infection Control and Hospital Epidemiology* 2001 **22** 607–612. (<https://doi.org/10.1086/501830>)
  - 27 Minetto MA, Lanfranco F, Botter A, Motta G, Mengozzi G, Giordano R, Picu A, Ghigo E & Arvat E. Do muscle fiber conduction slowing and decreased levels of circulating muscle proteins represent sensitive markers of steroid myopathy? A pilot study in Cushing's disease. *European Journal of Endocrinology* 2011 **164** 985–993. (<https://doi.org/10.1530/EJE-10-1169>)
  - 28 Stangl MK, Bocker W, Chubakov V, Ferrari U, Fischeder M, Gudermann T, Hesse E, Meinke P, Reincke M, Reisch N *et al.* Sarcopenia – endocrinological and neurological aspects. *Experimental and Clinical Endocrinology and Diabetes* 2019 **6** 8–22. (<https://doi.org/10.1055/a-0672-1007>)
  - 29 Sippel RS, Elaraj DM, Kebebew E, Lindsay S, Tyrrell JB & Duh QY. Waiting for change: symptom resolution after adrenalectomy for Cushing's syndrome. *Surgery* 2008 **144** 1054–1061. (<https://doi.org/10.1016/j.surg.2008.08.024>)
  - 30 Berr CM, Stieg MR, Deutschbein T, Quinkler M, Schmidmaier R, Osswald A, Reisch N, Ritzel K, Dimopoulou C, Fazel J *et al.* Persistence of myopathy in Cushing's syndrome: evaluation of the German Cushing's Registry. *European Journal of Endocrinology* 2017 **176** 737–746. (<https://doi.org/10.1530/EJE-16-0689>)
  - 31 Ragnarsson O & Johannsson G. Cushing's syndrome: a structured short- and long-term management plan for patients in remission. *European Journal of Endocrinology* 2013 **169** R139–R152. (<https://doi.org/10.1530/EJE-13-0534>)
  - 32 Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum A, Jr, Orlandini A, Seron P, Ahmed SH, Rosengren A, Kelishadi R *et al.* Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet* 2015 **386** 266–273. ([https://doi.org/10.1016/S0140-6736\(14\)62000-6](https://doi.org/10.1016/S0140-6736(14)62000-6))
  - 33 Moisey LL, Mourtzakis M, Cotton BA, Premji T, Heyland DK, Wade CE, Bulger E & Kozar RA. Skeletal muscle predicts ventilator-

- free days, ICU-free days, and mortality in elderly ICU patients. *Critical Care* 2013 **17** R206. (<https://doi.org/10.1186/cc12901>)
- 34 Arango-Lopera VE, Arroyo P, Gutierrez-Robledo LM, Perez-Zepeda MU & Cesari M. Mortality as an adverse outcome of sarcopenia. *Journal of Nutrition, Health and Aging* 2013 **17** 259–262. (<https://doi.org/10.1007/s12603-012-0434-0>)
- 35 Englesbe MJ, Lee JS, He K, Fan L, Schaubel DE, Sheetz KH, Harbaugh CM, Holcombe SA, Campbell DA, Jr, Sonnenday CJ *et al.* Analytic morphomics, core muscle size, and surgical outcomes. *Annals of Surgery* 2012 **256** 255–261. (<https://doi.org/10.1097/SLA.0b013e31826028b1>)
- 36 Englesbe MJ, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C, Holcombe SA, Wang SC, Segev DL & Sonnenday CJ. Sarcopenia and mortality after liver transplantation. *Journal of the American College of Surgeons* 2010 **211** 271–278. (<https://doi.org/10.1016/j.jamcollsurg.2010.03.039>)

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