CUSHING'S SYNDROME IN THE ELDERLY: DATA FROM THE EUROPEAN 1 **REGISTRY ON CUSHING'S SYNDROME** 2

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2 **Running head**: Aging in Cushing's syndrome

3

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6 **ABSTRACT**

Objective: To evaluate whether age-related differences exist in clinical characteristics,
diagnostic approach and management strategies in patients with Cushing's syndrome
included in the European Registry on Cushing's Syndrome (ERCUSYN).

10 **Design**: Cohort study.

Methods: We analyzed 1791 patients with CS, of whom 1234 (69%) had pituitary-dependent
CS (PIT-CS), 450 (25%) adrenal-dependent CS (ADR-CS) and 107 (6%) had an ectopic
source (ECT-CS). According to the WHO criteria, 1616 patients (90.2%) were classified as
younger (<65 years) and 175 (9.8%) as older (≥65 years).

15 **Results**:

Older patients were more frequently males and had a lower BMI and waist circumference as compared with the younger. Older patients also had a lower prevalence of skin alterations, depression, hair loss, hirsutism and reduced libido, but a higher prevalence of muscle weakness, diabetes, hypertension, cardiovascular disease, venous thromboembolism and bone fractures than younger patients, regardless of sex (p<0.01 for all comparisons). Measurement of UFC supported the diagnosis of CS less frequently in older patients as

compared with (p<0.05). 1 the younger An extra-sellar macroadenoma 2 (macrocorticotropinoma with extrasellar extension) was more common in older PIT-CS patients than in the younger (p<0.01). Older PIT-CS patients more frequently received 3 cortisol-lowering medications and radiotherapy as a first-line treatment, whereas surgery was 4 the preferred approach in the younger (p < 0.01 for all comparisons). When transsphenoidal 5 surgery was performed, the remission rate was lower in the elderly as compared with their 6 7 younger counterpart (p<0.05).

8 Conclusions:

9 Older CS patients lack several typical symptoms of hypercortisolism, present with more10 comorbidities regardless of sex, and are more often conservatively treated.

11

12 SIGNIFICANCE STATEMENT

Clinical presentation of Cushing's syndrome (CS) was different in older patients as compared 13 with that in the younger, with the former lacking some of the typical features of cortisol 14 excess while presenting with a greater burden of comorbidities and an elevated prevalence 15 of muscle weakness. Levels of urinary free cortisol were often within the normal range in the 16 elderly, and a conservative treatment was frequently chosen in them. Our data emphasize the 17 need of maintaining a high clinical suspicion of hypercortisolism in the general population, 18 19 while taking into account specific age-related differences in the presentation of symptoms. 20 Our data may contribute to reduce the delay to diagnosis in CS, which has been associated 21 with increased morbidity and mortality.

22

1 INTRODUCTION

Cushing's syndrome (CS) is usually caused by excessive ACTH release from a pituitary 2 corticotrope adenoma (Cushing's disease, CD) and, less frequently, by ectopic ACTH or 3 (very rarely) CRH production. CS can also be ACTH-independent when caused by cortisol-4 secreting adrenocortical tumors or hyperplasia (1). CS is most frequently diagnosed in 5 women (female to male ratio, 3-5:1) aged 40-50 years and is associated with a constellation 6 of symptoms and signs, including, among others, weight gain, centripetal fat deposition, 7 purple striae, skin thinning, muscle wasting and fatigue. Hypercortisolism is also related to 8 several comorbidities, such as type 2 diabetes mellitus, arterial hypertension, cardiovascular 9 disease, venous thromboembolism, mood disorders and osteoporosis which result in poor 10 quality of life (QoL) and elevated mortality (2, 3, 4). 11

Life expectancy has increased during the last decades and the general population is progressively growing older, especially in Western countries (5). Consequently, the number of elderly people with endocrine diseases rising and mean age of patients regularly followed in referral centers for low-prevalence diseases, such as CS, is older than in the past.

16 Advanced age at diagnosis of CS is associated with an elevated mortality, both 17 perioperatively and following long-term after remission (6, 7). Moreover, data from the 18 European registry on Cushing's Syndrome (ERCUSYN) showed that older age at diagnosis 19 predicted worse self-reported QoL more than one year after treatment (8).

20 Data on clinical presentation and management of CS in older patients are scarce. Some 21 authors have reported individual cases of older patients with CS (9, 10, 11, 12) but have not 22 focused on specific age-related differences in clinical presentation. Minniti et al. suggested 23 that the clinical picture of CD in older patients may be milder than in younger patients (13). Conversely, in a recent study, Qiao et al. showed that 45 CD patients older than 60 more
 commonly presented with a catabolic phenotype and cardiometabolic comorbidities as
 compared with younger patients (14).

Our study aimed to describe the age-related differences in clinical characteristics, diagnostic
approach, management strategies, treatment outcome and mortality in patients with CS
included in the European Registry on Cushing's Syndrome (ERCUSYN) the largest database
existing to date on this condition.

8

9 METHODS

10 Description of the database

ERCUSYN is a web-based, multicenter, observational study that enrolled 1972 patients from 11 57 centers in 26 European countries at the time of the study (between January 1st, 2000 and 12 January 31st, 2021). Patients were classified into four major etiologic groups: pituitary-13 dependent CS (PIT-CS), adrenal-dependent CS (ADR-CS; adrenal adenoma), CS from 14 ectopic source (ECT-CS) and CS from other etiologies (OTH-CS), mainly including cyclic 15 hypercortisolism. Etiologic classification was based on histologic documentation of ACTH-16 secreting or adrenal tumors. In case histological reports were not available, expert centers 17 involved confirmed diagnosis in their local multidisciplinary team meetings, based on 18 biochemical and clinical resolution of hypercortisolism after surgical resection, or, in patients 19 20 who were not operated on, based on biochemical test results and/or imaging.

A detailed description of the database layout has been provided elsewhere (7). Briefly, the "diagnosis" section contains information at diagnosis: baseline demographics and anthropometric characteristics, etiology of CS and diagnosis date, delay between onset of

symptoms and final diagnosis of CS, clinical features, concomitant pituitary hormone 1 2 deficiencies, menopausal status, comorbidities, such as cardiovascular disease (defined as a history of coronary heart disease or cerebrovascular accidents) and quality of life (QoL), the 3 latter being assessed using both the generic EuroOoL and the disease-generated CushingOoL 4 questionnaires. In this study, only EuroQoL measures will be shown, due to the low number 5 of CushingQoL questionnaires administered to older people across Europe. The "imaging" 6 subsection contains information on pituitary MRI ("microadenoma", "extrasellar 7 macroadenoma", "intrasellar macroadenoma", and "no visible adenoma"). The "treatment" 8 section contains information on surgery (type, date, number), RT (type, date), and medical 9 treatment (date, dose, duration, number). The "follow-up" section resembles the layout of the 10 "Diagnosis" section and contains information on clinical and hormonal status, including 11 concomitant pituitary hormone deficiencies and menopausal status on each follow-up visit. 12 The "death" section comprises information on the age of the deceased patients and the cause 13 of death. Diagnosis of autonomous cortisol secretion and adrenal carcinoma were exclusion 14 criteria of the ERCUSYN database. 15

Patients were grouped depending on their age at the time of diagnosis. Patients aged ≥ 65 were considered "elderly" and were compared with "younger" patients, aged <65 years. This classification was in accordance with the WHO definition (15). Data on MRI findings and remission rate in PIT-CS patients were also stratified, in women, based on the estrogen status and menopausal status. In particular, estrogen-sufficient women (premenopausal without gonadotropin deficiency) were compared with postmenopausal women or women with unreplaced gonadotropin deficiency. The ERCUSYN study was approved by the ethics committee of the Hospital Sant Pau, Barcelona, Spain, which is the coordinating centre of the project. In addition, the local ethics committee approval was obtained for each participating institution and all patients gave their informed consent, according to the EU *General Data Protection Regulation (GDPR)*. This research complies with the Declaration Of Helsinki. All the data inserted into the system were carefully monitored for inconsistencies and validated before starting statistical analysis.

7

8 Statistical analysis

For statistical analysis, GraphPad Prism® version 9 (Graph-Pad Software, San Diego, Calif., 9 USA) was used. Continuous data are presented as mean \pm SD, while categorical variables are 10 presented as absolute/relative frequencies. We performed statistical comparisons of 11 quantitative data with Student's t test or ANOVA. When variables were not normally 12 distributed, we used the Mann-Whitney U test. For statistical comparisons of dichotomous 13 data, we used the χ^2 test and, when the sample size was < 10 we used the exact Fisher test. 14 Comparison of remission rates depending on age were evaluated using Kaplan-Meier 15 16 analysis and compared using the log-rank test. All statistical tests were two sided with p values of <0.05 considered to be significant. 17

18

19 **RESULTS**

20

1- CHARACTERISTICS OF THE OVERALL POPULATION

At the time of the analysis, 1972 patients with CS were included in the database. One hundred and eighty-one patients were excluded because the cause of CS was classified as "not known", "other" or related to "illicit receptor expression". Finally, we analyzed 1791 CS patients classified as PIT-CS (n=1234), ADR-CS (n=450) or ECT-CS (n=107). The mean
age of the whole population was 44.7±14.1 years and 1397 (78%) were females. Onethousand six hundred and sixteen patients (90.2%) were classified as younger (<65 years)
and 175 (9.8%) were classified as elderly patients (≥ 65 years).

5

6 2- AGE-RELATED DIFFERENCES IN CLINICAL FEATURES AT 7 DIAGNOSIS

The clinical presentation at diagnosis, depending on age, is shown in Table 1. There was a 8 female preponderance in younger patients as compared with older [1289 (79.7%) vs. 107 9 (61.1%); p<0.01]. Elderly patients had lower BMI (26.7 ± 5.7 kg/m² vs. 29.7 ± 7.1 kg/m²; 10 p<0.01), lower waist circumference (97.1 \pm 10.8 vs. 103.1 \pm 16.5; p<0.01), lower prevalence of 11 weight gain [87 patients (49.7%) vs. 1184 patients (73.2%); p<0.01], higher prevalence of 12 hypertension [156 patients (89.1%) vs. 1084 patients (67.1%); p<0.01] and higher prevalence 13 of diabetes mellitus [84 patients (48%) vs. 446 patients (27.6%); p<0.01], in comparison to 14 younger patients. Elderly patients were less frequently depressed than younger ones [35] 15 (20%) vs. 538 (33.3%); p<0.01] and were less frequently followed by a psychiatrist [9 (5.1%) 16 vs. 170 patients (10.5%); p=0.02]. Elderly patients had lower prevalence of skin symptoms 17 [103 patients (58.8%) vs. 1123 (69.4%); p<0.01], hirsutism in females [23 (22%) vs. 668 18 (52%); p<0.01], hair loss in females [22 (21%) vs. 351 (27%); p=0.03], and loss of libido [14 19 20 (8%) vs. 325 (20.1%); p<0.01] in comparison to younger patients. Prevalence of fractures was higher in the elderly [38 (21.7%) vs. 217 (13.4%); p<0.01] in comparison to younger 21 22 patients.

23

3- AGE-RELATED DIFFERENCES IN CLINICAL FEATURES OF HYPERCORTISOLISM AT DIAGNOSIS BASED ON THE ETIOLOGY 3a- PIT-CS

Age-related clinical presentation in PIT-CS is shown in Figure 1 and Table 2. Of 1234 PIT-4 CS patients with data available, 103 patients (8.3%) were older, and 1131 (91.7%) were 5 younger. Fifty-six older and 889 younger patients were females (54% vs. 72%; p<0.01). The 6 commonest metabolic features in elderly patients as compared with their younger 7 counterparts were lower BMI, lower waist circumference, lower prevalence of weight gain, 8 higher prevalence of hypertension and higher prevalence of diabetes mellitus (p<0.01 for all 9 comparisons). Prevalence of muscle weakness in the older was greater as compared with that 10 in younger patients (p<0.01). Concerning psychiatric complications of PIT-CS, elderly 11 patients were less depressed and, accordingly, less frequently followed by a psychiatrist 12 (p<0.01 and p=0.03 respectively). Older females had lower prevalence of hirsutism and hair 13 14 loss, while low libido and higher prevalence of fractures were observed in the overall older 15 population as compared with younger (p<0.01 for all comparisons).

Data on cardiovascular morbidity were available in all 103 older and 1131 younger patients. Prevalence of cardiovascular disease at diagnosis was higher in the older as compared with the younger ([24/103 (23%) vs. 25/1131 (2%); p<0.01]. Ischemic heart disease was more frequently reported in the older as compared with the younger [19/103 (18.4%) vs. 20/1131 (1.5%); p<0.01]. Thrombosis was more frequently reported in the older as compared with the younger [26/103 (25.2%) vs. 59/1131 (5.2%); p<0.01)].

22

1 **3b- ADR-CS**

2 Age-related clinical presentation in ADR-CS is shown in Table 3.

Of 450 ADR-CS patients with available data, 52 (11.6%) were older and 398 (88.4%) younger. Thirty-eight older patients and 352 younger patients were females (73% vs. 88%; p<0.01). Prevalence of hypertension and type 2 diabetes was greater in the older as compared with the younger (p<0.01 for all comparisons). Older females had lower prevalence of hirsutism and hair loss (p<0.05). The differences in the prevalence of other clinical features between the two groups were not statistically significant, most probably due to the small number of patients included.

In the younger group, the proportion of women was lower in PIT-CS patients as compared 10 with ADR-CS patients [889 (72%) vs. 352 female patients (88%), respectively; p=0.04]. 11 12 Prevalence of hypertension was lower in PIT-CS as compared with ADR-CS [724 (64%) vs. 291 (73%); p<0.01]. Prevalence of hirsutism was higher in PIT-CS women as compared with 13 ADR-CS women [526 (46%) vs. 116 (29%), respectively; p<0.01]. The prevalence of skin 14 15 symptoms was higher in PIT-CS as compared with ADR-CS patients [818 (72%) vs. 238 (60%). The prevalence of weight gain was higher in PIT-CS as compared with ADR-CS 16 patients (904 (80%) vs. 226 (57%). respectively, p<0.01]. 17

Among elderly patients (>65 years old), the mean waist circumference was lower in PIT-CS
as compared with ADR-CS patients (95 cm vs. 103 cm, respectively; p=0.03). The mean
BMI was lower in PIT-CS as compared with ADR-CS patients (24 Kg/m² vs. 30 Kg/m²,
respectively; p=0.01).

1

2 **3c-ECT-CS**

Of 107 ECT-CS patients with data available, 20 (18.7%) were older and 87 (81.3%) were
younger patients. Prevalence of hypertension and type 2 diabetes was greater in the older as
compared with the younger [18 (90%) vs. 69 (79%) for hypertension and 18 (90%) vs. 33
(38%) for type 2 diabetes; p<0.01 for both comparisons]. The differences in the prevalence
of other clinical features between the two groups were not statistically significant, most
probably due to a smaller numbers of patients.

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10 4- SEX-RELATED DIFFERENCES IN OLDER PATIENTS AT DIAGNOSIS

Of 175 elderly patients with data available, 68 were males (38.8%) and 107 (61.2%) were 11 females. At diagnosis, female elderly patients had a significantly higher systolic blood 12 pressure as compared with their male counterparts (152±15 mmHg vs. 140±6; p<0.01) and 13 loss of libido was significantly less prevalent in elderly females in comparison with elderly 14 males [4 (4%) vs. 14 (21%); p<0.01] (Table 4). Older males had a significantly lower BMI 15 $(26\pm9 \text{ kg/m}^2 \text{ vs. } 29.6\pm6 \text{ kg/m}^2; \text{ p=0.02})$, higher prevalence of diabetes mellitus [36 (53%) vs. 16 17 112 (34%); p<0.01] and a lower prevalence of depression [9 (19%) vs. 130 (40%); p<0.01] 18 as compared with their younger counterpart (Table 4). Older females had a significantly 19 higher prevalence of hypertension [96 (90%) vs. 830 (64%); p<0.01], higher prevalence of 20 muscle weakness [63 (59%) vs. 615 (48%); p=0.01], higher prevalence of diabetes mellitus [56 (52%) vs. 354 (27%); p<0.01], lower prevalence of depression [23 (22%) vs. 408 (32%); 21 22 p=0.02], lower prevalence of weight gain [56 (53%) vs. 1019 (79%); p<0.01], and higher 23 prevalence of fractures [26 (24%) vs. 145 (11%); p=0.01] (Table 4).

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2	5- HEALTH-RELATED QUALITY OF LIFE AT DIAGNOSIS
3	Of 437 patients (24.4%) with EuroQoL data available, 34 (7.8%) were older and 403 (92.2%)
4	were younger. Older patients scored worse on several items of EuroQoL as compared with
5	younger patients, including mobility issues and self-care issues but they scored better on
6	anxiety/depression issues (p<0.05 for all comparisons).
7	
8	6- AGE-RELATED DIFFERENCES IN DIAGNOSIS AND MANAGEMENT
9	STRATEGIES IN PATIENTS WITH PIT-CS
10	6a- Diagnosis in elderly patients with PIT-CS
11	We also separately analyzed PIT-CS patients, who represented the largest etiologic group in
12	the ERCUSYN database.
13	Hormone assessment
14	Of the 943 patients with biochemical data available, 75 (8%) were older and 868 (92%) were
15	younger. In older patients with PIT-CS, UFC measurements supported the diagnosis of
16	hypercortisolism PIT-CS less frequently than in younger patients [(65/75 (87%) vs. 828/868
17	(95%); p<0.01]. The rest of hormone assessments were similar between younger and older
18	patients with PIT-CS.
19	Imaging

We had available information on pituitary MRI in 1113 patients (90%) of whom 1021 were
younger (90%) and 92 older (89%). The prevalence of a microadenoma was lower in the

older in comparison to the younger [36(39%) vs. 574 (56%); p<0.01]. Prevalence of an extra-
sellar macroadenoma was higher in older patients in comparison to the younger with PIT-CS
[16 (17.4%) vs. 103 (10.1%); p=0.02]. Corticotropinomas were not visualized on MRI in 219
younger patients (21.5%) vs. 23 older patients (25%); p=0.4.

Of 1113 patients with pituitary MRI data available, 810 patients were females (72.7%), of
whom 563 (69.5%) were estrogen-sufficient/premenopausal and 247 (30.5%) were estrogendeficient/ postmenopausal. Extrasellar macroadenomas were less prevalent in estrogen
sufficient/premenopausal women as compared with estrogen deficient/postmenopausal
women [37/563 (6.5%) vs. 39/247 (15.8%); p<0.01].

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11 6b- Choice of treatment in elderly patients with PIT-CS

Differences in management strategy in patient with PIT-CS, depending on age, are shown inTable 5.

Of the 1234 PIT-CS patients with data on first-line treatment available, 1082 (87.7%)
underwent pituitary surgery, of whom 71 were older (68.9%) and 1011 younger (89.3%)
(p<0.01). The rate of older patients who never received transsphenoidal surgery was higher
as compared with the younger [32 (31.1%) vs. 120 (10.6%); p<0.01)].

18 Cortisol-lowering medications were more frequently chosen as a first-line treatment in the 19 older as compared with the younger (41 (39.8%) vs. 307 (27.1%); p<0.01).

A total of 137 patients with PIT-CS were treated with radiotherapy (RT), of whom 120 younger (10.6%) and 17 older (13.6%) (p=0.06). Use of radiotherapy as a first line therapy 1 was more frequent in elderly patients as compared with younger patients (6 (35.3%) vs. 8
2 (6.6%); p<0.01).

The prevalence of an extrasellar adenoma was greater in patients who were conservatively

treated with first-line medical therapy as compared with that in the group of patients who

underwent first-line surgery [13/41 (31%) vs. 3/71 (4%), respectively; p<0.001]. 5 Thirty-eight (37%) older patients were diagnosed before 2010 and 65 (63%) after 2010. We 6 7 did not find any differences in the frequency of any modalities of first-line treatment in patients who received diagnosis of CD before 2010 as compared with those diagnosed after 8 2010 (p=0.8 for TSS; p=0.7 for both radiotherapy and medical treatment). However, more 9 CD patients with persistent/recurrent disease included after 2010 received medical therapy 10 as compared with those included before 2010 [52/65 (80%) vs. (12/37) (32%), respectively; 11 12 p<0.01].

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14 6c- Age-related differences in remission and relapse rate in PIT-CS patients

Of 1047 patients with PIT-CS who underwent transsphenoidal surgery with data available, 71 (6.8%) were older and 976 (93.2%) were younger. Remission rate was lower in the older as compared with the younger [37 (52%) vs. 636 (65%); p=0.03]. Relapse rates after successful pituitary surgery were not different in the older as compared with the younger (p=0.8). In elderly patients, remission rates were 48%, 51%, 51% and 51% at 1 year, 5 years, 10 years and 15 years respectively vs. 60%, 65.5%, 66.3% and 66.3% at 1 year, 5 years, 10 years and 15 years respectively in younger patients (p=0.04) (Figure 2). When only female patients without gonadotropin deficiency were analyzed and stratified
according to their reproductive status, estrogen-sufficient/premenopausal patients had higher
remission rate after the first transsphenoidal surgery as compared with that in estrogen
deficient/postmenopausal women [358/586 (61%) vs. 142/291 (48%); p<0.01)]. Relapse rate
was also higher in estrogen-sufficient as compared with that in estrogen-deficient patients
[73/358 (20%) vs. 18/142 (12%); p=0.04].

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7- AGE-RELATED DIFFERENCES IN MORTALITY

Among the 1791 patients included in the study, 67 (3.7%) died during the follow-up period.
As expected, a larger proportion of older patients had died at last follow-up as compared with
the younger [21/175 (12%) vs. 46/1616 (3%); p<0.01]. The causes of death were the
following: tumor progression (n=21; 31.3%), infections (n=12; 17.9%), cardiovascular
disease (n=5; 7.5%), cerebrovascular disease (n=5; 7.5%), thromboembolism (n=2; 3%) or
other causes (n=12; 17.9%). There were no age-related differences in the causes of death.
Active disease predicted mortality in the elderly [HR, 3.3 (95% CI, 1.2-8.4)].

In patients with PIT-CS and ADR-CS, proportion of older patients who died was higher than
that of the younger [14/103 (13%) vs. 22/1131 (2%); p<0.01 for PIT-CS; 3/52 (6%) vs. 4/398
(1%); p=0.04 for ADR-CS). In patients with ECT-CS, there were no age-related differences
in mortality rate between the groups.

Of 67 deceased patients, 29 (43.2%) died within 90 days from start of treatment. The proportion of elderly who died within 90 days from treatment did not differ from the proportion in younger patients [11/21 (52.4%) vs. 18/46 (39.1%); p=0.3]. 1

2 DISCUSSION

Our data from ERCUSYN demonstrated that the proportion of CS in patients older than 65 3 years was 9.8%, and there were age-specific differences in the clinical presentation of 4 endogenous hypercortisolism. Several typical symptoms of hypercortisolism were less 5 frequent in the older patients as compared with the younger, including weight gain, skin 6 alterations, hair loss, hirsutism, low libido and depression. On the contrary, the prevalence 7 diabetes. type 2 cardiovascular 8 of muscle weakness. hypertension, disease. thromboembolism and bone fractures was higher in the elderly. In the second part we only 9 analyzed PIT-CS patients because they represented the largest etiologic group which 10 provided the most significant results. Indeed, focusing on PIT-CS, older patients often had a 11 macroadenoma but less frequently underwent transsphenoidal surgery (TSS) as compared 12 with the younger. Instead, cortisol-lowering agents and radiotherapy were more often chosen 13 as a first-line therapeutic options in the former. 14

Our data also showed that aging attenuates the well-known female preponderance in the 15 prevalence of PIT-CS observed in adult population (14, 16). In fact, slightly more than half 16 17 of the elderly patients were females, whereas women represented almost three-quarters of 18 the younger patients. Because estrogens enhance corticotrope proliferation in vitro, and the 19 expression of the estrogen receptor beta (ER β) has been detected in the majority of ACTH-20 secreting adenomas, the reduction of the "gender-gap" we have found in aged patients with 21 PIT-CS may be due to the lack of estrogens in older women, and resembles that reported in 22 childhood (17, 18, 19). Accordingly, we have shown that estrogen-sufficient women with 23 PIT-CS presented with a higher relapse rate after the first TSS as compared with

postmenopausal patients, suggesting that corticotropinomas may have a more aggressive 1 2 biological behavior in the former. However, remission rate was also greater in estrogen-3 sufficient women as compared with their estrogen-deficient counterparts, likely due to the fact that the former more frequently had a microadenoma as compared with the latter. In fact, 4 older PIT-CS patients of both sexes more commonly had a macroadenoma and less frequently 5 6 experienced remission after TSS as compared with the younger population. These data are novel and in contrast with those by Qiao et al. who showed a tendency towards a lower female 7 to male ratio in the older as compared with the younger, but did not document any age-related 8 differences in both the adenoma size at diagnosis and the remission rate after surgery in 45 9 10 patients older than 60, as compared with 90 younger patients (14).

Higher prevalence of an extrasellar macroadenoma in our larger population of elderly 11 patients is an interesting finding. Although the time elapsed from the appearance of 12 symptoms to diagnosis, as reported by the patients, was similar between the older and the 13 younger population, a certain delay in the recognition of symptoms and consequent later 14 15 detection of the underlying pituitary lesion in this group of patients cannot be excluded. This 16 is in accordance with our results demonstrating that "red-flag symptoms" of CS, such as facial plethora, purple striae, easy bruising and central obesity, are often lacking in older 17 18 patients, making the early diagnosis of hypercortisolism more difficult in them than in the younger. Even the appearance of less specific symptoms of CS, such as weight gain, was not 19 20 as frequent in the older as it was in the younger, further contributing to reduce the probability 21 that an aged patient seeks medical advice to treat or prevent them. Furthermore, it is intuitive 22 that some of the most frequently reported symptoms or comorbidities in the elderly, such as muscle weakness, hypertension, type 2 diabetes and bone fractures, might have been 23

erroneously attributed to the aging process itself by clinicians, who may overlook other
 important clinical signs suggestive of cortisol excess and, therefore, exclude *a priori* other
 diagnoses.

Our data emphasize the need of maintaining a high clinical suspicion of hypercortisolism in
the general population, while taking into account specific age-related differences in the
presentation of symptoms.

Surprisingly, we found a lower prevalence of depression in the elderly with PIT-CS in 7 comparison to the younger. Several mechanisms associated with both aging and 8 hypercortisolism contribute to the development of depressive symptoms (20). Indeed, 9 depression was documented in 36% of Ercusyn patients overall, whereas Qiao et al. showed 10 that prevalence of mood disorders was around 29% in both younger and older patients. We 11 showed that depression was diagnosed in 18% of older PIT-CS patients vs. 35% of the 12 younger. A possible explanation for these discrepant results may be that severity of mood 13 disorders may be underestimated in the elderly due to their tendency to underreport 14 depressive symptoms (21). Indeed, affective symptoms in CS patients are often 15 underecognized by the clinicians, which may lead to an inaccurate estimation of the real 16 prevalence of depression in this condition (22). Moreover, major depression has been 17 demonstrated to occur less frequently in older subjects, thus further complicating the 18 recognition of symptoms (23). Additionally, younger patients perceiving Cushing-related 19 20 symptoms may be more impacted emotionally due to their physical and psychological limitations, than older patients who would conform more, considering them part of their 21 22 aging process.

We have shown that muscle weakness and myopathy were more common in older patients 1 2 as compared with the younger, whereas the latter more frequently presented with central obesity, hirsutism/hair loss and skin alterations including easy bruising, purple striae and thin 3 skin. Of note, a physiological skin thinning usually occurs with aging and, therefore, it may 4 5 be underestimated as a potential manifestation of cortisol excess during physical 6 examination. On the contrary, Qiao et al. reported more central obesity in the elderly along with more muscle wasting and did not find any age-related differences in the prevalence of 7 other typical signs and symptoms of hypercortisolism, such as fatigue and skin abnormalities 8 (14). Both cortisol excess and aging are known to cause sarcopenia, defined as low muscle 9 mass, impaired muscle quality and poor functionality (24, 25). While both conditions may 10 have concurred to increase the prevalence of muscle weakness observed in our population, 11 there may be age-related differences in the glucocorticoid receptor sensitivity in peripheral 12 tissues, making the elderly more prone to develop muscle impairment, as well as other 13 comorbidities, in the presence of excessive cortisol, as compared with the younger (26, 27, 14 28, 29). While studies in humans are needed to investigate this hypothesis, additional 15 mechanisms for muscle weakness and sarcopenia in CS might be lower sex hormone levels 16 due to cortisol suppression of the hypothalamic-pituitary-gonadal axis and suppression of 17 GH and IGF-1 secretion by excess cortisol, in addition to lower levels of IGF-1 in elderly 18 19 due physiological decline by aging. to Indeed, the rate of muscle wasting, as well as that of type 2 diabetes and hypertension, was 20 21 higher in older CS patients as compared with that in patients with non-functioning pituitary adenomas of the same age, suggesting that the negative, multisystemic effect of 22 hypercortisolism could prevails on that caused by aging alone (14). Moreover, a detrimental 23 effect of concomitant low IGF-I levels on muscle health cannot be excluded, although we did 24

not find any differences in the prevalence of GH deficiency between older and younger
patients (30). The paradoxical results on the lack libido-related complain in elderly patients
with CS may be explained by the fact that elderly patients under-report libido-related issues
and physicians probably also under-assess these issues. Indeed, although it is not fully
understood, the aging-related decrease in libido correlates with the physiological decrease in
sex hormone levels (31).

We have also described for the first time that there are differences in the management of PIT-7 CS between elderly patients and their younger counterparts throughout Europe. Although the 8 surgical resection of the corticotropinoma remains the first-line treatment of PIT-CS, elderly 9 patients were treated in a more conservative manner, undergoing surgery less frequently than 10 11 the younger whereas receiving more cortisol-lowering drugs and radiotherapy as first line treatments (32). When focusing on patients with micro adenomas, the proportion of patients 12 treated more conservatively remained higher in older patients as compared with their younger 13 14 counterparts. A more conservative approach relying on medical therapy or radiotherapy 15 instead of surgery may be advisable in the elderly with an elevated comorbidity load, which 16 may increase the risk of death or major postoperative complications. Accordingly, in a recent study focusing on the outcomes of transsphenoidal surgery in 123 elderly patients with 17 18 pituitary adenomas, Thakur et al. showed that this procedure is effective and safe in carefully selected subjects, being followed by a low complication rate and a postoperative readmission 19 20 rate of 11%, mostly for delayed hyponatremia (33). As a matter of fact, older patients had 21 more thromboembolism, cardiovascular diseases, hypertension and type 2 diabetes at 22 diagnosis as compared with the younger, which may potentially increase peri- and postoperative morbidity and mortality (7, 34, 35). However, longitudinal studies comparing 23

the long-term efficacy and safety of either approach are needed, especially in view of the
 growing proportion of elderly patients referred to endocrine units in the recent years.

Missing or incomplete information is a potential shortcoming of a multicenter registry like
the Ercusyn, but the proportion of patients with complete data was high and allowed creating
the largest dataset available to date. The database was also carefully reviewed for data quality
prior to data analysis, which guaranteed a satisfactory reliability of our results.

Another limitation is the lack of both quantitative data and standardized methods to evaluate 7 hormone levels. Indeed, we have shown that UFC measurements supported the diagnosis of 8 CS in the elderly less frequently than in the younger, suggesting that a milder hormone 9 10 elevation may develop in the former. This finding may be due to a milder hormone elevation in the former, although a concomitant renal impairment in the elderly may also play a role 11 To establish some hormone cut-offs potentially associated with a more suggestive clinical 12 picture in older patients would be helpful, to develop a diagnostic algorithm for early 13 recognition of hypercortisolism in this category of subjects. Yet, Ercusyn data cannot 14 currently address this point. 15

In conclusion, our study showed that clinical presentation of CS is different in older patients 16 as compared with that in the younger, with the former lacking some of the typical features of 17 18 cortisol excess while presenting with a greater burden of comorbidities and an elevated 19 prevalence of muscle weakness along with levels of UFC which are often within the normal 20 range. Moreover, although older patients frequently have a macroadenoma at diagnosis, a conservative, non-surgical management is more often chosen likely in the attempt to avoid 21 22 postoperative complications. Future studies are needed to evaluate the long-term effects of 23 each treatment in the elderly, and establish the safest strategy within an individualized approach. 24

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1 LEGENDS

- 2 Figure 1. Common clinical presentation of patients with PIT-CS, depending on age. This
- 3 picture represents some age-related differences in clinical presentation. A detailed
- 4 description of all the features found is provided in the text
- 5 Figure 2. Disease free survival of younger and older patients after successful
- 6 transsphenoidal surgery (Kaplan-Meier analysis).
- 7 **Table 1.** Comparison of clinical presentations at diagnosis in elderly patients (>65 years
- 8 old) with CS versus younger patients (<65 years old) with CS.
- 9 Table 2. Comparison of clinical presentations at diagnosis in elderly patients (>65 years
- 10 old) with PIT-CS versus younger patients (<65 years old) with PIT-CS.
- 11 **Table 3.** Comparison of clinical presentations at diagnosis in elderly patients (≥ 65 years
- 12 old) with ADR-CS versus younger patients (<65 years old) with ADR-CS.
- 13 Table 4. Comparison of clinical presentations at diagnosis in elderly patients (>65 years
- 14 old) with CS versus younger patients (<65 years old) with CS, depending on age.
- p value^a: Comparison of initial clinical presentation between males and females among
 younger patients (<65 years old) with CS.
- 17 p value^b: Comparison of initial clinical presentation between males and females among 18 older patients (\geq 65 years old) with CS.
- Table 5. Comparison of management strategies in elderly patients (≥65 years old) with
 PIT-CS versus younger patients (<65 years old) with PIT-CS.
- 21

	< 65 years old	<u>></u> 65 years old	p value
Number of patients, n(%)	1616 (90.2)	175 (9.8)	-
PIT-CS, n(%)	1131 (70)	103 (58.8)	<0.01
ADR-CS, n(%)	398 (24.6)	52 (29.7)	0.1 loaded
ECT-CS, n(%)	87 (5.4)	20 (11.5)	<0.01 htt
Age (year), mean+/-SD	42+/-12	69.6+/-4.7	<0.01 <0.01
Female, n(%)	1289 (79.7)	107 (61.1)	<0.01 demic.c
Onset of symptoms (year), mean+/-SD	2.9+/-3.3	3.1+/-4.8	0.5 om
ON DEX cortisol (nmol/L), mean+/-SD	496+/-375	436+/-317	0.3 ^(ejendo)
BMI, mean+/-SD	29.7+/-7.1	26.7+/-5.7	<0.01
Waist circumference (cm), mean+/-SD	103.1+/-16.5	97.1+/- 10.8	<0.01
Hypertension, n(%)	1084 (67.1)	156 (89.1)	<0.01
SBP (mmHg), mean+/-SD	140+/-21	149+/-22	<0.01 ^{1093/eje}
DBP (mmHg), mean+/-SD	88+/-14	84+/-12	<0.01
Muscle weakness, n(%)	821 (50.9)	101 (57.7)	0.09 0.09
Diabetes mellitus, n(%)	446 (27.6)	84 (48)	<0.01
Depression, n(%)	538 (33.3)	35 (20)	<0.01 gue
Loss of libido, n(%)	325 (20.1)	14 (8)	<0.01 ^{st on} 15
females), n(%)	351 (27.2)	22 (20.7)	0.03 Februa
Hirsutism (only for females), n(%)	668 (51.8)	23 (21.5)	<0.01
Skin symptoms, n(%)	1123 (69.4)	103 (58.8)	<0.01
Weight gain, n(%)	1184 (73.2)	87 (49.7)	<0.01
Fractures, n(%)	217 (13.4)	38 (21.7)	<0.01

Followed by a psychiat	rist,		
n(%)	170 (10.5)	9 (5.1)	

Table 1. Comparison of clinical presentations at diagnosis in elderly patients (>65 years

old) with CS versus younger patients (<65 years old) with CS.

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	< 65 years old	> 65 years old	n value
Number of patients $n(%)$	1121 (01 7)	103 (8 3)	
Age (year) means (SD	1001/122		-0.01
Age (year), mean+/-SD	40.9+/-12.2	70.2+7-4.7	<0.01
Female, n(%)	889 (72)	56 (54.3)	<0.01
Unset of symptoms (year),	2.122		0.5
mean+/-SD	3+/-3.2	2.6+/-3.6	0.5
UFC/24h, mean+/-SD	898+/-1219	900+/-899	0.6
ON DEX cortisol (nmol/L),			
mean+/-SD	496+/-375	436+/-317	0.3
BMI, mean+/-SD	29.7+/-20.6	24.2+/-12.7	<0.01
Waist circumference (cm),			
mean+/-SD	103.9+/-16.7	95+/- 10.4	<0.01
Hypertension, n(%)	724 (64)	93 (90.2)	<0.01
SBP (mmHg), mean+/-SD	138+/-20.2	149+/-22	<0.01
DBP (mmHg), mean+/-SD	87+/-13.7	86+/-14.1	0.7
Muscle weakness, n(%)	551 (48.7)	61 (59.2)	0.04
Diabetes mellitus, n(%)	307 (23.1)	42 (40.7)	<0.01
Depression, n(%)	394 (34.8)	19 (18.4)	<0.01
Loss of libido, n(%)	241 (21.3)	5 (4.8)	<0.01
Hair loss (only for females),			
n(%)	242 (27.2)	13 (26.5)	0.2
Hirsutism (only for females),			
n(%)	524 (58.9)	13 (26.5)	<0.01
Skin symptoms, n(%)	818 (72.3)	67 (65)	0.1
Weight gain, n(%)	904 (79.9)	53 (51.4)	<0.01
Fractures, n(%)	154 (13.6)	26 (25.2)	<0.01
Followed by a psychiatrist, n(%)	119 (10.5)	4 (3.8)	0.03

Table 2. Comparison of clinical presentations at diagnosis in elderly patients (>65 years

old) with PIT-CS versus younger patients (<65 years old) with PIT-CS.

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	< 65 years old	<u>></u> 65 years old	p value
Number of patients, n(%)	398 (88.4)	52 (11.6)	-
Age (year), mean+/-SD	44.6+/-11.3	67.8+/-3.1	<0.01
Female, n(%)	352 (88.4)	38 (73.1)	<0.01
Onset of symptoms (year),			
mean+/-SD	2.7+/-3.5	3.7+/-5.3	0.9
BMI, mean+/-SD	29.9+/-6.7	30.2+/-5.4	0.5
Waist circumference (cm),			
mean+/-SD	102.4+/-16.6	103.4+/-11.8	0.5
Hypertension, n(%)	291 (73.1)	45 (86.5)	0.03
SBP (mmHg), mean+/-SD	142+/-19	144+/-20	0.7
DBP (mmHg), mean+/-SD	89+/-13	82+/-8	0.3
Muscle weakness, n(%)	202 (50.7)	24 (46.1)	0.5
Diabetes mellitus, n(%)	112 (28.1)	26 (50)	<0.01
Depression, n(%)	118 (29.6)	10 (19.2)	0.5
Loss of libido, n(%)	67 (16.8)	6 (11.5)	0.4
Hair loss (only for			
females), n(%)	97 (27.5)	6 (17.1)	0.03
Hirsutism (only for			
females), n(%)	116 (32.9)	8 (21)	0.02
Skin symptoms, n(%)	238 (59.7)	23 (44.2)	0.03
Weight gain, n(%)	226 (56.7)	26 (50)	0.3
Fractures, n(%)	49 (12.3)	9 (17.3)	0.3
Followed by a psychiatrist,			
_n(%)	46 (11.5)	4 (7.7)	0.5

Table 3. Comparison of clinical presentations at diagnosis in elderly patients (>65 years old) with ADR-CS versus younger patients (<65 years old) with ADR-CS.

	< 65 years old FEMALES	< 65 years old MALES	<u>></u> 65 years old FEMALES	<u>></u> 65 years old MALES	p value ^a	p value ^b
Number of patients, n(%)	1291	325	107	68	-	-
Age (year), mean±SD	42±11	42±12	68±4	69±4	0.9	0,8
Onset of symptoms (year), mean±SD	2±2	2±2	3±4	2±5	0.7	0.07 0.07
BMI, mean+/-SD	28±16.4	29.6±6	26.8±8.8	26±9*	0.1	0.8 htt
Waist circumference (cm), mean±SD	102±17	105±11	96±10	97±10	0.09	0.6 0.6
Weight gain, n(%)	1019 (79)	252 (78)	56 (53)**	34 (50)	0.5	0.7 0.7
Muscle weakness, n(%)	615 (48)	206 (63)	63 (59)**	41 (60)	<0,01	0.8 0.8
SBP (mmHg), mean+/-SD	139±21	147±20	152±15	140±6	<0,01	<0.01 <0.01
DBP (mmHg), mean+/-SD	87±13	91±15	83±20	84±11	0,02	0.7 ance-art
Hypertension, n(%)	830 (64)	254 (78)	96 (90)**	60 (88)	<0.01	0.7 0.7
Diabetes mellitus, n(%)	354 (27)	112 (34)	56 (52)**	36 (53)*	0.01	0.9 0. 9
Fractures, n(%)	145 (11)	81 (25)	26 (24)**	13 (19)	<0.01	0.4 ejendo
Depression, n(%)	408 (32)	130 (40)	23 (22)**	9 (19)*	<0.01	0.2 0.2
Loss of libido, n(%)	214 (17)	112 (35)	4 (4)	14 (21)	<0.01	<0.01

Table 4. Comparison of clinical presentations at diagnosis in older (>65 years old) versus younger (<65 years old) CS patients, depending on gender.

p value^a: Male vs. female younger patients

p value^b: Male vs. female older patients

*p<0.05 vs. younger male patients

**p<0.05 vs. younger female patients

	<65 years old	<u>></u> 65 years old	p value
No pituitary surgery, n(%)	120 (10)	32 (31)	<0.01
1 pituitary surgery, n(%)	804 (71)	60 (58)	<0.01
2 or more pituitary surgeries, n(%)	207 (18)	11 (10)	0.05
Medical therapy as first line, n(%)	307 (27)	41 (39)	<0.01
Bilateral adrenalectomy, n(%)	56 (4)	5 (4)	1 lload
RT, n(%)	120 (10)	17 (13)	0.06 🗒
RT as first line therapy, n(%)	8 (7)	6 (35)	<0.01 ^{on}
RT as second line therapy, (%)	112 (93)	11 (65)	<0.01 ^{nttps}

4 Table 5. Comparison of management strategies in elderly patients (>65 years old) with

- 5 PIT- CS versus younger patients (<65 years old) with PIT-CS.





