

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

Vincent Amodru¹, Antoine Tabarin², Frederic Castinetti³, Stylianos Tsagarakis⁴, Miklos Toth⁵, Richard A Feelders⁶, Susan M Webb¹, Martin Reincke⁷, Romana Netea-Maier⁸, Darko Kastelan⁹, Atanaska Elenkova¹⁰, Dominique Maiter¹¹, Oskar Ragnarsson¹², Alicia Santos¹, Elena Valassi^{13,14,15}

¹IIB-Sant Pau and Department of Endocrinology, Hospital Sant Pau, Dept Medicine, UAB, and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBER-ER, Unidad 747), ISCIII, Barcelona, Spain.

²Department of Endocrinology, Diabetes and Nutrition, University of Bordeaux, Bordeaux, France. ³Aix-Marseille Université, Institut National de la Santé et de la Recherche Médicale INSERM U1251, Marseille Medical Genetics, Marseille, France and Assistance Publique Hôpitaux de Marseille (APHM), Hôpital de la Conception, Marseille, France. ⁴Evangelismos Hospital, Athens, Greece. ⁵Department of Internal Medicine and Oncology, Semmelweis University, Budapest, Hungary. ⁶Erasmus University Medical Centre, Rotterdam, The Netherlands. ⁷Medizinische Klinik und Poliklinik IV, Campus Innenstadt, Klinikum der Universität München, Ludwig-Maximilians-Universität München, Munich, Germany.

⁸Department of Internal Medicine, division of Endocrinology, Radboud University Medical Center, Nijmegen, The Netherlands. ⁹Department of Endocrinology, University Hospital Zagreb, Zagreb, Croatia. ¹⁰Medical University of Sofia, Sofia, Bulgaria. ¹¹UCL Cliniques Universitaires St Luc, Brussels, Belgium. ¹²Department of Endocrinology, Sahlgrenska University Hospital, Gothenburg, Sweden. ¹³Endocrinology and Nutrition Department, Germans Trias i Pujol Hospital and Research Institute, Badalona, Spain; ¹⁴Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER); ¹⁵Universitat Internacional de Catalunya (UIC), Barcelona, Spain

Introduction

In the last decades, life expectancy has improved worldwide, and the number of elderly patients referred to endocrine clinics has progressively increased. Data on clinical presentation and management of Cushing's syndrome (CS) in older patients are scarce. Our study was aimed at evaluating whether age-related differences exist in terms of clinical characteristics, diagnostic approach and management strategies in patients with CS included in the European Registry on Cushing's Syndrome (ERCUSYN).

Material and Methods

We performed a retrospective, observational, multicenter study based on the ERCUSYN registry.

Results

In this cohort study, 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). Of the older patients, 8% had PIT-CS, 12% ADR-CS and 19% ECT-CS. At diagnosis, older patients with CS were more frequently males and had a lower BMI and waist circumference as compared with younger patients, they 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 (Table 1 and Table 2). Regarding clinical presentation at diagnosis in the subgroups, we also found significant differences comparing older patients and younger patients with PIT-CS (Table 3 and Figure 1) and with ADR-CS (Table 4). Measurement of UFC, the most commonly used test, supported the diagnosis of CS less frequently in older patients as compared with the younger ($p < 0.05$). An extra-sellar macroadenoma was more commonly found in older PIT-CS patients than in the younger ($p < 0.01$). Older PIT-CS patients more frequently received cortisoid-lowering medications and radiotherapy as a first-line treatment, whereas surgery was the preferred approach in the younger $p < 0.01$ for all comparisons (Table 5). However, when transsphenoidal surgery was performed, the remission rate was lower in the elderly as compared with their younger counterparts $p < 0.05$ (Figure 2).

Table 1. Comparison of clinical presentations at diagnosis in elderly patients (>65 years old) with CS versus younger patients (<65 years old) with CS.

	< 65 years old	> 65 years old	p value
Number of patients, n(%)	1616 (90.2)	175 (9.8)	-
Age (year), mean+/-SD	42+/-12	69.6+/-4.7	<0.01
Female, n(%)	1289 (79.7)	107 (61.1)	<0.01
Onset of symptoms (year), mean+/-SD	2.9+/-3.3	3.1+/-4.8	0.5
ON DEX cortisol (nmol/L), mean+/-SD	496+/-375	436+/-317	0.3
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
DBP (mmHg), mean+/-SD	88+/-14	84+/-12	<0.01
Muscle weakness, n(%)	821 (50.9)	101 (57.7)	0.09
Diabetes mellitus, n(%)	446 (27.6)	84 (48)	<0.01
Depression, n(%)	538 (33.3)	35 (20)	<0.01
Loss of libido, n(%)	325 (20.1)	14 (8)	<0.01
Hair loss, n(%)	377 (23.3)	29 (17.4)	0.04
Hirsutism, n(%)	668 (41.3)	29 (17.4)	<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 psychiatrist, n(%)	170 (10.5)	9 (5.1)	0.02

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

	< 65 years old	> 65 years old	p value
Number of patients, n(%)	1131 (91.7)	103 (8.3)	-
Age (year), mean+/-SD	40.9+/-12.2	70.2+/-4.7	<0.01
Female, n(%)	889 (72)	56 (54.3)	<0.01
Onset of symptoms (year), 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, n(%)	261 (23.1)	18 (17.4)	0.2
Hirsutism, n(%)	526 (46.5)	16 (15.5)	<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 5. Comparison of management strategies in elderly patients (>65 years old) with PIT-CS versus younger patients (<65 years old) with PIT-CS.

	<65 years old	>65 years old	p value
No pituitary surgery, n(%)	120 (10.6)	32 (31.1)	<0.01
1 pituitary surgery, n(%)	804 (71.1)	60 (58.2)	<0.01
2 or more pituitary surgeries, n(%)	207 (18.3)	11 (10.7)	0.05
Medical therapy as first line, n(%)	307 (27.1)	41 (39.8)	<0.01
Bilateral adrenalectomy, n(%)	56 (4.9)	5 (4.8)	1
RT, n(%)	120 (10.6)	17 (13.6)	0.06
RT as first line therapy, n(%)	8 (6.6)	6 (35.3)	<0.01
RT as second line therapy, (%)	112 (93.4)	11 (64.7)	<0.01

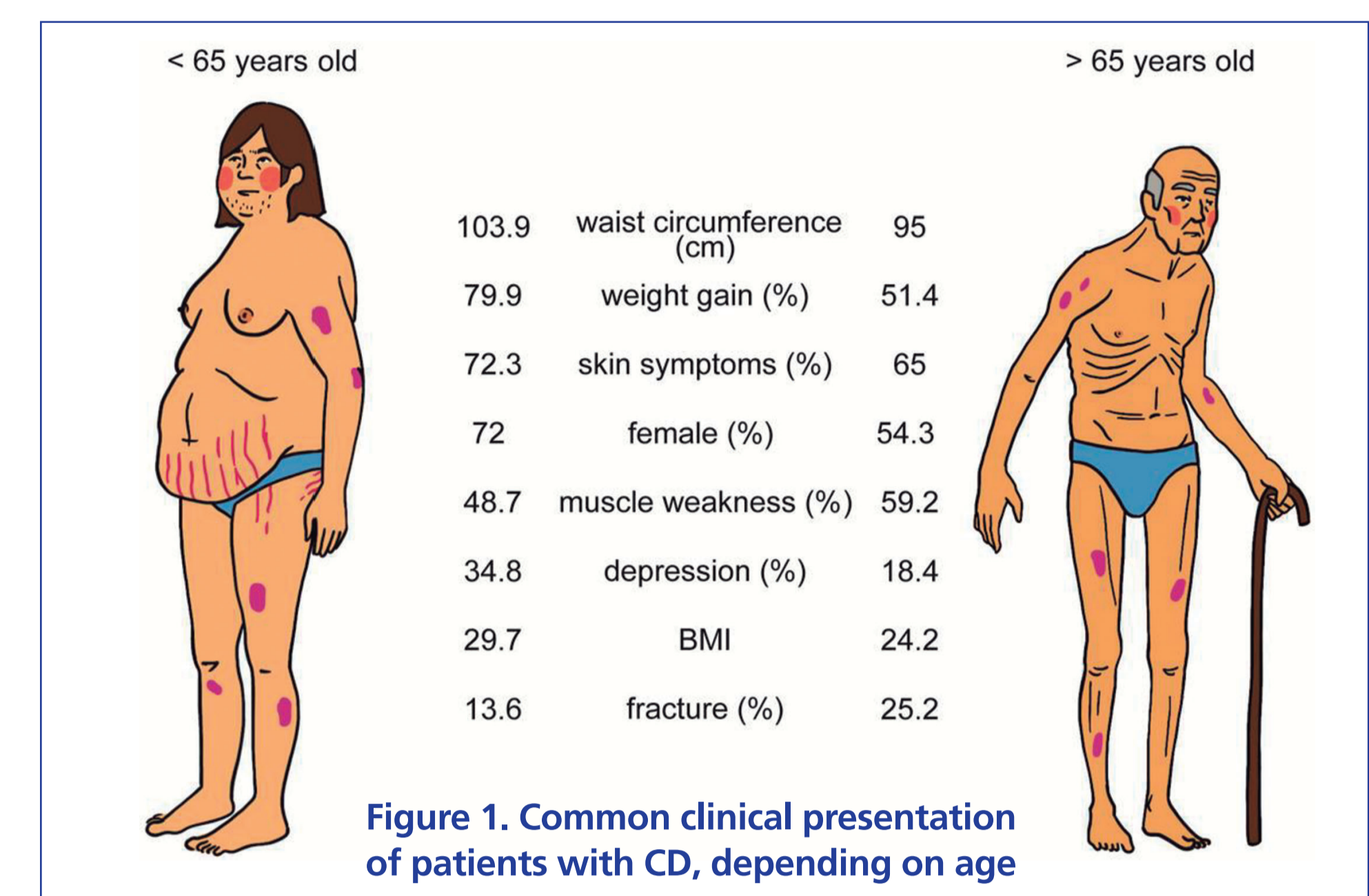


Figure 1. Common clinical presentation of patients with CD, depending on age

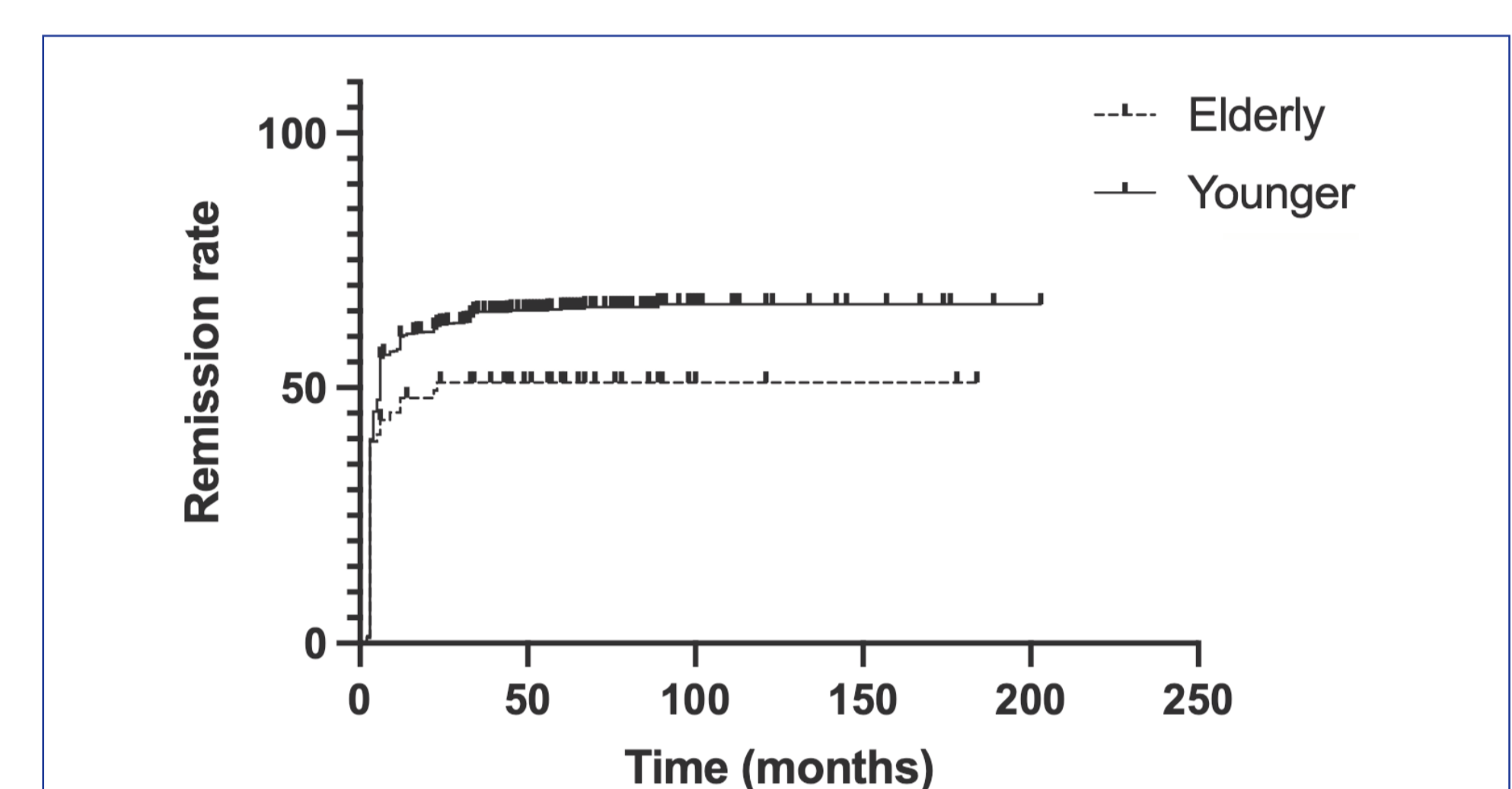


Figure 2. Patients remaining in remission over time (Kaplan-Meier analysis) Disease-free survival in Kaplan-Meier curve between older and younger patients

Table 2. Comparison of clinical presentations at diagnosis in elderly patients (>65 years old) with CS versus younger patients (<65 years old) with CS, depending on gender.

	< 65 years old FEMALES	< 65 years old MALES	> 65 years old FEMALES	> 65 years old MALES	p value ^a	p value ^b
Number of patients, n(%)	1291	325	107	68	-	-
Age (year), mean+/-SD	42.2±11.2	42.1±12.1	68.9±4.4	69.6±4.5	0.9	0.8
Onset of symptoms (year), mean+/-SD	2.8±2.9	2.5±2.6	3.6±4.9	2.9±5.2	0.7	0.07
BMI, mean+/-SD	28.1±16.4	29.6±5.7	26.8±8.8	26.1±9.3	0.1	0.8
Waist circumference (cm), mean+/-SD	102.5±17.5	105.7±11.9	96.3±10.5	97.8±10.1	0.09	0.6
Hypertension, n(%)	830 (64.3)	254 (78.1)	96 (89.7)	60 (88.2)	<0.01	0.7
SBP (mmHg), mean+/-SD	139±21	147±20	152±15	140±6	<0.01	<0.01
DBP (mmHg), mean+/-SD	87±13	91±15	83±20	84±11	0.02	0.7
Muscle weakness, n(%)	615 (47.6)	206 (63.4)	63 (58.8)	41 (60.3)	<0.01	0.8
Diabetes mellitus, n(%)	354 (27.4)	112 (34.4)	56 (52.3)	36 (52.9)	0.01	0.9
Depression, n(%)	408 (31.6)	130 (40)	23 (21.5)	9 (19.1)	<0.01	0.2
Loss of libido, n(%)	214 (16.5)	112 (34.5)	4 (3.7)	14 (20.5)	<0.01	<0.01
Hair loss, n(%)	311 (24.1)	68 (20.9)	20 (18.7)	7 (10.3)	0.2	0.2
Hirsutism, n(%)	568 (44)	142 (43.6)	23 (21.5)	10 (14.7)	0.9	0.2
Skin symptoms, n(%)	897 (69.4)	226 (69.5)	65 (60.7)	43 (63.2)	0.9	0.7
Weight gain, n(%)	1019 (78.9)	252 (77.5)	56 (52.3)	34 (50)	0.5	0.7
Fractures, n(%)	145 (11.2)	81 (24.6)	26 (24.3)	13 (19.1)	<0.01	0.4

Table 4. 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	> 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, n(%)	102 (25.6)	6 (11.5)	0.02
Hirsutism, n(%)	116 (29.1)	8 (15.4)	0.04
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

Conclusions

There are significant age-related differences in clinical presentation, management and surgical outcome of CS. Older patients lack several typical symptoms of hypercortisolism and present with an increased comorbidity burden regardless of gender. Conservative management is often the preferred approach in older CS patients.