Endocrine (2023) 80:142–151
https://doi.org/10.1007/s12020-022-03261-y

ORIGINAL ARTICLE

Systemic comorbidities of acromegaly in real-life experience: which difference among young and elderly patients?

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Received: 1 August 2022 / Accepted: 10 November 2022 / Published online: 29 November 2022
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Abstract

Introduction Acromegaly is a rare but potentially life-threatening disease, if not promptly managed, for the systemic complications due to the GH/IGF-I hypersecretion. According to the increased population life span, the number of older acromegaly patients is growing. We aim to investigate clinical features of elderly acromegaly (elderly-ACRO) and to identify the risk factors for the occurrence of comorbidities in elderly-ACRO.

Materials and methods A retrospective and multi-center study was performed on acromegaly patients. Acromegaly comorbidities were compared among elderly-ACRO (>65 years), young acromegaly patients (young-ACRO if ≤65 years) and a control group of age and gender-matched subjects.

Result Fifty of the 189 enrolled patients were elderly-ACRO (26.5%). Cardiovascular, metabolic, neurological/psychiatric and joint/articular disorders, nodular thyroid disease, sleep apnoea syndrome and skeletal fragility occurred more frequently in elderly-ACRO as compared to controls. Cardiovascular and metabolic disorders, nodular thyroid disease occurred significantly more frequently in elderly-ACRO as compared to young-ACRO and controls. On the other hand, neurological/psychiatric, joint/articular disorders and bone fragility occur with a similar frequency among elderly and young-ACRO. We found that elderly-ACRO had an increased risk for the occurrence of systemic arterial hypertension ($p < 0.001$, OR: 5.4 95% IC:2.6–10.9), left ventricular hypertrophy ($p = 0.01$, OR: 3 95%IC: 1.5–5.8) and metabolic disorders ($p = 0.006$, OR: 4.1 95%IC: 2–8.3).

Conclusion Our results may suggest that some acromegaly comorbidities may be predominantly due to acromegaly "per-se" rather than to aging. On the contrary, cardiovascular and metabolic disorders seem to be due to aging as well.

Keywords Growth hormone · IGF-I · Bone fragility

Introduction

Acromegaly is a rare but potentially life-threatening disease, if not promptly managed. Life span is reduced in patients with active disease and in those affected by acromegaly-related comorbidities. In this view, the aims of the care of acromegaly patients are to reach the biochemical control of GH and IGF-I hypersecretion, to remove/reduce the tumor mass and to diagnose and manage acromegaly-related comorbidities [1]. Chronic exposure to GH and IGF-I hypersecretion is in fact responsible of the onset of systemic complications, associated to increased mortality and reduced quality of life [2]. Cardiovascular, respiratory, metabolic, joint/articular disorders, skeletal fragility and neoplasia involved a not-negligible percentage of acromegaly

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s12020-022-03261-y.

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patients. However, data on frequency and risk factors of systemic complication in elderly patients with acromegaly is limited and controversial [3], although of increasing interest. According to the increased life span of general population, the number of older acromegaly patients is expected to grow in the next years and physicians will need to know how to treat these patients.

It is widely recognised that acromegaly phenotype in older patients is milder as compared to that observed in younger acromegaly patients [4–6], with an increased risk of misleading or delayed diagnosis.

In this study, we aim to investigate the clinical features of acromegaly in elderly patients, in order to improve the knowledge of acromegaly in elderly patients. Moreover, we aim to identify risk factors for the occurrence of comorbidities in the clinical setting of elderly acromegaly patients.

Material and Methods

A retrospective, cross-sectional, observational and multicenter study was performed on acromegaly patients. The study was approved by Institutional Ethical Committees.

Objectives

The primary objective of the study was to compare the frequency of acromegaly-related comorbidities (ACRO-comorbidities) among elderly and young acromegaly patients.

The secondary objective of the study was to compare the frequency of ACRO-comorbidities among elderly-ACRO and among a control group of age and gender-matched subjects, enrolled with a 1:1 ratio.

In order to reach these objectives, the study endpoints were the frequencies of systemic arterial hypertension, left ventricular hypertrophy, arrhythmias, nodular thyroid disease, metabolic, neurological/psychiatric and joint/articular disorders, sleep apnea syndrome (SAS), bone fragility and neoplasia in acromegaly patients and in the control group. The confounders were gender, age, GH and IGF-I levels at acromegaly diagnosis, tumor dimension and invasiveness, disease status, GH and IGF-I level at last follow-up, and length of active disease.

Inclusion/exclusion criteria

Acromegaly patients were consecutively enrolled according to the following inclusion and exclusion criteria.

Inclusion criteria:

1. Diagnosis of acromegaly between 2000 and 2020;
2. follow-up at the Pituitary Unit of the Gemelli Hospital IRCCS, Università Cattolica del Sacro Cuore in Rome and at the Endocrinological center of the Azienda Ospedaliera Universitaria of Ferrara, Italy;
3. cases with availability of all data required for the study;
4. patients who agreed to participate to the study, by signing an informed consent.

Exclusion criteria

All patients who died were excluded from the study.

Data collection

According to the retrospective design of the study, the presence and diagnosis of each comorbidity were searched in patient's charts. Patients were considered affected by systemic arterial hypertension in cases of elevated screening blood pressure (systolic pressure ≥130 mmHg and/or diastolic pressure ≥80 mmHg) [7]. Left ventricular hypertrophy was diagnosed by performing a 2D echocardiography and was defined in cases of left ventricular mass >102 g/m^2 for men and >88 g/m^2 for women [7]. Arrhythmia was diagnosed by electrocardiography (ECG) or 24-hours ECG Holter, that was performed when clinically indicated. Obstructive sleep apnea syndrome was diagnosed though full-night polysomnography (PSG) or split-night PSG. Metabolic disorders were defined in cases of dyslipidemia, glucose intolerance, impaired fasting glucose, and diabetes mellitus. Bone fragility was diagnosed in patients with osteoporosis or spontaneous vertebral fractures that were investigated by thoraco-lumbar spine radiographs. Joint/articular disorders were defined in the presence of self-reported joints pain (resting or movement), or joints stiffness or functional impairment [8], that were further confirmed by the presence of bone deformities and signs of acute/chronic inflammation at joint ultrasound/radiographs.

Neurological/psychiatric disorders were defined according to the clinical history of patients and concomitant treatments. Patients underwent neurological, neurocognitive and psychiatric evaluation when clinically indicated.

According to disease status, patients were classified cured/controlled or affected by active disease. Acromegaly was defined:

– cured in patients off-therapy for at least six consecutive months with normal age and gender-adjusted IGF-I values and random GH was below 1.0 ng/mL and with GH nadir <0.1 ng/mL in not-diabetic patients;
– controlled in patients treated with medical therapy, with normal age and gender-adjusted IGF-I values and random GH < 1.0 ng/mL [9];

Table 1 Acromegaly disease features at disease diagnosis and during follow-up according to the age groups (elderly vs young acromegaly)

	Study population	Elderly acromegaly	Young acromegaly	*p*-value
Gender				
Females *n*, (%)	100 (52.9%)	31 (62%)	69 (49.6%)	0.133
Males *n*, (%)	89 (47.1%)	19 (38%)	70 (50.4%)	
Age at ACRO diagnosis, median (IQR)	43 (19)	57 (15)	37 (17.5)	<0.001
GH at ACRO diagnosis ng/mL, median (IQR)	11.3 (28)	7.9 (11)	17.1 (4)	<0.001
IGF x ULN at ACRO diagnosis, median (IQR)	2.7 (1.3)	2.7 (0.9)	2.7 (1.9)	0.749
Hypopituitarism				
No n, (%)	120 (63.5%)	30 (60%)	90 (64.7%)	0.55
Yes n, (%)	69 (36.5%)	20 (40%)	49 (35.3%)	
Central hypothyroidism				
No *n*, (%)	151 (79.8%)	37 (74%)	114 (82.1%)	0.435
Yes *n*, (%)	38 (20.2%)	13 (26%)	25 (17.9%)	
Central hypoadrenalism				
No *n*, (%)	141 (74.6%)	40 (80%)	101 (72.7%)	0.324
Yes *n*, (%)	48 (25.4%)	10 (20%)	38 (27.3%)	
Central hypogonadism				
No *n*, (%)	166 (87.8%)	45 (90%)	32 (87.1%)	0.482
Yes *n*, (%)	23 (12.2%)	5 (10%)	18 (12.9%)	
Tumor dimension				
Micro-adenoma *n*, (%)	38 (20.1%)	17 (34%)	21 (15.1%)	0.005
Macro-adenoma *n*, (%)	151 (79.9%)	33 (66%)	118 (84.9%)	
Invasiveness				
Invasive *n*, (%)	66 (37.7%)	15 (32.6%)	51 (39.5%)	0.405
Not invasive *n*, (%)	109 (62.3%)	31 (67.4%)	78 (60.5%)	
Residual disease				
No *n*, (%)	63 (41.2%)	21 (48.8%)	42 (38.2%)	0.229
Yes *n*, (%)	90 (58.8%)	22 (51.2%)	68 (61.8%)	
Disease status				
Active *n*, (%)	15 (7.9%)	3 (6%)	12 (8.6%)	0.555
Cured/controlled *n*, (%)	174 (92.1%)	47 (94%)	127 (91.4%)	
Length of active disease, median (IQR)	12 (11)	17 (11)	10 (10)	<0.001

– active in patients treated with medical therapy, IGF-I concentrations above the normal ranges for age and gender, and with random GH > 1.0 ng/mL [10].

In patients with discordant GH and IGF-I levels, disease control was defined on the basis of IGF-I levels. Indeed, according to the last 2020 consensus conference on acromegaly management [9], IGF-I levels were considered to best reflect disease clinical activity.

Patients on treatment with Peg-V were evaluated only by serum IGF-I [9]. IGF-I was expressed as IGF-I upper limit of normal (ULN), according to normative data for each center laboratory. GH and IGF-I were measured in all centers using chemiluminescent immunometric assays (Immulite 2000, Siemens Healthcare, Erlangen, Germany). The standard for GH was IS 80/505 until 2010, IS 98/574 afterwards. The standard for IGF-I was IS 02/254. Coefficients of variation were below 5% for both assays.

The length of active acromegaly was estimated as the number of months between the time at which two consecutive values of IGF-I within the normal ranges for age and gender were reached and the time of acromegaly diagnosis.

Statistical analysis

The patients' cohort was described in its clinical and demographic features using descriptive statistics. Normality of

continuous variables was checked using Kolmogorov-Smirnov test. Quantitative variables were expressed as median and range and qualitative variables as absolute and percentage frequency. Chi-square test (or Fisher exact test when necessary) and Mann-Whitney non-parametric tests were used to compare categorical and quantitative un-paired data.

To reach the primary objective of the study, acromegaly patients were divided in two groups: elderly patients aged > 65 years (group A) and young patients aged <65 years (group B), at last follow-up. The frequency of ACRO-comorbidities was compared between group A and group B. The secondary objective of the study was to compare the frequency of ACRO-comorbidities among elderly-ACRO (group A) and among a control group of age and gender-matched subjects with a 1:1 ratio.

Control group included patients that referred to an outpatient endocrinological and internal medicine clinic and were consecutively and retrospectively enrolled if aged >65 years and if all data required for this study were available. The patients affected by secondary hypertension, secondary osteoporosis, Cushing syndrome, hyperprolactinemia, hypopituitarism, hyperthyroidism, primary hypothyroidism, hyperparathyroidism were ruled out from the control group.

Statistical analyses were performed using SPSS software version 24.0 for Windows.

Results

A total of 189 patients entered the study: 100 were females (52.9%). 50 patients aged >65 years (26.5%) and the remaining 139 were <65 years (73.5%), at last follow-up visit. Acromegaly was diagnosed in 14 patients >65 years (7.4%). Acromegaly features among young and elderly group are summarized in Table 1.

Systemic complications of acromegaly

Among the whole study population, 111 patients were affected by cardiovascular diseases (58.7% of cases): in particular, arterial hypertension occurred in 77 patients (40.7%), left ventricular hypertrophy in 66 patients (34.9%) and arrhythmias in 22 cases (11.6%). 69 patients were affected by sleep apnoea syndrome (SAS) (36.5% of cases) and 47 patients by neurological/psychiatric (24.9 of cases) disorders. Glucose and lipid metabolisms were impaired in a total of 85 patients (45% of cases): more in detail 25 patients were diagnosed with impaired fasting glucose (13.2% of cases), 19 patients with impaired glucose tolerance (10%) and 41 patients with diabetes mellitus (21.6%). Dyslipidaemia occurred in 59 patients (31.2% of cases). Nodular thyroid disease was diagnosed in 88 patients (46.6% of cases), joint/articular disorders in 87 patients (46% of cases), and bone fragility in 104 patients (55% of cases). Neoplasia was diagnosed in 45 patients (23.8%): 21 cases of breast tumors (46.7%), 7 cases of prostate tumors (15.5%), 5 cases of colon neoplasia (11.1%), 5 cases of thyroid neoplasia (11.1%), 3 cases of uterus/ovary tumors (6.7%), 3 cases of neuroendocrine neoplasia (6.7%) and a case of hematologic neoplasia (2.2%).

Cardiovascular disorders frequency (systemic arterial hypertension, left ventricular hypertrophy, arrhythmias),

Table 2 Comorbities in acromegaly patiens according to age groups (elderly vs young acromegaly)

	Study population	Elderly acromegaly	Young acromegaly	*p*-value
Systemic arterial hypertension				
Yes, *n* (%)	77 (40.7%)	35 (70%)	42 (30.2%)	<0.001
No, *n* %	112 (59.3%)	15 (30%)	97 (69.8%)	
Left ventricle hypertrophy				
Yes, *n* (%)	66 (34.9%)	27 (54%)	39 (28.1%)	0.001
No, *n* %	123 (65.1%)	23 (46%)	100 (71.9%)	
Arrhythmias				
Yes, *n* (%)	22 (11.6%)	13 (26%)	9 (6.5%)	<0.001
No, *n* %	167 (88.4%)	37 (74%)	130 (93.5%)	
Metabolic disorders				
Yes, *n* (%)	85 (45%)	35 (70%)	50 (36%)	<0.001
No, *n* %	104 (55%)	15 (30%)	89 (64%)	
SAS				
Yes, *n* (%)	69 (36.5%)	26 (52%)	43 (30.9%)	0.008
No, *n* %	120 (63.5)	24 (48%)	96 (69.1%)	
Neurological/ psychiatric disorders				
Yes, *n* (%)	47 (24.9%)	15 (30%)	32 (23%)	0.214
No, *n* %	142 (75.1%)	35 (70%)	107 (77%)	
Nodular thyroid disease				
Yes, *n* (%)	88 (46.6%)	30 (60%)	58 (41.7%)	0.026
No, *n* %	101 (53.4%)	20 (40%)	81 (58.3%)	
Joint/articular disorders				
Yes, *n* (%)	87 (46%)	27 (54%)	60 (43.2%)	0.187
No, *n* %	102 (54%)	23 (46%)	79 (56.8%)	
Bone fragility				
Yes, *n* (%)	104 (55%)	31 (62%)	73 (52.5%)	0.248
No, *n* %	85 (45%)	19 (38%)	66 (47.5%)	
Neoplasia				
Yes, *n* (%)	45 (23.8%)	12 (24%)	33 (23.7%)	0.971
No, *n* %	144 (76.2%)	38 (76%)	106 (76.3%)	

SAS sleep apnea syndrome

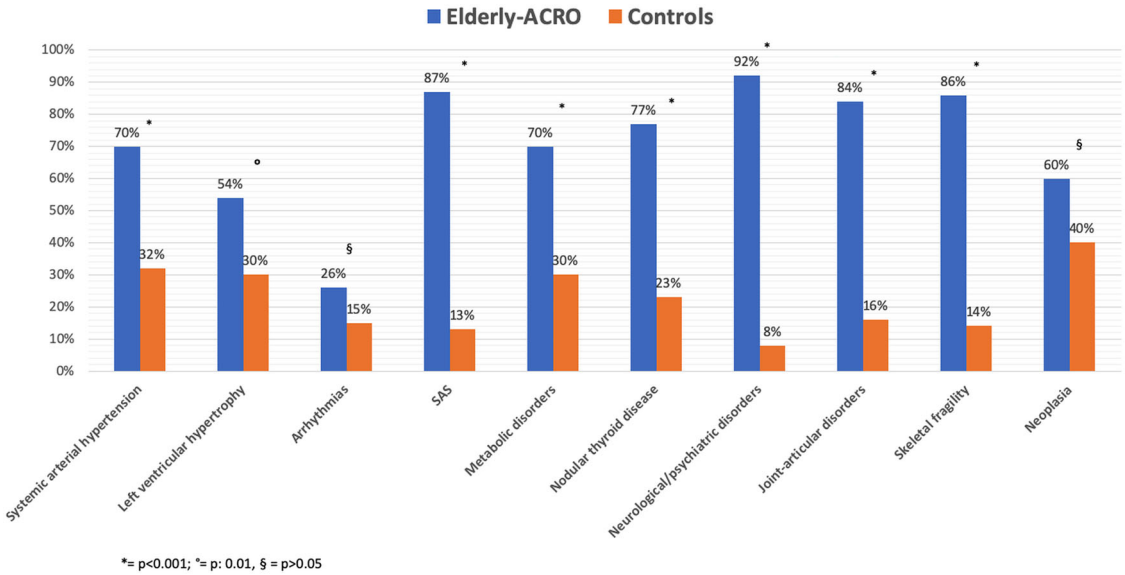

Fig. 1 Frequencies of systemic complications at last evaluation, among elderly-ACRO and controls $*p < 0.001$, $§p > 0.05$

metabolic disorders, and nodular thyroid disease was higher in elderly-ACRO as compared to young-ACRO, as shown in Table 2. SAS was rare in young-ACRO, with an increased frequency in elderly-ACRO ($p = 0.008$). On the contrary, neurological/psychiatric, joint/articular disorders, and bone fragility occurred with a similar frequency in elderly and young-ACRO.

Comparing elderly-ACRO patients with a control group of age and gender matched subjects, we found a significantly higher frequency of cardiovascular, metabolic, neurological/psychiatric and joint/articular disorders, nodular thyroid disease, SAS and bone fragility in acromegaly patients, as shown in Fig. 1.

Acromegaly outcome

At last follow-up visit, only 15 patients out of the 189 enrolled were affected by active acromegaly (7.9%). Seventy-seven patients were on treatment with first-generations SSAs (40.7%), 39 patients with GH antagonist (Pegvisomant) (20.6%), alone or in combination with first-generation SSA, 2 patients with dopamine agonist (1.1%), 7 patients with Pasireotide Lar (3.7%) and 5 patients with Pasireotide Lar in combination with Pegvisomant. 59 patients were considered cured and did not require additional treatments (31.2%). No difference was found between young and elderly acromegaly with regard to treatment history, as shown in Supplementary Table 1.

Similarly, no difference was identified between the two groups with regard to therapeutic history, as shown in Table 1. 144 patients underwent pituitary surgery (79% of young-ACRO and 66% of elderly-ACRO groups, p = 0.06), 133 patients were treated with first-generation SSA (72.7% of young-ACRO and 64% of elderly-ACRO groups, $p = 0.25$), 35 patients were treated with Pegvisomant (18.7% of young-ACRO and 18% of elderly-ACRO groups, $p = 0.912$), 12 with dopamine-agonist (7.2% of young-ACRO and 4% of elderly-ACRO groups $p = 0.427$), 7 with Pasireotide Lar (4.3% of young-ACRO and 2% of elderly-ACRO groups, $p = 0.319$) and 5 with Pasi-Lar plus Pegvisomant (none of elderly-ACRO and 3.6% of young-ACRO groups, $p = 0.126$). GH levels at acromegaly diagnosis were higher in young-ACRO as compared to elderly-ACRO, 17.1 ng/mL (IQR: 4) vs. 7.9 ng/mL (IQR: 11; $p < 0.001$), respectively. Although the majority of patients in this series carried a macroadenoma, a significant percentage of elderly-ACRO was affected by microadenomas ($p = 0.005$). Moreover, tumoral cell Ki67 was inversely correlated with patients' age at the time of acromegaly diagnosis ($p = 0.007$ r: −0.325).

Clinical features of acromegaly patients diagnosed > 65 years

Among the 14 patients diagnosed with acromegaly >65 years, 7 were males and 7 females ($p = 0.82$). Median age at diagnosis was 75 years (IQR: 8). At diagnosis, median GH levels were 4.5 ng/dL (IQR: 11) and IGF-I x ULN was 2 (IQR: 1.5). Nine patients (64.3%) carried a macroadenoma. Invasive tumours were detected in only two patients (14.3% of cases). Five patients (35.7%) underwent surgical removal of the pituitary tumour, 10 patients were treated with first generation SSA (57.1%), four patients with Pegvisomant (28.4%), 2 with DA (14.3%). Median Ki67 was 2% (IQR:

0.5). At last visit, 13 patients were considered cured/controlled (92.9%). In particular, 8 patients were still on treatment with first generation SSA (57.1%) and 4 patients with Pegvisomant (28.6%). Ten patients (71.5%) were affected by systemic arterial hypertension, 8 (57.1%) by left ventricular hypertrophy, 5 (35.7%) by arrhythmias, 11 (78.6%) by metabolic disorders, 9 (64.3%) by SAS, 5 (35.7%) by neurological/psychiatric disorders, 13 (92.9%) by nodular thyroid disease, 11 (78.6%) by joint/articular disorders and bone fragility. Four patients (28.6%) had a history of neoplasia. All patients diagnosed with cardiovascular, metabolic, neurological/psychiatric disorders, nodular thyroid disease, skeletal fragility and SAS during follow-up were affected by the same disorder at acromegaly diagnosis. On the other hand, among the 11 patients with joint/articular disorders at the end of the study, joint/articular disorders were already identified in 8 cases at the time of acromegaly diagnosis (73% of cases).

Risk factors for occurrence of systemic complications

We investigated the possible risk factors for occurrence of systemic complications in acromegaly with a univariate model (Supplementary Table 2). The factors that reached statistical significance in the univariate analysis entered the logistic regression, as shown in Fig. 2. We found that elderly-ACRO had an increased risk for the occurrence of systemic arterial hypertension ($p < 0.001$, OR: 5.4 95%IC: 2.6–10.9), left ventricular hypertrophy ($p = 0.01$, OR: 3 95%IC: 1.5–5.8) and metabolic disorders ($p = 0.006$ OR: 4.1; 95%IC: 2–8.3) and that patients diagnosed with acromegaly >65 years had an increased risk for the occurrence of nodular thyroid disease ($p = 0.013$ OR: 1.2 95%IC: 1.1–1.3) and joint/articular disorders ($p = 0.023$ OR:4.7 95%IC: 1.3–17.7). In addition, we found that female patients are at higher risk for occurrence of joint/articular disorders ($p = 0.016$; OR:1.4; 95%IC:1.1–2) and that patients with a long-term active acromegaly have an increased risk to develop a second neoplasia ($p = 0.02$; OR: 3; 95%IC:1.0–9), independently of age. In particular an active disease longer than 33 months (AUC: 0.747 $p = 0.008$ Sensibility: 77% specificity 60%) is associated with a 5-fold higher risk of second neoplasia (OR: 5 95%CI: 1.3–20.5, $p = 0.01$).

Discussion

Acromegaly is a chronic and systemic disease, associated with several complications that may increase disease-related mortality and compromise quality of life [1–3]. It is generally assumed that older acromegaly patients are affected by a mild disease phenotype [4–6]. In this study, we investigated the clinical features of acromegaly in elderly patients as compared to those of young ones and we tried to identify the risk factors for the occurrence of comorbidities in elderly acromegaly.

Cardiovascular disease and hypertension are frequent comorbidities in acromegaly patients [2] and age is considered a risk factor, together with persistence of GH/IGF-I hypersecretion, long-standing disease, smoke, obesity, dyslipidaemia [11]. Similarly, left ventricular hypertrophy is more frequently observed in acromegaly patients aged >50 years than in younger ones [12]. In particular, patient's age seems to act as a major determinant for this disorder [13]. Older age has been associated also to an increased impaired glucose metabolism risk in acromegaly [14–17] although evidences are not completely consistent [3, 18, 19]. In particular, Espinosa et al. [20] demonstrated that patients' age correlated with the occurrence of diabetes mellitus but not with impaired fasting glucose and impaired glucose tolerance.

Older age is a risk factor also for the occurrence of SAS in the general population. Acromegaly is per-se a condition that increases SAS risk [21].

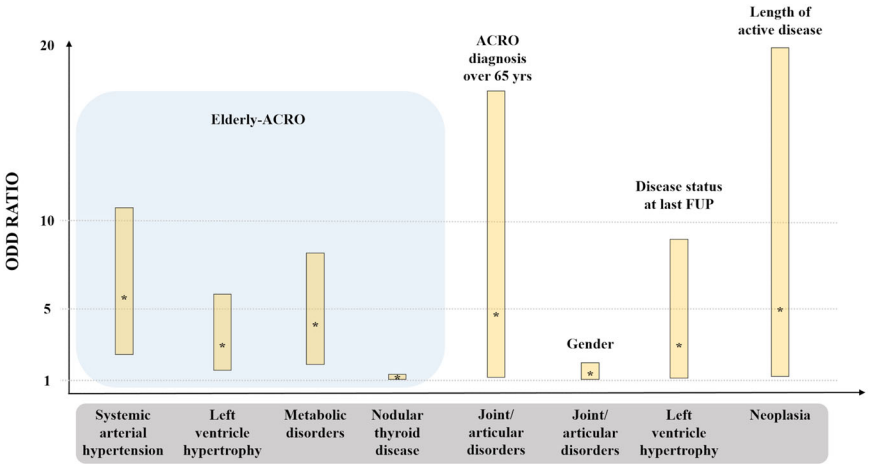

Fig. 2 Graphic representation of results of the logistic regression, for the occurrence of systemic acromegaly comorbidities. The bars represent the 95%IC, the asterisk the OR

Skeletal fragility, joint and bone complications are frequent in acromegaly [22–24]. Older age is considered a risk factor for primary osteo-arthrosis, which might be present in up to 30% of patients over 60 years [25, 26]. Bone and musculoskeletal diseases have been associated with worse geriatric outcomes and physical performance in a cohort of older acromegaly patients [27]. However, a clear correlation between age and skeletal fragility was not established: most of the available evidence seems to rule out an effect of age on vertebral fracture risk in acromegaly [3].

In this cohort, we found that frequency of neurological/psychiatric, joint/articular disorders and skeletal fragility was higher in elderly acromegaly then in controls but similar in elderly and young acromegaly patients. On the contrary, cardiovascular and metabolic disorders, nodular thyroid disease and SAS occurred more frequently in elderly-ACRO then in young-ACRO and in controls. This finding may suggest that neurological/psychiatric, joint/articular disorders, and skeletal fragility are predominantly due to GH/IGF-I hypersecretion rather than to aging. On the other hand, the occurrence of cardiovascular, metabolic disorders, nodular thyroid disease and OSAS seems to be influenced by both GH/IGF-I hypersecretion and aging.

Interestingly, in this study, we did not find a difference in the frequency of neoplasms between elderly and young acromegaly patients that was detected in ~24% of the patients, despite it is well known that cancer is an age-dependent disease. In addition, we confirm that duration of active acromegaly represents a factor risk for the occurrence of neoplasia. This may be due to the strict oncological surveillance that we conducted routinely in the clinical management of acromegaly patients. In fact, according to our clinical practice, acromegaly patients annually underwent screening for neoplasia, performing prostate specific antigen dosage, urinalysis, faecal occult blood test, thyroid, and abdominal ultrasound and breast radiography. Endoscopic examinations, such as gastroscopy and pan-colonoscopy, are instead performed every two or three years or also annually in cases of previous detection of colon lesions.

In our centres, all acromegaly patients are followed-up with a straight surveillance for the occurrence of acromegaly-related comorbidities. More in detail at our pituitary centres, all acromegaly patients underwent a close follow-up, in agreement with the 2003 Consensus Conference on the diagnosis and treatment of acromegaly complications. In particular, at diagnosis all patients underwent glucose and lipid metabolism assessment, echocardiography, electrocardiogram, colonscopy, bone densitometry, sleep assessment, blood pressure monitoring [28]. Moreover, during follow-up, screening for comorbidities was conducted according to the timing that was suggested by guidelines or closer, if clinically indicated [29].

In our multicentre and retrospective series, we found that GH levels at acromegaly diagnosis were significantly lower in elderly acromegaly patients and in those diagnosed > 65 years, as compared to those observed and diagnosed in young patients. An inverse correlation between basal GH levels and age at acromegaly diagnosis was already described in previous studies [30, 31]. The lower GH and IGF-I levels in elderly acromegalic patients may be due to the physiological reduction in GH and IGF-I secretion during aging but also to a different tumour biology [32, 33]. As in normal aging, this phenomenon could be due to the reduction in hypothalamic GHRH release and to alterations in age-related plasma concentrations of sex steroids [34, 35]. Moreover, several authors reported that elderly-ACRO carried frequently smaller and enclosed tumours [36–38], with a possible negative correlation between tumour size and patient's age. Similarly, in our series, a significant percentage of elderly-ACRO carried microadenomas.

Moreover, we found an inverse correlation between the Ki67 Li and patients' age at the time of acromegaly diagnosis. As Ki67 is widely recognised as a biomarker of tumoral proliferation [39], the lower values identified in elderly-ACRO may suggest a more benign tumoral behaviour in this subset of patients.

However, in our study, we found that elderly-ACRO are affected more frequently by systemic comorbidities as compared to a control group of age and gender-matched subjects, as shown also by other authors [40, 41].

This finding allows us to confirm that GH and IGF-I hypersecretion plays a crucial role in the development of disease complications, as cardiovascular, metabolic, neurological/psychiatric, and joint/articular disorders, nodular thyroid disease, SAS and skeletal fragility.

Actually, data on the role of aging in the development of comorbidities in acromegaly are not conclusive [3]. In fact, the results of previous studies are difficultly comparable for methodological issues, as study designs, selection of patients' cohort, definition of disease functional status and of complications. In this view, our study suggested that cardiovascular, metabolic, neurological disorders may represent an interesting clinical scenario, in which acromegaly should be suspected both in young individuals and in elderly ones with multiple acromegaly-related comorbidities.

A limitation of our study is its retrospective design.

An interesting finding of this study concerns the therapeutic choice that did not differ between elderly and young acromegaly patients. In fact, a similar percentage of patients underwent pituitary surgery, treatment with first-generation SSA and Pegvisomant.

Data on surgical treatment in elderly acromegaly are few but encouraging [42–45], providing a remission rate of

around 74% of cases [46], without severe perioperative complications [47]. The higher remission rates achieved in elderly acromegaly patients may be due to a mild tumour behaviour in this subset of patients, as somatotroph tumors are usually smaller and less aggressive in older patients and consequently more likely to be totally removed. Anyway, a proper anaesthesia risk must be evaluated preoperatively and surgery must be performed by an expert pituitary neurosurgical team [3].

Finally, in this cohort, elderly-ACRO were treated both with Pegvisomant and Pasireotide Lar, as second line medical treatments. This finding may encourage the use of both these treatments for a tailored and personalized therapy [48], also in elderly acromegaly patients, resulting safe as suggested also by a previous report [49]. In this cohort, no elderly patient required a combination treatment with Pegvisomant and Pasireotide Lar [49], as all patients reached acromegaly control with conventional therapies, according to a mild tumoral behaviour.

Our data proved that cardiovascular and metabolic disorders, nodular thyroid disease and SAS occurred more frequently in elderly-ACRO then in young-ACRO and in controls and that the frequency of neurological/psychiatric, joint/articular disorders, skeletal fragility are higher in elderly acromegaly then in controls. These finding may suggest that neurological/psychiatric and articular disorders and skeletal fragility are predominantly due to GH/IGF-I hypersecretion rather than to aging. On the other hand, the occurrence of cardiovascular and metabolic disorders, nodular thyroid disease, and SAS seems to be influenced by both GH/IGF-I hypersecretion and aging.

In conclusion, our results underline that aging represents an additional risk factor for the occurrence of comorbidities in acromegaly. The high frequency of cardiovascular/metabolic disorders, nodular thyroid disease and SAS reflects the need for a prompt screening in particular in elderly patients. Finally, our study confirms that systemic complications of acromegaly have to be screened, investigated, and diagnosed, in all acromegaly patients and particularly in elderly ones.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethics All procedures performed in the study were in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by Institutional Review Board of the Gemelli Hospital, Catholic University of the Sacred Heart, Rome, and of Azienda Ospedaliera Universitaria of Ferrara.

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