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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur et
de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas à
corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres, je
rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime
si je suis fidèle à mes
promesses.
Que je sois couvert
d'opprobre et méprisé de mes
confrères
si j'y manque.

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RESUME

Introduction. L'acromégalie est une pathologie endocrinienne due à une sécrétion excessive d'hormone de croissance, elle est responsable de nombreuses complications notamment cardio-vasculaires et cancéreuses. L'objectif de notre étude était d'estimer la prévalence et l'incidence de l'acromégalie et de ses complications à l'échelle nationale.

Méthodes. A partir de la base de données PMSI (Programme de Médicalisation des Systèmes d'Information) ont été extraites les informations des patients adultes ayant eu au moins un séjour hospitalier entre 2012 et 2021 avec un code diagnostique d'acromégalie, permettant ainsi d'estimer la prévalence de la maladie. Une validation de notre algorithme d'extraction a été effectuée en faisant une revue locale des dossiers de patients extraits. Une cohorte des nouveaux patients a ensuite été conduite sur la période 2015-2020 permettant d'estimer l'incidence de l'acromégalie, la prévalence et le délai d'apparition des complications. L'impact de l'âge au diagnostic, du sexe, et de la présence d'un diabète a été analysé par comparaison des sous-groupes.

Résultats. Au total, 7943 patients ont été identifiés avec une valeur prédictive positive de notre méthode estimée à 87%. La prévalence estimée était de 10.4/100 000 en France, l'incidence annuelle était de 0.76/100 000 habitants/an. Au cours d'un suivi de 4.3 ± 3.2 ans, 530 patients sont décédés, soit une mortalité de 1.6% par an. Le parcours de prise en charge retrouvait 43% de chirurgie et 4% de radiothérapie. Les complications les plus fréquentes étaient l'hypertension artérielle (43%), l'apnée du sommeil (34,3%) et le diabète (31,3%). Celles-ci étaient présentes avant le diagnostic dans 76% des cas pour l'HTA et le diabète et 56% pour l'apnée du sommeil. Le sexe masculin, un âge au diagnostic supérieur à 50 ans et le diabète étaient associés à un risque augmenté de complications, principalement cardiovasculaires.

Conclusion. Cette étude a permis d'estimer pour la première fois l'incidence et la prévalence de l'acromégalie en France. Malgré certaines limitations inhérentes à l'utilisation des bases médico-administratives hospitalières, l'étude des parcours des patients était possible, retrouvant un taux de complications plus important, un âge au diagnostic plus élevé, et moins d'actes thérapeutiques que dans la littérature. Ce qui pourrait refléter une prise en charge sub-optimale des patients sur l'ensemble du territoire en comparaison aux données publiées des cohortes de patients issues des centres spécialisés.

Mots clés : Acromégalie ; cohorte nationale ; épidémiologie ; adénome hypophysaire

ABSTRACT

Introduction. Acromegaly is an endocrine disease caused by the hypersecretion of growth hormone. It is responsible for numerous complications, notably cardiovascular diseases and cancers. The objective of our study was to estimate the prevalence and incidence of acromegaly and its complications through a national retrospective cohort.

Methods. By using the French database PMSI, data were extracted about adult patients who had at least one hospital stay between 2012 and 2021 with a diagnosis code of acromegaly. A validation of our extraction algorithm was performed by conducting a local review of extracted patient records. We estimated the prevalence of the disease from all the patients identified in the database. A cohort of new patients was then conducted over the period 2015-2020 allowing us to estimate the incidence of acromegaly, the time to onset and the prevalence of complications. The impact of gender, age at diagnosis, and presence of diabetes was analysed by subgroup comparison.

Results. A total of 7 943 patients were identified with a positive predictive value of our method estimated at 87%, resulting in a prevalence of 10.4/100 000 in France, in accordance with data previously described in other countries. The annual incidence was 0.76/100 000 inhabitants/year. During a follow-up of 4.3 ± 3.2 years, 530 patients died, resulting in a 1.6% per year mortality. The treatment strategy involved surgery for 43% of patients and 4% underwent radiotherapy. The most frequent complications were hypertension (43%), sleep apnoea (34.3%) and diabetes (31.3%), they were present before diagnosis in 76% of cases for hypertension and diabetes and 56% for sleep apnoea. Male gender, age at diagnosis higher than 50 years old and diabetes were associated with an increased risk of complications, mainly cardiovascular.

Conclusion. This study is the first to estimate the incidence and prevalence of acromegaly in France. Despite limitations inherent to administrative databases, it was possible to ensure a follow-up of patients, finding higher prevalence of complications, a higher age at diagnosis, and less use of therapeutic procedures than in previous studies. This could reflect suboptimal treatment strategy around the country in comparison with published data from specialized expert centers.

Keywords: **Acromegaly; pituitary; epidemiology; national cohort**

ABBREVIATIONS

CCAM: Classification Commune des Actes Médicaux

CNIL: Commission Nationale de l'Informatique et des Libertés),

DNRP: Danish National Registry of Patients

GH: Growth Hormone

HTA: Hypertension artérielle

ICD-10: International Classification of Diseases 10th revision

IGF-1: Insulin-like Growth Factor 1

INSEE: Institut National de la Statistique et des Etudes Economiques

MRI: Magnetic Resonance Imaging

PMSI: Programme de Médicalisation des Systèmes d'Information

PPV: Predictive Positive Value

RSS: Résumé de Sortie Standardisé

SAS: Statistical Analysis System

SD: Standard Deviation

TSH: Thyroid-Stimulating Hormone

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I - PREAMBULE

L'acromégalie est une pathologie endocrinienne due à un excès d'hormone de croissance (Growth Hormone GH) et d'insulin-like growth factor 1 (IGF-1), le plus souvent secondaire à un adénome hypophysaire secrétant de la GH (1).

La maladie se caractérise par un syndrome dysmorphique prédominant sur les mains, les pieds et le visage, mais aussi par de nombreuses complications systémiques secondaires aux taux élevés de GH et d'IGF-1. Plusieurs complications cardiovasculaires sont classiquement décrites avec l'hypertension artérielle (HTA), la cardiopathie hypertrophique (secondaire à l'HTA mais également par effet direct de la GH), l'insuffisance cardiaque, les valvulopathies à type de régurgitation, les troubles du rythme, les syndromes coronariens aigus et les accidents vasculaires cérébraux (2–4). D'autres complications systémiques sont possibles avec notament le diabète sucré, le syndrome d'apnée du sommeil obstructif, des céphalées, des syndromes radiculaires avec principalement celui du canal carpien, des douleurs articulaires et des fractures vertébrales (5,6). Une augmentation du risque de néoplasie associée à l'acromégalie a été discutée et reste débattue, le cancer colorectal étant le premier à être incriminé, suivi du cancer de la thyroïde, de la prostate et du sein (7–9). Enfin, l'adénome hypophysaire lui-même peut provoquer des troubles du champ visuel, ou être responsable d'une production excessive d'autres hormones en cas d'adénomes dits mixtes, comme la prolactine, le cortisol en cas de sécrétion d'hormone adénocorticotrope (ACTH) ou la thyréostimuline (TSH) (5).

L'acromégalie est considérée comme une maladie rare, avec une prévalence estimée à 10/100 000 habitants mais variable selon les pays (10). Il est cependant possible que la prévalence soit sous-estimée, la lenteur d'installation du syndrome dysmorphique rendant en effet les patients difficiles à identifier. Le retard diagnostique moyen est estimé à 7 ans, mais il existe une proportion difficilement quantifiable de patients malades non diagnostiqués (11,12). Du fait de la rareté de la maladie, il est difficile d'obtenir des groupes de patients suffisamment importants pour avoir des statistiques fiables concernant la fréquence de survenue des complications, ou sur l'épidémiologie de la maladie en elle-même.

Le Programme de Médicalisation des Systèmes d'Information (PMSI) est un dispositif mis en place afin de quantifier l'activité des établissements de santé en France. Son utilisation actuelle répond à un objectif budgétaire : le financement des établissements de santé étant dépendant du système de tarification à l'activité, une évaluation précise selon une nomenclature standardisée de l'activité est nécessaire afin d'estimer en conséquence le budget à allouer à chaque établissement. L'Agence Technique de l'Information sur l'Hospitalisation (ATIH) reçoit donc les données des séjours d'hospitalisation réalisés par l'ensemble des établissements hospitaliers français, du secteur public et du secteur privé. Ces données sont recueillies sous la forme d'un Résumé de Sortie Standardisé (RSS), qui utilise un système de codage des pathologies prises en charge et des actes de soins effectués selon la 10ème version de la Classification

Internationale des Maladies (CIM-10) et la Classification Commune des Actes Médicaux (CCAM).

Bien qu'initialement conçue et utilisée pour des considérations administratives et financières, une base de données recensant l'ensemble des séjours hospitaliers en France constitue une source conséquente d'informations pouvant être utilisées dans un but épidémiologique. En effet, bien qu'anonymisées, les données du PMSI d'un même patient sont liées entre elles, permettant de réaliser un suivi au fil des différentes hospitalisations. Ceci, associé à l'effectif considérable que représente l'ensemble des patients hospitalisés, permet donc d'analyser des cohortes de patients à grande échelle qui seraient autrement impossibles à mettre en place en recherche clinique classique.

L'acromégalie est une pathologie apparaissant comme pertinente à étudier via la base de données du PMSI pour plusieurs raisons. D'une part, le système de recueil national offre un effectif large qui résout la difficulté de recrutement des patients due à la rareté de la maladie. La plupart des patients acromégales sont susceptibles d'être hospitalisés au moins une fois dans leur parcours de soins, que ce soit pour confirmer le diagnostic, ou à des fins de traitement ou de suivi, ce qui est un autre facteur favorisant un recrutement efficace des patients (13). Les nombreuses complications de l'acromégalie peuvent ensuite être suivies pour chaque patient en recherchant leur survenue lors de leurs différentes hospitalisations, et ce même si celles-ci ne sont pas le motif initial de recours aux soins, les diagnostics associés pouvant modifier la prise en charge étant également renseignés dans la base. Enfin, la stratégie thérapeutique peut au moins en partie être l'objet d'études, car si les traitements médicamenteux ne font pas partie des données accessibles, les actes chirurgicaux et ceux de radiothérapie qui peuvent être pratiqués sur l'adénome hypophysaire sont renseignés et analysables.

Au vu des informations nouvelles sur l'acromégalie que pourrait offrir une base de données médico-administrative nationale, et du fait qu'aucune étude n'a à ce jour utilisé ce type d'outil pour cette pathologie en France, nous avons réalisé un travail de recherche avec plusieurs objectifs : estimer la prévalence et l'incidence de la maladie par un recrutement se voulant exhaustif, et décrire pour les patients retrouvés leurs caractéristiques dont la survenue des complications et les traitements effectués.

II - INTRODUCTION

Acromegaly is an endocrine disease caused by the hypersecretion of growth hormone (GH), from a pituitary adenoma in most cases, associated with the elevation of insulin-like growth factor 1 (IGF-1) (1).

The disease is characterized by physical deformations predominantly on hands and feet as well as the face, but also by numerous systemic complications secondary to high levels of GH and IGF-1: complications of the cardiovascular system involving arterial hypertension, cardiac hypertrophy, heart failure, cardiac valve disease, arrhythmia, acute coronary syndromes, and strokes, but also diabetes, obstructive sleep apnoea, headaches, radicular syndrome such as carpal tunnel, arthropathy and vertebral fractures (5). An increased risk of neoplasia associated with acromegaly has been discussed and remains debated, colorectal cancer being the first to be incriminated followed by thyroid, prostate, and breast cancer (7,8,14). Lastly, the pituitary adenoma itself can cause visual field impairment, or be responsible for an excessive production of other pituitary hormones such as prolactin, thyroid-stimulating hormone (TSH), or cortisol in the case of mixed adenomas (6). Overall, an increased risk of mortality has initially been described due to cardiovascular and neoplastic affections (15), but recent large cohort studies tend to show a decrease in the mortality rate, credited to changes in treatment patterns (16–18).

Acromegaly is considered a rare disease, having prevalence and incidence which vary among countries, with estimation of 2.8-13.7 cases per 100 000 people and 0.2-1.1 cases / 100 000 people/year respectively (10). A possible underestimation of those numbers has already been evoked, as the slow manifestation of symptoms can make the patients difficult to identify, with an average delay in diagnosis of 7 years when the disease is not simply overlooked (11,12). Because of this rarity, getting robust epidemiological data is quite challenging, and national databases and registries can be an interesting tool to achieve that goal (19). As most patients with acromegaly are prone to be hospitalized even for a brief period at some point in their life, be it for diagnosis purpose, treatment, or follow-up (13), hospital stay records could be a strong source of information about those patients.

The main objectives of the present study were to estimate the contemporary epidemiology of acromegaly in France using an exhaustive analysis of national hospital databases, and to describe patient characteristics.

The secondary objectives were to describe whether acromegaly-associated comorbidities and complications were described before or after acromegaly diagnosis, and compare complications occurrence between subgroups of interest.

III - METHODS

1- *Source population*

We identified patients with acromegaly from the PMSI (Programme de Médicalisation des Systèmes d'Information): the French national hospitalization database. PMSI is a medico-administrative database, which aims to compile information about every inpatient hospitalization in each French healthcare facility from their discharge abstract. PMSI gathers administrative information (age, gender, place of residence, duration of hospital stay), medical diagnoses following the codes from the International Classification of Diseases (ICD-10) with the affection that led to hospitalization being reported as "main diagnosis" and comorbidities reported as "associated diagnoses", and medical procedures such as imaging test or surgery using the French nomenclature of medical acts CCAM (Classification Commune des Actes Médicaux). Even though data are anonymized, multiple hospital stays of a single patient are linked, allowing to get a longitudinal record for each patient (20–22). Data are progressively classified and made unavailable after 10 years, so at any given time one can only access to data of hospitalizations that happened during the last 10 years.

2- *Patient selection and data collection*

Data extraction was performed in April 2022, available data ran from 01/01/2012 to 12/31/21. We included all patients who had ICD-10 diagnosis E 22.0 "Acromegaly and pituitary gigantism" coded in their chart at least one time, whether it was a main or an associated diagnosis for hospitalization. For each patient, the stay where the acromegaly code appeared for the first time was called the "index stay" of the patient. All other events could appear before the index stay, at the same of the index stay or thereafter. We decided to consider any event to be anterior to the acromegaly diagnosis if its first occurrence was declared before or at the same time as the index stay, and posterior if it appeared later.

A validation of our algorithm was carried out by extracting the local files of the University Hospital Center of Tours in order to verify that the included patients had a real acromegaly. Half of the false-positive patients were erroneously diagnosed during childhood or puberty while we did not find any true positive diagnosed during that period (detailed results below in "case verification"), leading us to exclude all patients who were diagnosed with acromegaly before the age of 18.

Epidemiological outcomes were measured as follows:

- Prevalence: patient with at least one acromegaly code over the period was defined as a prevalent case. The prevalence rate was estimated as the total number of patients with acromegaly divided by the mean French population at that time - as available from the French National Institute of Statistics and Economic Studies (Institut National de la Statistique et des Etudes Economiques *INSEE*) - adjusted to the positive predictive value (23) ;

- The incidence was estimated over the 2015-2020 period in order to exclude prevalent cases. Patients having their first ICD-10 code of Acromegaly between January 1st, 2015 and December 31st, 2021 (without any acromegaly diagnosis during the 2012-2014 period) were defined as an incident case. The incidence was estimated as the number of incident cases divided by the total French population of each year ;
- Case fatality defined as the percentage of hospital death among the total prevalent cases over the decade.

Sociodemographic data was collected: age at diagnosis and age at death, gender, obesity, dyslipidemia. For each patient, the adapted Charlson score was calculated according to a previously published method (24).

Comorbidities and complications were defined as described in the *appendix 1*. Treatment patterns such as a pituitary surgery or radiotherapy were also collected. Because radiotherapy codes are not specific of a location, we defined patients who underwent pituitary radiotherapy as those who had radiotherapy while not having a malignant neoplasm diagnosed before. Complications, comorbidities and treatments were analysed only for patients diagnosed during the 2015-2020 period in order to have long-enough follow-ups before and after diagnosis.

3- Outcomes

The main objectives of the study were:

- To identify acromegaly cases diagnosed between 2012 and 2021 to assess the annual incidence in France, and evaluate acromegaly prevalence.
- To describe patient characteristics at diagnosis and the incidence of complications of acromegaly, including those which appeared before and after the diagnosis of acromegaly was made.
- To assess treatment modalities by searching which patients underwent pituitary surgery or radiotherapy.

Secondary objectives were:

- To distinguish for each complication code if they tend to appear before or after the main diagnosis of acromegaly, and for those which appear after to determine the time interval between acromegaly diagnosis and appearance of complications.
- To compare patients in order to evaluate if complications were more likely to appear depending on patient characteristics: gender, age at diagnosis and diabetes, and if they were associated with death.

4- Statistical analysis

Qualitative variables were presented as count and percentage, and quantitative variables as means and standard deviations (SD). Student t-test was used to search for association of age at diagnosis and age at death with categorical variables, while association of complications with gender, diabetes, age at diagnosis and death status was searched using Chi-squared test. All the analyses were performed using SAS (SAS institute Inc., Cary, North Carolina, USA), version available on the national PMSI website at the moment of the analyses.

5- Ethics

Our study was conducted following the Reference Methodology MR-005 established by the CNIL (Commission Nationale de l'Informatique et des Libertés), the French authority ensuring data protection, which granted access to PMSI data (authorization number F20211104105727 registered on Health Data Hub). As the study was retrospective, using anonymized data without consequence on medical care, patients were not informed and written consent was not needed.

IV – RESULTS

1- *Local cases verification*

A local case validation was carried out in our teaching hospital by a physician working in the endocrinology department, by checking the medical charts of 132 patients selected in the hospital discharge database. After verification, 102 patients were confirmed cases, resulting in a 77% Predictive Positive Value (PPV) (Table 1). Patients younger than 18 years old accounted for 15 of the 30 false positives while there was not any true positive among them, so they were ruled out of the study, increasing our PPV to 87%. Almost all patients who had an acromegaly code more than once were confirmed cases, and all of them were confirmed cases when acromegaly code was found more than two times in their hospital resumes increasing even more the PPV to 97% and 100%. Because 23 of the 102 true positives had only one code registered in their files, we chose to keep patients with only one code in order not to rule out confirmed cases for the following analysis, and therefore sticking to a PPV of 87%.

Table 1. Accuracy of acromegaly ICD- 10 code for hospital stays, according to the number of times the code is used and to the age at first diagnosis

	Comfirmed diagnosis/Number of cases	PPV
≥ 1 time, any age	102/132	77%
≥ 1 time, ≥ 18 years old	102/117	87%
≥ 2 times, any age	79/81	97.5%
≥ 2 times, ≥ 18 years old	79/81	97.5%
> 2 times, any age	60/60	100%
> 2 times, ≥ 18 years old	60/60	100%

2- *Acromegaly epidemiology*

8 231 patients having at least one diagnosis code of acromegaly in their chart were found in the database during the 2012-2021 period, and 7 943 remained after applying our 18-year-old age at diagnosis limit (Figure 1). With our positive predictive value of 87% we estimated there would be 6 910 patients with actual acromegaly in France, corresponding to a prevalence of 10.4/100 000.

A total of 3 551 incident cases occurred over the 2015-2020 period (Table 2), giving an average number of 592 new patients each year and 515 after correcting with PPV, giving an annual incidence rate in France of 0.76/100 000.

Mean follow-up was 4.26 ± 3.18 years for all patients, and 2.51 ± 1.93 years for patients diagnosed between 2015 and 2020. Eventually, 530 patients died during follow-up (Table 2), giving a case fatality rate for all patients of 1.6% each year.

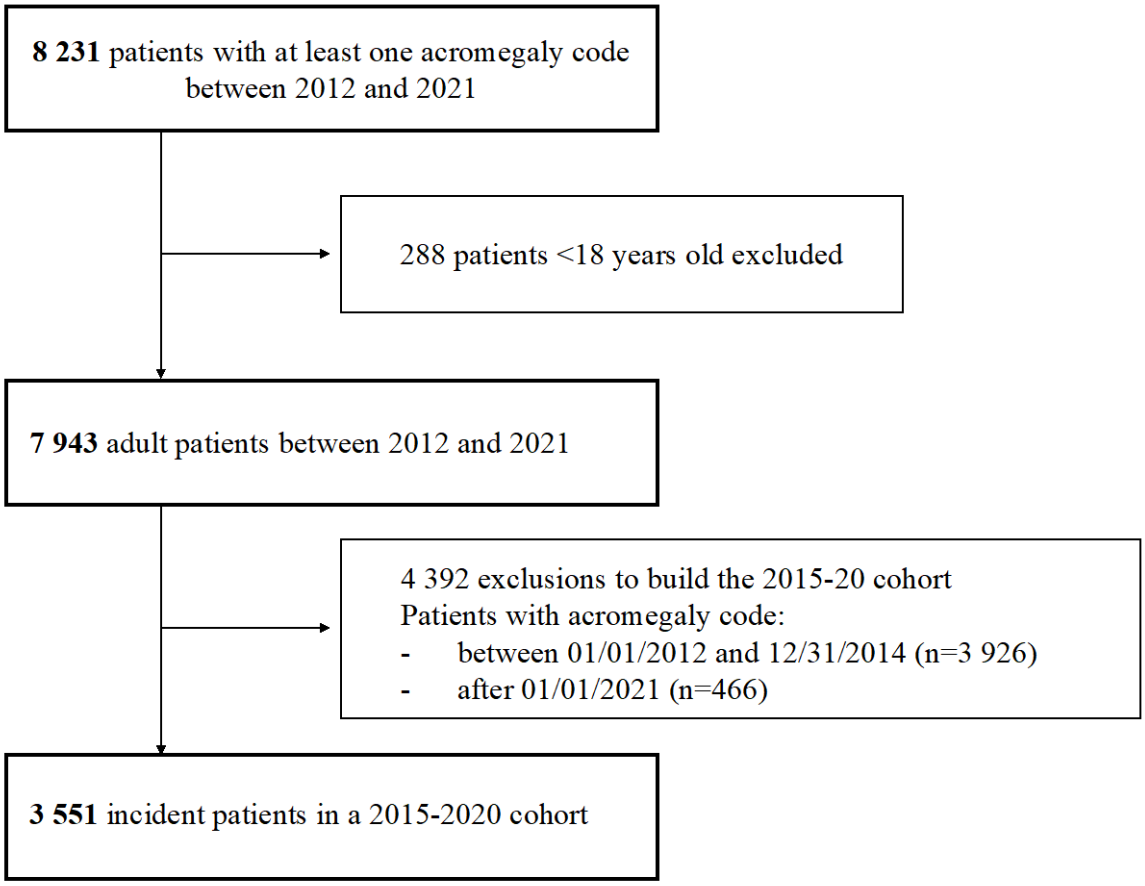

Figure 1. Flowchart of study population

Table 2. Incident cases of acromegaly and number of deaths by year

	New cases	Deaths
2012	2 096	27
2013	1 098	28
2014	732	43
2015	666	51
2016	623	48
2017	627	59
2018	566	77
2019	598	59
2020	471	85
2021	466	53
Total	7 943	530

3- *Patients characteristics, complications, treatment patterns*

Table 3 shows patients characteristics, prevalence of complications during follow-up including mortality, and number of patients that underwent surgery, radiotherapy or both. There was a slight female predominance with almost 55% of patients being women. Mean age at diagnosis was 53 years old. Hypertension, sleep apnoea, diabetes and hypopituitarism were the most frequent complications (43.0%, 34.3%, 31.3% and 26.4% respectively).

There were 1 528 patients who underwent surgery, among whom 85 (5.5%) had a bimodal treatment with radiotherapy associated to surgery and 1 443 only had surgery reported in their files. 57 patients had radiotherapy without surgery, representing 40% of the 142 patients who had radiotherapy. 1 966 patients had neither surgery nor radiotherapy reported during any of their hospitalization, representing 55% of patients being treated with medication or not being treated at all, at the time of the study.

4- *Time distribution of complications*

Table 4 depicts for each complication the number of patients for whom that condition appeared before or at the same time of acromegaly diagnosis. Are also displayed the mean time interval between acromegaly diagnosis and complication appearance, calculated for complications that appeared after acromegaly diagnosis.

Diabetes, cardiovascular complications (except for heart valve disease and heart failure), carpal tunnel syndrome, hyperprolactinemia and visual fields defects were more often observed before acromegaly diagnosis than after (ranging from 50% to 77%), while diabetes insipidus and colonic polyps were observed after acromegaly diagnosis in most cases (54% and 70% respectively).

When considering complications and comorbidities that happened after acromegaly diagnosis, mean time interval was shorter for diabetes insipidus, visual field defect and hyperprolactinemia (233, 321 and 361 days respectively), while breast cancer, myocardial infarction and prostate cancer had the longest time of appearance after acromegaly diagnosis (772, 745 and 707 days respectively).

Table 3. Characteristics of patients with a first diagnosis of acromegaly between 01/01/2015 and 12/31/2020

	n	%
All patients	**3 551**	***100***
Demographics		
Female	1 944	*54.7*
Age at diagnosis, mean ± std	53.1 ± 16.2	
Endocrine conditions		
Diabetes	1 110	*31.3*
Type 1	24	*0.7*
Type 2	996	*28.0*
Other or unknown type	90	*2.5*
Hyperprolactinemia	369	*10.4*
Hypopituitarism	939	*26.4*
Diabetes insipidus	276	*7.8*
Cardiovascular conditions		
Hypertension	1 526	*43.0*
Hypertrophic cardiomyopathy	81	*2.3*
Coronary artery disease	348	*9.8*
Myocardial infarction	67	*1.9*
Heart failure	253	*7.1*
Stroke	152	*4.3*
Cardiac arrhythmia	290	*8.2*
Atrial fibrillation	273	*7.7*
Ventricular tachycardia/fibrillation	30	*0.8*
Heart valve diseases (any)	175	*4.9*
Aortic valve stenosis	58	*1.6*
Aortic valve regurgitation	46	*1.3*
Mitral valve regurgitation	97	*2.7*
Tricuspid valve regurgitation	30	*0.8*
Neoplasia		
Colonic polyp	638	*18.0*
Cancer (any)	586	*16.5*
Thyroid	81	*2.3*
Breast	76	*2.1*
Colorectal	48	*1.4*
Prostate	44	*1.2*
Kidney	33	*0.9*
Urinary tract	30	*0.8*
Other conditions		
Sleep apnoea syndrome	1 217	*34.3*
Carpal tunnel syndrome	277	*7.8*
Headache	514	*14.5*
Visual field defect	176	*5.0*
Treatments	**1 682**	***47.4***
Surgery	1 528	*43.0*
Radiotherapy	142	*4.0*
Surgery and radiotherapy	85	*2.4*
Death	**186**	***5.2***
Mean age at death (STD)	71.6 ± 12.2	

Table 4. Complications before acromegaly and time interval between acromegaly diagnosis and complications if they occurred after acromegaly diagnosis

	Complication diagnosed before acromegaly		Time interval between acromegaly diagnosis and complication occurrence (days)
	n	%	
Endocrine conditions			
Diabetes	852/1 110	*76.8%*	393.5 ± 459.1
Hyperprolactinemia	234/369	*63.4%*	361.0 ± 410.9
Hypopituitarism	512/939	*54.5%*	397.7 ± 442.6
Diabetes insipidus	126/276	*45.7%*	233.2 ± 300.7
Cardiovascular conditions			
Hypertension	1 172/1 526	*76.8%*	389.1 ± 437.1
Hypertrophic cardiomyopathy	47/81	*58.0%*	565.8 ± 612.7
Coronary artery disease	219/348	*62.9%*	579.8 ± 537.4
Myocardial infarction	40/67	*59.7%*	744.9 ± 570.5
Heart failure	121/253	*47.8%*	575.0 ± 555.8
Stroke	83/152	*54.6%*	681.9 ± 603.0
Cardiac arrhythmia	193/290	*66.6%*	528.4 ± 560.7
Atrial fibrillation	179/273	*65.6%*	527.3 ± 554.6
Ventricular tachycardia/fibrillation	18/30	*60.0%*	502.8 ± 602.0
Heart valve diseases (any)	90/175	*51.4%*	623.4 ± 537.6
Aortic valve stenosis	29/58	*50.0%*	580.9 ± 485.5
Aortic valve regurgitation	19/46	*41.3%*	715.2 ± 629.6
Mitral valve regurgitation	51/97	*52.6%*	697.0 ± 561.4
Tricuspid valve regurgitation	12/30	*40.0%*	658.5 ± 523.1
Neoplasia			
Colonic polyp	188/638	*29.5%*	603.6 ± 567.6
Cancer (any)	328/586	*56.0%*	484.9 ± 528.7
Thyroid	42/81	*51.9%*	388.0 ± 400.3
Breast	41/76	*53.9%*	771.8 ± 673.4
Colorectal	21/48	*43.8%*	451.6 ± 539.7
Prostate	25/44	*56.8%*	706.9 ± 607.5
Kidney	14/33	*42.4%*	683.0 ± 569.1
Urinary tract	16/30	*53.3%*	683.2 ± 527.9
Other conditions			
Sleep apnoea syndrome	685/1 217	*56.3%*	379.7 ± 442.8
Carpal tunnel syndrome	212/277	*76.5%*	492.9 ± 534.2
Headache	263/514	*51.2%*	375.8 ± 443.0
Visual field defect	116/176	*65.9%*	321.8 ± 354.1

5- *Differences among sub-categories (gender, age at acromegaly diagnosis, diabetes, death)*

Tables 5, 6, 7 and 8 show patient characteristics according to gender, age at diagnosis, diabetes status, and death occurrence during follow-up respectively. Age at diagnosis was not significantly different between men and women, but patients with diabetes and those who died during follow-up were diagnosed at a significantly older age.

Men had higher rates of most cardiovascular affections except for hypertension and stroke, higher rates of cancer except for thyroid and breast cancer, and higher rates of hypopituitarism and sleep apnoea. Women had higher rates of headaches and breast cancer. Mortality during follow-up was higher among men than women (6.8% versus 3.9%) with a younger age at death. There was no difference in treatment patterns between men and women.

Patients who were 50 or older when they had acromegaly diagnosed had higher rates of almost all the complications and comorbidities that we analysed except for thyroid cancer and carpal tunnel syndrome. They were less frequently treated with significantly lower rates of surgery and radiotherapy, and had higher mortality rate (8.2% versus 0.9% for those diagnosed before the age of 50).

Patients with diabetes had higher rates of all cardiovascular complications, hypopituitarism, overall cancer and specifically thyroid cancer, and sleep apnoea. Significantly fewer patients had pituitary surgery when having diabetes than when not having diabetes. Mortality was higher for patients with diabetes but age at death was not different between patient with or without diabetes.

Patients who died during the follow-up were older at baseline, mostly men and had significantly higher prevalence of diabetes, hyperprolactinemia, hypopituitarism, most cardiovascular complication except hypertrophic cardiomyopathy, all types of cancer and more specifically urinary tract cancer and colorectal cancer as well as colonic polyp, and carpal canal syndrome. The number of patients who had pituitary surgery or radiotherapy was lower among patients who died during the follow-up (8.6% and 0.5% respectively) than those who were still alive at the end of follow-up (44.9% and 4.2% respectively).

Table 5. Characteristics of incident patients according to gender

	Female	Male	P value
All patients	n= 1944	n= 1607	
Demographics			
Age at diagnosis, mean ± std	53.6 ± 16.4	52.5 ± 15.9	0.0583
Endocrine conditions			
Diabetes	595 (30.6%)	515 (32.0%)	0.3567
Hyperprolactinemia	192 (9.9%)	177 (11.0%)	0.2688
Hypopituitarism	430 (22.1%)	509 (31.7%)	**<0.0001**
Diabetes insipidus	153 (7.9%)	123 (7.7%)	0.8106
Cardiovascular conditions			
Hypertension	810 (41.7%)	716 (44.6%)	0.0835
Hypertrophic cardiomyopathy	30 (1.5%)	51 (3.2%)	**0.0012**
Coronary artery disease	132 (6.8%)	216 (13.4%)	**<0.0001**
Myocardial infarction	22 (1.1%)	45 (2.8%)	**0.0003**
Heart failure	106 (5.5%)	147 (9.1%)	**<0.0001**
Stroke	75 (3.9%)	77 (4.8%)	0.1713
Cardiac arrhythmia	119 (6.1%)	171 (10.6%)	**<0.0001**
Atrial fibrillation	113 (5.8%)	160 (10.0%)	**<0.0001**
Ventricular tachycardia/fibrillation	10 (0.5%)	20 (1.2%)	**0.0180**
Heart valve diseases (any)	75 (3.9%)	100 (6.2%)	**0.0012**
Aortic valve stenosis	23 (1.2%)	35 (2.2%)	**0.0199**
Aortic valve regurgitation	16 (0.8%)	30 (1.9%)	**0.0062**
Mitral valve regurgitation	39 (2.0%)	58 (3.6%)	**0.0035**
Tricuspid valve regurgitation	12 (0.6%)	18 (1.1%)	0.1032
Neoplasia			
Colonic polyp	305 (15.7%)	333 (20.7%)	**0.0001**
Cancer (any)	282 (14.5%)	304 (18.9%)	**0.0004**
Thyroid	48 (2.5%)	33 (2.1%)	0.4090
Breast	76 (3.9%)	0 (0%)	**<0.0001**
Colorectal	19 (1.0%)	29 (1.8%)	**0.0336**
Prostate	0 (0%)	44 (2.7%)	**<0.0001**
Kidney	8 (0.4%)	25 (1.6%)	**0.0004**
Urinary tract	7 (0.4%)	23 (1.4%)	**0.0005**
Other conditions			
Sleep apnoea syndrome	565 (29.1%)	652 (40.6%)	**<0.0001**
Carpal tunnel syndrome	167 (8.6%)	110 (6.8%)	0.0535
Headache	318 (16.4%)	196 (12.2%)	**0.0005**
Visual fields defect	91 (4.7%)	85 (5.3%)	0.4058
Treatments			
Surgery	828 (42.6%)	700 (43.6%)	0.5625
Radiotherapy	72 (3.7%)	70 (4.4%)	0.3235
Surgery and radiotherapy	40 (2.1%)	45 (2.8%)	0.1496
Death	76 (3.9%)	110 (6.8%)	**<0.0001**
Mean age at death (STD)	75.0 ± 9.9	69.4 ± 13.2	**0.0021**

Table 6. Characteristics of incident patients according to age at diagnosis

	<50 years old	≥50 years old	P value
All patients	n= 1 443	n= 2 108	
Demographics			
Female	765 (53.0%)	1 179 (55.9%)	0.0865
Age at diagnosis, mean ± std	37.0 ± 8.6	64.1 ± 9.5	
Endocrine conditions			
Diabetes	292 (20.2%)	818 (38.8%)	**<0.0001**
Hyperprolactinemia	207 (14.3%)	162 (7.7%)	**<0.0001**
Hypopituitarism	452 (31.3%)	487 (23.1%)	**<0.0001**
Diabetes insipidus	173 (12.0%)	103 (4.9%)	**<0.0001**
Cardiovascular conditions			
Hypertension	207 (14.3%)	162 (7.7%)	**<0.0001**
Hypertrophic cardiomyopathy	452 (31.3%)	487 (23.1%)	**<0.0001**
Coronary artery disease	173 (12.0%)	103 (4.9%)	**<0.0001**
Myocardial infarction	6 (0.4%)	61 (2.9%)	**<0.0001**
Heart failure	20 (1.4%)	233 (11.1%)	**<0.0001**
Stroke	19 (1.3%)	133 (6.3%)	**<0.0001**
Cardiac arrhythmia	20 (1.4%)	270 (12.8%)	**<0.0001**
Atrial fibrillation	17 (1.2%)	256 (12.1%)	**<0.0001**
Ventricular tachycardia/fibrillation	3 (0.2%)	27 (1.3%)	**0.0006**
Heart valve diseases (any)	30 (2.1%)	145 (6.9%)	**<0.0001**
Aortic valve stenosis	6 (0.4%)	52 (2.5%)	**<0.0001**
Aortic valve regurgitation	7 (0.5%)	39 (1.9%)	**0.0004**
Mitral valve regurgitation	18 (1.2%)	79 (3.7%)	**<0.0001**
Tricuspid valve regurgitation	6 (0.4%)	24 (1.1%)	**0.0208**
Neoplasia			
Colonic polyp	157 (10.9%)	481 (22.8%)	**<0.0001**
Cancer (any)	114 (7.9%)	472 (22.4%)	**<0.0001**
Thyroid	25 (1.7%)	56 (2.7%)	0.0701
Breast	15 (1.0%)	61 (2.9%)	**0.0002**
Colorectal	2 (0.1%)	46 (2.2%)	**<0.0001**
Prostate	1 (0.1%)	43 (2.0%)	**<0.0001**
Kidney	9 (0.6%)	24 (1.1%)	0.1163
Urinary tract	1 (0.1%)	29 (1.4%)	**<0.0001**
Other conditions			
Sleep apnoea syndrome	382 (26.5%)	835 (39.6%)	**<0.0001**
Carpal tunnel syndrome	99 (6.9%)	178 (8.4%)	0.0840
Headache	277 (19.2%)	237 (11.2%)	**<0.0001**
Visual fields defect	87 (6.0%)	89 (4.2%)	**0.0148**
Treatments			
Surgery	793 (55.0%)	735 (34.9%)	**<0.0001**
Radiotherapy	88 (6.1%)	54 (2.6%)	**<0.0001**
Surgery and radiotherapy	56 (3.9%)	29 (1.4%)	**<0.0001**
Death	13 (0.9%)	173 (8.2%)	**<0.0001**

Table 7. Characteristics of incident patients according to diabetes

	Diabetes	No diabetes	P value
All patients	n= 1 110	n= 2 441	
Demographics			
Female	595 (53.6%)	1 349 (55.3%)	0.3567
Age at diagnosis, mean ± std	58.1 ± 14.4	50.9 ± 16.4	**<0.0001**
Endocrine conditions			
Hyperprolactinemia	106 (9.5%)	263 (10.8%)	0.2676
Hypopituitarism	321 (28.9%)	618 (25.3%)	**0.0241**
Diabetes insipidus	73 (6.6%)	203 (8.3%)	0.0727
Cardiovascular conditions			
Hypertension	737 (66.4%)	789 (32.3%)	**<0.0001**
Hypertrophic cardiomyopathy	45 (4.1%)	36 (1.5%)	**<0.0001**
Coronary artery disease	190 (17.1%)	158 (6.5%)	**<0.0001**
Myocardial infarction	39 (3.5%)	28 (1.1%)	**<0.0001**
Heart failure	135 (12.2%)	118 (4.8%)	**<0.0001**
Stroke	64 (5.8%)	88 (3.6%)	**0.0032**
Cardiac arrhythmia	130 (11.7%)	160 (6.6%)	**<0.0001**
Atrial fibrillation	122 (11.0%)	151 (6.2%)	**<0.0001**
Ventricular tachycardia/fibrillation	15 (1.4%)	15 (0.6%)	**0.0262**
Heart valve diseases (any)	79 (7.1%)	96 (3.9%)	**<0.0001**
Aortic valve stenosis	30 (2.7%)	28 (1.1%)	**0.0007**
Aortic valve regurgitation	16 (1.4%)	30 (1.2%)	0.6038
Mitral valve regurgitation	43 (3.9%)	54 (2.2%)	**0.0049**
Tricuspid valve regurgitation	10 (0.9%)	20 (0.8%)	0.8056
Neoplasia			
Colonic polyp	219 (19.7%)	419 (17.2%)	0.0650
Cancer (any)	230 (20.7%)	356 (14.6%)	**<0.0001**
Thyroid	34 (3.1%)	47 (1.9%)	**0.0353**
Breast	24 (2.2%)	52 (2.1%)	0.9515
Colorectal	21 (1.9%)	27 (1.1%)	0.0602
Prostate	17 (1.5%)	27 (1.1%)	0.2881
Kidney	14 (1.3%)	19 (0.8%)	0.1645
Urinary tract	14 (1.3%)	16 (0.7%)	0.0675
Other conditions			
Sleep apnoea syndrome	529 (47.7%)	688 (28.2%)	**<0.0001**
Carpal tunnel syndrome	88 (7.9%)	189 (7.7%)	0.8487
Headache	148 (13.3%)	366 (15.0%)	0.1924
Visual fields defect	55 (5.0%)	121 (5.0%)	0.9979
Treatments			
Surgery	433 (39.0%)	1 095 (44.9%)	**0.0011**
Radiotherapy	44 (4.0%)	98 (4.0%)	0.9429
Surgery and radiotherapy	24 (2.2%)	61 (2.5%)	0.5427
Death	**79 (7.1%)**	**107 (4.4%)**	**0.0007**
Mean age at death (STD)	72.1 ± 11.6	71.4 ± 12.8	0.6895

Table 8. Characteristics of incident patients according to death status at the end of the follow-up

	Alive	Deceased	P value
All patients	n= 3 365	n= 186	
Demographics			
Female	1 868 (55.5%)	76 (40.9%)	**<0.0001**
Age at diagnosis, mean ± std	52.2 ± 15.8	70.3 ± 12.2	**<0.0001**
Endocrine conditions			
Diabetes	1 031 (30.6%)	79 (42.5%)	**0.0007**
Hyperprolactinemia	360 (10.7%)	9 (4.8%)	**0.0108**
Hypopituitarism	904 (26.9%)	35 (18.8%)	**0.0154**
Diabetes insipidus	268 (8.0%)	8 (4.3%)	0.0693
Cardiovascular conditions			
Hypertension	1 396 (41.5%)	130 (69.9%)	**<0.0001**
Hypertrophic cardiomyopathy	73 (2.2%)	8 (4.3%)	0.0580
Coronary artery disease	304 (9.0%)	44 (23.7%)	**<0.0001**
Myocardial infarction	56 (1.7%)	11 (5.9%)	**<0.0001**
Heart failure	188 (5.6%)	65 (34.9%)	**<0.0001**
Stroke	122 (3.6%)	30 (16.1%)	**<0.0001**
Cardiac arrhythmia	224 (6.7%)	66 (35.5%)	**<0.0001**
Atrial fibrillation	210 (6.2%)	63 (33.9%)	**<0.0001**
Ventricular tachycardia/fibrillation	23 (0.7%)	7 (3.8%)	**<0.0001**
Heart valve diseases (any)	151 (4.5%)	24 (12.9%)	**<0.0001**
Aortic valve stenosis	42 (1.2%)	16 (8.6%)	**<0.0001**
Aortic valve regurgitation	41 (1.2%)	5 (2.7%)	0.0844
Mitral valve regurgitation	89 (2.6%)	8 (4.3%)	0.1774
Tricuspid valve regurgitation	28 (0.8%)	2 (1.1%)	0.7243
Neoplasia			
Colonic polyp	615 (18.3%)	23 (12.4%)	**0.0409**
Cancer (any)	485 (14.4%)	101 (54.3%)	**<0.0001**
Thyroid	78 (2.3%)	3 (1.6%)	0.5307
Breast	74 (2.2%)	2 (1.1%)	0.3026
Colorectal	39 (1.2%)	9 (4.8%)	**<0.0001**
Prostate	39 (1.2%)	5 (2.7%)	0.0665
Kidney	30 (0.9%)	3 (1.6%)	0.3182
Urinary tract	25 (0.7%)	5 (2.7%)	**0.0048**
Other conditions			
Sleep apnoea syndrome	1 161 (34.5%)	56 (30.1%)	0.2190
Carpal tunnel syndrome	271 (8.1%)	6 (3.2%)	**0.0169**
Headache	495 (14.7%)	19 (10.2%)	0.0899
Visual fields defect	170 (5.1%)	6 (3.2%)	0.2640
Treatments			
Surgery	1 512 (44.9%)	16 (8.6%)	**<0.0001**
Radiotherapy	141 (4.2%)	1 (0.5%)	**0.0133**
Surgery and radiotherapy	45 (2.8%)	40 (2.1%)	0.1496

V - DISCUSSION

1- Main results

The present study is to our knowledge the first to present an overview of the epidemiology of unselected patients with acromegaly in France, as the disease has mainly been studied by expert centers (16) but using a national database to screen as many patients as possible is a premiere in France.

After estimating the PPV of our algorithm to 87%, we estimated there would be 6 910 patients with acromegaly in France, with a prevalence of 10.4/100 000, an incidence of 0.76/100 000 and a case fatality of 1.6% each year. Those results are in accordance with previous observational studies from other countries (10).

Among the 3 551 patients that were analysed, we found a slight female predominance, and the most frequent comorbidities were hypertension, sleep apnoea, diabetes, hypopituitarism, and colonic polyps. Those characteristics are similar to those described in previous smaller epidemiological studies about acromegaly from other countries, supporting that PMSI can be used as a tool with good reliability to describe patients with acromegaly (12,17,25,26).

One difference between our study and literature was the mean age at diagnosis of 53 years, which is higher than results of previous data where mean age at diagnosis was around 45 years in most studies (10,19). The other main difference between our results and previous studies is the lower proportion of patients who underwent surgery or radiotherapy based on the 2015-2020 cohort, since 43% of patients had surgery and 4% of patients had radiotherapy in our study, versus 60 to 80% of patients who had surgery in literature and proportions of radiotherapy treated patients very different from one country to another but always far higher than the 4% we found (16,17).

This reflects the nature of our analysis not being limited to selected patients seen in tertiary centers, and including possibly older and sicker patients with late diagnosis and many comorbidities for whom complex explorations or an aggressive management is not deemed reasonable. It is also possible that the lower use of surgery or radiotherapy in our analysis reflects an inappropriate underuse of these therapeutic methods that should be improved in future years.

Another possible explanation for these two differences could be the 10 years limit of PMSI hindsight: as the first year with available data was 2012, the patients with acromegaly diagnosed before that year appeared to us as “new cases” when they first had acromegaly coded in their chart during the 2012-2021 period. This could explain the mean age at diagnosis being possibly overestimated because of patients who had acromegaly diagnosed before 2012 at a younger age, but with a first acromegaly diagnosis code only appearing later in our data. The same goes for the proportion of patients that underwent surgery or radiotherapy: we found lower surgery rate than expected, but any surgery or radiotherapy performed before 2012 would be lacking of available data, resulting in an underestimation of the surgery rate for older acromegaly cases as

surgery is ideally done shortly after acromegaly diagnosis. That 10 years limit of PMSI hindsight should also be taken into consideration when looking at the high numbers of new cases per year at the beginning that quickly decreased, as most of the "new cases" between 2012 and 2014 are most likely patients that were already diagnosed.

2- Study limitations

Our study suffers from several limitations. It was a retrospective observational study, so potential bias regarding the validity of the data cannot be totally ruled out, with possible underestimation of comorbid conditions (27). However, as the coding is used for reimbursement and financial purposes with regular controls, a good reliability is still to be expected. For example Carre et al. established that PPV and sensibility were 89% and 73% respectively for thyroid cancer using the PMSI (28). Dal et al. evaluated accuracy of ICD diagnosis in the Danish National Registry of Patients (DNRP) for acromegaly, finding a PPV between 53 and 75% depending of used criteria (29), and our local files review showed a PPV of 87%.

As PMSI is used for financial purposes and was not designed for medical research, the main downside of this database is the lack of notable medical information that would have been relevant to obtain but could not be found. Used medication is not recorded, so we could not establish if patients were prescribed somatostatin analogs, GH receptor antagonists, or dopamine agonists. Blood tests like IGF-1 and GH levels were also not available, hence we could not determine disease status (cured or controlled versus uncontrolled disease) which is an important prognosis factor of mortality and occurrence of complications (18). We could not either get access to magnetic resonance imaging (MRI) reports to collect pituitary adenoma size. Also, some affections that do not require hospitalization suffer from an increased risk of under-declaration, so complications such as hypertension, sleep apnoea, diabetes, and carpal tunnel syndrome could be underestimated, while we simply didn't look for arthropathy or dyslipidaemia.

Finally, outpatients with acromegaly who were never hospitalized did not appear in our study, which could cause a selection bias, and also result in an underestimation of acromegaly prevalence and incidence. Nonetheless, we expect those patients to be uncommon as one hospitalization is often needed for diagnosis purpose. Surgery also requires hospitalization, and patients who don't undergo surgery are in most cases recused because of frailty or comorbidities, and are therefore likely to have been hospitalized for another reason.

Events included were only in-hospital and we were not able to analyse data for out-of-hospital deaths. Nonetheless, one might consider that the present analysis provides valuable information since French data show that hospital deaths account for almost 70% of all deaths in France (30).

3- *Study strengths and peculiarities*

The main strength of our study is the patients' recruitment: by using a national database that covers healthcare facilities from the entire country we were able to get a consequent number of patients that would be difficult to reach with other methods, and that represents one of the biggest cohorts of patients with acromegaly to our knowledge. Patients were included from any healthcare facility in France, thus preventing a potential bias of enrolling patients from only one center and being closer to a "real life" description of the current situation of patients with acromegaly.

We found higher complication rates and lower treatment rates than those already reported in France (16), namely higher proportion of patients suffering from diabetes, most cardiovascular comorbidities baring valve diseases, cancer and sleep apnoea. This could be explained by the fact that previous studies were conducted with patients included in the French acromegaly registry from expert centers, while our study included patients from the entire French territory with possibly sub-optimal treatment that could explain higher complication rates. Despite the obvious underestimation of surgery and radiotherapy of our study as stated above, it remains plausible that not all patients have access to such treatments which are performed in few centers. Such results could emphasize the importance of addressing patients with acromegaly in expert centers to improve medical care.

Our inclusion criteria (patients with at least one acromegaly diagnosis code in their chart, being 18 years old or older at first diagnosis) can be a matter of discussion. One could say that stricter criteria, with a required number of 2 diagnosis codes would have improved our PPV and retained only confirmed cases of acromegaly (29). We intentionally chose a lower cut-off, even though our PPV dropped from 97.5 to 87%, for several reasons. First, our local file review showed that 22.5% of confirmed cases of acromegaly only had one diagnosis code in their hospital records, so a cut-off of two would have make us miss a significant proportion of patients and underestimate the incidence and prevalence of acromegaly. Another reason is that in case we retained patients who were hospitalized at least twice, we would have selected only the more severe patients with comorbidities, biasing and possibly overestimating complications occurrence. The decision of ruling out patients with a first diagnosis before the age of 18 was made after we saw that there were no confirmed cases among our local files for those patients, as it seemed that pediatrics erroneously used the "acromegaly and pituitary gigantism" for children with tall stature. We possibly missed some real cases of very young onset acromegaly by doing that, but those are exceptional (10).

Another methodological choice that could require explanations is the decision we made to only retain patients with a first diagnosis of acromegaly between 2015 and 2020 to analyse incidence and patient characteristics. Reasons for that selection are the 2012-2014 period incidence being potentially flawed by patients diagnosed before 2011 and being erroneously considered as new cases at their first hospitalization (this phenomenon decreasing over time as seen in Table 2.).

Patients diagnosed in 2021 were ruled out to keep patients who had at least one year to declare a complication after acromegaly appearance, as available data ran up to December 31st of 2021.

4- Consequences of the results

One of the main issues in the management of acromegaly is the diagnosis or early detection of patients, which is difficult due to the insidious and progressive development of the disease (6,11). The time interval in diagnosis is estimated at seven years on average, so systemic complications are often already present at the time of diagnosis, and are in most cases the reason that makes the clinician evoke acromegaly in the first place (5,17).

The fact that most cardiovascular complications with potential severity (myocardial infarction, stroke) often appeared before the time acromegaly diagnosis was made, and the high median age at diagnosis of 53 years old that we found are still concerning results. This could highlight a higher delay of diagnosis and therefore treatment than expected, with clinical consequences: mortality in patients with acromegaly is no longer higher than in general population if the disease is cured or controlled, but if patients remain untreated because of diagnosis latency they are at risk of cardiovascular complications with higher mortality (31–33).

VI - CONCLUSION

In this nationwide study we estimated for the first time acromegaly prevalence and incidence in France with a tool that was yet to be used for that specific disease, and found similar results than those already described in previous studies from other countries. Patients were older than expected when acromegaly diagnosis was made, and the percentage of patients who underwent surgery or radiotherapy was lower. These results support the need to raise awareness about the disease in order to shorten the diagnosis delay, and to refer to a specialized center for treatment management.

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VIII - SUPPLEMENTARY DATA

Appendix 1. Diagnosis and therapeutic procedures according to ICD-10 CCAM codification

Diagnosis/treatment	**ICD-10 / CCAM code**
Endocrine conditions	
Acromegaly	E220: Acromegaly and pituitary gigantism
Pituitary adenoma	D352: Benign neoplasm of other and unspecified endocrine glands: Pituitary gland D 443: Neoplasm of uncertain or unknown behaviour of endocrine glands: pituitary gland
Diabetes of any type	E10-E14: Diabetes mellitus
Type 1 diabetes	E10: Type 1 diabetes mellitus
Type 2 diabetes	E11: Type 2 diabetes mellitus
Other type of diabetes	E12: Malnutrition-related diabetes mellitus E13: Other specified diabetes mellitus E14: Unspecified diabetes mellitus
Hyperprolactinaemia	E221: Hyperprolactinaemia
Hypopituitarism	E230: Hypopituitarism
Post-treatment hypopituitarism (pituitary surgery or radiotherapy)	E893: Postprocedural hypopituitarism
Diabetes insipidus	E232: Diabetes insipidus
Cardiovascular conditions	
Hypertension	I10: Essential (primary) hypertension I11: Hypertensive heart disease I12: Hypertensive renal disease I13: Hypertensive heart and renal disease I15: Secondary hypertension
Heart failure	I110: Hypertensive heart disease with (congestive) heart failure I130: Hypertensive heart and renal disease with (congestive) heart failure I132: Hypertensive heart and renal disease with both (congestive) heart failure and renal failure

	I50: Heart failure J81: Pulmonary oedema R570: Cardiogenic shock
Hypertrophic cardiomyopathy	I421: Obstructive hypertrophic cardiomyopathy I422: Other hypertrophic cardiomyopathy
Coronary artery disease	I20: Angina pectoris I21: Acute myocardial infarction I22: Subsequent myocardial infarction I23: Certain current complications following acute myocardial infarction I24: Other acute ischaemic heart diseases I25: Chronic ischaemic heart disease
Cardiac Arrhythmias	I472: Ventricular tachycardia I48: Atrial fibrillation and flutter I49: Other cardiac arrhythmias
Stroke	G45: Transient cerebral ischaemic attacks and related syndromes I63: Cerebral infarction l64: Stroke, not specified as haemorrhage or infarction
Aortic valve stenosis	I060: Rheumatic aortic stenosis I062: Rheumatic aortic stenosis with insufficiency I350: Aortic (valve) stenosis I352: Aortic (valve) stenosis with insufficiency
Aortic regurgitation	I061: Rheumatic aortic insufficiency I351: Aortic (valve) insufficiency
Mitral regurgitation	I051: Rheumatic mitral insufficiency I340: Mitral (valve) insufficiency
Tricuspid regurgitation	I071: Tricuspid insufficiency (rheumatic) I361: Nonrheumatic tricuspid (valve) insufficiency I36: Nonrheumatic tricuspid (valve) stenosis with insufficiency
Cardiac valve disease (any type)	Aortic valve stenosis, Aortic insufficiency, Mitral valve stenosis, Mitral insufficiency, Tricuspid valve stenosis, Tricuspid insufficiency
Neoplasia	
Cancer of any type	C00-C97: Malignant neoplasms
Colorectal cancer	C18: Malignant neoplasm of colon C19: Malignant neoplasm of rectosigmoid junction C20: Malignant neoplasm of rectum C21: Malignant neoplasm of anus and anal canal
Colonic polyp	D12: Benign neoplasm of colon, rectum, anus and anal canal
Thyroid cancer	C73: Malignant neoplasm of thyroid gland
Breast cancer	C50: Malignant neoplasm of breast
Prostatic cancer	C61: Malignant neoplasm of prostate
Kidney cancer	C64: Malignant neoplasm of kidney, except renal pelvis
Urinary tract cancer	C65: Malignant neoplasm of renal pelvis C66: Malignant neoplasm of ureter C67: Malignant neoplasm of bladder

	C68: Malignant neoplasm of other and unspecified urinary organs
Other complications and comorbidities	
Sleep apnoea	G473: Sleep apnoea
Carpal tunnel syndrome	G560: Carpal tunnel syndrome
Headache	R51: Headache
Visual field defects	H534: Visual field defects
Treatments and therapeutic actions	
Pituitary surgery	KANB001: functional hypophysiolysis transsphenoidal way KAFE900: Pituitary lesion removal by transsphenoidal video surgery KAFA001: Pituitary lesion removal by transsphenoidal approach KAFA002: Pituitary lesion removal by craniotomy
Pituitary radiotherapy	Z510: Radiotherapy session ZZNL051: External irradiation session using a dedicated machine producing photons with intensity modulation and control of the target position by imaging ZZNL054: External irradiation session using a linear accelerator with intensity modulation and control of the target position by imaging ZZNL055: External irradiation in stereotactic conditions using a dedicated machine producing photons with imaging guidance, without synchronization with breathing, in one single dose ZZNL059: External irradiation in stereotactic conditions using a dedicated machine producing photons with imaging guidance, without synchronization with breathing, in one single dose ZZNL060: External irradiation in stereotactic conditions using a dedicated machine producing photons with imaging guidance, with synchronization with breathing, ZZNL061: External irradiation session using a machine with a less than 5 megavolts power ZZNL063: External radiation session using linear accelerator of 5 megavolts or more power, equipped with an image-guided repositioning system

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Résumé :

Introduction. L'acromégalie est une pathologie endocrinienne due à une sécrétion excessive d'hormone de croissance, elle est responsable de nombreuses complications notamment cardio-vasculaires et cancéreuses. L'objectif de notre étude était d'estimer la prévalence et l'incidence de l'acromégalie et de ses complications à l'échelle nationale.

Méthodes. A partir de la base de données PMSI (Programme de Médicalisation des Systèmes d'Information) ont été extraites les informations des patients adultes ayant eu au moins un séjour hospitalier entre 2012 et 2021 avec un code diagnostique d'acromégalie, permettant ainsi d'estimer la prévalence de la maladie. Une validation de notre algorithme d'extraction a été effectuée en faisant une revue locale des dossiers de patients extraits. Une cohorte des nouveaux patients a ensuite été conduite sur la période 2015-2020 permettant d'estimer l'incidence de l'acromégalie, la prévalence et le délai d'apparition des complications. L'impact de l'âge au diagnostic, du sexe, et de la présence d'un diabète a été analysé par comparaison des sous-groupes.

Résultats. Au total, 7943 patients ont été identifiés avec une valeur prédictive positive de notre méthode estimée à 87%. La prévalence estimée était de 10.4/100 000 en France, l'incidence annuelle était de 0.76/100 000 habitants/an. Au cours d'un suivi de 4.3 ± 3.2 ans, 530 patients sont décédés, soit une mortalité de 1.6% par an. Le parcours de prise en charge retrouvait 43% de chirurgie et 4% de radiothérapie. Les complications les plus fréquentes étaient l'hypertension artérielle (43%), l'apnée du sommeil (34,3%) et le diabète (31,3%). Celles-ci étaient présentes avant le diagnostic dans 76% des cas pour l'HTA et le diabète et 56% pour l'apnée du sommeil. Le sexe masculin, un âge au diagnostic supérieur à 50 ans et le diabète étaient associés à un risque augmenté de complications, principalement cardiovasculaires.

Conclusion. Cette étude a permis d'estimer pour la première fois l'incidence et la prévalence de l'acromégalie en France. Malgré certaines limitations inhérentes à l'utilisation des bases médico-administratives hospitalières, l'étude des parcours des patients était possible, retrouvant un taux de complications plus important, un âge au diagnostic plus élevé, et moins d'actes thérapeutiques que dans la littérature. Ce qui pourrait refléter une prise en charge sub-optimale des patients sur l'ensemble du territoire en comparaison aux données publiées des cohortes de patients issues des centres spécialisés.

Mots clés : Acromégalie ; cohorte nationale ; épidémiologie ; adénome hypophysaire

Jury :

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