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Insulin-like growth factor-1, growth hormone and disease outcomes in acromegaly: A population study

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Abstract

Context: A lack of consensus remains about the relative importance of insulin-like growth factor-1 (IGF-1) and growth hormone (GH) in predicting adverse outcomes in patients with acromegaly.

Objective: To describe the differing association between IGF-1 and GH and major disease outcomes in acromegaly.

Design: Retrospective cohort study.

Patients: United Kingdom National Health Service patients with acromegaly who had an IGF-1 and/or a GH measurement recorded following diagnosis, prior to December 2019.

Measurements: A composite endpoint including all-cause mortality (ACM), type 2 diabetes (DM), major adverse cardiovascular events (MACE) or cancer was the primary outcome. These outcomes were also analysed individually. Follow-up period was capped at 5 years.

Results: A maximum of 417 cases and 332 cases were eligible for the IGF-1 and GH analyses, respectively, comprising 1041.5 and 938.9 years of follow-up. There was a direct association between increased IGF-1 concentration and adjusted event risk for the composite endpoint (hazard ratio [HR] = 1.2; 95% confidence interval [CI] = 1.02-1.5); in GH, the HR was 1.1 (1.0-1.2). For the individual endpoints in relation to IGF-1 level, the HRs were ACM (1.2; 0.93-1.5), MACE (1.2; 0.64-2.1), DM (1.53; 1.09-2.2) and cancer (1.3; 0.95-1.7). For GH, the HRs were ACM (1.1; 0.97-1.2), MACE (0.99; 0.73-1.3), DM (1.1; 0.99-1.2) and cancer (0.90; 0.66-1.2).

Conclusions: In this contemporary data set with extended follow-up, IGF-1 and GH concentrations showed an association with major adverse outcomes from acromegaly.

KEYWORDS
acromegaly, cardiovascular diseases, diabetes mellitus type 2, growth hormone, Insulin-like growth factor 1, mortality, neoplasms

1 | INTRODUCTION

Acromegaly is a rare disease, with an estimated prevalence and annual incidence of 2.8 to 13.7, and 0.2 to 1.1 cases per 100,000 people, respectively.[1] In addition to characteristic skeletal overgrowth, patients with acromegaly are at increased risk of several adverse outcomes, including type 2 diabetes (DM), cardiovascular disease, cerebrovascular disease, obstructive sleep apnoea and cancer,[2,3] leading to increased mortality in the presence of active disease.[4]

Treatment is aimed at normalising growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels, since good biochemical control not only improves symptoms but also reduces morbidity and mortality. Consensus statements thus recognise a nadir GH concentration of <1 μg/L after an oral glucose tolerance test, and normalised age- and sex-adjusted IGF-1 level as key treatment goals, since this helps reduce the impact of comorbidities and restores mortality risk close to that of the general population.[5,6] However, uncertainty remains as to whether GH or IGF-1 better predicts disease outcomes, which generates challenges in clinical practice in selecting the most appropriate marker of control, especially in the context of discordant results. In a 2008 meta-analysis, reduction of both GH and IGF-1 to target levels was shown to reduce the standardised mortality ratio to normal[6] whereas other studies have identified elevated GH but not IGF-1 as a predictor of mortality.[7]

The advent of newer assays for GH and IGF-1, and wide variability between assays adds to this inherent complexity.[8,9] The problem of inter-assay variation in GH measurement led to a recommendation in 2004 that the recombinant DNA-derived standard (IS 98/574) should be adopted as the primary calibrant for GH assays and that laboratories should adopt mass units for reporting GH results.[10] The need to revisit disease outcomes in an era of modern GH and IGF-1 assays, as recommended by consensus guidelines[11] would thus appear to be timely.

In light of these uncertainties, we sought to re-examine adverse outcomes in patients with acromegaly in a large, real-world data set reflecting contemporary practice in the United Kingdom. Our objective was to investigate the discriminatory potential of IGF-1 and GH in predicting major morbidity and mortality in acromegaly, hypothesising that both markers would be associated with adverse outcomes.

2 | METHODS

2.1 | Study design

This was a retrospective observational study using data from the UK National Health Service. Data were accessed via the Clinical Practice Research Datalink (CPRD)[12] and linked to Hospital Episode Statistics (HES) data. Data were available to December 2019. Overall, 75% of patients included were diagnosed in 2010 or later.

The CPRD datalink combines the longitudinal, anonymised electronic healthcare records from over 1900 UK primary care practices using either Vision or EMIS practice management software (the source of the GOLD and Aurum data sets, respectively).[12] The primary care dataset includes a sample of 16 million currently registered individuals and is representative of the UK population in terms of age, sex and ethnicity.[12] Records are pseudo-anonymised and contain information including demographics, medical history (diagnoses), symptoms, test results, drug treatments and health-related data such as smoking and alcohol consumption.

For over seven million patients registered with participating English practices, their CPRD records can be linked to the HES secondary care data source. HES data records diagnoses according to the 10th revision of the International Classification of Disease (ICD-10) and procedures according to the UK Office of Population Censuses and Surveys Classification of Interventions and Procedures, version 4 (OPCS-4).

2.2 | Study population

Patients were selected who had a diagnosis of acromegaly, and at least one IGF-1 measurement that included a laboratory reference range or at least one GH measurement. High inter-assay variability necessitated the inclusion of a reference range for analysis of IGF-1 readings, whereas this was not a requirement for GH measurements.

CPRD and linked HES data record only those tests requested in primary care. This is a limitation of this study method, as both IGF-1 and GH would be expected to be collected routinely in secondary care. Due to this limitation, relatively few IGF-1/GH measurements meeting the necessary criteria could be identified. Of those patients in the IGF-1 and GH analysis groups, 58% and 67% had ≤2 usable readings available, respectively. Given the relative paucity of IGF-1 and GH records, the last observed measurement in the patient's record was designated the index date. These measurements were required to follow the patient's diagnosis of acromegaly.

All patients were required to have at least 365 days of clinical records available prior to index date, be 'research acceptable' according to the CPRD quality standard[12] and be eligible for HES linkage. Attrition diagrams demonstrating exclusion criteria for IGF-1 and GH analysis groups are provided in Figure 1A and Figure 1B, respectively.

Patients were followed from the date of their last reported IGF-1 or GH measurement until their censor date, which was defined as the earliest of patient transfer from an included practice, practice's last data collection date, death or five years' post-index date.

2.3 | IGF-1 and GH measurements

For IGF-1 effect analysis, a patient's last available IGF-1 measurement was calibrated by the co-recorded reference range (age- and sex-adjusted). The term 'IGF-1 ratio' refers to the recorded value as a

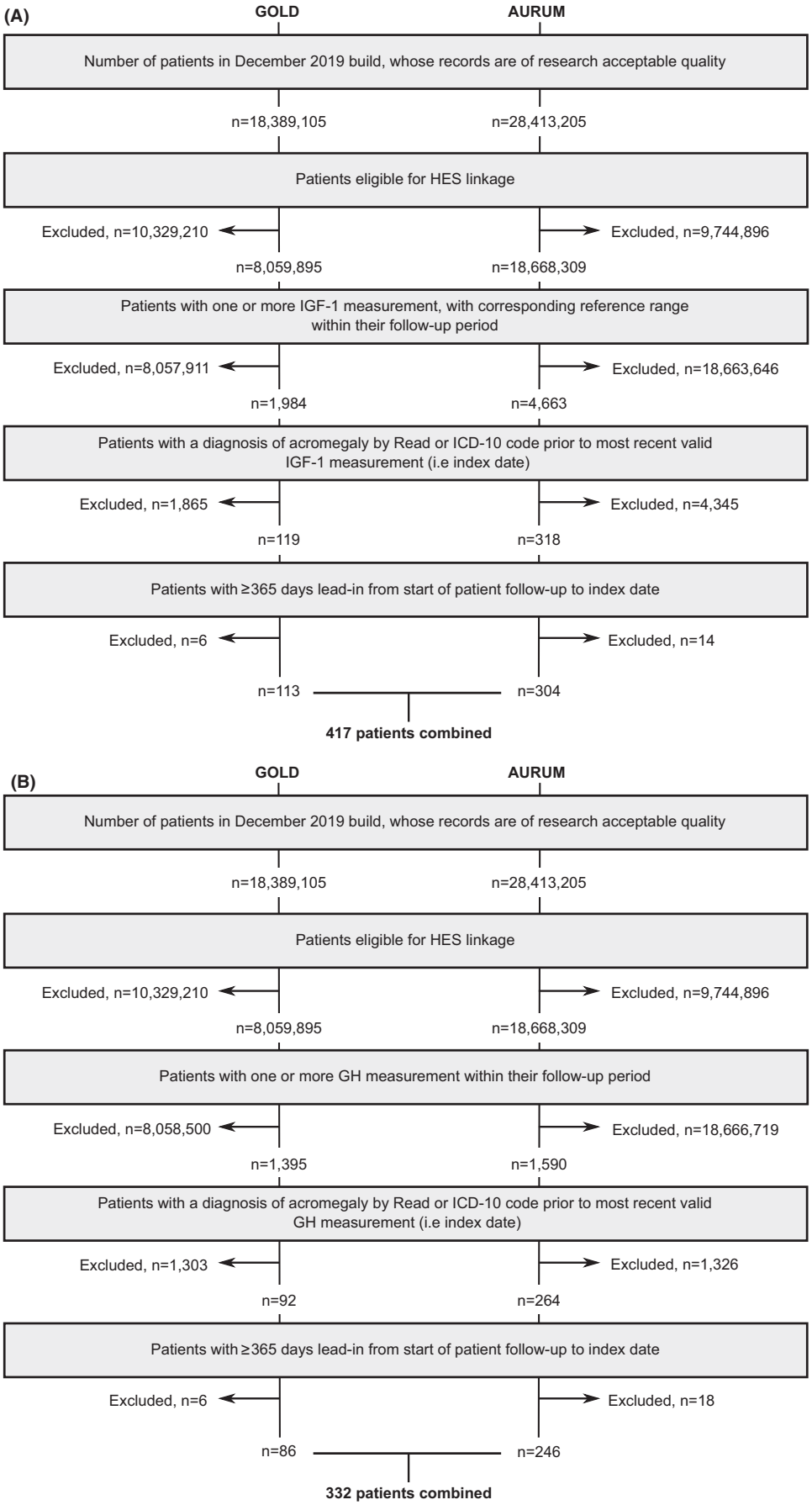

FIGURE 1 Attrition Charts demonstrating inclusion criteria for a) IGF-1 analysis cohort and b) GH analysis cohort [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Baseline characteristics of cases with relevant IGF-1 records included in the analysis, by clinical endpoint

		Composite		ACM[a]		DM		MACE[c]		Cancer	
Characteristic	**Parameter**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Total	N	417		417		309		328		289	
Age (years)	Mean, SD	60.35, 14.161		60.35, 14.161		59.59, 14.172		58.12, 13.776		58.37, 14.136	
Gender	Female	207	49.64%	207	49.64%	150	48.54%	167	50.91%	137	47.40%
	Male	210	50.36%	210	50.36%	159	51.46%	161	49.09%	152	52.60%
IMD[d]	Quintile 1	108	28.88%	108	28.88%	73	23.62%	69	21.04%	64	22.15%
	Quintile 2	102	27.27%	102	27.27%	80	25.89%	85	25.91%	73	25.26%
	Quintile 3	90	24.06%	90	24.06%	65	21.04%	75	22.87%	59	20.42%
	Quintile 4	74	19.79%	74	19.79%	59	19.09%	65	19.82%	58	20.07%
	Quintile 5	43	11.50%	43	11.50%	32	10.36%	34	10.37%	35	12.11%
Charlson Index	Mean, SD	2.319, 2.132		2.319, 2.132		1.867, 1.888		1.805, 1.700		1.564, 1.632	
BMI Category	Normal	18	4.32%	18	4.32%	11	3.56%	15	4.57%	13	4.50%
	Underweight	1	0.24%	1	0.24%	1	0.32%	1	0.30%	1	0.35%
	Overweight	33	7.91%	33	7.91%	25	8.09%	22	6.71%	18	6.23%
	Obese	36	8.63%	36	8.63%	19	6.15%	29	8.84%	28	9.69%
	Severely Obese	13	3.12%	13	3.12%	8	2.59%	10	3.05%	9	3.11%
	Very Severely Obese	11	2.64%	11	2.64%	4	1.29%	9	2.74%	9	3.11%
	Missing	305	73.14%	305	73.14%	241	77.99%	242	73.78%	211	73.01%
Smoking Status	Never	228	54.68%	228	54.68%	168	54.37%	185	56.40%	156	53.98%
	Prior	108	25.90%	108	25.90%	78	25.24%	79	24.09%	68	23.53%
	Current	76	18.23%	76	18.23%	59	19.09%	59	17.99%	61	21.11%
	Missing	5	1.20%	5	1.20%	4	1.29%	5	1.52%	4	1.38%
Alcohol Status	Never	259	62.11%	259	62.11%	191	61.81%	198	60.37%	180	62.28%
	Prior	17	4.08%	17	4.08%	11	3.56%	12	3.66%	15	5.19%
	Current	141	33.81%	141	33.81%	107	34.63%	118	35.98%	94	32.53%
Prior Transsphenoidal Surgery	Yes	175	41.97%	175	41.97%	176	56.96%	195	59.45%	166	57.44%
	No	242	58.03%	242	58.03%	133	43.04%	133	40.55%	123	42.56%
Prior Pituitary Radiotherapy	Yes	57	13.67%	57	13.67%	40	12.94%	47	14.33%	36	12.46%
	No	360	86.33%	360	86.33%	269	87.06%	281	85.67%	253	87.54%
Prior SSA[e] Prescription	Yes	120	28.78%	120	28.78%	76	24.60%	86	26.22%	72	24.91%
	No	297	71.22%	297	71.22%	233	75.40%	242	73.78%	217	75.09%
Prior Pegvisomant Prescription	Yes	32	7.67%	32	7.67%	21	6.80%	26	7.93%	21	7.27%
	No	385	92.33%	385	92.33%	288	93.20%	302	92.07%	268	92.73%

Note: BMI category definitions—Underweight: BMI <18.5, Normal: 18.5 ≥ BMI <25, Overweight: 25 ≥ BMI <30, Obese: 30 ≥ BMI <35, Severely Obese: 35 ≥ BMI <40, Very Severely Obese: BMI ≥40

[a]All-Cause Mortality.; [b]Type 2 Diabetes Mellitus.; [c]Major Adverse Cardiac Events.; [d]Index of Multiple Deprivation.; [e]Somatostatin Analogue.

TABLE 2 Baseline characteristics of cases with relevant growth hormone records included in the analysis, by clinical endpoint

		Composite		ACM[a]		DM[b]		MACE[c]		Cancer	
Characteristic	**Parameter**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Total	N	332		332		259		256		239	
Age (years)	Mean, SD	59.11, 14.410		59.11, 14.410		58.46, 14.50		56.86, 14.002		57.46, 14.244	
Gender	Female	158	47.59%	158	47.59%	122	47.10%	122	47.66%	110	46.03%
	Male	174	52.41%	174	52.41%	137	52.90%	134	52.34%	129	53.97%
IMD[d]	Quintile 1	82	24.70%	82	24.70%	60	23.17%	56	21.88%	59	24.69%
	Quintile 2	69	20.78%	69	20.78%	54	20.85%	58	22.66%	47	19.67%
	Quintile 3	60	18.07%	60	18.07%	47	18.15%	46	17.97%	39	16.32%
	Quintile 4	72	21.69%	72	21.69%	62	23.94%	61	23.83%	55	23.01%
	Quintile 5	49	14.76%	49	14.76%	36	13.90%	35	13.67%	39	16.32%
Charlson Index	Mean, SD	2.12, 1.924		2.12, 1.924		1.82, 1.863		1.738, 1.737		1.418, 1.372	
BMI Category	Normal	8	2.41%	8	2.41%	5	1.93%	5	1.95%	4	1.67%
	Underweight	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%
	Overweight	24	7.23%	24	7.23%	19	7.34%	15	5.86%	12	5.02%
	Obese	16	4.82%	16	4.82%	10	3.86%	15	5.86%	12	5.02%
	Severely Obese	6	1.81%	6	1.81%	3	1.16%	5	1.95%	4	1.67%
	Very Severely Obese	6	1.81%	6	1.81%	2	0.77%	5	1.95%	6	2.51%
	Missing	272	81.93%	272	81.93%	220	84.94%	211	82.42%	201	84.10%
Smoking Status	Never	217	65.36%	217	65.36%	170	65.64%	167	65.23%	160	66.95%
	Prior	62	18.67%	62	18.67%	47	18.15%	46	17.97%	40	16.74%
	Current	30	9.04%	30	9.04%	23	8.88%	25	9.77%	22	9.21%
	Missing	23	6.93%	23	6.93%	19	7.34%	18	7.03%	17	7.11%
Alcohol Status	Never	240	72.29%	240	72.29%	189	72.97%	185	72.27%	179	74.90%
	Prior	11	3.31%	11	3.31%	7	2.70%	7	2.73%	8	3.35%
	Current	81	24.40%	81	24.40%	63	24.32%	64	25.00%	52	21.76%
Prior Transsphenoidal Surgery	Yes	210	63.25%	210	63.25%	163	62.93%	175	68.36%	154	64.44%
	No	122	36.75%	122	36.75%	96	37.07%	81	31.64%	85	35.56%
Prior Pituitary Radiotherapy	Yes	56	16.87%	56	16.87%	40	15.44%	44	17.19%	39	16.32%
	No	276	83.13%	276	83.13%	219	84.56%	212	82.81%	200	83.68%
Prior SSA[e] Prescription	Yes	106	31.93%	106	31.93%	73	28.19%	80	31.25%	70	29.29%
	No	226	68.07%	226	68.07%	186	71.81%	176	68.75%	169	70.71%
Prior Pegvisomant Prescription	Yes	2	0.60%	2	0.60%	2	0.77%	2	0.78%	2	0.84%
	No	330	99.40%	330	99.40%	257	99.23%	254	99.22%	237	99.16%

Note: BMI category definitions—Underweight: BMI <18.5, Normal: 18.5 ≥ BMI <25, Overweight: 25 ≥ BMI <30, Obese: 30 ≥ BMI <35, Severely Obese: 35 ≥ BMI <40, Very Severely Obese: BMI ≥40.

[a]All-Cause Mortality.; [b]Type 2 Diabetes Mellitus.; [c]Major Adverse Cardiac Events.; [d]Index of Multiple Deprivation.; [e]Somatostatin Analogue.

ratio of the upper value in the normal reference range. Similarly, for GH effect analysis, a patient's last available GH measurement was used. GH assays were calibrated since 2008 against the International Standard (IS)-recombinant human growth hormone, IS 98/574. Both IGF-1 ratio and GH measurements were entered into analysis as continuous variables.

2.4 | Clinical outcomes

The primary outcome was the time to a composite endpoint incorporating all-cause mortality (ACM), incident type 2 diabetes (DM), major adverse cardiovascular event (MACE) or cancer. Secondary endpoints were incident DM, MACE, cancer and all-cause mortality. The MACE outcome was defined as myocardial infarction, heart failure, stroke or angina. A composite endpoint was selected as the primary outcome to gain the best overall perspective of adverse outcomes and to increase statistical strength within the relatively small sample size. Singular secondary endpoints were included to ensure no overwhelming difference in one outcome was responsible for the composite outcome result.

2.5 | Statistical analysis

Baseline characteristics were analysed by study cohort (IGF-1 and GH) and missing data are reported in Table 1. The null hypotheses assumed there was no association between either IGF-1 or GH and any of the described outcomes. Hypotheses were tested using extended Cox proportional hazards regression modelling, adjusting for age and gender. IGF-1 ratio and GH measurements were entered as continuous variables. The proportional hazards assumption was evaluated. For incident outcomes of diabetes, MACE and cancer, patients were excluded from analysis if they had any record of a previous diagnosis.

All data management was performed using Microsoft SQL Server, and statistical analyses were performed in R, version 4.0.3.

3 | RESULTS

3.1 | Patient disposition

Since we excluded some patients from each endpoint due to a need for incident events, the number of cases varied by group (Tables 1 and 2). A cohort of 417 and 332 patients were identified who met the inclusion criteria for the IGF-1 and GH effect analysis, respectively. Major exclusions included the absence of linked hospital data eligibility and a lack of IGF-1 reference values for the IGF-1 analysis. A total of 199 patients were eligible for both IGF-1 and GH effect analyses, with 95 of those having corresponding IGF-1 and GH measurements.

3.2 | Baseline characteristics

Among 417 patients eligible for the IGF-1 analysis, 50% were male and the median age was 60 (SD 14) years. The greatest proportion of patients fell within Quintile-1 (26%), Quintile-2 (24%) and Quintile-3 (22%) of the Index of Multiple Deprivation (IMD). The mean Charlson Comorbidity Index (CCI) score of patients was 2.3 (SD 2.1) (Table 1). With regard to smoking status, 55% of patients reported never having smoked, 26% were prior smokers and 18% were current smokers. Within this group, 62% of patients reported never having been alcohol users, and 34% reported being current alcohol drinkers (Table 1).

Of the 332 patients eligible for the GH analysis, 52% were male and the mean age was 59 (SD 14) years (Table 2). The majority of patients were classified within Quintile-1 (25%), Quintile-2 (21%) or Quintile-4 (22%) of the IMD. The mean CCI score for this group of patients was 2.1 (SD 1.9). In terms of smoking status, 65% reported never having smoked, while 9% were current smokers, and 19% were prior smokers. Overall, 72% of patients reported never having drunk alcohol, and 24% reported being current alcohol drinkers (Table 2).

A comparison of the baseline characteristics of patients in the IGF-1 and GH cohorts showed they differed only in smoking status ($P < .05$), alcohol status ($P < .05$) and prior recorded pegvisomant prescription ($P < .05$). All other characteristics were comparable across the cohorts.

3.3 | Primary and secondary outcomes

The primary outcome was recorded in 417 individuals in the IGF-1 cohort and 332 individuals in the GH cohort during 1041.5 and 938.9 person-years of follow-up, respectively (Figure 2). At five years, over 35% of patients had experienced at least one of the serious clinical events.

Death was the most commonly occurring endpoint (Table 3), seen in 51 (12.2%) patients in the IGF-1 cohort, and 46 (13.9%) of the GH cohort. Event rates for other components of the primary endpoint were lower and are reported in Table 3.

The adjusted hazard ratios for the primary and secondary endpoints across the IGF-1 and GH cohorts are shown in Figure 3. Of note, both elevated IGF-1 and GH were associated with increased risk of the composite endpoint (IGF-1 HR = 1.20, 95% CI 1.02-1.50; GH HR = 1.10, 1.00 to 1.20).

Beyond a significant association with the primary endpoint, elevated IGF-1 conferred a 1.5 times excess risk of incident type 2 diabetes. No other components of the primary endpoint demonstrated a significant association with IGF-1 when analysed individually (Figure 3). In the GH analysis, no component endpoint was found to be significantly associated with GH. Visual comparison of the patterns of association in Figure 3 shows a generally more evident pattern of increased risk using IGF-1 than when using GH as a biochemical metric.

4 | DISCUSSION

In this large study embedded in contemporary clinical practice in the UK, IGF-1 and GH were predictive of adverse outcome in acromegaly. Elevated IGF-1 was associated with an increased risk of a composite endpoint comprising mortality, diabetes, MACE and cancer. Increased IGF-1 ratio was also associated with increased incidence of type 2 diabetes as an individual clinical endpoint. GH measurements were associated with an increased risk of the composite outcome, but not with any individual clinical endpoint.

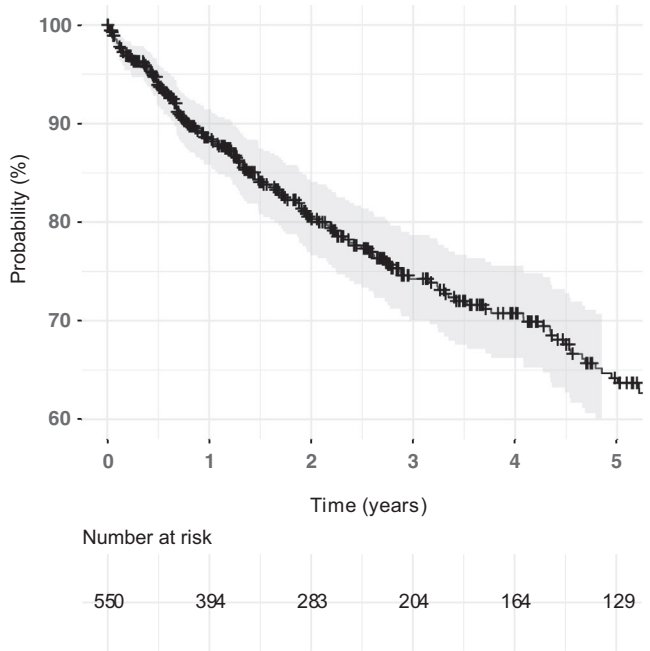

FIGURE 2 Kaplan-Meier survival curve illustrating the probability of progression to the composite clinical endpoint (including all-cause mortality, type 2 diabetes, major adverse cardiovascular events and cancer) [Colour figure can be viewed at wileyonlinelibrary.com]

Previous studies have shown that both elevated GH and IGF-1 are associated with disease outcomes in patients with acromegaly. Previous meta-analyses concluded that elevations in both GH and IGF-1 were associated with increased mortality,[4,5] albeit that the GH threshold identified (<2.5 μg/L) related largely to measurements undertaken by radioimmunoassay and at a time when calibration against a uniform GH standard had not been widely adopted. A normal age- and sex-adjusted serum IGF-1 at last follow-up was associated with a standardised mortality ratio (SMR) of 1.1 (95% CI 0.9-1.4) compared with an SMR of 2.5 (1.6-4.0) for patients with continued IGF-1 elevation.[9] Other studies had previously identified GH as a major determinant of mortality in multivariate analyses.[4,5,13-15] In contrast, the data on IGF-1 are less consistent, with some,[6,16,17] but not all[7,13] studies identifying IGF-1 as a significant independent predictor of mortality. The number of patients with IGF-1 measurements performed and available for analysis was significantly lower in many earlier studies which might in part account for these discrepant findings. Inter-assay variation is likely another significant factor,[18] which we sought to minimise by only including those IGF-1 measurements with a defined upper reference value (age- and sex-adjusted) and expressing IGF-1 elevation as an IGF-1 ratio. More recent studies have shown that elevated GH at last follow-up[19,20] and/or elevated IGF-1 at last follow-up[21] was predictive of mortality. Neither GH nor IGF-1 were predictive of mortality as an individual outcome in our study, likely as we were underpowered to demonstrate an association with singular outcomes.

Diabetes is a frequent comorbidity in acromegaly with a prevalence of 12%-37%.[22] Our data confirm a high incidence of diabetes in patients with acromegaly, with an event rate equivalent to cancer and exceeding that of MACE in our population. IGF-1, but not GH, was significantly associated with incident diabetes in our study, although the hazard ratio for GH-approached statistical significance. Our data could not be explained by any major imbalance between the GH and IGF-1 groups with respect to patient or treatment characteristics, which were very similar with the exception of a slightly

TABLE 3 Total follow-up, events and unadjusted event rates per thousand person-years

Outcome	Cases (n)	Follow-up (years)	Events (n)	Event rate	95% CI	
IGF-1						
Composite endpoint	417	1041.5	100	96.0	78.5	116.3
All-cause mortality	417	1172.7	51	43.5	32.7	56.7
Type 2 diabetes	309	839.8	21	25.0	15.9	37.6
MACE[a]	328	926.3	9	9.7	4.7	17.8
All cancers	289	808.8	20	24.7	15.5	37.5
Growth hormone						
Composite endpoint	332	938.9	84	89.5	71.7	110.1
All-cause mortality	332	1042.9	46	44.1	32.7	58.3
Type 2 diabetes	259	772.3	18	23.3	14.3	36.1
MACE[a]	256	814.5	9	11.1	5.4	20.3
All cancers	239	768.0	16	20.8	12.3	33.1

[a]Major Adverse Cardiac Events.

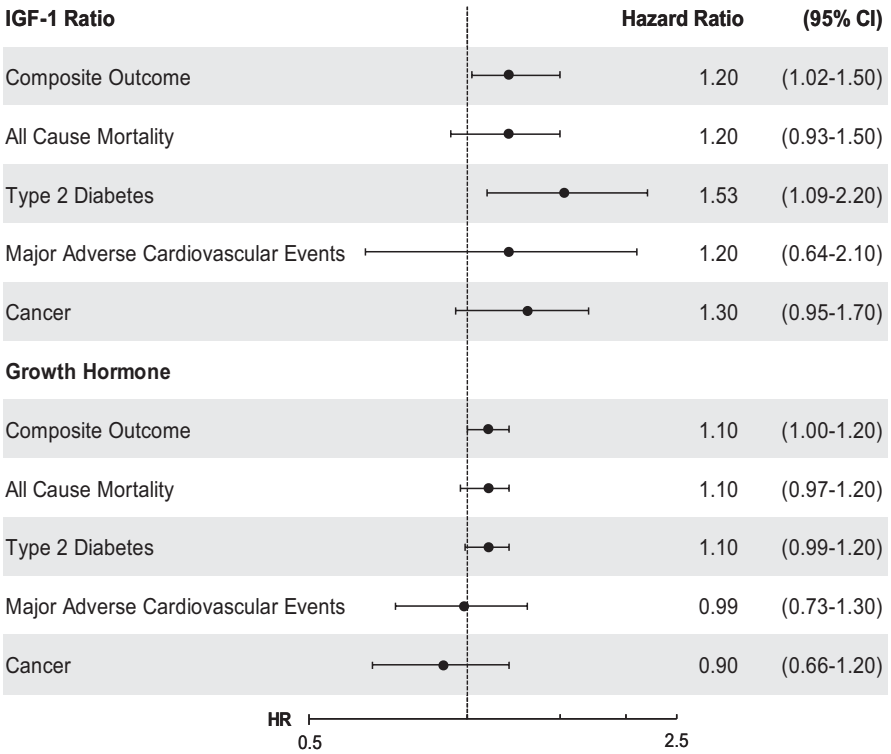

FIGURE 3 Forest plot of adjusted hazard ratios (aHRs) describing the relationship between IGF-1 ratio and growth hormone (GH) measurements with clinical endpoints. All HRs presented were adjusted for age and gender [Colour figure can be viewed at wileyonlinelibrary.com]

greater number treated previously with pegvisomant in the IGF-1 group as might be anticipated. Our data contrast with findings from the French Acromegaly Registry in which neither GH nor IGF-1 were predictive for the presence of diabetes.[23] However, our observations are consistent with previous cross-sectional data in which high plasma IGF-1, but not GH, concentrations at diagnosis were independently associated with hyperglycaemia[24] and with another registry study in which glucose values (basal or post-glucose tolerance test) correlated significantly with IGF-1 alone.[25] Furthermore, plasma IGF-1 concentration in acromegaly is the strongest predictor of insulin sensitivity.[26,27] IGF-1 concentrations thus appear to be a better marker of diabetes risk than GH values in acromegaly, perhaps as they represent an integrated measure of GH excess, and IGF-1 normalisation may therefore be an important metabolic treatment goal.

Cardiovascular disease, including hypertension and cardiomyopathy, is highly prevalent in patients with acromegaly and traditionally considered a major cause of premature death. However, we found a low number of cardiovascular events during the follow-up period of our study and were thus unable to demonstrate an association between either IGF-1 or GH with MACE as an outcome. A recent analysis of 19 national acromegaly registries, including more than 16,000 patients, has shown that cardiovascular mortality has decreased markedly over time,[28] in line with similar trends in the general population.[29] Demonstrating an effect of biochemical control on cardiovascular outcomes in contemporary practice is thus challenging and will likely require prospective, international collaborative efforts involving large numbers of patients. Registry data[30] and a systematic review[30] have also confirmed that cancer has now become a leading cause of death in patients with acromegaly, paralleling the decline in cardiovascular mortality. Consistent with this, we found a higher event rate for cancer compared with cardiovascular disease in our study population, although neither IGF-1 nor GH was associated with incident events at the conventional level of statistical significance. Our findings are in agreement with data from the German Acromegaly Registry, comprising 6656 person-years of follow-up, which in addition to showing no difference in overall cancer incidence compared with the general population found no relationship between either GH or IGF-1 and incident disease.[31]

Our study has a number of strengths, including the population-based design which is less subject to any bias that may be apparent in targeted studies.[30] This allowed us to compare the effects of markers of disease control on serious, clinically relevant outcomes in a 'real-world' setting in an unselected manner. The study was undertaken in an era of modern GH and IGF-1 immunoassays, reflecting contemporary endocrine practice; hence, our results are likely to be generalizable to the wider population of patients with acromegaly. The study also benefited from a good duration of follow-up and careful adjustment for potential confounders. However, our study also has some limitations. While we intentionally exploited the improved population coverage offered by the most recent CPRD release to capture a large number of patients with acromegaly at study outset, our sample size was affected by missing data, particularly biochemical measures, and by application of a number of exclusion criteria to ensure high-quality cases. Consistent with the secular trends for improved disease control and outcomes in acromegaly reported elsewhere,[30] the event rate for individual outcomes was also comparatively low over the follow-up period, hence the need for a composite primary outcome in order to increase statistical power. A larger sample size may have revealed statistically significant

differences that our study was insufficiently powered to obtain. Nevertheless, it is worth noting that, collectively, progression to any endpoint was high. This serves as a reminder of the importance of screening for, and treating, comorbidities in this population, in line with recent consensus recommendations,[32] in addition to targeting good biochemical control. Another limitation also arises from the use of last available IGF-1 and GH readings to classify patients, under the assumption that these readings would remain stable over the length of follow-up. Further work could use a method of cumulative exposure to classify a patient's biochemical status. Finally, comparison of baseline characteristics demonstrated a significant difference in smoking status, alcohol status and prior recorded pegvisomant prescription between the IGF-1 and GH analysis groups. These factors were not controlled for in the cox proportional hazards models due to the relatively low number of outcome events.

In summary, IGF-1 and GH concentrations predicted incident major disease outcomes in this large population-based study of patients with acromegaly, within a 5-year follow-up period. Our data support the use of IGF-1 alongside GH for biochemical monitoring and suggest that normalisation of GH and IGF-1 is needed in order to optimise disease outcomes.

CONFLICT OF INTEREST

DAR and JA consulted for Pfizer in relation to this study. JB and SW are employed by Pfizer and hold stock and/or stock options in that company. CC, CP, SJJ, MT and EB are employed by Pharmatelligence, a consultancy that receives funding from the pharmaceutical industry and other healthcare organisations, contracted by Pfizer to conduct the current study.

AUTHOR CONTRIBUTION

This study was conceived by DAR, JA, SW, JB, EB, MT, SJJ, CDP and CC. CDP and EB wrote the statistical analysis plan. MT, EB and SJJ carried out the analysis and collected the data. MT, CC and DAR produced the initial draft of the manuscript. All authors contributed to the revision of the manuscript and accepted the final version.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

ETHICS APPROVAL

Research carried out using CPRD data was approved by the MHRA Independent Scientific Advisory Committee (ISAC approval number 19_254).

DATA AVAILABILITY STATEMENT

Restrictions apply to the availability of some or all data generated or analysed during this study to preserve patient confidentiality or because they were used under licence. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided. CPRD data are available upon application after ISAC approval through a licenced organisation (Pharmatelligence). Source data are not publicly available. This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. HES data - Copyright © (2020), re-used with the permission of The Health & Social Care Information Centre. All rights reserved. The OPCS Classification of Interventions and Procedures, codes, terms and text is Crown copyright (2016) published by Health and Social Care Information Centre, also known as NHS Digital and licensed under the Open Government Licence available at www.nationalarchives.gov.uk/doc/open-government-licence/open-government-licence.html

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REFERENCES

1. Lavrentaki A, Paluzzi A, Wass JA, Karavitaki N. Epidemiology of acromegaly: review of population studies. *Pituitary*. 2017;20:4-9.
2. Sherlock M, Ayuk J, Tomlinson JW, et al. Mortality in patients with pituitary disease. *Endocr Rev*. 2010;31:301-342.
3. Sughrue ME, Chang EF, Gabriel RA, Aghi MK, Blevins LS. Excess mortality for patients with residual disease following resection of pituitary adenomas. *Pituitary*. 2011;14:276-283.
4. Dekkers OM, Biermasz NR, Pereira AM, Romijn JA, Vandenbroucke JP. Mortality in acromegaly: a meta-analysis. *J Clin Endocrinol Metab*. 2008;93:61-67.
5. Holdaway IM, Bolland MJ, Gamble GD. A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. *Eur J Endocrinol*. 2008;159:89-95.
6. Holdaway IM, Rajasoorya RC, Gamble GD. Factors influencing mortality in acromegaly. *J Clin Endocrinol Metab*. 2004;89:667-674.
7. Ayuk J, Clayton RN, Holder G, Sheppard MC, Stewart PM, Bates AS. Growth hormone and pituitary radiotherapy, but not serum insulin-like growth factor-I concentrations, predict excess mortality in patients with acromegaly. *J Clin Endocrinol Metab*. 2004;89:1613-1617.
8. Chanson P, Arnoux A, Mavromati M, et al. Reference values for IGF-1 serum concentrations: comparison of six immunoassays. *J Clin Endocrinol Metab*. 2016;101:3450-3458.
9. Pokrajac A, Wark G, Ellis AR, Wear J, Wieringa GE, Trainer PJ. Variation in GH and IGF-I assays limits the applicability of international consensus criteria to local practice. *Clin Endocrinol (Oxf)*. 2007;67:65-70.
10. Wieringa GE, Barth JH, Trainer PJ. Growth hormone assay standardization: a biased view? *Clin Endocrinol (Oxf)*. 2004;60(5):538-539.
11. Giustina A, Barkhoudarian G, Beckers A, et al. Multidisciplinary management of acromegaly: a consensus. *Rev Endocr Metab Disord*. 2020;21:667-678.
12. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015;44:827-836.
13. Kauppinen-Mäkelin R, Sane T, Reunanen A, et al. A nationwide survey of mortality in acromegaly. *J Clin Endocrinol Metab*. 2005;90:4081-4086.
14. Mestron A, Webb SM, Astorga R, et al. Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry (Registro Espanol de Acromegalia, REA). *Eur J Endocrinol*. 2004;151:439-446.
15. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study.

United Kingdom Acromegaly Study Group. *J Clin Endocrinol Metab*. 1998;83:2730-2734.
16. Swearingen B, Barker FG, Katznelson L, et al. Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. *J Clin Endocrinol Metab*. 1998;83:3419-3426.
17. Biermasz NR, Dekker FW, Pereira AM, et al. Determinants of survival in treated acromegaly in a single center: predictive value of serial insulin-like growth factor I measurements. *J Clin Endocrinol Metab*. 2004;89:2789-2796.
18. Strasburger CJ. IGF-I and mortality in patients with acromegaly. *J Endocrinol Invest*. 2005;28:78-80.
19. Arosio M, Reimondo G, Malchiodi E, et al. Predictors of morbidity and mortality in acromegaly: an Italian survey. *Eur J Endocrinol*. 2012;167:189-198.
20. Ritvonen E, Löyttyniemi E, Jaatinen P, et al. Mortality in acromegaly: a 20-year follow-up study. *Endocr Relat Cancer*. 2016;23:469-480.
21. Mercado M, Gonzalez B, Vargas G, et al. Successful mortality reduction and control of comorbidities in patients with acromegaly followed at a highly specialized multidisciplinary clinic. *J Clin Endocrinol Metab*. 2014;99:4438-4446.
22. Hannon AM, Thompson CJ, Sherlock M. Diabetes in patients with acromegaly. *Curr Diab Rep*. 2017;17:8.
23. Fieffe S, Morange I, Petrossians P, et al. Diabetes in acromegaly, prevalence, risk factors, and evolution: data from the French Acromegaly Registry. *Eur J Endocrinol*. 2011;164:877-884.
24. Alexopoulou O, Bex M, Kamenicky P, Mvoula AB, Chanson P, Maiter D. Prevalence and risk factors of impaired glucose tolerance and diabetes mellitus at diagnosis of acromegaly: a study in 148 patients. *Pituitary*. 2014;17:81-89.
25. Petrossians P, Daly AF, Natchev E, et al. Acromegaly at diagnosis in 3173 patients from the Liège Acromegaly Survey (LAS) Database. *Endocr Relat Cancer*. 2017;24:505-518.
26. Niculescu D, Purice M, Coculescu M. Insulin-like growth factor-I correlates more closely than growth hormone with insulin resistance and glucose intolerance in patients with acromegaly. *Pituitary*. 2013;16:168-174.
27. Reid TJ, Jin Z, Shen W, et al. IGF-1 levels across the spectrum of normal to elevated in acromegaly: relationship to insulin sensitivity, markers of cardiovascular risk and body composition. *Pituitary*. 2015;18:808-819.
28. Maione L, Chanson P. National acromegaly registries. *Best Pract Res Clin Endocrinol Metab*. 2019;33:101264.
29. Bhatnagar P, Wickramasinghe K, Wilkins E, Townsend N. Trends in the epidemiology of cardiovascular disease in the UK. *Heart*. 2016;102:1945-1952.
30. Bolfi F, Neves AF, Boguszewski CL, Nunes-Nogueira VS. Mortality in acromegaly decreased in the last decade: a systematic review and meta-analysis. *Eur J Endocrinol*. 2018;179:59-71.
31. Petroff D, Tönjes A, Grussendorf M, et al. The Incidence of Cancer Among Acromegaly Patients: Results From the German Acromegaly Registry. *J Clin Endocrinol Metab*. 2015;100:3894-3902.
32. Giustina A, Barkan A, Beckers A, et al. A Consensus on the diagnosis and treatment of acromegaly comorbidities: an update. *J Clin Endocrinol Metab*. 2020;105:dgz096.

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