Research Square

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Long-Term Metabolic Effects of Recombinant Human Growth Hormone Therapy in Childhood-Onset Craniopharyngioma Survivors

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Abstract

Background

Hypothalamic obesity (HO) is a debilitating sequela of paediatric craniopharyngioma (CP) in survivors. Concerns regarding tumour recurrence often delay the initiation of recombinant human growth hormone (rhGH) therapy. This study aimed to evaluate the long-term metabolic safety of rhGH replacement in paediatric CP survivors, focusing on body mass index (BMI) trajectories and survival outcomes.

Methods

In this single-centre retrospective cohort study, we included 53 patients diagnosed with CP before age 18 and followed for up to 26 years. Patients were categorised into two groups: a rhGH-treated group (TrG; ≥ 12 months, n = 30) and a non-treated control group (Control; n = 23), despite all having growth hormone deficiency. Longitudinal BMI z-score (z-BMI) trajectories were analysed using linear mixed-effects models adjusting for hypothalamic tumour grade and baseline obesity status. Overall and recurrence-free survival were assessed using Kaplan-Meier and landmark analyses.

Results

Forty-three of 53 (81.1%) patients were diagnosed with panhypopituitarism after surgery. The prevalence of metabolic syndrome did not differ significantly between groups, whereas the prevalence of low HDL cholesterol was higher in the control group ($p = 0.047$). In multivariable analysis, grade 2 tumours were independently associated with higher z-BMI trajectories ($p < 0.001$), and baseline z-BMI was significantly associated with long-term z-BMI trajectories during rhGH treatment ($p < 0.001$). Landmark analyses demonstrated no significant differences in overall or recurrence-free survival between the groups ($p = 0.630$ and $p = 0.480$, respectively).

Conclusions

rhGH therapy was associated with relatively stable z-BMI trajectories over time in paediatric CP survivors, without evidence of increased recurrence or mortality.

Background

Craniopharyngioma (CP) is a rare, benign epithelial tumour that arises in the sellar and suprasellar regions near critical structures, such as the hypothalamus and pituitary gland, and predominantly affects the paediatric population [1, 2]. Despite excellent long-term survival rates—often exceeding 90% at 10 years—the disease and its treatment are associated with profound and lifelong morbidities, particularly hormonal deficiencies and hypothalamic dysfunction [1, 3]. Endocrine sequelae, including growth

hormone deficiency (GHD), adrenal insufficiency, hypothyroidism, hypogonadism, and diabetes insipidus, are observed in most children following diagnosis and treatment, reflecting the central role of the hypothalamic-pituitary axis in the pathophysiology of CP [1, 4].

Hypothalamic obesity (HO) is a distinctive, highly morbid, and refractory phenotype of weight gain caused by altered energy balance, affecting approximately half of the survivors of childhood CP and is tightly linked to tumour location, grade, and the extent of hypothalamic damage [5–7]. The hypothalamus plays a pivotal role in regulating energy expenditure and appetite. Previous studies report that up to 50% of patients with CP develop HO, with approximately 20% already being obese at diagnosis [8]. To date, the management of HO remains challenging because of its poor response to diet, physical exercise, and/or medications, with substantial ramifications on quality of life, morbidity, and mortality [9]. Unlike adults, children with hypopituitarism tend to experience earlier and more rapid weight gain, placing them at greater risk of severe metabolic complications. Moreover, ongoing growth and pubertal hormone changes may further exacerbate the clinical burden of HO in children [10].

GHD is another common sequela of CP, and recombinant human growth hormone (rhGH) replacement is the standard treatment for improving height and metabolic outcomes [11–13]. Safety concerns regarding tumour recurrence or progression associated with rhGH have largely been addressed by large cohort studies and systematic reviews, which found no significant increase in recurrence risk with proper rhGH replacement therapy [13–15]. Nonetheless, the effect of rhGH therapy on metabolic profiles and the risk of HO remains underexplored and controversial [16, 17]. Longitudinal data on body mass index (BMI) trajectories and metabolic risk in paediatric CP survivors receiving rhGH are limited, especially in Asian populations, where genetic and ethnic factors may influence metabolic responses [17–19]. Furthermore, patient and caregiver surveys consistently highlight that the prevention and management of HO should be the highest research priority, even over concerns regarding tumour recurrence [17].

This study aimed to investigate the prevalence of endocrine and metabolic comorbidities over a long-term follow-up period and evaluate the effects of prolonged rhGH therapy on BMI z-scores (z-BMI) and BMI outcomes during the transition from childhood to adult rhGH replacement therapy, particularly with respect to obesity status at diagnosis. The study leveraged detailed long-term, single-centre data to clarify whether rhGH therapy affects BMI trajectories in the context of obesity risk stratification and to identify variables that modify treatment outcomes.

Methods

Patients, data collection, and measurements

This retrospective cohort study enrolled paediatric patients aged < 18 years, who were pathologically diagnosed with CP between January 1994 and December 2021 at the Samsung Medical Centre, South Korea. Medical and biometric data, including height, weight, BMI, laboratory tests, and dual-energy X-ray absorptiometry findings, were extracted from the medical records. Obesity status at diagnosis was

determined using age- and sex-specific BMI percentiles, calculated as weight in kilograms divided by height in meters squared (kg/m^2), according to the World Health Organization growth standards. Participants were categorised into three groups: normal (< 85th percentile), overweight (85th to < 95th percentile), and obesity (≥ 95th percentile). These categorical thresholds corresponded to z-BMI values ≤ 1.0 standard deviation (SD), 1.0 < z-BMI ≤ 2.0 SD, and > 2.0 SD, respectively. While these categories were used for baseline stratification, z-BMI was treated as a continuous variable in the subsequent longitudinal mixed-effects model analysis to ensure statistical granularity [20].

Fasting blood samples were collected to measure lipid profiles, glucose, insulin, haemoglobin A1c, and hormone levels, including insulin-like growth factor 1, growth hormone (GH), adrenocorticotropic hormone (ACTH), cortisol, luteinizing hormone, follicle-stimulating hormone, prolactin, free thyroxine (fT4), triiodothyronine and thyroid stimulating hormone (TSH). All laboratory analyses were performed at the Samsung Medical Centre. The Institutional Review Board of the Samsung Medical Centre approved this study (IRB No. SMC 2022-10-051). Given the retrospective nature of the study, the requirement for informed consent was waived by the IRB. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Definitions of endocrine and metabolic illnesses

Pituitary hormone deficiencies were defined as follows: ACTH or TSH deficiency was considered present if patients required glucocorticoids or thyroxine replacements, respectively. When both were required, glucocorticoids were administered first, followed by thyroxine. Gonadotropin deficiencies were noted in premenopausal female patients with amenorrhea and non-elevated gonadotropin levels, as well as women who were currently receiving oestrogen prescriptions in the form of hormone replacement therapy or oestrogen-containing contraceptive pills. In male patients, gonadotropin deficiency was defined by ongoing testosterone replacement therapy at the most recent evaluation. GHD was diagnosed when GH stimulation test results were indicative of GH deficiency (peak serum GH < 10 μg/L in two or more drug challenge tests) [21]. Central hypothyroidism was defined as a fT4 level < 0.75 ng/dL and non-elevated TSH levels (not increased by > 5 mU/L). In the thyrotropin-releasing hormone stimulation test, secondary hypothyroidism was indicated by a low basal serum fT4 level with inappropriately normal or low TSH levels [22]. Anterior panhypopituitarism was considered when the levels of three or more pituitary hormones were insufficient. Patients prescribed maintenance desmopressin were classified as having central diabetes insipidus.

Metabolic syndrome was defined according to the modified National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria adopted for paediatric populations. Because patients with unavailable waist circumference data were included, metabolic syndrome was identified by the presence of three or more of the following four components: (1) hypertriglyceridemia (≥ 150 mg/dL), (2) low high-density lipoprotein (HDL) cholesterol (< 40 mg/dL for both sexes, or < 50 mg/dL for girls aged ≥ 16 years), (3) impaired fasting glucose (≥ 100 mg/dL or known diabetes mellitus), and (4) hypertension

(blood pressure ≥ 90 percentile for age, sex and height in children and adolescents; ≥ 130/90 mmHg in adult; or use of anti-hypertensive medication) [23]. Diabetes mellitus was diagnosed according to the American Diabetes Association guidelines, and dyslipidaemia was defined as the receipt of pharmacological treatment for lipid abnormalities despite lifestyle modifications [24].

Tumour grading of CP

Tumour grade was classified according to the degree of hypothalamic involvement. The posterior hypothalamic nuclei were localised in the lateral walls of the third ventricle, beginning at the level of the mammillary bodies and extending posteriorly. Grade 0 CP was defined as a lack of contact with the floor of the third ventricle. Grade 1 CP referred to tumours contacting or compressing the hypothalamus anterior with the mammillary bodies. Grade 2 CP was defined as tumours causing dislocation, compression, or destruction of the hypothalamus, beginning at the level of the mammillary bodies or dorsal to them [25].

Survival outcomes

Overall survival (OS) and recurrence were calculated after the initial CP treatment. CP recurrence was diagnosed by neuroimaging. After initial therapy, recurrence was defined as the reappearance or progression of CP. Follow-up neuroimaging was performed regularly, based on the surgeon's preference and clinical judgement.

Group definition based on treatment duration

Patients were categorised into two groups based on the duration of rhGH replacement therapy. Patients who received rhGH replacement therapy for at least 12 consecutive months, a duration deemed sufficient to induce stable metabolic adaptation and discernible change in body composition, were assigned to the GH-treated group (TrG, n = 30).

The control group (Control, n = 23) comprised patients who remained rhGH-naïve throughout the follow-up period. Patients who received rhGH for less than 12 months (n = 6) were excluded from the analysis due to potential confounding effects of transient or insufficient exposure, which may not adequately reflect the sustained metabolic impact of rhGH replacement [26].

Statistical analysis

Baseline characteristics are presented as numbers and percentages for categorical variables and as medians with interquartile ranges (IQRs; Q1–Q3) for continuous variables. The TrG and control group were compared using Fisher's exact test for categorical variables, and the Wilcoxon rank-sum test for continuous variables. Kaplan-Meier analyses were used to estimate the OS and recurrence-free survival

(RFS), and survival curves were compared using the log-rank test. To account for potential immortal time bias associated with the timing of rhGH initiation, a landmark analysis was performed, with the landmark set at 2 years post-surgery. The longitudinal mixed-effects model was performed using data with at least two documented z-BMI measurements to ensure a robust assessment of trajectories.

A smoothing plot was used to confirm the pattern of BMI change over time. Linear mixed-effects models with random intercepts were employed to analyse the longitudinally measured z-BMI. The models included treatment duration, tumour grade, type or surgery, and baseline z-BMI as fixed effects to adjust for potential confounders and estimate their independent associations with z-BMI patterns. Furthermore, to determine whether the rate of change in z-BMI over time differed across obesity groups, a model was constructed including treatment duration, degree of obesity (baseline z-BMI), and their interaction term (treatment duration × baseline z-BMI) as fixed effects. *P*-values were corrected using Bonferroni's method due to multiple testing.

All statistical analyses were performed using R (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria) and Rex software (version 3.6.3, RexSoft Inc., Seoul, South Korea). p-values < 0.05 were considered statistically significant.

Results

Clinical characteristics of all participants

Among 77 patients identified with childhood-onset CP, 12 were excluded due to insufficient baseline data: nine lacked BMI data at diagnosis, two lacked anthropometric measurements at the initiation of rhGH therapy, and one had an indeterminate tumour grade owing to missing baseline radiographic imaging. Of the remaining 65 patients, 12 were further excluded to maintain cohort homogeneity (6 discontinued rhGH therapy or received non-continuous treatment, and 6 received rhGH for less than 12 months). Consequently, 53 patients were included in the final statistical analysis (TrG, n = 30; Control, n = 23) (Fig. 1).

Figure 1. Flowchart for patient enrolment.

Abbreviation: BMI, body mass index; GH, recombinant human growth hormone treatment; TrG, patients treated with GH for ≥ 1 year.

In the total cohort (n = 53), 29 (54.7%) were male (TrG, 16 [53.5%]; Control, 13 [56.5%]), and the median age at diagnosis was 9.7 (interquartile range [IQR] 5.4, 12.4; TrG, 8.2 [4.5, 11.2]; Control, 12.4 [5.4, 15.3]) years. The median follow-up period was 10.8 (IQR, 3.5, 15.3) years. For the subgroup analysis of TrG, the median interval from surgery to the initiation of rhGH therapy was 1.2 (IQR, 1.0, 1.8) years. Forty-four (83.0%) patients had grade 2 (G2) hypothalamic involvement, all with adamantinomatous histology. At diagnosis, the median height and BMI z-scores (z-BMI) were within the normal reference ranges. Regarding primary treatments, 37 of 53 (69.8%) underwent surgery only, whereas 16 (30.2%) received

surgery followed by adjuvant radiotherapy. The baseline clinical characteristics and distribution of obesity status are detailed in Table 1.

Table 1. Baseline characteristics of childhood-onset craniopharyngioma patients at diagnosis stratified by recombinant human growth hormone (rhGH) treatment status.

	Total patients (n = 53)	TrG (n = 30)	Control (n = 23)	*p*-value
Sex (Male)	29 (54.7%)	16 (53.3%)	13 (56.5%)	> 0.999
Age (year)	9.7 (5.4, 12.4)	8.2 (4.5, 11.2)	12.4 (5.4, 15.3)	0.011
Height z-score	-0.929 (-1.830, -0.038)	-1.649 (-2.769, -0.864)	-0.164 (-0.944, 0.300)	< 0.001
BMI z-score	0.452 (-0.410, 1.781)	0.434 (-0.430, 1.198)	0.653 (-0.228, 2.095)	0.353
Obesity status[#] (n) Normal Overweight Obesity	34 (64.2%) 4 (5.7%) 15 (26.4%)	20 (66.7%) 3 (10.0%) 7 (23.3%)	14 (60.9%) 1 (4.3%) 8 (34.8%)	0.613
Tumour grade G0 G1 G2	7 (13.2%) 2 (3.8%) 44 (83.0%)	5 (16.7%) 0 (0.0%) 25 (83.3%)	2 (8.7%) 2 (8.7%) 19 (82.6%)	0.304
Initial treatment Op Op + RT	37 (69.8%) 16 (30.2%)	23 (76.7%) 7 (23.3%)	14 (60.9%) 9 (39.1%)	0.347
Degree of resection GTR STR Biopsy	22 (41.5%) 24 (45.3%) 7 (13.2%)	14 (46.7%) 10 (33.3%) 6 (20.0%)	8 (34.8%) 14 (60.9%) 1 (4.3%)	0.083
Histological subtype Adamantinomatous Papillary Unknown	48 (90.6%) 3 (5.7%) 2 (3.8%)	26 (86.7%) 2 (6.7%) 2 (6.7%)	22 (95.7%) 1 (4.3%) 0 (0.0%)	0.274

Abbreviations: TrG, rhGH treatment group (≥ 1 year); BMI, body mass index; IQR, interquartile range; rhGH, recombinant human growth hormone treatment; G0, Grade 1 tumour; G1, Grade 1 tumour; G2, Grade 2 tumour; Op, operation; RT, radiotherapy; GTR, gross total resection; STR, subtotal resection.

[#]Assessing obesity status using body mass index (BMI) percentiles: normal (< 85th), overweight (85th to < 95th), and obesity (≥ 95th), corresponding to BMI z-score (z-BMI) ≤ 1.0, 1.0 < z-BMI ≤ 2.0, and > 2.0 SD, respectively.

Note: The categorical values are presented as percentages (%) and the continuous variables as medians (interquartile ranges). Statistical significance between the TrG and control groups was determined using the Wilcoxon rank-sum test for continuous variables (age and z-scores). For categorical variables, the chi-square test or Fisher's exact test was employed as appropriate based on cell frequencies.

Endocrine profiles during the perioperative period

At a median of 19 (IQR, 9.5–203) days after surgery, 47 of 53 patients (88.7%) underwent complex pituitary hormone stimulation testing. Owing to the retrospective nature and potential risks of invasive testing, formal hormonal stimulation testing was not routinely performed in all patients. For patients unable to undergo formal testing due to clinical contraindications or missing retrospective data, hormone deficiency was determined based on basal pituitary hormone levels measured within 1 month of diagnosis or surgery, together with documented initiation of hormone replacement therapy. Forty-three of 53 (81.1%) patients were diagnosed with panhypopituitarism and received treatment with at least three hormones in addition to rhGH. The details of the hormonal deficiency are described in Table 2.

Table 2. Hormonal status on perioperative period.

Types of hormones	IGF-1D/GHD[#]	AI/ACTHD[†]	TSHD	LHD	FSHD	PRLD	DI
Before surgery	14/53 (26.4%)	15/53 (28.3%)	6/53 (11.3%)	9/53 (17.0%)	9/53 (17.0%)	1/53 (1.9%)	3/53 (5.7%)
After 1st surgery	45/53 (84.9%)	43/53 (81.1%)	34/53 (64.2%)	29/53 (54.7%)	27/53 (50.9%)	23/53 (43.4%)	50/53 (94.3%)

Abbreviation: IGF-1D, low insulin-like growth factor-1 below the normal range for their age and gender; GHD, growth hormone deficiency; AI, adrenal insufficiency; ACTHD, adrenocorticotropic hormone deficiency; TSHD, thyroid-stimulating hormone deficiency; LHD, luteinizing hormone deficiency; FSHD, follicle stimulating hormone deficiency; PRLD, prolactin deficiency; DI, diabetes insipidus.

[#]In this population, some patients were included when their clinical condition precluded GH stimulation or a combined pituitary test, and their insulin-like growth factor-1 level measured within 1-month post-surgery fell below the normal range for their age and sex.

[†]In this population, some patients were included when their clinical condition precluded ACTH stimulation or combined pituitary test, and their early morning cortisol level measured within 1-month post-surgery fell below the normal range for their age.

Overall and recurrence-free survival rates over time in each group

Data were analysed to identify differences in OS and RFS rates between groups (Fig. 2). Kaplan-Meier survival analyses were performed to compare the oncological safety of long-term rhGH therapy between the TrG and control groups. To account for potential immortal time bias, a landmark analysis was performed at 2 years post-surgery, by which all patients in the TrG had initiated rhGH therapy.

No significant difference in OS was observed between groups either at the time of surgery ($p = 0.290$, log-rank test) or in the landmark analysis ($p = 0.630$, log-rank test) (Fig. 2a and 2b). RFS curves showed a statistically significant difference between the TrG and control groups over the overall follow-up period ($p = 0.007$). However, this difference was not significant in the landmark analysis ($p = 0.480$) (Fig. 2c and 2d).

Figure 2. OS and RFS between groups treated with rhGH for ≥ 1 year (TrG) and Control.

a. The OS rate across time between groups across all time periods ($p = 0.290$).

b. The OS rate over time between groups from the intervention start point (landmark) between groups ($p = 0.630$).

c. The RFS rate over time between groups across all time periods ($p = 0.007$).

d. The RFS rate over time between groups from the landmark ($p = 0.480$).

rhGH, recombinant human growth hormone; RFS, recurrence-free survival; OS, overall survival.

Comparison of metabolic comorbidities

The prevalence of metabolic syndrome was 6.7% in the TrG and 13.0% in the control group ($p = 0.642$). Among the individual components, the TrG exhibited a significantly lower frequency of low HDL cholesterol than the control group ($p = 0.047$; 26.7% vs. 56.5%). Other metabolic components showed no significant differences between the groups, including hypertriglyceridemia ($p > 0.999$; 50.0% vs. 52.2%), impaired fasting glucose ($p > 0.999$; 16.7% vs. 13.0%), and hypertension ($p > 0.999$; 6.7% vs. 4.3%). None of the patients with hypertension required anti-hypertensive medications. Detailed metabolic parameters associated with metabolic syndrome are summarised in Table 3.

Table 3. Prevalence of metabolic comorbidities at final follow-up between groups.

Metabolic abnormality*	TrG (n = 30)	Control (n = 23)	*p*-value
High Triglycerides	15 (50.0%)	12 (52.2%)	> 0.999
Low HDL cholesterol	8 (26.7%)	13 (56.5%)	0.047
Pharmacologically treated hyperlipidaemia	1 (3.3%)	4 (21.7%)	0.158
IFG#	5 (16.7%)	3 (13.0%)	> 0.999
DM type 2	1 (3.3%)	1 (4.3%)	> 0.999
Hypertension	2 (6.7%)	1 (4.3%)	> 0.999
Metabolic syndrome	2 (6.7%)	3 (13.0%)	0.642

Abbreviation: HDL, high-density lipoprotein; IFG, Impaired fasting glucose; DM, diabetes mellitus.

*Serum triglycerides ≥ 150 mg/dL; HDL cholesterol < 40 mg/dL for both sexes, or < 50 mg/dL for girls aged ≥16 years; Fasting glucose ≥ 100 mg/dL; blood pressure ≥ 90 percentile for age, sex and height or use of antihypertensive medication; defined as presence of ≥ 3 criteria as per modified NCEP-ATP III guidelines.

Note: Variables are presented as frequency (%). The *p*-value was calculated using Fisher's exact test.

Factors associated with z-BMI trends and longitudinal trajectories

To identify the clinical determinants affecting the longitudinal trends in z-BMI during rhGH treatment, a multivariable mixed-effects model was generated (Table 4). Tumour grade and baseline z-BMI were significant independent predictors. Patients with Grade 2 tumours exhibited significantly higher z-BMI trends compared to those with Grade 0 tumours (β = 1.150, p < 0.001). Additionally, baseline z-BMI was strongly associated with follow-up z-BMI levels throughout the treatment period (β = 0.533, p < 0.001).

Table 4. Multivariable analysis of BMI z-score (z-BMI) pattern trends during rhGH treatment after adjusting for variables over time

Effect	Estimate (β)	SE	DF	*t*-value	*p*-value
Treatment duration (months)	-0.006	0.006	181	-1.02	0.310
Tumour grade (G2 vs. G0)	1.150	0.229	181	5.02	< 0.001
Type of surgery#	0.196	0.233	181	0.84	0.402
z-BMI	0.533	0.062	181	8.58	< 0.001

Abbreviation: SE, standard error; DF, degree of freedom; G2, grade 2 tumour; G0, grade 0 tumour.

#Classified into transsphenoidal approach and transcranial approach.

Note: Data were analysed using a linear mixed-effects model to evaluate the impact of clinical factors on the outcome. 'Estimate' represents the beta (β) regression coefficient. For categorical variables, the following were used as reference groups: Grade 0 for tumour grade, transsphenoidal approach, and z-BMI at diagnosis.

Longitudinal changes in z-BMI over 48 months in the TrG are depicted in Figure 3. When stratified by the degree of obesity at diagnosis, z-BMI trajectories consistently reflected the findings from the multivariable mixed-effects model (Fig. 3-2). Specifically, while no significant longitudinal change over 48 months in z-BMI was observed among patients with normal weight at diagnosis (n = 20, β = 0.005, p = 0.481), a significant interaction was observed between time and the obese group (β = -0.052, p = 0.033), indicating that the obese group demonstrated a significantly different longitudinal z-BMI trajectory, characterized by a steeper decline, compared to normal weight group. In contrast, the interaction between time and the overweight group did not reach statistical significance (β = -0.039, p = 0.137).

Discussion

In this single-centre, long-term cohort study of childhood-onset CP survivors, rhGH therapy (TrG) was associated with favourable BMI trajectories, particularly in patients with pre-existing obesity, and was not associated with an increased risk of tumour recurrence. Consistent with the literature, the high prevalence of panhypopituitarism and hierarchical pattern of hormonal deficits in our cohort, predominantly GHD and diabetes insipidus, followed by adrenal and thyroid insufficiencies, reflects the substantial impact of radical resection on the hypothalamic-pituitary axis and underscores the need for multidisciplinary follow-up [27,28].

HO remains the most debilitating sequela in CP survivors and is characterised by rapid, refractory weight gain resulting from impaired energy homeostasis. Our findings confirm that extensive hypothalamic involvement and preoperative obesity are major determinants of adverse weight trajectories, consistent with recent cohort studies [8]. Specifically, among patients receiving rhGH therapy, our multivariable analysis suggested that grade 2 tumours and baseline z-BMI were associated with longitudinal BMI trajectories.

Previous studies evaluating metabolic parameters, including insulin sensitivity, lipid profile, and fat distribution, have typically required at least 6 to 12 months of rhGH therapy to demonstrate meaningful effects. Accordingly, we defined a minimum treatment duration of 12 months for inclusion in the TrG [26]. While prior studies have reported improvements in body composition and height velocity with rhGH in paediatric CP survivors, reports of its long-term effects on BMI are inconsistent [29]. In our cohort study, z-BMI trends over time during rhGH treatment tended to decline, albeit not significantly. Although the sample size was small, a decreasing trend in z-BMI was observed in the subgroup of patients who were overweight or obese at diagnosis. In contrast, patients with normal baseline BMI showed relatively stable z-BMI trajectories without significant change in the subgroup analysis. These findings suggest that rhGH may exert a favourable lipolytic effect, particularly in high-risk patients with existing HO. This

implies that rhGH may be especially beneficial in mitigating further weight gain in children already on a path toward obesity, a finding supported by previous long-term studies in European cohorts [16].

We reproduced these patterns in a single-centre Asian cohort, demonstrating that hypothalamic damage leads to similar metabolic consequences across ethnic groups. While multivariable analysis did not identify rhGH therapy as an independent statistically significant factor for z-BMI reduction after adjustments, subgroup analysis provided clinically meaningful evidence that rhGH can modulate adverse BMI trajectories in high-risk patients. Beyond its established role in promoting linear growth, rhGH may exert lipolytic and metabolic regulatory effects.

Regarding metabolic outcomes, we used the modified NCEP-ATP III criteria for paediatric populations because some waist circumference data were unavailable. In our study, we observed a distinct clinical benefit regarding lipid profiles in the treatment group. Specifically, the significantly higher rate of low HDL cholesterol in the control group suggests that long-term treatment may help maintain HDL levels, a crucial factor in cardiovascular health. The high incidence of hypertriglyceridemia across both groups reflects the underlying metabolic vulnerability of the study population. Otherwise, there was no significant difference in the incidence of metabolic syndrome between groups, suggesting that rhGH treatment did not adversely impact overall metabolic status, even considering the small number of cases.

Safety concerns regarding tumour recurrence remain a major barrier to rhGH therapy. In the RFS analysis, statistically significant differences were observed immediately following surgery, suggesting that rhGH therapy might confer a benefit. However, landmark analysis, designed to reduce selection bias in the recurrence populations, showed no significant difference between the TrG and control groups. These findings indicate that initiation of rhGH therapy after radiological stability does not adversely affect recurrence risk. According to previously published guidelines, initiating rhGH therapy is recommended in patients with CP, after radiological stability has been confirmed for 3 to 6 months [30]. Although full consensus was only recently achieved, there appears to be agreement that initiating treatment for at least 6 months in radiologically stable CP tumours with residual lesions, and in children with severe growth and metabolic disorders, does not significantly affect the recurrence rate [14,31]. Our overall and landmark analyses further support these recommendations.

We acknowledge some limitations of our study, primarily the baseline demographic differences. The TrG population was significantly younger at diagnosis compared with the control group, which might have contributed to the lower prevalence of metabolic syndrome observed in the TrG. However, it is noteworthy that the TrG also presented with a significantly lower height z-score at diagnosis, reflecting a more pronounced growth deficit that clinically necessitated rhGH initiation. To explore potential age-related bias, a subset of eight patients was followed into adulthood without evidence of emerging metabolic abnormalities, suggesting sustained stability rather than transient age-related effects. The modest sample size, inherent to the rarity of CP, and the limited number of patients followed into adulthood represent additional limitations.

The strengths of this study include a follow-up of up to 26 years, rigorous z-score modelling, and evaluation in an Asian population with this rare disease, where long-term data remain scarce. Moreover, studies addressing long-term metabolic changes in response to rhGH therapy in a single-centre CP cohort are extremely rare, making this study noteworthy. Although some associations may not have reached statistical significance due to limited statistical power, further studies with larger cohorts are warranted to validate these findings. Despite these limitations, the relatively homogeneous nature of our single-centre cohort may partially mitigate these concerns.

In conclusion, rhGH therapy in paediatric CP survivors appears safe and does not exacerbate HO. Rather than promoting weight gain, rhGH therapy appears to confer a protective effect by improving BMI trajectories in patients with pre-existing overweight or obesity and maintaining a significantly lower prevalence of metabolic syndrome compared with untreated controls. These findings support early and rhGH replacement to optimise both linear growth and long-term metabolic health in this high-risk population.

Abbreviations

HO Hypothalamic obesity

CP craniopharyngioma

rhGH recombinant human growth hormone

BMI body mass index

z-BMI BMI z-score

GHD growth hormone deficiency

TSH thyroid stimulating hormone

GH growth hormone

ACTH adrenocorticotropic hormone

HDL high-density lipoprotein

OS Overall survival

RFS recurrence-free survival

Declarations

Clinical trial number

Not applicable.

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Statement of Ethics

Study approval statement: The Institutional Review Board of the Samsung Medical Centre approved this study (IRB No. SMC 2022-10-051).

Consent to participate statement: Given the retrospective nature of the study, the requirement for informed consent was waived by the IRB.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Data Availability Statement

All data generated or analysed during this study are included in this published article.

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Figures

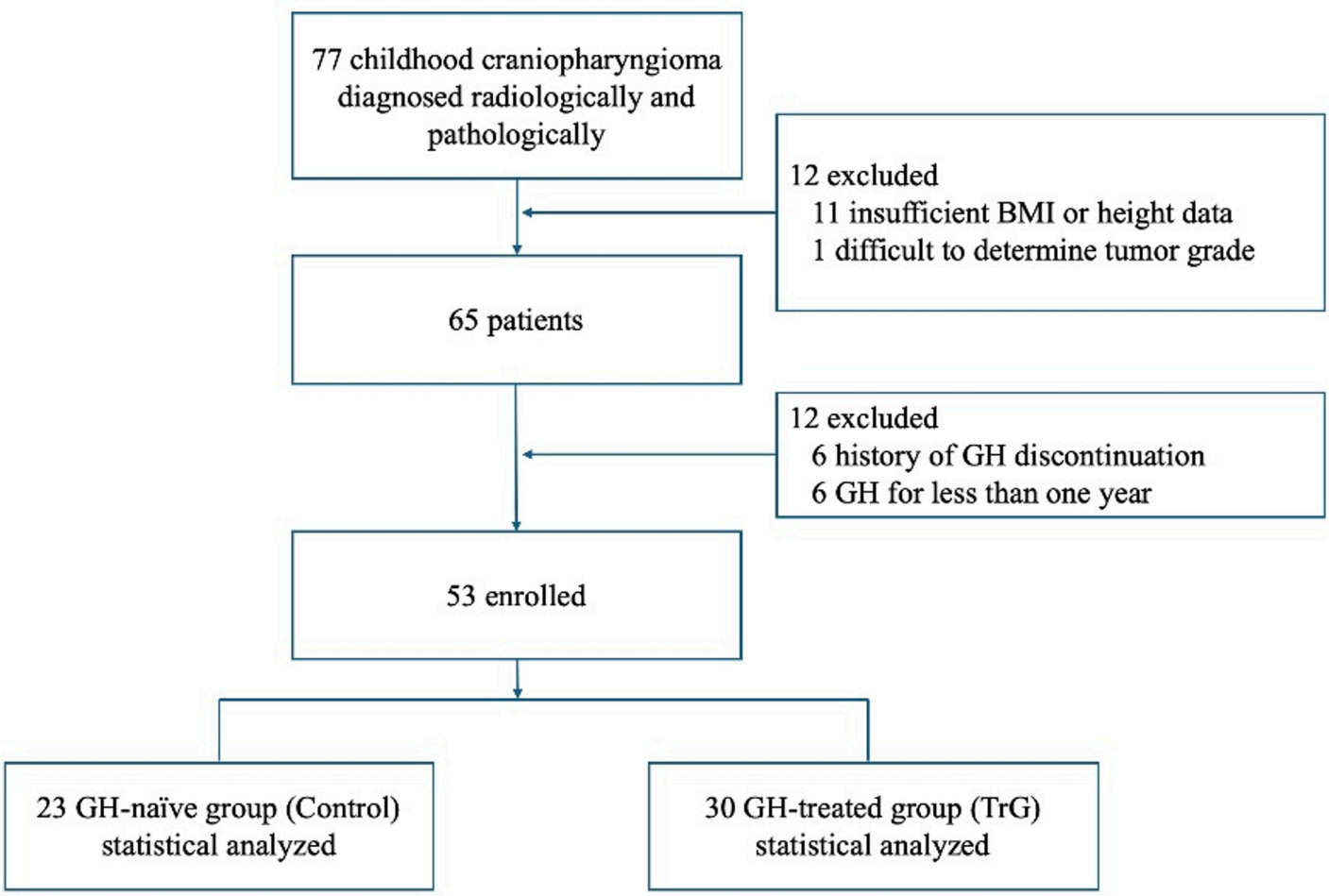


Figure 1

Flowchart for patient enrolment.

Abbreviation: BMI, body mass index; GH, recombinant human growth hormone treatment; TrG, patients treated with GH for ≥ 1 year.

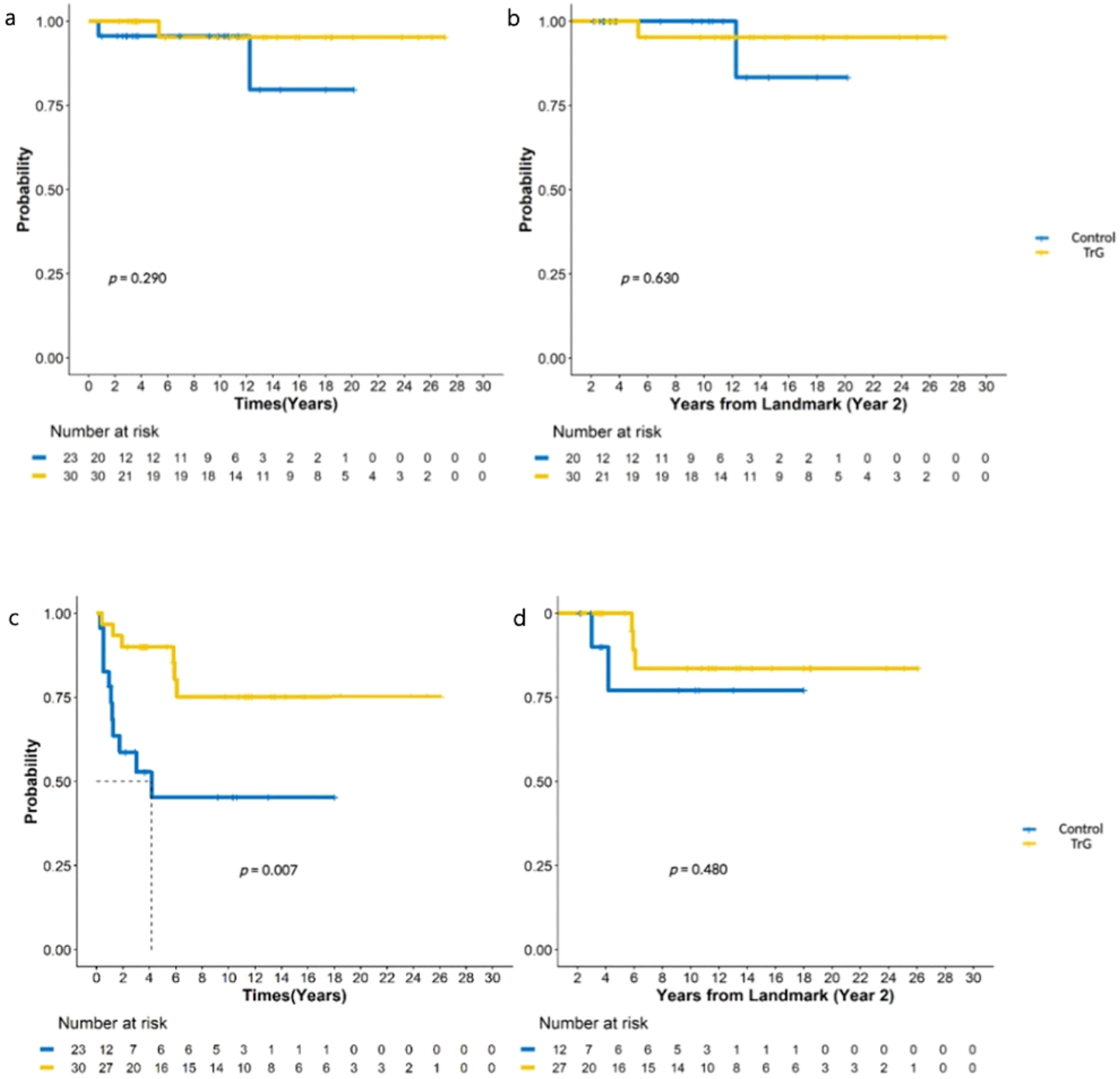


Figure 2

OS and RFS between groups treated with rhGH for ≥ 1 year (TrG) and Control.

a. The OS rate across time between groups across all time periods (p = 0.290).

b. The OS rate over time between groups from the intervention start point (landmark) between groups (p = 0.630).

c. The RFS rate over time between groups across all time periods (p = 0.007).

d. The RFS rate over time between groups from the landmark (p= 0.480).

rhGH, recombinant human growth hormone; RFS, recurrence-free survival; OS, overall survival.

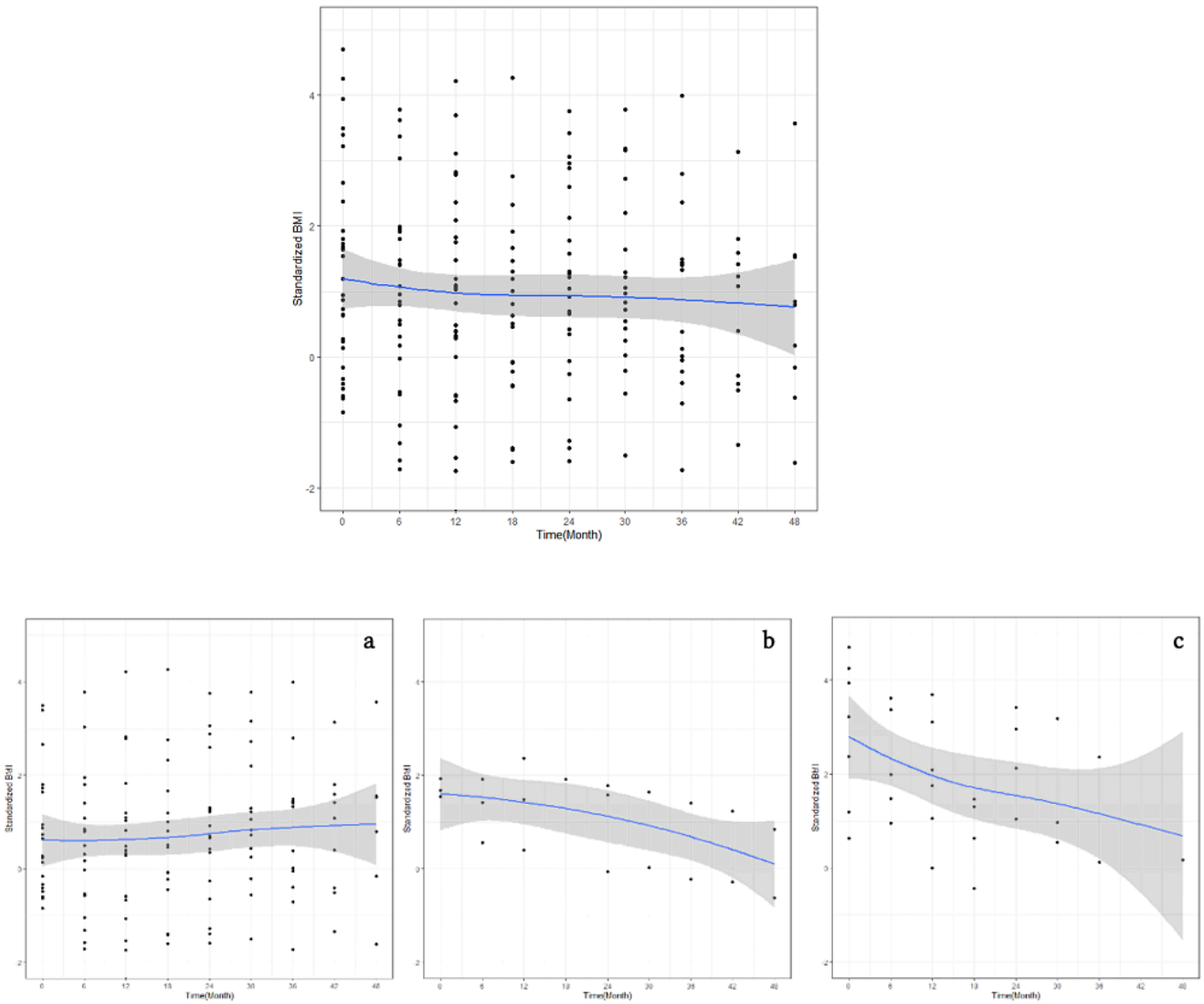


Figure 3

BMI z-score (z-BMI) pattern changes by degree of obesity at diagnosis during rhGH treatment (TrG).

Figure 3-1. z-BMI patterns in total TrG patients (n = 30, β = -0.008, p = 0.195).

Figure 3-2.

a. z-BMI pattern in the TrG with normal weight (n = 20, β = 0.005, p = 0.481).

b. z-BMI pattern in the TrG with overweight (n = 3, β = -0.024, p < 0.001).

c. z-BMI pattern in the TrG with obesity (n = 7, β = -0.049, p = 0.005).

Note**:** Interaction effect of time x Degree of obesity at diagnosis: time x (overweight vs. normal weight), β = -0.039, $p^{\dagger}$ = 0.137; time x (obesity vs. normal weight), β = -0.052, $p^{\dagger}$ = 0.033 (p-values† were corrected using Bonferroni's method due to multiple testing).