Journal of Endocrinological Investigation (2022) 45:1709–1717
https://doi.org/10.1007/s40618-022-01808-4

ORIGINAL ARTICLE

Isolated childhood growth hormone deficiency: a 30-year experience on final height and a new prediction model

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Received: 16 February 2022 / Accepted: 21 April 2022 / Published online: 14 May 2022

Abstract

Purpose We aimed to evaluate the near-final height (nFHt) in a large cohort of pediatricpatients with growth hormone deficiency (GHD) and to elaborate a new predictive method of nFHt.

Methods We recruited GHD patients diagnosed between 1987 and 2014 and followed-up until nFHt. To predict the values of nFHt, each predictor was run in a univariable spline.

Results We enrolled 1051 patients. Pre-treatment height was −2.43 SDS, lower than parental height (THt) (−1.09 SDS, $p < 0.001$). The dose of recombinant human GH (rhGH) was 0.21mg/kg/week at start of treatment. nFHt was −1.08 SDS (height gain 1.27 SDS), higher than pre-treatment height ($p < 0.001$) and comparable to THt. 1.6% of the patients were shorter than −2 SDS from THt. The rhGH dose at nFHt was 0.19 mg/kg/week, lower than at the start ($p < 0.001$). The polynomial regression showed that nFHt was affected by gender, THt, age at puberty, height at puberty, age at the end of treatment ($F = 325.37$, $p < 0.0001$, R^2 87.2%).

Conclusion This large national study shows that GHD children can reach their THt. The rhGH/kg/day dose significantly decreased from the start to the end of the treatment. Our model suggests the importance of a timely diagnosis, possibly before puberty, the beneficial effect of long-term treatment with rhGH, and the key-role of THt. Our prediction model has a very acceptable error compared to the majority of other published studies.

Keywords Growth hormone deficiency · Final height · Prediction · Growth · Growth hormone retesting · Insulin-like growth factor 1 · LMG method

Introduction

The main goal of recombinant human GH (rhGH) treatment is to improve growth to achieve the target height, which can have positive impacts on the long-term psychosocial status [1, 2]. The main indication for this therapy in childhood is GH deficiency (GHD) [3, 4]. RhGH is administered subcutaneously 6 or 7 days/week with a dose of 25–50 μg/kg/day, usually until final height (FHt) or near-FHt (nFHt) is achieved [3, 4]. Several studies have shown that patients reach a normal FHt, although it is frequently below the target height.

Most papers have reported data on small cohorts [5–11], and only a few studies involved very large cohorts in population-based studies [12] or international database studies [13, 14]. In particular, results from the French and the KIGS databases show that the height gain at FHt ranges from 1 [12] to 1.6 SDS [14] and that FHt may be below the target height [12, 13]. A subsequent analysis on a larger cohort from the KIGS database demonstrated the achievement of target height in most of patients [14].

Members of the Study Group on Physiopathology of growth processes of ISPED are listed in the acknowledgements section.

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Several factors have been suggested to affect the response to the therapy [14–16], and some prediction models have been proposed to support clinicians in clinical practice [17–19]. The aim of this study was to evaluate the nFHt in a large cohort of GHD patients treated over the last 30 years with rhGH and the magnitude of patients achieving parental height (THt). Furthermore, we investigated the factors that are most important in determining nFHt and their use in a new predictive method.

Methods

In this retrospective multicentre study, we recruited GHD patients who were diagnosed between 1987 and 2014 and followed-up by one of the Italian tertiary centres for GHD treatment. The diagnostic criteria were (a) short stature defined as height (Ht) ≤ − 3 SDS *or* Ht < − 2 SDS and growth rate (GR) < − 1 SDS *or* GR < − 2 SDS over 1 year *or* < − 1.5 SDS over 2 years, irrespective of Ht; and (b) peak GH < 10 ng/mL in 2 different standard stimulation tests. The inclusion criteria were a start of treatment before July 2014 (when a different GH cut off after stimuli was proposed due different standards used for the assay), regular follow-up every 6 ± 1 months until nFHt was reached (GR < 2 cm/year) *or* bone age ≥ 14 years for girls and ≥ 16 years for boys. The exclusion criteria were a medical history of neoplasia, irradiation, or any other chronic diseases that could affect growth; other associated pituitary hormone deficiency; or therapy discontinuation for more than 2 months.

The data collection included patients' standing Ht (using a wall-mounted Harpenden Stadiometer), weight, THt [(mother's Ht + father's Ht)/2 + 6.5 cm for males or − 6.5 cm for females], body mass index (BMI), bone age at diagnosis (Greulich and Pyle's method), age at puberty onset (testicular volume ≥ 4 ml in males, breast development ≥ 2nd Tanner stage in females). At diagnosis, all patients underwent MRI of the hypothalamic-pituitary area. The area was classified as abnormal in case of ectopic posterior pituitary, or empty sella, or other pituitary anomalies (adenohypophysis hypoplasia, pituitary stalk interruption, Rathke cleft cyst, thin pituitary stalk), otherwise it was considered normal.

Serum IGF1 was assayed every 12 months at each centre local laboratory. As compared to the local laboratory reference, it was classified as low if < − 2 SDS, normal if between − 2 and 2 SDS, or high if > 2 SDS.

The study was approved by the Ethics Committee of Azienda Ospedaliero-Universitaria Policlinico di Bari, which was the coordinating centre (study number 5377), and by the local ethics committees of every other centre. The study was conducted according to the Declaration of Helsinki for human studies.

Treatment

The dose of rhGH was titrated every 6–12 months according to clinical and biochemical parameters to optimize growth velocity and to avoid high IGF1, impairment of glucose tolerance, headache. Serum IGF1 levels were used to monitor adherence to the treatment and response to dose change [4].

GH retesting

GH retesting was carried out in all patients by repeating GH stimulation tests at the attainment of nFHt after at least 1 month after therapy discontinuation. Permanent GHD was diagnosed when peak GH levels were below 6 ng/ml after an insulin tolerance test or 19 ng/ml after a test with GHRH plus arginine (GHRH + arginine).

Statistical analysis

Ht was expressed as cm and as SDS (Ht SDS), and BMI was expressed as SDS (BMI SDS) using the Growth Calculator® based on Italian reference data. Continuous data that were non-normally distributed were described using medians and interquartile ranges (IQRs), and non-parametric tests were used as appropriate to compare independent or paired groups. Qualitative variables were described as counts and percentages, and the chi-squared test, Fisher's exact test, or McNemar's test was used as appropriate to compare independent or paired proportions. Correlations between quantitative variables were evaluated by Spearman's correlation coefficient.

To predict the values of nFHt and as nFHt SDS, each predictor was run in a univariable spline. Next, for each predictor, the corresponding polynomial transformation was identified and tested in a linear regression to evaluate the distribution of residual and statistical significance. A multivariable polynomial model was applied to all statistically significant predictors in the previous analysis. Predictors that were not statistically significant or had a level of collinearity higher than 5 were removed from the model to define the final model.

To predict final value of nFHt, a multivariable polynomial linear regression model was fitted with sex, THt, age, Ht at puberty, and age at the end of the treatment as linear, square, and cubic values (model M1). To predict the final value of SDS, another multivariable polynomial linear regression model was fitted with sex, duration of the therapy as linear and square, square of age at the beginning of the therapy, square of bone age at the beginning

of the therapy, Ht SDS at puberty, THt SDS as linear and cubic values, and Ht SDS at 12 months after the beginning of the therapy as linear and cubic values (model M2). To run both models, the data set was split into two parts: a training set (70% of the whole sample) and a validation set (30% of the whole sample).

Models M1 and M2 were run using SAS Software for Windows. The results of validation were determined with a bootstrap method, and the results on the validation set were described with medians and IQRs of R-squared, residual mean square error (RMSE), and coefficient of variation (CV) values. The RELAIMPO package in R was also used to fit the model and determine the importance of predictors. The result of the estimation using the Lindeman, Merenda, and Gold (LMG) method was used to describe the results. *P* values < 0.05 were considered statistically significant.

Results

Data at start of treatment

We recruited 1051 patients (62.7% males and 37.3% females), 65.8% were of Italian origin and 1.7% has other ethnicities (missing data for 32.4% of the patients). The median (IQR, interquartile range) chronological age was 11.0 (8.7/12.8) years, which was statistically different from the bone age of 9.5 (6.8/11.4) years ($p < 0.001$) (data available in the medical records for 921 patients). Ht was − 2.43 (− 2.80/− 2.01) SDS, which was significantly lower than the THt of − 1.09 (− 1.63/− 0.48) SDS ($p < 0.001$). Data about pubertal development were available for 861 patients: 183 were pubertal (21.2%) and 678 prepubertal (78.7%). The rhGH dose was 0.21 (0.19/0.23) mg/kg/week (Table 1).

The maximum peak GH after the stimulation test (available for 944 patients) was 6.0 (4.0/7.9) ng/ml. Pre-treatment IGF1 (available for 839 patients) was low in 316 of them (37.7%). Patients with low IGF1 were older at diagnosis than patients with normal IGF1 ($p = 0.001$). Ht was not different between patients with low or normal IGF1, but nFHt was higher in patients with lower pre-treatment IGF1. However, the gap between THt and nFHt was not different between patients with low or normal IGF1 (suppl. Table 1).

Brain MRI records were available for 911 patients (86.7%, missing data in the medical records for 140 patients). They were normal in 701 patients (76.9%) and abnormal in 210 patients (23.1%; ectopic pituitary in 25 patients). Patients with abnormal MRI were younger, shorter, showed lower peak GH, and had larger delay in bone age than patients with normal MRI (suppl. Table 2).

Data at near-final height

nFHt was − 1.08 (− 1.64/− 0.50) SDS, which is significantly higher than Ht SDS at start of treatment ($p < 0.001$) and comparable to THt SDS (Fig. 1 and Table 1). The Ht gain during the treatment (defined as the difference between nFHt and Ht at start of treatment) was 1.27 (0.84/1.79) SDS. It was higher in patients with low IGF1 than in patients with normal IGF1 ($p < 0.001$). nFHt SDS was above mean THt SDS, above THt SDS − 1 SDS, and above THt SDS -2 SDS in 49.5%, 88.2%, and 98.4% of patients, respectively. nFHt was comparable to THt both in patients with normal pre-treatment IGF1 than with low pre-treatment IGF1. The rhGH dose was 0.19 (0.16/0.21) mg/kg/week, which is lower than at the start ($p < 0.001$).

There was a low inverse correlation between nFHt SDS and bone age at diagnosis ($r = -0.075$, $p = 0.022$). On the contrary, nFHt SDS showed a positive correlation with the following variables: THt SDS ($r = 0.449$, $p < 0.001$), Ht SDS at diagnosis ($r = 0.505$, $p < 0.001$), Ht SDS at puberty ($r = 0.590$, $p < 0.001$), age at nFHt ($r = 0.112$, $p < 0.001$), rhGH dose at the end of treatment ($r = -0.109$, $p = 0.002$), and treatment duration ($r = 0.114$, $p < 0.001$).

Regression analysis

nFHt

The polynomial regression to predict nFHt (Table 1) was run on 342 patients, which resulted in statistical significance ($F = 325.37$, $p < 0.0001$), and the value of R^2 was 87.2%. The contribution of each statistically significant predictor to the final R^2 was 0.18 for THt, 0.16 for Ht at puberty, 0.12 for age at the end of the treatment as linear, 0.12 for square, and 0.11 for cubic values, 0.1 for sex and 0.02 for age at puberty. These results suggest that THt, Ht at puberty, and age at the end of treatment are the most important variables to predict nFHt (Table 2).

The validation analysis was run on 146 subjects, and the fitting resulted in a median R^2 of 76.7% (IQR 74.9/78.9%), RMSE of 4.7 (4.5/4.9), and CV of 3.58 (2.9/4.7). The correspondence between observed and estimated values in the validation was illustrated by a scatter plot (Suppl. Figure 1), in which data points were distributed along the perfect correspondence line without showing a trend or bias for the estimation.

nFHt SDS

The polynomial regression to predict the nFHt SDS was run on 163 subjects and resulted in statistical significance ($F = 42.64$, $p < 0.0001$) and an R^2 of 58.8%. The contribution

Table 1 Auxological data at start and end of treatment

		All patients	Males	Females	Males vs female *p*
At start of treatment	Age (years)	11.0 (8.7/12.8) N: 1051	11.5 (8.7/13.6) N: 659	10.5 (8.6/11.9) N: 392	< 0.001
	Bone age (years)	9.5 (6.8/11.4) N: 921	10.0 (6.5/12.0) N: 572	9.0 (7.0/10.5) N: 349	< 0.001
	Height (SDS)	− 2.43 (− 2.80/− 2.01) N: 1051	− 2.37 (− 2.76/− 1.93) N: 659	− 2.52 (− 2.88/− 2.11) N: 392	< 0.001
	BMI (SDS)	− 0.64 (− 1.36/0.24) N: 553	− 0.64 (− 1.35/0.26) N: 335	− 0.63 (− 1.42/0.19) N: 218	0.340
	rhGH dose (mg/kg/week)	0.21 (0.19/0.23) N: 833	0.21 (0.19/0.23) N: 521	0.21 (0.19/0.23) N: 312	0.887
At end of treatment	Age (years)	15.9 (14.7/16.9) N: 1042	16.5 (15.5/17.3) N: 653	14.8 (14.0/15.8) N: 389	< 0.001
	Height (SDS)	− 1.08 (− 1.64/− 0.50) N: 1051	− 1.03 (− 1.62/− 0.43) N: 659	− 1.19 (− 1.72/− 0.58) N: 392	0.014
	BMI (SDS)	− 0.31 (− 1.06/0.49) N: 465	− 0.31 (− 1.00/0.47) N: 291	− 0.30 (− 1.10/0.55) N: 174	0.553
	rhGH dose (mg/kg/week)	0.19 (0.16/0.21) N: 818	0.19 (0.16/0.21) N: 504	0.20 (0.17/0.22) N: 314	< 0.001
Parental height (SDS)		− 1.09 (− 1.64/− 0.48) N: 1006	− 1.12 (− 1.63/− 0.58) N: 632	− 1.00 (− 1.63/− 0.39) N: 374	0.057
Age at puberty (years)		12.2 (11.2/13.3) N: 848	12.7 (11.7/13.7) N: 521	11.6 (10.6/12.4) N: 327	< 0.001
Height at puberty (SDS)		− 1.85 (− 2.37/− 1.24) N: 764	− 1.75 (− 2.29/− 1.13) N: 461	− 1.97 (− 2.49/− 0.141) N: 303	0.003

Values are reported as median and IQR.

N number of patients, *BMI* body mass index.

of each statistically significant predictor to the final R^2 was 0.15 for Ht SDS after 12 months of treatment, 0.12 for Ht SDS at puberty, 0.09 for THt, 0.04 for square value of age when starting therapy, 0.05 for duration of therapy, 0.03 for square value of duration of therapy and cubic value of THt, 0.011 for square value of pre-treatment bone age and 0.005 for sex (suppl. Table 3). The cubic value of Ht SDS at 12 months was not removed even though it was not statistically significant to hold the polynomial relation of this predictor with respect to the nFHt. These results suggest that Ht SDS during the follow-up is an important factor to consider for prediction of nFHt SDS.

The validation was run on 89 subjects, and the fitting had an R^2 of 32.4% (23%/41%), RMSE of 7.8 (7.3/8.2), and CV of 4.9 (4.6/5.1). The correspondence between observed and estimated values in the validation was illustrated by a scatter plot (Suppl. Figure 2). Data points were more dispersed with respect to the perfect correspondence line, which could be interpreted as bias in the prediction by the model.

GH retesting

Data about GH retesting were available for 698 patients. GH secretion was normal in 579 patients (83%), while 119 patients (17%) were diagnosed with permanent GHD. Patients with permanent GHD presented larger chronological age at nFHt, BMI SDS at diagnosis, Ht gain, and

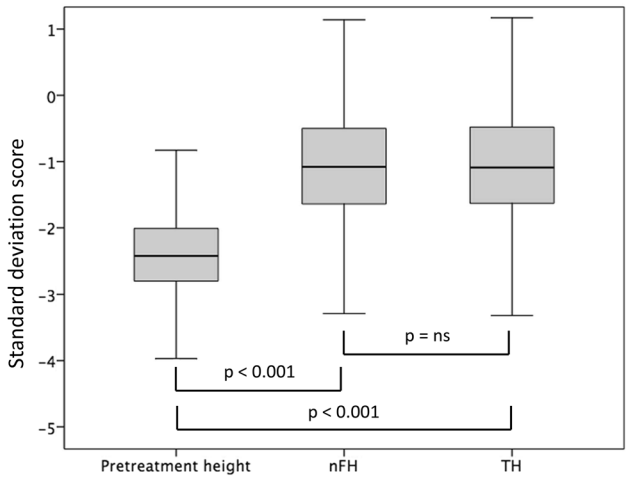

Fig. 1 The box plot displays the values of height at start of treatment (pretreatment height), near final height (nFHt) and parental height (TH). The values are reported as standard deviation score.

treatment duration than patients with transient GHD (Suppl. Table 4).

Discussion

The most important finding of our study is that the median nFHt is similar to the THt, gaining 1.27 SDS as compared to Ht at diagnosis. In our cohort, the age at diagnosis was 11 years, consistent with most studies on the topic, which show that it ranges between 10 and 11 years [17–20], or even later [21]. Only a few papers report an age of 8 years in females and 9 years in males [22, 23].

In our patients, pre-treatment Ht was about − 2.4 SDS, which is lower than what was reported by a recent Italian study (-1.9 SDS) [19] but similar to the French registry [24]. Other studies on large cohorts reported that Ht at diagnosis was even worse, ranging from − 2.9 to − 2.7 SDS [25].

Based on the KIGS® database, Reiter et al. [13] reported pre-treatment Ht of − 2.6 SDS and − 2.4 SDS in 200 White females and 351 White males, respectively. In both genders, the gain at nFHt was 1.6 SDS, but the FHt was below the mean by 0.5 and 0.2 SDS in females and males, respectively. A few years later, Darendeliler et al. [14] found an Ht gain of 1.6 SDS in 1619 patients from the same database, but interestingly, they reported that the parental-adjusted Ht SDS at nFHt was -0.1 SDS.

At the beginning of the 2000s, Carel et al. showed that the nFHt in 1232 GHD children was − 1.6 SDS, which is below the mid-parental height of − 1.1 SDS, with an Ht gain of 1.1 SDS [12]. In our patients, the Ht gain was 1.27 SDS, but the most important point is that they reached their THt, and only 1.6% of them were shorter than 2 SDS from THt.

The median dose of rhGH at the start was 0.21 mg/kg/week in our study, which is similar to other studies on Caucasian patients [4, 13, 21, 26, 27], but lower than in a US study [25, 28]. The dose was progressively reduced to 0.19 mg/kg/week by the end of treatment. This finding was confirmed in both permanent and transient GHD patients, suggesting that the dose reduction is not due to the GH secretion status or the IGF1 classification. The dose was reduced during the follow-up according to clinical and biochemical parameters, and the regression analysis ruled out that the initial dose affected nFHt. The adherence to the treatment was monitored by periodical serum IGF1 measurement [4] and assessed by interview or digital device when available [29].

Both patients with normal or low pre-treatment IGF1 achieved THt, confirming the efficacy of rhGH treatment independently of the GH reserve. A limitation of this study is the lack of data on IGF1 SDS. The patients were recruited from different centres with different analysis kits and reference ranges. Thus, IGF1 was classified as normal or low based on the reference range provided by each centre. Previous predictive models demonstrated a negative correlation between IGF1 SDS and height gain [17, 23, 30, 31]. Similarly, in our study patients with low pre-treatment

Table 2 (model M1) Results of the regression to predict near final height, regression coefficient and LMG estimation for each predictor

Variable	Parameter estimate	Standard error	Pr>|t|	Relative importance LMG estimation
Intercept	− 191.19	58.05	0.0011	–
Sex	2.82	0.67	< 0.0001	0.35254
Parental height	0.35	0.047	< 0.0001	0.28954
Age at puberty	− 3.03	0.237	< 0.0001	0.28093
Height at puberty	0.66	0.04	< 0.0001	0.31830
Age at the end of the treatment	35.49	11.22	0.0017	0.00010794
Square age at the end of the treatment	− 1.81	0.72	0.0129	0.00002659
Cubic age at the end of the treatment	0.03	0.01	0.0344	0.00010285

IGF1 presented a larger height gain than the other ones. In contrast, other papers did not confirm this finding [31, 32]. Pre-treatment IGF1 did not enter in our prediction models.

Permanent GHD was observed in 17% of our patients. Interestingly, patients with persistent GHD required longer treatment by 0.9 years, likely due to the larger bone-age delay (1.9 vs 1.4 years), so they were older at the stop of therapy. From a clinical point of view, this finding suggests that a longer period of replacement therapy is suggestive of permanent rather than transient GHD. Both patients with permanent or transient GHD reached their THt.

The correlation analysis shows that in GHD paediatric patients the nFHt will be the higher in dependence of some clinical variables such the parents' height and the height at diagnosis and at puberty. Similarly, also the treatment duration, the age and the dose of rhGH at attainment of nFHt positively affect the nFHt, but the correlation coefficient is lower. On the contrary, the patients with younger bone age at diagnosis will be the higher at the end of treatment.

We propose a new prediction model for nFHt. Most models predict the short-term response to treatment [23, 32–35] or the total pubertal growth [31], but a few papers propose a statistical model to predict FHt or nFHt [17–19]. We obtained 2 different models through the polynomial regression: one that predicts nFHt and one that predicts nFHt SDS.

The first model showed good reliability in both the training set (R^2 87.2%) and the validation set (R^2 76.7%) with a median RMSE of 4.7 cm. Thus, it had better predictions of nFHt than the second model (R^2 58.8%). To reach this level of fitting, it was trained and validated with a regression after data transformation, because the simple linear multiple regression did not fit the data. Splines were used, suggesting that a non-linear model should be used to fit these data, and this choice let us reach those fitting levels.

Different models are used to evaluate growth, and solutions are used to overcome the issue of linearity [36]. The model used for the prediction was a spline to evaluate each predictor, and then we chose the best polynomial model in the multivariable regression. Recently, models based on a neural network have been used to predict targets. The variables that were entered into the model were age at the end of treatment, THt, Ht, age at puberty, and gender. The first three were the most relevant in terms of Ht prediction. Our model seems slightly less precise than a neural model based on 10 variables (RMSE 0.5 SD, about 3 cm) proposed by Smyczyńska et al. [17] and the model by Migliaretti et al. [19]. However, our prediction appears more efficient with respect to the result of the model by the NordiNet® International Outcome Study [18], which used a method more similar to our regression. Most models predict FH SDS. Notably, our prediction model for nFHt was more predictive than the model of nFHt SDS.

Our study has some limitations. First, sex-hormone priming before GH testing was not routinely performed in all patients, which likely resulted in overestimation of the GHD patients, especially in the case of constitutional delay of growth and puberty. This bias equally affects all the papers on the topic, so this limitation is well acknowledged. Diagnosis of GHD in patients with delayed puberty is a challenging issue and the subject of ongoing debate [37]. Second, the long period of time (30 years) could be another limitation. Third, this is a retrospective study and thus we collected only the data available in the medical records. We did not report about some data, such as the rate of organic disorders or GHD after brain tumours [38] or drop-out. The height at diagnosis and near final height were available for all patients, but data about MRI, GH peak, IGF1, bone age, and other variables were not available for statistical analysis in all patients, even if they were used in the clinical assessment.

On the other hand, a strength of this paper is the large size of the cohort. Only data from the KIGS database and the French registry were based on such large cohorts. A limitation of international studies is the recruitment of patients from different countries, so the data may not always be comparable because of patients' features and non-homogeneous national regulatory issues.

In conclusion, we have demonstrated that paediatric patients with GHD can reach their parental height, and the median height gain was 1.27 SDS during the treatment. Patients with permanent GHD may require a longer period of treatment. The rhGH dose significantly was decreased during the follow-up on the basis of clinical and biochemical parameters. Our data suggest that the age at diagnosis can be improved in Italy. Our model suggests the importance of a timely diagnosis, possibly before the onset of puberty, and the beneficial effect of long-term treatment with rhGH as modifying variables in the medical history of these children. The other significant unmodifiable variable that affects nFHt is the parental height. Our prediction model of nFHt has a very acceptable error (4.7 cm) compared to the majority of other published studies, as well as the greatest sample size.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40618-022-01808-4.

Acknowledgements The Members of the Study Group on Physiopathology of growth processes of ISPED are as follows: Bruzzi Patrizia (Modena), Capalbo Donatella (Napoli), Fatti Letizia Maria (Milano) (0000-0002-1219-8953), Luongo Caterina (Napoli), Moro Mirella (Milano) (0000-0003-1645-547X), Pellegrin Maria Chiara (Trieste), Pepe Giorgia (Messina), Predieri Barbara (Modena), Sangiorgio Arianna (Milnao), Salvatoni Alessandro (Varese), Sartori Chiara (Reggio Emilia), Timpanaro Tiziana (Catania), Trombatore Jessica (Messina), Zucchini Stefano (Bologna), Zuccotti Gianvincenzo (Milano). The listed members are considered as authors of the paper.

Declarations

Conflict of interest None to declare. We would like to thank patients and their parents for joining the study.

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