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Comparison of Methods used for Final Height Prediction in Patients with Central Precocious Puberty

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What is already known on this topic?

The Bayley-Pinneau and Roche-Wainer-Thissen methods are commonly used for predicting final/target height.

What this study adds?

The Bone Age Percentile Curve Projected Height Estimation (BAPCPHE) method is a method of estimating final height by extrapolating the bone age percentile to the end of the percentile curve at 18 years of age. The BAPCPHE is more practical for use in outpatient settings, and was found to be effective in predicting target height.

ABSTRACT

Objective: Various methods may be used to estimate target height in patients diagnosed with precocious puberty. These methods include the Bayley-Pinneau (BP) and Roche-Wainer-Thissen (RWT) methods. In addition to these methods, in our clinic, we routinely use a practical approach based on the percentiles in growth charts. In this method, the bone age percentile is projected to the end of the percentile curve (at 18 years of age) to estimate the final adult height. We have named this method Bone Age Percentile Curve Projected Height Estimation (BAPCPHE). The aim of this study was to retrospectively compare the effectiveness of these three methods in predicting target height in patients treated for central precocious puberty and who have reached their final height in our pediatric endocrinology clinic.

Methods: Fifty female patients were included. The predicted adult heights (PAH) were calculated at treatment initiation, at the end of the first, second, and third years of treatment, and at the time of final height attainment using the BP, RWT, and BAPCPHE methods, based on the patients' heights and bone ages.

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Results: When the agreement between the PAH calculated by three methods and the final height was analyzed using intraclass correlation coefficient, significant agreement was found for PAH using the BAPCPHE method in the third year. Among the methods, the strongest agreement with final height and PAH was observed with the BP method at the end of treatment, followed by the BAPCPHE method.

Conclusion: The BAPCPHE method allows estimation of PAH quickly, making it a valuable tool in the outpatient setting. Given its simplicity and accuracy, we find the BAPCPHE method preferable.

Keywords: Precocious puberty, predicted adult height, bone age, Bayley-Pinneau, Roche-Wainer-Thissen

Introduction

Puberty is a transitional phase in children characterized by accelerated growth, the development of secondary sexual characteristics, and physical and psychosocial maturation (1). Precocious puberty (PP) refers to the onset of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys (2). Early initiation of treatment in central PP (CPP) management is effective in preserving adult height and hence, the assessment of predicted target height is important in the follow-up of patients with CPP (3).

Various methods are used to estimate predicted adult height (PAH) in patients diagnosed with PP. The Bayley-Pinneau (BP) method estimates final height using the child's current height and bone age, determined according to the Greulich and Pyle bone atlas (4). The Roche-Wainer-Thissen (RWT) method predicts adult height based on height, weight, mid-parental height (MPH) (calculated from measured parental heights), and bone age recorded during a single pediatric visit (5). Given that the BP and RWT methods are time consuming in practice, we sought a faster, more practical method. It should also be kept in mind that the bone atlas data used were based on data from the 1930-1950 period in the United States of America (USA), when puberty started later. The final height estimates made with the data from this atlas may not be suitable for the children from different populations and the present time. In addition to these methods, a practical approach employed in our clinic involves a method based on growth percentile curves, numerically defined by Neyzi and Saka (6). Using the percentile curves, bone age is plotted, and the projection of the percentile line at age 18 years is considered the predicted final height. We have termed this method the Bone Age Percentile Curve Projected Height Estimation (BAPCPHE).

In this study, we aimed to retrospectively compare the effectiveness of BAPCPHE and two other commonly used methods (BP, RWT) for estimating PAH in patients diagnosed with CPP who underwent treatment and had achieved their final height.

Methods

Patients diagnosed with CPP, followed up and treated, without any additional chronic diseases, and who had reached their final height (defined as bone age ≥14 years in girls and growth velocity <2 cm/year) who gave consent fort his study were included. Leuprolide acetate 3.75 mg/month or 11.25 mg/3 months was used as the treatment in all cases. Exclusion criteria were defined as the presence of additional chronic diseases, history of mass/trauma/radiotherapy in the hypothalamic-pituitary region, syndromic disorders, or treatment for other conditions. Patients who discontinued treatment were also excluded from the study.

A total of 2,000 patients who applied for suspected early puberty, to the pediatric endocrinology outpatient clinic of our hospital between 2015 and 2023 were screened using patient files and the hospital information system. From these, female patients meeting the above study criteria were selected.

Ethical approval for the study was obtained from İstanbul Medeniyet University, Göztepe Prof. Dr. Süleyman Yalçın City Hospital Clinical Research Ethics Committee (approval number: 2023/0966, date: 20.12.2023). Informed consent was also obtained from the participating patients.

Demographic characteristics, medical history, anthropometric measurements, pubertal findings (Tanner stages), laboratory results, imaging studies, parental heights, and MPH values of the patients were retrospectively collected from patient files. The heights of the parents of the patients who came to our outpatient clinic were measured in our clinic. In rare cases, the heights of parents who could not come to our outpatient clinic were measured in a health institution close to them and recorded.

The treatment initiation date was considered as month 0. Heights, height standard deviation scores (SDS), body weights, body weight SDS values, and bone ages were recorded at months 12, 24, and 36 following the start of treatment, as well as at the end of treatment.

MPH was calculated using the following formula:

- For girls: [mother's height (cm)+father's height (cm)-13]/2
- For boys: [mother's height (cm)+father's height (cm)+13]/2

The age at final height attainment, final height, and final height SDS values were recorded for all patients.

Height was measured using a Harpenden stadiometer with a precision of 0.1 cm (SECA, Hamburg, Germany). Height SDS were calculated using reference data prepared for Turkish children through the Anthropometry Calculation Program (Child Metrics), an online tool developed by the Pediatric Endocrinology and Diabetes Association (*Çocuk Endokrinolojisi ve Diyabet Derneği*-ÇEDD) based on the standards published by Neyzi et al. (7).

Body mass index (BMI) was classified as follows: underweight (<5th percentile), normal weight (5th-85th percentile), overweight (85th-95th percentile), and obese (>95th percentile). A BMI SDS>2 SDS was defined as obesity (8,9).

Breast and pubic development were classified using the Tanner staging system during physical examinations performed by a pediatric endocrinologist (10,11). The presence or absence of axillary hair was also recorded.

Basal levels of follicle stimulating hormone (FSH), luteinising hormone (LH) and estradiol (E2), as well as stimulated LH and FSH levels, were assessed. Basal LH, FSH, and E2 tests were conducted between 8:00 and 10:00 AM. A basal LH level of ≥0.3 IU/L was considered significant for diagnosis. In cases with non-diagnostic basal LH levels and/or ambiguous clinical findings, a luteinizing hormone releasing hormone stimulation test was administered. A peak LH level of ≥5 IU/L or a peak LH/FSH ratio >0.66 was considered consistent with PP (12,13,14).

A single-view radiograph of the left hand and wrist was obtained for all patients. All bone age measurements were determined by two pediatric endocrinologists (Reader 1 and Reader 2) using the Greulich-Pyle bone age atlas (15). A bone age-to-chronological age ratio of >1.2 was considered indicative of CPP, and a reduction in this ratio during follow-up was interpreted as a positive response to treatment (16).

Final height predictions based on patients' heights and bone ages at the start of treatment, at the first, second, and third years of treatment, and at the time of final height attainment were calculated using the BP, RWT, and BAPCPHE methods.

BP and RWT predictions were performed using the PAH calculation tool integrated into the Child Metrics application (4,5).

For the BAPCPHE method, PAH was calculated, as illustrated in Figure 1. The patient's current bone age and height were plotted on Neyzi's growth percentile chart for Turkish children. The corresponding percentile was then tracked along the growth curve until the age of 18 years. The final projected value was recorded as the patient's PAH.

Statistical Analysis

Descriptive data in the study are presented as frequency and percentage, and continuous data are expressed as mean±standard deviation or median (minimum-maximum)

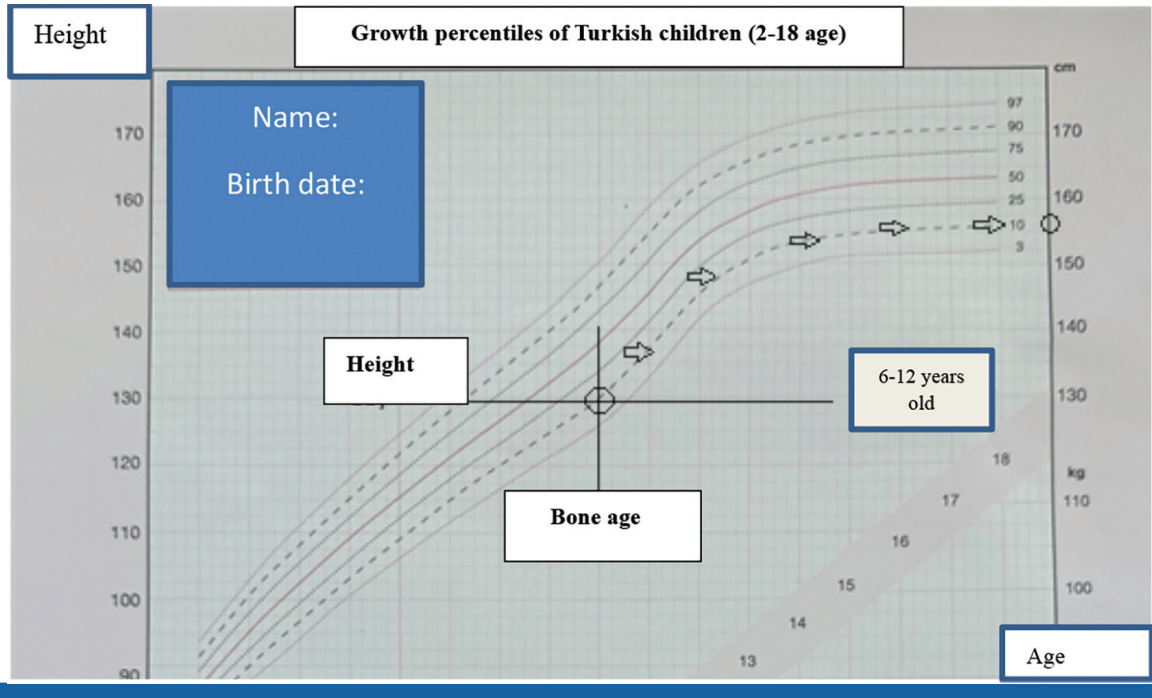

Figure 1. BAPCPHE method for calculating predicted target height
BAPCPHE: Bone Age Percentile Curve Projected Height Estimation

values, as appropriate. For categorical variables, the McNemar-Bowker test was used for comparisons of dependent groups, while the chi-square and Fisher's exact tests were applied for independent groups where appropriate. The normality of the distribution of measurements was assessed using the Kolmogorov-Smirnov test and histogram plots. The difference between measurements with a normal distribution was compared using a one-sample t-test. For measurements that did not show normal distribution, the Mann-Whitney U test was used for comparisons between groups. The level of agreement between two pediatric endocrinologists to determine bone age was assessed using the intraclass correlation coefficient (ICC). ICC was also used to assess the agreement between the PAH, calculated using the three different prediction methods (BP, RWT, and BAPCPHE), and the actual final height achieved by the same individuals. Bonferroni correction was applied for post-hoc analyses. Analyses were performed using IBM SPSS Statistics, version 20 (IBM Inc., Armonk, NY, USA).

Results

The study was conducted with a total of 50 female patients. The mean age at which the first symptoms appeared was 7.16±0.84 years. The mean age at onset of thelarche was 7.3±0.7 years, while the mean age at onset of pubarche was 8.7±1.6 years. The mean age at onset of axillary hair was 9.3±1.6 years. The mean height SDS at the start of treatment was 1.43±1.24, the mean weight SDS was 1.13±0.92, and the mean BMI SDS was 0.69±0.74.

The mean bone age at the start of treatment was calculated to be 9.7±1.7 years.

When evaluating Tanner stages, 72% (n=36) of patients were in stage T2 and 28% (n=14) were in stage T3. In terms of pubarche stages, 56% (n=28) were in stage P1, 36% (n=18) in stage P2, 6% (n=3) in stage P3, and 2% (n=1) in stage P4. Regarding axillary hair presence, 60% (n=30) of patients had no axillary hair, while 40% (n=20) had axillary hair.

When examining BMI distributions at presentation, no patients were classified as underweight. Most (n=34, 68%) of patients were within the normal weight range, 22% (n=11) were overweight, and 10% (n=5) were obese.

The mean age at the start of treatment was 8.3±1.0 years, and the mean treatment duration was 28.4±11.9 months.

The mean age at the end of the treatment was 10.65±0.27 years. At this time, the median height SDS was 0.84 (-1.06-3.2) SDS, the mean weight SDS was 1.17±0.82, and the mean BMI SDS was 0.93±0.

The mean bone age at the end of the treatment was 11.4±0.9 years. The average age of final growth was achieved at 14.1±0.7 years, and the mean final height was 163.0±6.4 cm. The final height SDS was 0.46±1.10.

The mean difference between final height and MPH was 4.3 (-5.6-19) cm, and the mean difference between final height SDS and MPH SDS was 1.29±0.94 SDS. The mean difference between MPH and initial height was 24.4±20.3 cm, and the mean difference between MPH SDS and initial height SDS was -2.11±1.49 SDS. The mean difference between final height and initial height was 26.5±7.6 cm, and the mean difference between final height SDS and initial height SDS was -0.96±1.08 SDS.

The ICC between Reader 1 and Reader 2 for the bone age measurements at the first, second and third year of treatment were 0.986 [95% confidence interval (CI)=0.939-0.981, p<0.001], 0.976 (95% CI=0.945-0.989, p<0.001) and 0.975 (95% CI=0.857-0.995, p<0.001), respectively.

The relation between final height prediction techniques and final height was evaluated using the ICC. At the end of the third year of treatment, all parameters, except for the PAH using the BAPCPHE method, had a significant correlation with final height. The level of agreement was ranked from highest to lowest, and the highest correlation with final height was observed with the BP model at treatment completion. There was a high agreement between final height and PAH calculated according to BP model at treatment completion, the RWT model at the end of the second year, and the BP model at the end of the third year, respectively. A poor agreement was found between final height and PAH calculated according to BAPCPHE model at the end of the first year and at the start of treatment, and a moderate level of agreement was observed with other parameters, subsequently (Table 1).

When statistical significance of differences between final height and PAH using three different methods was examined, it was found that final height was significantly shorter than the BP predicted adult height at the end of the second year, third year, and at treatment completion (p=0.007, p=0.036, and p=0.004, respectively). No significant difference was found between final height and the other two model predictions of adult height (Table 2).

When comparing the treatment initiation age according to the achievement of target height, patients who reached the BP predicted adult height at the end of the first year had a significantly lower median treatment initiation age compared to those who did not (p=0.032). Patients who reached the RWT predicted adult height at the end of the third year had a significantly higher median treatment initiation age compared to those who did not (p=0.038). No significant relationship was found between treatment initiation age and other target height achievements.

When comparing the treatment duration according to the achievement of target height, patients who reached the RWT predicted adult height at the end of the third year had a significantly shorter median treatment duration compared to those who did not (p=0.038). No significant relationship was found between treatment duration and other target height achievements.

Table 1. Analysis of the agreement between predicted adult height calculation methods and final height

	ICC	p value
BP predicted adult height at treatment initiation	0.504	**<0.001**
RWT predicted adult height at treatment initiation	0.639	**<0.001**
BAPCPHE predicted adult height at treatment initiation	0.262	**0.032**
BP predicted adult height at the end of the 1st year of treatment	0.582	**<0.001**
RWT predicted adult height at the end of the 1st year of treatment	0.656	**<0.001**
BAPCPHE predicted adult height at the end of 1st year of treatment	0.268	**0.030**
BP predicted adult height at the end of the 2nd year of treatment	0.686	**<0.001**
RWT predicted adult height at the end of the 2nd year of treatment	0.734	**<0.001**
BAPCPHE predicted adult height at the end of 2nd year of treatment	0.449	**0.003**
BP predicted adult height at the end of the 3rd year of treatment	0.727	**0.006**
RWT predicted adult height at the end of the 3rd year of treatment	0.608	**0.024**
BAPCPHE predicted adult height at the end of 3rd year of treatment	0.488	0.076
BP predicted adult height at the end of treatment	0.749	**<0.001**
RWT predicted adult height at the end of treatment	0.676	**<0.001**
BAPCPHE predicted adult height at the end of treatment	0.566	**<0.001**

p<0.005 is considered statistically significant.
ICC: intraclass correlation coefficient, BP: Bayley-Pinneau method, RWT: Roche-Wainer-Thissen method, BAPCPHE: Bone Age Percentile Curve Projected Height Estimation

Table 2. Analysis of the difference between final height and predicted target heights assessed by three different methods

	Target height	Final height	p value*
	Target height-Final height	Target height-Final height	
BP predicted adult height at treatment initiation	163.2±6.4	163.0±6.4	0.861
RWT predicted adult height at treatment initiation	164.1±4.9	163.0±6.4	0.250
BAPCPHE predicted adult height at treatment initiation	163.1±5.6	163.0±6.4	0.948
BP predicted adult height at the end of the 1st year of treatment	164.0±6.2	163.0±6.4	0.297
RWT predicted adult height at the end of the 1st year of treatment	163.3±4.4	163.0±6.4	0.776
BAPCPHE predicted adult height at the end of 1st year of treatment	163.4±6.0	163.0±6.4	0.694
BP predicted adult height at the end of the 2nd year of treatment	**165.6±7.4**	**163.0±6.4**	**0.007**
RWT predicted adult height at the end of the 2nd year of treatment	163.0±4.9	163.0±6.4	0.965
BAPCPHE predicted adult height at the end of 2nd year of treatment	164.2±6.4	163.0±6.4	0.208
BP predicted adult height at the end of the 3rd year of treatment	**165.0±5.1**	**163.0±6.4**	**0.036**
RWT predicted adult height at the end of the 3rd year of treatment	163.0±2.8	163.0±6.4	0.965
BAPCPHE predicted adult height at the end of 3rd year of treatment	164.3±4.2	163.0±6.4	0.172
BP predicted adult height at the end of treatment	**165.8±6.1**	**163.0±6.4**	**0.004**
RWT predicted adult height at the end of treatment	162.9±4.4	163.0±6.4	0.878
BAPCPHE predicted adult height at the end of treatment	164.4±4.9	163.0±6.4	0.141

*p<0.005 is considered statistically significant.
BP: Bayley-Pinneau method, RWT: Roche-Wainer-Thissen method, BAPCPHE: Bone Age Percentile Curve Projected Height Estimation

Discussion

In the present study, we retrospectively evaluated 50 female patients diagnosed with idiopathic CPP, treated with gonadotropin releasing hormone (GnRH) analogs, and followed until they reached their final height. Our aim was to assess the accuracy of three different methods for estimating final height.

The study by Baek et al. (17) in South Korea, which included 71 female CPP patients, reported an average treatment duration of 27.9±9.0 months, a mean treatment initiation age of 8.5±0.7 years, and a mean MPH of 161.6±3.6 cm. Their findings indicated a significant increase in PAH from 158.7±4.1 cm before treatment to 163.8±4.7 cm afterward, by using the BP method (17). Similarly, in our study, the PAH at treatment initiation was 163.2±6.4 cm using the BP method, increasing to 165.8±6.1 cm in the post-treatment period. These findings suggest that treatment effectively halts bone age advancement, contributing to increased PAH, in line with the literature.

Wu et al. (18) developed a predictive model in 2023 to estimate target height in 258 Chinese girls with idiopathic CPP. This model incorporated variables, such as height SDS at diagnosis, bone age-adjusted height SDS, and MPH. Unlike traditional models, it used bone age-adjusted height SDS instead of the peak LH/FSH ratio as a diagnostic factor. Bone age was assessed using the Greulich-Pyle atlas and Tanner-Whitehouse (TW) methods. The model's predicted target heights closely matched the final heights observed in the cohort.

Studies comparing different methods for predicting final height have shown variability in accuracy. For instance, a study including short-statured girls who did not receive GnRH therapy found that the BP method was the most accurate among three methods (BP, TW, and RWT) (19). Joss et al. (20) reported that the BP method provided reliable predictions, while the TW method overestimated final height by 3.9 cm and the RWT method by 6.3 cm. In contrast, Brämswig et al. (21) argued that BP, TW, and RWT methods were equally inadequate in predicting adult height in patients with PP.

Quiroga et al. (22) compared the BP and RWT methods in a cohort of 93 girls with CPP who reached their final height without GnRH treatment. They found that the BP method underestimated the predicted target height by 1.01 cm, while the RWT method overestimated it by 0.96 cm. Despite these differences, they recommended the BP method for its simplicity and practical application in predicting height in cases of early puberty (22).

Akın Kağızmanlı et al. (23) found that while the RWT method provided predictions close to the final height, the BP method produced the smallest difference between PAH and final height, making it the preferred method.

Jang et al. (24) studied 206 patients with CPP and reported an MPH of 160.26±3.62 cm. Using the BP method, PAH at diagnosis was 155±5.71 cm, while the final height was 159.3±4.26 cm. The mean initial height was 133.9±5.15 cm, with a mean final height increase of 25.4 cm (24).

In a study by Matias et al. (25) involving 138 patients, the BP and TW methods were compared. The mean final height was 173.6±5.31 cm. The TW method predicted a mean target height of 168.6±6.17 cm and the BP method predicted 172.5±5.12 cm. The BP method's predictions were significantly closer to the final height (25).

In the present study, the mean difference between final height and MPH was 4.3 (-5.6-19) cm, while the final height SDS-MPH SDS difference was 1.29±0.94 SDS. The mean difference between final height and initial height was 26.5±7.6 cm, and the SDS difference was -0.96±1.08 SDS. PAH at treatment initiation was 163.2±6.4 cm using the BP method, 164.1±4.9 cm using the RWT method, and 163.1±5.6 cm using the BAPCPHE method, respectively. ICC analysis revealed that the BP method showed the highest correlation with final height, followed by the RWT and BAPCPHE methods. All three methods demonstrated satisfactory accuracy in predicting final height.

When assessing the ICC between target height prediction methods and final height at the third year of treatment, all parameters except the BAPCPHE-predicted target height showed significant correlation. The BP method based on post-treatment bone age exhibited the highest agreement with final height. Strong agreement was observed between final height and post-treatment BP predictions, second-year RWT predictions, and third-year BP predictions. Moderate correlation was noted with other parameters, while a weak correlation was found with first-year and baseline BAPCPHE predictions.

The differences between all these studies can be attributed to the content of the methods and the patient profile. For example, the inclusion of weight in the RWT method causes obesity to affect the assessment of PAH. We did not evaluate our obese patients with subgroup analyses. The age at presentation of obese patients may have influenced the relationship between RWT/BP methods and age at treatment initiation.

There are a few published studies evaluating the efficacy of PAH methods within the treatment period. In the present study, we found that all three methods were effective and gave similar PAH results during treatment. The method we use is not affected by either obesity or MPH. In addition, the fact that bone ages were evaluated by two different specialists and consistency was found between the evaluations strengthened the results of our study. We believe that the BAPCPHE method has benefits because it is easy to use in practice and the final height estimates are in

agreement with the final height during the whole treatment process.

Study Limitations

This study has several limitations. It is a retrospective study involving a relatively small patient cohort receiving varying doses of GnRH analogs at different pubertal stages. The RWT method recommends horizontal height measurement, whereas our study used standing height measurements due to its retrospective design. Factors such as obesity-related bone age advancement were not analyzed, limiting insights into its potential contribution to final height. CPP is more prevalent in girls. Our study cohort had no male patients achieving final height. The heights of the parents who could not come to our outpatient clinic were not measured in our outpatient clinic but in another health institution close to them. This may have created an error in the calculation of mid parenteral height.

Conclusion

In clinical practice, the BAPCPHE method's practical application allows for quick and easy target height estimation, making it a valuable tool in outpatient settings. Given its simplicity and accuracy, we found the BAPCPHE method preferable.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from İstanbul Medeniyet University, Göztepe Prof. Dr. Süleyman Yalçın City Hospital Clinical Research Ethics Committee (approval number: 2023/0966, date: 20.12.2023).

Informed Consent: Informed consent was obtained from the participating patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Nisa Nur Turan, Aşan Önder Çamaş, Burçin Çiçek, Merve Nur Hepokur, Hamdi Cihan Emeksiz, Concept: Nisa Nur Turan, Aşan Önder Çamaş, Design: Nisa Nur Turan, Aşan Önder Çamaş, Data Collection or Processing: Nisa Nur Turan, Aşan Önder Çamaş, Burçin Çiçek, Merve Nur Hepokur, Hamdi Cihan Emeksiz, Analysis or Interpretation: Nisa Nur Turan, Aşan Önder Çamaş, Literature Search: Nisa Nur Turan, Aşan Önder Çamaş, Merve Nur Hepokur, Writing: Nisa Nur Turan, Aşan Önder Çamaş, Hamdi Cihan Emeksiz.

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