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ORIGINAL ARTICLE

Complex nutritional deficiencies in a large cohort of Italian patients with Cornelia de Lange syndrome spectrum

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Abstract

Cornelia de Lange syndrome Spectrum (CdLSp) is characterized by intellectual disability, facial dysmorphisms, and growth impairment. Although eating difficulties are a well-known feature of the disease, there is no data regarding the nutritional deficiencies of these patients. The food intake was tracked using a dietary transcription provided by the family/caregivers, biochemical nutritional parameters were measured with laboratory tests and through an accurate clinical evaluation of the incidence of qualitative and quantitative imbalances in a cohort of 73 patients with CdLSp ware determined. Of these 73, 62 (85%) subjects provided a complete and detailed dietary transcription. In the studied population, a quantitative caloric imbalance in 47/62 (76%) subjects was observed. The caloric intake was low in 27/62 (43%) subjects whereas excessive in 20/62 (33%). Only 15/62 (24%) had an optimum caloric intake. Regarding micronutrients, a calcium intake deficiency in 32% of the patients (20/62) was observed. Blood tests revealed a low iron level in 22/73 (30%) of the patients and 25(OH)D deficiency in 49/73 (67%). Serum hypocalcemia was not evidenced. Qualitative and quantitative imbalances resulted in more frequent than expected in CdLSp patients. A qualitative imbalance was more prevalent in younger patients while in older patients prevailed mainly a quantitative disproportion. We found no statistically meaningful correlation between dietary imbalances, genetic, or clinical parameters. Our findings highlight the need for further studies to evaluate the basal metabolic rate of CdLSp patients and find a correlation with their growth impairment.

KEYWORDS

caloric intakes, CdLS, qualitative nutritional deficiency, quantitative nutritional deficiency

1 | INTRODUCTION

Cornelia de Lange Syndrome (CdLS) is a rare genetic condition characterized by typical facial features, growth impairment, developmental delay, intellectual disabilities, and major malformations. Due to the wide phenotype variability of these patients, an International Consensus Statement has recently defined CdLS phenotype as a spectrum (Kline et al., 2018).

Within the CdLS spectrum (CdLSp) are included the classic and nonclassic CdLS phenotypes. Most patients harbor a pathogenic variant in a cohesin function-relevant gene (*NIPBL*, *SMC1A*, *SMC3*, *RAD21*, *BRD4*, *HDAC8*, *ANKRD11*), identifying CdLSp as a cohesinopathy

(Borck et al., 2004; Deardorff et al., 2007; Gil-Rodríguez et al., 2015; Mannini, Liu, Krantz, & Musio, 2010; Olley et al., 2018; Parenti, Gervasini, Pozojevic, Graul-Neumann, et al., 2016; Parenti, Gervasini, Pozojevic, Wendt, et al., 2016). Approximately 15–20% of the individuals with classic features have mosaic *NIPBL* variants (Ansari et al., 2014; Baquero-Montoya et al., 2014; Huisman, Redeker, Maas, Mannens, & Hennekam, 2013).

From an early age in life, individuals with CdLSp may suffer from a wide range of medical problems. Among them, gastrointestinal complications and feeding difficulties are certainly the most frequent ones. Particularly, CdLSp patients suffer from dysphagia and gastroesophageal reflux disease (GERD; Bull, Fitzgerald, Heifetz, & Brei, 1993; Cates, Billmire, Bull, & Grosfeld, 1989; Kline et al., 2007; Luzzani, Macchini, Valadè, Milani, & Selicorni, 2003; Macchini et al., 2010) which could lead to food refusal and difficult/deficient nutrients' intake. Several reports evidenced that GERD, vomiting, and esophagitis are more frequent in patients with a classical phenotype, generally associated with NIPBL truncating mutations (Huisman et al., 2013; Luzzani et al., 2003; Nizon et al., 2016).

Feeding difficulties are frequently evident in newborns/infants with CdLSp and these difficulties generally evolve with time. A recent study evidenced that nutritional devices are generally used by CdLSp patients during first months/years of life and that most of these patients (93.1%) achieved a normal oral nutrition through time (Decimi et al., 2018).

For all of the above reasons, the involvement of a dietician support in the medical team is mandatory for these patients (Kline et al., 2018) as it is for other fragile children.

Children with neurological disabilities usually have feeding difficulties and gastrointestinal symptoms commonly resulting in malnutrition with qualitative/quantitative deficiencies and growth failure (Calis, Veugelers, Rieken, Tibboel, & Evenhuis, 2010; Penagini et al., 2015; Sangermano et al., 2014).

In 2017, the European Society of Gastroenterology, Hepatology, and Nutrition (ESPGHAN) published a consensus statement (ESPGHAN guidelines) on the diagnosis and management of gastrointestinal and nutritional complications in children with neurological disability. The purpose of this consensus was to provide a nutritional guideline and management of gastrointestinal symptoms and nutritional interventions for children with neurological disabilities (Romano et al., 2017).

Besides, from a few reports on Down Syndrome (DS), there is not enough scientific data published on nutrition and other syndromes. The great majority of the available studies regard cerebral palsy (CP) which is the most frequent nongenetic disease associated with disability.

To the best of our knowledge, this is the first report describing the prevalence of quantitative and qualitative nutritional problems in a large cohort of CdLSp patients that studies the correlation of these and some characteristics of the syndrome (pathogenic variant, severity score), auxological parameters, and nutritional parameters.

The aims of this study were, first, to define the prevalence of quantitative and qualitative nutritional deficiencies in our cohort and the distribution of these problems according to patient's age; second, to evaluate the nutritional status of these patients analyzing biochemical parameters; third, to correlate the presence of nutritional imbalances with auxological parameters and Body Mass Index (BMI); and last but not least, to correlate the nutritional problems with the clinical and molecular findings in our patients.

2 | PATIENTS AND METHODS

This retrospective study evaluated 73 patients, with a clinical diagnosis of CdLSp according to the diagnostic criteria published by Kline et al., 2007. All patients fulfilled also the new diagnostic criteria recently published (Kline et al., 2018). Children with a nasogastric tube or gastrostomy feeding tube were excluded.

The patients were assessed once a month on specific sessions called "De Lange Day" organized at the Clinical Genetics Department of Pediatric Clinic Foundation MBBM in San Gerardo Hospital in Monza from March 2013 to February 2016.

All subjects underwent molecular testing of known genes related to CdLSp (*NIPBL SMC1A*, *SMC3*, *HDAC8*, *ANKRD11*, *RAD21*). By the time, this study was conducted, *BDR4* gene was not known as a CdLSp-related gene; therefore, no patient was analyzed for pathogenic variants of *BDR4* gene. To compare the nutritional data with the genotype, we defined four genotypic classes: Patients with *NIPBL* truncated mutations, patients with other *NIPBL* nontruncated mutations, patients with mutations in other cohesion related genes (*SMC1A*, *SMC3*, *HDAC8*, *ANKRD11*, and *RAD21*) and patients with normal genetic screening who had only a clinical diagnosis in accordance with international indications.

In addition, patients of the cohort were classified based on the disease severity using the "scoring system" published by Kline et al. (2007) (severe, moderate, and mild). At the clinical evaluation, the patients' weight and length/height were recorded on specific CdLS growth charts (Kline et al., 1993). BMI was categorized according to the extended International Obesity Task Force (IOTF) criteria (Cole & Lobstein, 2012). Unfortunately, skin-fold thickness was not measured in all patients so this parameter was not used to evaluate the nutritional status of the cohort.

To investigate the presence of nutritional problems, parents/caregivers were required to record over 3 days the precise amount of each ingredient used to prepare every meal to calculate and evaluate the exact nutritional intake.

The nutritional intake was calculated after an accurate study (calories and micro/macronutrients intakes per day) of the patients' food dairy. To estimate the dietary intake parents/caregivers were supposed to list and weight the ingredients of each meal. The daily nutritional intake of each participant was determined by summing the nutritional intake of each meal. The caloric and proteic intake of each subject were evaluated based on the values suggested by CdLS Foundation (www.CdLSusa.org) and the lipidic intake was evaluated based on the Italian Reference for nutrients and energy intake according to age (LARN) of the Italian Society of Human Nutrition (SINU, 2014).

Biochemical nutritional parameters were studied measuring 25-hydroxy vitamin D [25(OH)D], iron, and calcium serum levels (Romano et al., 2018). Levels of 25(OH)D under 30 ng/ml (Antonucci, Locci, Clemente, Chicconi, & Antonucci, 2018; Hovsepian, Amini, Aminorroaya, Amini, & Iraj, 2011), iron concentration level under 49 mg/dl and serum calcium under 8.20 mg/dl were considered low.

Chi-square test was performed to assess the presence of statistically significant associations between the different variables analyzed (with or without Yates correction). Statistical significance was set at $p < .05$.

3 | RESULTS

3.1 | Clinical data

Seventy-three patients (35 males, 38 females) with a mean age of 11 years were evaluated. Table 1 summarizes genetic and clinical data of this cohort, including the severity score distribution and the auxological data. Based on the BMI, only 36/73 (50%) patients were between 10th and 90th percentiles for general population. Of these 73, 31 (42%) had a BMI under the 10th percentile, whereas 6 (8%) had a BMI over the 90th percentile.

3.2 | Prevalence of nutritional imbalances

Of these 73, 62 (85%) patients provided a complete and detailed food diary. Quantitative caloric imbalances were observed in 47/62 (76%) of these patients.

Regarding the type of caloric imbalance, 27/62 (43%) had a hypocaloric diet, while 20/62 (33%) had an excess of calories in their diets. Only 15/62 (24%) had a regular caloric intake. Collected data showed a qualitative imbalanced diet in 48/62 patients (77%; Table 1).

In particular, an imbalanced protein intake was present in 42 patients. Among subjects, 29/62 (47%) had an imbalanced protein intake exclusively. Then, 13/62 (21%) had both proteins and lipids intake altered, and 6/62 subjects (10%) had only the lipid intake altered. Regarding protein alterations, all 42 patients presented an excess of protein intake. Whereas for lipids, 5/19 (26%) had a low lipid intake and 14/19 (74%) had a high-fat diet. Table 1 summarizes the macronutrient intake distribution.

A micronutrients deficiency (iron, 25(OH)D, and calcium) was evidenced by assessing the food diary the laboratory workup of the cohort.

By analyzing the food diary from 62 patients, a deficient calcium intake in 20/62 patients (32%) was evidenced. Nevertheless, none of the patients showed serum calcium alterations.

49/73 (67%) had a low serum concentration of 25(OH)D, but none had a particular history of bone fractures. We could not determine the bone density as DEXA scan was not performed. Regarding iron level, blood tests showed that 22/73 patients (30%) had a low iron level. In 50% (11/22) of these, a low sideremia was associated with microcytic anemia.

Quantitative nutritional imbalances were classified according to patient's age: 5/11 (45%) children under 6 years of age, 9/38 (24%) between 6 and 15 years old, and 1/13 (8%) more than 15 years old had a normal caloric intake. No significant results emerged from the statistical analysis (chi-square test, p value = .07; Table 2).

Regarding micronutrients, a statistically significant analysis (chi-square test, p value = .05) showed that hypovitaminosis D was more frequent in the group of 6–15 years old with an incidence of 33/42 (78%; Table 3).

TABLE 1 Genetic, severity score, auxological parameters, and distribution of the alterations of macronutrients in the analyzed population distribution of CdLS cohort

Genotypic classes	*N* (%)
Mutation identified	47/73 (64)
NIPBL truncating mutation	15/47 (32)
NIPBL not truncating mutation	24/47 (51)
NIPBL mutation (total)	39/47 (82)
Mutation in genes different from *NIPBL*	8/47 (17)
No mutation identified, Clinical diagnosis (Kline et al.)	26/73 (36)
Severity score	
Mild	28/73 (38)
Moderate	27/73 (37)
Severe	18/73 (25)
Weight	
<25°	7/73 (9)
25–90°	48/73 (66)
>90°	18/73 (25)
Height	
<25°	9/73 (12)
25–90°	51/73 (70)
>90°	12/73 (16)
BMI	
<10°	31/73 (42)
10–90°	36/73 (50)
>90°	6/73 (8)
Caloric intake	
Hypocaloric	27/62 (43)
Normocaloric	15/62 (24)
Hypercaloric	20/62 (33)
Macronutrient imbalances	
Protein imbalance (isolated)	29/62 (47)
Protein and lipid imbalances	13/62 (21)
Lipid imbalance (isolated)	6/62 (10)

3.3 | Correlations between nutritional imbalances, characteristics of the syndrome, and growth

A significant correlation (chi-square test, p value = .03) between the severity score and vitamin D deficiency was found (Table 3). Then,

TABLE 2 Distribution of caloric intakes in different age groups

Age	Hypocaloric intakes	Normocaloric intakes	Hypercaloric intakes	Total	*p* value
<6 years	1/11 (10%)	5/11 (45%)	5/11 (45%)	11	.07
6–15 years	19/38 (50%)	9/38 (24%)	10/38 (26%)	38	
>15 years	7/13 (54%)	1/13 (8%)	5/13 (38%)	13	
Total	27	15	20	62	

TABLE 3 Distribution of 25(OH)D status in different age groups and correlation to different severity score

	Hypovitaminosis D	Normal vitamin D	Total	*p* value
Age				
<6 aa	5/15 (33%)	10/15 (67%)	15	.05
6–15 aa	33/42 (78%)	9/42 (22%)	42	
>15 aa	11/16 (68%)	5/16 (32%)	16	
Severity score				
Mild	19/28 (68%)	9/28 (32%)	28	.03
Moderate	14/27 (52%)	13/27 (48%)	27	
Severe	16/18 (89%)	2/18 (11%)	*18*	
Total	49	24	73	

TABLE 4 Correlation between quantitative nutritional imbalance and genotype, severity score and BMI

	Hypocaloric intakes	Normocaloric intakes	Hypercaloric intakes	Total	*p* value
Mutations					
NIPBL truncating	4/12 (33%)	3/12 (25%)	5/12 (42%)	12	.70
NIPBL not truncating	10/22 (46%)	6/22 (27%)	6/22 (27%)	22	
Other genes	3/7 (43%)	3/7 (43%)	1/7 (14%)	7	
Clinical diagnosis	10/21 (48%)	3/21 (14%)	8/21 (38%)	21	
Severity score					
Mild	12/26 (46%)	5/26 (19%)	9/26 (35%)	26	.83
Moderate	8/21 (38%)	7/21 (33%)	6/21 (28%)	21	
Severe	7/15 (47%)	3/15 (20%)	5/15 (33%)	15	
Total	27	15	20	62	
BMI					
< 10°	10/27 (37%)	7/15 (47%)	9/20 (45%)	26	.55
10–90°	16/27 (60%)	7/15 (47%)	8/20 (40%)	31	
>90°	1/27 (3%)	1/15 (6%)	3/20 (15%)	5	
Total	27	15	20	62	

19/28 (68%) patients with a mild severity score, 14/27 (52%) patients with a moderate score, and 12/15 (89%) patients with a severe score had a vitamin D deficiency.

There was no correlation between the molecular classification/severity of the disease and the quantitative nutritional imbalance (Table 4).

From the analysis, no statistically significant relationship emerged (Chi-square test, *p* value = .55) between the BMI and the nutritional intakes (Table 4). Among patients with BMI <10th percentile: 10/27 (37%) had a low caloric intake, 7/15 (47%) had a normal caloric intake, and 9/20 (45%) had a high caloric intake. Between patients with a normal BMI: 16/27 (60%) had a low caloric intake, 7/15 (47%) had a normal caloric intake, and 8/20 (40%) had a high caloric intake. Among those with a BMI > 90th percentile: 1/27 (3%) had a low caloric intake, 1/15 a normal caloric intake (6%), and 3/20 (15%) a high caloric intake. No statistically significant relationship was found between the caloric intakes and the genetic framework of the subjects (Chi-square test, *p* value = .70; Table 4).

4 | DISCUSSION

Children with disabilities generally have nutritional problems. Dysphagia and GERD are the most frequent disorders among these children,

leading to a difficult introduction of nutrients. It is well known that parents/caregivers often present significant difficulties in feeding these subjects.

Not enough scientific data is available in the literature, nevertheless, this situation may lead to growth failure due to malnutrition and dietary imbalances, increased susceptibility to infections, and raised hospitalization and mortality rates. Most of what has been published, to date, are related to children with DS and CP.

A study aimed to analyze the nutritional status of a group of young DS adults showed a high prevalence of overweight and obesity with reduced intakes of proteins, fats, fibers, and some vitamins and minerals (Soler Martin & Xandri Graupera, 2011). Other studies described overweight/obesity in more than half of their subjects, confirming excessive intakes of macronutrients and a deficient intake of vitamins and minerals (vitamins A and C along with calcium and zinc) in DS patients compared to controls. Frequently, high serum triglycerides and low HDL-cholesterol levels are also observed in this population (Mazurek & Wyka, 2015; O'Neill, Shults, Stallings, & Stettler, 2005; Smarkandy, Mohamed, & Al-Hamdan, 2012).

A study of the nutritional intake and anthropometric status of individuals with intellectual disabilities of different etiologies evidenced that obesity was more prevalent in people with intellectual disabilities, especially in patients with DS (Hoey et al., 2017).

Kilpinen-Loisa et al. (2009) studied the nutrient intake in 54 children with motor disability (CP in 59% of cases). The mean energy intake was less than 80% of the recommended diary caloric intake, particularly in severely disabled children (Kilpinen-Loisa et al., 2009). Another study, conducted in 99 CP patients aged between 18 and 36 months, evidenced a lower caloric intake in patients with severe motor dysfunction (Benfer et al., 2015).

To date, there is no published data about nutritional intakes in patients with CdLSp. In this report, we investigated the nutritional alterations in a cohort of 73 CdLSp patients. Of these 73, 62 (85%) provided us with a complete and detailed dietary transcription.

In 27/62 (43%) of CdLSp patients was evidenced by a low caloric intake. Similarly, to what was observed by Kilpinen-Loisa et al. in patients with motor disabilities, half of the patients 15/27 (55%) with a low caloric intake had a moderate–severe gravity score.

Regarding the macronutrient intake, a study of the dietary patterns in 90 children with CP showed that between 2 and 13 years old, 52% had a low carbohydrates intake, 53% had an adequate proteins intake and 43% had a high lipids intake (Lopes, Amancio, Araújo, Vitalle, & Braga, 2013). Another study in 30 children with neuromotor disabilities, aged between 2 and 15 years, evidenced an imbalanced macronutrient intake with and increased intake of lipids and proteins and a reduced intake of carbohydrates (Sangermano et al., 2014). A similar dietary pattern, high on lipids and proteins, was found in the studied cohort.

Interestingly, by assessing micro and *macronutrient* intakes, a decreased normocaloric intake was evidenced with aging. Although statistical correlation was not significant, the observed trend could be explained by the following hypothesis: (a) through time, less attention to diet might be paid by both medical staff and family; (b) feeding plans at school could be difficult to monitor; and (c) lower patient compliance. All of the above could difficult a proper caloric intake of these patients.

Lopes et al. described a similar phenomenon on 90 CP children aged between 2 and 13 years old: The youngest group (age range: 2–3 years old), presented a nutritional intake in accordance with standard recommendations; on the other hand, older children (age range: 9–13 years old) presented a lower caloric intake (Lopes et al., 2013).

In the studied population, 30% of the subjects had a low iron level, half of these had an associated microcytic anemia. Iron deficiency anemia is a well know condition observed in neurologically impaired children, possibly due to iron deficit which might be worsened by GERD.

A high incidence of anemia in patients with CP (age range: 8–29 years) was found in Papadopoulos et al. (2008). Other studies compared micronutrient levels in children affected by CP with neurologically normal control and evidenced that iron serum levels were significantly lower in children with CP (Hillesund, Skranes, Trygg, & Bøhmer, 2007; Kalra, Aggarwal, Chillar, & Faridi, 2015). Similar data were reported in DS: Low iron and ferritin serum levels, high zinc serum levels, and a normal vitamin B12 and folic acid levels (Concolino et al., 2001; Soler Martin & Xandri Graupera, 2011).

Esophagitis and gastroesophageal reflux disease, which frequently affect CdLSp patients, could lead to blood loss which might not be evident at first. Occult bleeding worsens iron deficiency (Bermejo & García-López, 2009; Stein et al., 2016). Not enough data about GERD in syndromic conditions have been published. ESPGHAN guidelines mention only CdLSp as a genetic condition at high risk of GERD (Romano et al., 2017).

Hypovitaminosis D was found in 67% of studied cohort with a higher prevalence between 6 and 15 years. Nevertheless, it seems that hypovitaminosis is a more transversal condition rather than a specific deficit of children with disabilities, as it is a constant in 30–50% of the American and European children and in 50% of the adolescents (Holick, 2007). A more recent study in children with autism spectrum disorder showed a significant low level 25(OH)D also in this cohort (Arastoo et al., 2018).

Patients with impaired mobility have a higher risk of fractures due to more fragile bones in comparison to general population. This situation reflects the need for greater attention to 25(OH)D vitamin levels in children with disabilities. Despite the 25(OH)D serum levels evidenced in the studied patients, none had a positive history of bone fractures.

Calcium intake and blood levels of calcium were also assessed. A Norwegian study evidenced low calcium intakes among 35% of non-supplemented children, with no evidence of low serum calcium levels (Hillesund et al., 2007). Similarly, 32% of the children from the studied cohort had a low calcium intake with normal serum levels.

As shown, no statistically significant correlation was found in any of the analyzed parameters apart from a more prevalent hypovitaminosis D in patients with severe disability scores. Therefore, the

more severe the disease is the higher the prevalence of 25(OH)D deficiency.

The correlation between quantitative nutritional imbalances and the patients' severity score was not statistically significant probably because of two main reasons: (a) It is possible that our population is not big enough to evidence significant differences when classified and (b) feeding problems are so frequent in CdLSp patients that they might affect almost the totality of them.

Among the 15 patients with a normocaloric diet, we observed that 12 had a mild or moderate phenotype. This indicates that it is possible to ensure a balanced caloric intake in patients with a milder phenotype.

A very interesting data that emerged from this study is that an imbalanced nutritional intake does not affect directly the patient's BMI. The great majority of patients with a low BMI had a normal/high caloric intake evidenced by the food diary. This data suggests that growth is only moderately influenced by the caloric intake in these patients. Unfortunately, there is no data regarding the metabolic rate of the different genomic groups of CdLSp patients not even of CdLSp patients in general.

Regarding the matter, Leoni et al. (2016) evidenced using indirect calorimetry that individuals with Costello syndrome have increased resting energy expenditure. This reflects an increased cellular basal metabolism, age independent, and might be possibly related to the molecular defect itself.

The concept of increased cellular metabolism should be considered in every genetic disease associated with growth deficiency in which calorimetric studies are missing or are difficult to carry out. Moreover, increased metabolic rates in conditions with neurological impairment have been related to a high level of physical activity, as in CdLSp patients (Penagini et al., 2015). Therefore, once a low caloric intake is ruled out through an accurate dietary record, an increased basal metabolism should be considered as the main cause of failure to thrive and weight gain. To achieve a greater understanding of the matter, further studies on metabolic rate measurements, whereas possible, must be conducted.

This study may have some limitations as the dietary intake was assessed based on the food diary reported by parents/caregivers, therefore there may be bias regarding the reported caloric intake of the cohort. In fact, parents and caregivers may provide nutritional information that could be inaccurate in terms of both quality and quantity. Despite this, a 3-day dietary record is still a valid method to study the eating habits of these children when integrated into their home environment. Moreover, no prior researches on this specific topic are available in the literature; it could be a limit because of the lack of comparison.

5 | CONCLUSIONS

Our results highlight that patients with CdLSp may have both quantitative and qualitative unbalanced nutrition problems. Apart from the clinical severity and genomic background, most patients appear to have evident alterations in their diets. Qualitative imbalances are more prevalent in younger patients while quantitative anomalies are more evident in the older ones.

The lack of correlation between the patients' BMIs and the nutritional imbalances suggest a major influence of genetics regarding growth in CdLSp patients. Further studies must be conducted to evaluate the basal metabolic rate of these special patients.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Valentina Decimi collected data; Barbara Parma and Paola Cianci wrote the manuscript with support from Milena Mariani, Maria Cristina Provero, Caterina Funari, Silvia Tajè, Erika Apuril, Anna Cereda, Roberto Panceri, Silvia Maitz, and Chiara Fossati. Angelo Selicorni supervised the whole project. All authors discussed the results and contributed to the final manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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