# Quality of Life & Phonatory and Morphological Outcomes in Cognitively Unimpaired Adolescents With Pierre Robin Sequence – A Cross-sectional Study in a 72-patient Series

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# Quality of life & phonatory and morphological outcomes in cognitively unimpaired adolescents with Pierre Robin sequence – a cross-sectional study in a 72-patient series

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**Authors‘ contributions** : Béatrice Thouvenin (BT), Véronique Soupre, Laurence Vaivre-Douret and Véronique Abadie (VA) designed the study. VA was the study PI. VA and BT wrote the manuscript. Charlotte Henry-Mestelan et Béatrice Thouvenin are the psychologists who saw the children and conducted the interviews. Christel Chalouhi, Nancy Végas et Katia Lind are the pediatricians at the reference centre for rare disease who organized the examinations. Bachar Houssamo is the orthodontist who made the orthodontic assessment. Aurélie Royer and Cécile Chappuis are the speech-therapists who designed the protocol and saw the children. Jeanne Amiel is the geneticist who saw all the families. Véronique Soupre, Arnaud Picard and Gérard Couly are the surgeons who operated the children. Marie-Anne Caillaud performed the statistical analyses. All the authors corrected the draft and approved the final manuscript.

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All authors are informed about and agree with these declaration

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**Competing interests**

All authors have no financial or non-financial competing interests to declare regarding this study.

**Ethics approval and consent to participate**

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**Abstract**

We assessed the phonatory and morphological outcome of 72 cognitively unimpaired adolescents with Pierre Robin Sequence (PRS), studied their generic (Kidscreen-52), oral (COHIP-SF19) and vocal (VHI-9i) qualities of life (QoL), and sought to identify determinants of these outcomes. Two-thirds of our adolescents retained low or moderate phonation difficulties but risk factors for them were not identified. For 14%, esthetic results were considered disharmonious with no link to neonatal retrognathia severity. Only two-stage surgery appeared to have a role in improving esthetic results. The generic QoL of these adolescents was slightly lower than that of control patients, especially in dimensions concerning physical well-being, relationships and autonomy. Patients with non-isolated PRS had lower results than those with isolated PRS. Phonatory and morphological sequelae had no impact on generic QoL. Only non-isolated PRS and a low oral QoL had an impact on generic QoL. The oral QoL of these adolescents was comparable to that of control patients and significantly better than that of children with craniofacial malformations. The oral QoL of the adolescents with non-isolated PRS, was significantly worse than that of control patients and close to that of children with craniofacial malformations. The vocal QoL of our subjects was better than that of patients with other voice pathologies and better when phonation was good.

Keywords :

Pierre Robin Sequence; generic quality of life; oral QoL; vocal QoL; adolescent; outcome

## INTRODUCTION

Pierre Robin sequence (PRS) is a rare and complex facial malformation that occurs in roughly one out of 10,000 births. It associates retrognathia, glossoptosis, airway obstruction and frequently posterior U-shaped cleft palate (CP) [1]. The pathophysiological origin of the embryonic sequence of events leading to the disorder appears heterogeneous [2,3]. A family history of PRS is present in 10 to 15% of cases, possibly involving mutations upstream of the SOX9 gene, which participates in embryonic mandible development among other roles [4,5]. Neonates with PRS experience breathing and feeding issues, including upper airway obstruction due to the posterior position of the tongue and to glossopharyngeal/laryngeal hypotonia, suckling and swallowing difficulties and gastroesophageal reflux [6,7]. Because of these functional disorders, the first year of an infant with PRS is marked by many burdensome medical necessities, such as prolonged hospitalization, mother/child separation, nasogastric or gastrostomy tube feeding and the management of upper airway obstruction. In the Parisian protocol, this latter comprises prone positioning, continuous positive airway pressure (CPAP), nasopharyngeal tube, or tracheostomy according to case severity [8,9]. Patients usually improve progressively during the first two years of life. In PRS with CP, one or two-stage primary surgery, according to the surgical team and the CP width, are performed between the ages of 6 and 18 months.

Nearly half of children with PRS also have associated malformations resulting in syndromic PRS often affecting their cognitive development. In contrast, those whose PRS is isolated or associated with Stickler syndrome have a good cognitive prognosis. However, in a previous prospective longitudinal study spanning 12 years, we showed that such children had good cognitive development, but retained phonatory disorders, especially hypernasality, for about half of them [10].

A number of teams have looked at the negative impact of cleft lips/palates on quality of life (QoL), particularly as concerns self-esteem [11-14]. In contrast, only two studies have been published on QoL in PRS patients who have posterior, non-visible clefting [15,16]. The authors of the first study, concerning younger children (4 to 11 years of age), reported that self-esteem in their PRS group was

comparable to that of their control group but underlined that this dimension should be evaluated in adolescents. Those of the more recent second study demonstrated a satisfactory generic QoL in 17 adolescents with PRS. Nonetheless, both families and health providers report self-esteem issues, inhibitions, and social integration difficulties in some teenagers affected by PRS, even those with normal cognitive and scholastic capacities. The hypernasality and face morphology issues they still carry could contribute to these issues, as the voice and face are major elements of social communication.

The primary objective of the study we report here was to analyze generic and specific (vocal and oral) QoL in cognitively unimpaired adolescents with PRS, and identify determinants of any differences that may exist between QoL in this setting and that in the general population. Those determinants were defined as either current: particularly any phonatory or facial morphology sequelae still present in adolescence; or early: particularly PRS type (isolated or not), neonatal anatomic characteristics (cleft width, retrognathia degree), neonatal functional impairment severity (respiratory, orodigestive) and cleft palate surgery procedure (one or two-stage).

Our secondary objectives were to describe phonatory and morphological outcomes in a large monocentric cohort of PRS patients as they pass through the important period of adolescence, and analyze early determinants of any phonatory or morphological sequelae that they may still be carrying.

Finally, we also compared two surgical protocols for cleft repair (in one or two-stage primary surgery) to assess complications incidence (palatal fistulae) and functional results in terms of facial morphology and phonation. Indeed, in our series, two protocols for cleft palate repair were used. The first consisted of uranostaphylorrhaphy as per the Veau-Wardill technique [17] deployed in a single intervention at 9 months of age regardless of cleft width (Necker Hospital), and the second intravelar veloplasty as per Sommerlad [18], at 6 to 8 months with closure of the hard palate during the initial surgery for narrow clefts, or during a second surgery at 12 to 18 months (median age 15 months), for larger clefts (Trousseau Hospital). These two techniques for cleft palate repair and the results they

confer have never been compared in the setting of PRS and their deployment in other types of cleft lip/palate remains controversial [19-24].

## PATIENTS AND METHODS

### Patients

All adolescents born between 01 July 1997 and 01 July 2007 (i.e., aged 12 to 18 years during the study period) and admitted during the neonatal period to Necker Hospital or Trousseau Hospital for PRS were included. The PRS cases could be isolated or associated with an underlying Stickler syndrome or with other minor bone malformations not threatening cognitive development. All the children had been seen by the genetics team. Children with more than two years of schooling delay were excluded, as were those who experienced serious underlying organic disease potentially deleterious to QoL.

The Île-de-France Ethics Committee II and the French national agency for medicines and health products safety (ANSM) approved the study protocol on 05 July 2016.

### Methods

Patients were received for a day of examinations by the team of the French Rare Diseases Reference Center. The examinations included:

**1. A phonation assessment** performed by a speech therapist blinded to clinical data. This assessment included: a) a Glatzel mirror test for nasal air emission, responsible for hypernasality; b) a vocal quality evaluation (hypernasality, vocal strength, hoarseness) and a phonation evaluation as per the Borel-Maisonny classification [25,26]:

- Ph1: normal phonation
- Ph1/2: occasional nasal air emission (NAE); good intelligibility
- Ph2B: constant but non-audible NAE; good intelligibility
- Ph2/1: constant and audible NAE; improvement on effort

- Ph2: constant and audible NAE; no improvement on effort
- Ph2M: constant NAE hampering intelligibility or with synkinesis and/or forcing
- Ph2/3 or 3/2 (depending on the predominant mode): constant NAE; occasional compensatory mechanisms (glottal stops, pharyngeal friction); poor intelligibility
- Ph 3: constant compensatory mechanisms; no intelligibility

The phonation assessment enabled the classification of phonatory impairment into three groups as follows.

Mild: no NAE on Glatzel mirror test, normal voice, Borel-Maisonny phonation 1/2

Moderate: NAE on Glatzel mirror test, abnormal voice, Borel-Maisonny phonation 2b

Severe: NAE on Glatzel mirror test, abnormal voice, Borel-Maisonny phonation 2m, 2/3 or 3

**2. A morphological assessment** performed by an orthodontist to analyze any chin projection or dentofacial defects and note malocclusion according to Angle's classification. This clinical assessment permitted a classification of orthodontic abnormalities into 3 groups, i.e., minor/absent, moderate or severe. Thereafter, the moderate and severe orthodontic abnormality groups were pooled for further analyses as only one patient fell within the latter.

Furthermore, neutral portrait and profile photographs were taken the day of the examination, for independent, morphological analyses by two female assessors (a pediatrician and a maxillofacial surgeon) blinded to all neonatal and surgical data. They subjectively classified esthetic results as good, moderate or bad with the possibility of a shared consensus judgment in cases of disagreement. Maxillomandibular lateral and frontal teleradiographs were taken and analyzed in another work.

3. **An assessment of generic and specific (vocal & oral) QoL**. Responses were collected during psychologist-led semi-directive interviews. Life traumas that may have modified QoL for the patient (death of a close family member, parental separation, etc.) were also identified.

The four following questionnaires were used:

**KIDSCREEN-52: generic QoL**

The adolescent version of KIDSCREEN-52 was conceived for teens aged 12 to 18 years who may be healthy, chronically ill or socioeconomically disadvantaged. The KIDSCREEN questionnaires have been translated into 38 languages. Numerous European data are available for them, particularly control group results that supplement general population results obtained during the standardization of the instrument [27]. KIDSCREEN-52 is the complete version, comprising 52 items. Responses are chosen from a 5-point scale ranging from "never / not at all" to "always / extremely." The KIDSCREEN-52 provides no global score. Its results are expressed for each of ten dimensions: “physical well-being,” “psychological well-being,” “moods & emotions,” “self-perception,” “autonomy,” “parent relations & home life,” “financial resources,” “social support & peers,” “school environment,” “social acceptance (bullying).” The results from the adolescents in the present series were compared first to the T-score mean of 50 established in the general population used for KIDSCREEN validation, and second to the weighted mean of control subjects from different studies in which the KIDSCREEN-52 was used to evaluate children with disease. These latter values were reported in a meta-analysis [28]. Of the cited studies, we retained only those wherein the complete instrument was used and the subjects were aged ≥12 years [29-35].

**Multiscore Depression Inventory for Children**

The Multiscore Depression Inventory for Children (MDI-C) is a 15 to 20-minute self-report instrument for measuring depression and its features in children aged 8 to 17 years. Its French adaptation was used here. The MDI-C has high test-retest reliability, good internal consistency and satisfactory concurrent validity with the Revised Children's Manifest Anxiety Scale [36]. It comprises 79, short, true/false items worded in such a way as to be easily understood by children. Its total score ranges from 0 to 79 and measures the severity of depression symptoms across 8 subscales: “anxiety,” “self-esteem,” “sad mood,” “instrumental helplessness,” “social introversion,” “low energy,” “pessimism” and “defiance”. The instrument's raw scores are standardized with distinct profiles for sex and age groups (8–10, 11–13, 14–17 years). For each of the subscales and the global score, there

are three levels of symptomatology. Global scores from 56 to 65, from 66 to 75 and above 75 indicate respectively mild, moderate and severe depression.

**Child Oral Health Impact Profile: oral QoL**

The Child Oral Health Impact Profile (COHIP) is a questionnaire designed specifically to assess the impact of orofacial abnormalities on QoL. It was first validated in the United States and Canada and thereafter in numerous countries. The full COHIP comprises 34 items but a short-form 19-item version of it (COHIP-SF19) was developed by the instrument's authors for subjects aged 7 to 19 years [37]. The short and long versions show good equivalence. The COHIP-SF19 is expressed as a global score, and oral, functional, socio emotional sub-scores. The initial scoring was reversed (never=0 to almost all of the time=4) as it is done currently by the authors of the COHIP-SF19 [38]. Thus, the higher the score, the lower the oral QoL. The results derived from our subjects were compared to those of other studies that employed the COHIP-SF19, with score conversion when necessary. Of these, five reported global results from children of the general population, aged similarly to ours, and were thus considered as controls [37, 39-42]. No studies have been published using the COHIP in children with PRS. We compared our results to those of four series of children with craniofacial conditions [37, 43].

**The Voice Handicap Index: vocal QoL**

The Voice Handicap Index (VHI) is a QoL questionnaire exploring the physical, functional or emotional impact of voice disorders regardless of etiology. The instrument was first validated in English in the United States and thereafter in a range of languages. The original VHI developed by Jacobson et al. counted 30 items. In 2009 a shorter, international, nine-item version called the Voice Handicap Index 9 international (VHI-9i), was derived from it for subjects aged ≥12 years. The VHI and VHI-9i have shown very good correlation. Responses to the nine questions are noted on a scale from 0 (never) to 4 (always) and the total score ranges from 0 to 36 [44]. Scores from 0 to 5, from 6 to 10, from 11 to 16 and from 17 to 36, indicate respectively no, mild, moderate and severe vocal disorders [45, 46]. Those thresholds were used to interpret the VHI-9i results of the present cohort

and compare them to results reported in four other series on adult patients with voice disorders [45,47-49]. Of note, the pathological settings of these other studies were functional or organic dysphonias, settings different from the present cases of velopharyngeal insufficiency.

**Collected clinical data**

- Socioeconomic status as per the French National Institute of Statistics and Economic Studies and geographic origin of the parent(s).
- Birth term and measurements. Apgar score.
- Intrauterine growth restriction (IUGR) was noted when birth weight was below the $10^{th}$ percentile.
- Neonatal functional impairment severity classified as per Couly and modified by Cole [50]. Neonates for whom airway obstruction was treated by prone positioning and suckling difficulties by facilitation means (soft-nipple bottles, vertical positioning, thickened milk, etc.) were classified as grade 1; those for whom the airway obstruction was judged tolerable (PCO2 <50 mm Hg, SaO2 >90% >95% of the time, AHI <10/h if PSG was done) in prone position and without ventilatory support but tube feeding was justified for more than eight days were classified grade 2; and those for whom airway obstruction necessitated an intervention (intubation, nasopharyngeal airway, non-invasive ventilation or tracheostomy) were classified grade 3. In Paris and between 01 July 1997 and 01 July 2007 (period during which the study subjects were neonates), tracheostomy was the preferred technique for severe cases.
- Cleft palate width, categorized as complete (or large), incomplete (or narrow) or soft-palate.
- Degree of neonatal retrognathia measured clinically as the distance between the two alveolar ridges in the awake, calm baby, cradled in a semi-seated position (45°; holding the back and neck) by the examiner. Measurements were categorized as minor (inferior alveolar ridge <5 mm from superior alveolar ridge), moderate (5–9 mm) or major (≥10 mm).
- Palate surgery: 1 or 2 stage primary surgery.

- Fistula sequelae.
- Secondary pharyngoplasty for rhinolalia resistant to speech therapy.
- Final diagnosis: Isolated PRS; PRS within a collagenopathy; PRS associated with other malformations without cognitive disability.
- Severe congenital myopia >10 diopters and/or retinal detachment.
- Hearing deficit treated with hearing aids.

**Statistical analysis**

All calculations were done with SAS for Windows (v 9.4; SAS Institute Inc). Statistical significance was set at $p<0.05$. No adjustments for multiplicity were done. Descriptive data analyses were conducted depending on the nature of the considered criterion. For quantitative data, this included the number of observed (and missing, if any) values, mean and standard deviation (SD), median and first and third quartiles, and minimums and maximums. For qualitative data, this included the number of observed (and missing, if any) values and the number and percentage of patients per class. Generalized linear models were used to identify prognostic factors and/or current explicative factors. Univariate comparisons between groups were carried out considering the chi-square test, the Fisher exact test or the Mann-Whitney test depending on the nature of the studied criterion. One sample t-tests and/or signed-rank tests were considered for comparisons with the literature data. Finally, agreement between the assessment of patient photographs and the severity of the facial morphological abnormalities as determined under orthodontic examination was evaluated by the weighted kappa.

**RESULTS**

**General patient characteristics**

There were 101 patients compatible with the inclusion criteria. Of them, 27 were excluded. This included 20 families lost to follow-up and seven who did not wish to participate (three for distance issues and four for inability or non-desire to participate). The remaining 74 patients' families did agree to enroll their adolescents in the study. Of these, one patient was unable to undergo the complete

speech evaluation and another was retroactively re-qualified as a case of isolated cleft palate. Thus, the present study counted 72 cases.

The 72 (38 females, 34 males) included patients were aged between 12 and 18 years (mean: 14.4 years (SD: 1.8 years), median: 14 years). There were 59 (82%) cases of isolated PRS, 9 of Stickler syndrome and 4 of moderate bone malformation not related to a collagen gene defect (2 well-tolerated, molecularly non-explored epiphyseal dysplasias, 1 ossicle abnormality and 1 abnormality affecting the nasal bones). These 13 latter cases were grouped and labeled as "non-isolated PRS" for the purposes of this study. Eight of the nine Stickler syndrome cases had severe myopia (>10 diopters) and two deafness treated with hearing aids. Dominant inheritance was present in 10% of isolated PRS cases and 38% of non-isolated PRS cases.

The socioeconomic distribution of the patients' families reflected the general Paris region population, which has a larger proportion (42%) of managerial/executive and intellectual professions than the general French population (26.5%, corrected for working-age status of the families of the adolescents in the study). Similarly, the proportion of patients with at least one parent of foreign origin (33%) was similar to that of the general population of parents of children aged 11 to 18 years in the Île-de-France administrative region [51].

**Neonatal phenotype**

Globally, the patients were born full-term (mean weeks of amenorrhea (WA)=39.1; SD=1.4) at normal weight (mean birth weight=3303 g, SD=532 g). The rates of prematurity (4.2%) and IUGR (11%) were similar to those of the general population [52,53]. Mean Apgar scores were 9.1 (SD=2.1) at one minute and 9.7 (SD=1.0) at five minutes. At birth, 40% of the babies were transferred to neonatal intensive care or a specialized pediatric unit. By definition, all included patients were born with at least posterior cleft palate, i.e., 61 (85%) with a large or complete cleft palate, 6 (8%) with a narrow or incomplete cleft palate and 5 (7%) with soft palate cleft. Concerning retrognathia, 22 (31%) cases were classified as major, 31 (43%) moderate and 19 (26%) minor.

Functional impairment severity during the first weeks of life was grade 1 for 26 (36%) cases, grade 2 for 33 (46%) and grade 3 for 13 (18%) cases. Tracheostomy was required for 9 of the 13 grade-3 cases (12.5% of the series). There were 17 (25%) infants who required enteral nutrition via a nasogastric tube or gastrostomy for ≥6 months, another 24 (35%) who needed enteral nutrition via a nasogastric tube for <6 months, and 27 (40%) who were able to bottle feed (data missing for four cases). None were able to be breastfeed.

Clinically, with the exception of a higher functional impairment severity grade in the non-isolated PRS group compared to the isolated PRS group (p=0.016), there were no statistically significant differences between the above early infancy data, be it in terms of isolated or non-isolated PRS (Table I), sex, or considered age groups (12–14 and 15–18 years; data not shown).

**Surgical itinerary**

A one-stage surgery for CP repair was used in 57 (79%) cases. Specifically, 40 infants underwent uranostaphylorrhaphy at Necker Hospital and 17 intravelar veloplasty with closure of the hard palate in one-stage surgery at Trousseau Hospital. The remaining 15 (21%) infants underwent intravelar veloplasty with closure of the hard palate in two interventions at the latter hospital. In each hospital, nearly all surgeries were performed by a single surgeon. Follow-up surgery was necessary in 13 (18%) cases for fistula repair. PRS type, cleft width, neonatal functional impairment severity grade, and surgery type were not found to be risk factors for residual fistula. A "center" effect was however detected with a significantly higher fistula rate among infants who underwent surgery at Trousseau Hospital (OR=12.9, 95% CI [2.7, 83.7]). Intravelar veloplasty with closure of the hard palate had a clearly higher rate of residual fistula compared to uranostaphylorrhaphy.

Secondary pharyngoplasty was needed between the ages of six and twelve years for 18 (25%) subjects to correct persistent significant rhinolalia. PRS type, cleft width, neonatal functional impairment severity grade, and surgery type were not found to be risk factors for secondary pharyngoplasty (p>0.05 for all factors).

**Current phonation**

Speech assessments were completed for 70 of the 72 adolescents included in the study. Phonatory impairment was absent in 23 (33%) patients, mild in 19 (27%), moderate in 28 (40%) and severe in none. Nasal air emission or hypernasality, as determined by a Glatzel mirror test and Borel-Maisonny classification, was the most frequently encountered sequela (present in 61 cases). The quality of phonation of the adolescents who had previously undergone secondary pharyngoplasty was identical to that of adolescents who had not. However, the former tended to have lower quality vocal projection and inferior vocal strength compared to the latter. Phonatory assessment results are summarized in Table II.

In multivariate logistic regression considering PRS type, cleft size, neonatal degree of retrognathia, neonatal functional impairment severity, surgery type, center and socioeconomic status (which may influence the quality of speech therapy management), only non-isolated PRS appeared to be indicative of good phonation at adolescence. Given the counterintuitive nature of that finding, two different analyses were carried out, both providing the same result: In the first, the 18 adolescents with a history of pharyngoplasty were included in the severe phonatory impairment group (OR=4.4, 95% CI [1.3, 16.9]), and in the second, the presence or absence of secondary pharyngoplasty was added as an adjustment factor (OR=4.0, 95% CI [1.1, 17.0]).

These results suggest that two-thirds of newborns with PRS may retain low or moderate phonation difficulties but do not yield determinants for them.

**Current morphology**

The portrait and profile photographs were interpretable for all of the adolescents except one. As subjectively judged by two of the team's physicians, 35 (49%) of the adolescents had harmonious faces (good esthetic result), 26 (37%) mildly disharmonious faces with a somewhat receded chin (moderate esthetic result), and 10 (14%) sufficiently disharmonious faces (bad esthetic result: significantly receded chin, cervico-chin angulation defect, etc.) to justify a suggestion for genioplasty.

The portrait and profile photographs of the ten adolescents (7 males) judged disharmonious are presented in Figure 1. Only one female subject had undergone a condyloplasty before the study. She was subjectively (without knowledge of the previous surgery) placed in the moderate results group.

Of the 67 adolescents who had a complete orthodontic assessment, 35 (52%) were judged as having a good orthodontic state and 32 (48%) as having a moderate orthodontic state. None had a bad state (or severe abnormalities). More precisely, 45% of the subjects had dentofacial disharmony, 31% an insufficiently projected mandible, 45% a narrow mandible and 39% a narrow maxilla. The orthodontic assessment in the present study was clinical; teleradiography results were the subject of another work. The results of the subjective esthetic assessment and those of the orthodontic assessment were not in total agreement (weighted Kappa=-0.006 95% CI [-0.226, 0.213]).

In a multivariate logistic regression analysis considering sex, PRS type (isolated or not), cleft size (large or not), degree of neonatal retrognathia (minor, moderate or major), neonatal functional impairment severity (grade 1, 2 or 3) and surgery type (1 or 2-stage), only this latter was identified as an early prognostic factor (p=0.038) of esthetic results at adolescence. Thus, correcting for other factors, the two-interventions protocol (intravelar veloplasty with postponed closure of the hard palate when CP was large) was 4.7 times more likely to give good morphological results at adolescence than the one-stage intervention (uranostaphylorrhaphy or intravelar veloplasty with concomitant hard palate closure) (OR-associated 95% CI [1.3, 20.7]). Interestingly, the esthetic results of cases with Stickler syndrome were not different from those of the other cases. The better esthetic results conferred by the two-stage protocol did not carry over to the orthodontic results. Indeed, none of the considered factors (PRS type, cleft size, neonatal degree of retrognathia, neonatal functional impairment severity, surgery type) were found to have a statistically significant prognostic value for that endpoint.

Neither neonatal retrognathia degree nor obstruction severity degree was predictive of less-satisfactory esthetic results in the present series. Only the two-stage surgical protocol, the objective

of which is to avoid maxillary growth defects, appeared to have a role in improving esthetic results at adolescence.

**Generic QoL**

The results of the KIDSCREEN questionnaire suggested that overall, the adolescents in the study had a good generic QoL. In both parametric and non-parametric analyses, none of the QoL score results significantly differed from the instruments reference score of 50, except for the "moods & emotions" and "autonomy" dimensions, which were respectively higher and lower. For the 8 other dimensions, most of the results were insignificantly inferior to 50. The comparison of the results from our series to those of the control group extracted from the 2019 meta-analysis by Silva et al. showed a less favorable tendency with significant differences for the dimensions "physical well-being," "autonomy," "financial resources," "social support & peers," and "school environment." However, when only isolated PRS cases were considered, only the dimensions "physical well-being" and "financial resources" were concerned by this statistical inferiority. The results were less favorable for adolescents with non-isolated PRS, whose scores for the instrument's ten dimensions ranged from one to six points less than those of adolescents with isolated PRS. (Table III).

**Depression**

The mean responses to the MDI-C instrument showed that severe depression was not present in the total, isolated PRS or non-isolated PRS populations of the study. As a reminder, mild moderate and severe depression are indicated by MDI-C scores of 56 to 65, 66 to 75, and >75 respectively. The mean total score was 47.6 ± 10 for all subjects. Sub-group scores were: 46.9 ± 9.7 for the isolated PRS subjects; 52.2 ± 11.3 for the non-isolated PRS subjects; 47 ± 8.5 for females; 48 ± 11.8 for males; 50.7 ± 11.5 for subjects aged 12–14 years; and 46 ± 8.5 for those aged 15–18 years. At the individual level, mild depression was present in eleven adolescents (scores from 56 to 62) and moderate depression in three (scores of 66, 67 and 68). There were no cases of severe depression. A total 19% of the series had symptoms of depression but 0% had severe depression. These findings compare favorably to the general population, wherein rates for severe depression range from 4–5% and those

for depressive mood, or symptoms of depression reach 30%, especially during adolescence [54,55]. Considering the instruments subscales in decreasing order of the number of study subjects reaching the threshold score of 56, "anxiety" was the most frequent symptom (26.7% of subjects) followed by "self-esteem" (25.7%) and "instrumental helplessness" (25.3%). "Pessimism" and "defiance" were the least-frequent symptoms.

**Oral-specific quality of life**

The mean global score for the COHIP-SF19 was 17.5 (SD=8.9). Oral QoL was better in subjects with isolated PRS (mean=16.1, SD=7.3) than it was in subjects with non-isolated PRS (mean=24.2, SD=12.5). The COHIP-SF19 results of the present study were compared to those of the Australian study by Agnew et al. on 222 seven to eighteen-year-old children with orofacial clefts or velopharyngeal insufficiency [43]. In that Australian work, mean COHIP-SF19 scores were 23.5 (SD=12.2) in 45 children with cleft palate, 25.6 (SD=13.9) in 28 children with velopharyngeal insufficiency, and 28.6 in 36 children with bilateral cleft lip and palate. Broder et al. reported a mean COHIP-SF19 score of 22.3 (SD=11.4) in 839 seven to eighteen-year-old American children with craniofacial conditions [37]. The weighted mean of the scores of subjects with craniofacial malformations and the same age range as the present series was 25.7 and that of the control group was 15.4.

The global COHIP-SF19 scores of the adolescents with isolated PRS in the present work were comparable to those of control cases and significantly better than those of children affected by craniofacial malformations. The sub-scores of the COHIP dimensions "oral health" and "social-emotional well-being" of the isolated PRS cases were similar to those of controls, but the sub-scores of the former for the dimension "functional well-being" were discretely worse than those of the latter. The oral-specific QoL for the adolescents with non-isolated PRS in our series was significantly worse than that of the control cases and close to that of children affected by craniofacial malformations (Table IV).

**Vocal-specific quality of life**

For the present series of 72 adolescents, the mean of the VHI-9i results was 7.5 (SD=5.4; median=6.5), i.e., a "mild vocal disorder" as per the scale established by the instrument's authors. The vocal QoL of adolescents with isolated PRS was better than that of adolescents with non-isolated PRS in all three VHI-9i dimensions, even if the type of PRS was not identified as a significant factor in the multivariate analysis (Table V). No differences were observed between the sexes or age groups. Interestingly, the evaluation by the speech therapist had pointed to a higher incidence of phonatory impairment in the isolated PRS cases, in contradiction thus with the results of the VHI-9i. This finding may suggest that adolescents with non-isolated PRS perceive their own vocal disorders as being worse than they objectively are.

The VHI-9i responses from the present series indicate a better vocal QoL than those reported in the literature do for patients with voice-affecting pathologies (Table VI) [45, 46, 48, 56]. It is interesting—and logical—to note that the adolescents assessed by the speech therapist as having no phonation impairment had a mean total VHI-9i score less than six (5.8 ± 4.7), indicating a normal voice, whereas those assessed with low or moderate impairment were above that threshold (7.9 ± 5.1) indicating a mild phonation disorder.

**Early risk factors and current determinants of generic and specific quality of life in cognitively unimpaired adolescents with Pierre Robin sequence. Results of multivariate regression analysis:**

Generic QoL. KIDSCREEN results can only be considered dimension by dimension. For the "physical well-being" dimension, non-isolated PRS was an early risk factor of reduced QoL, but severe neonatal anatomical malformations (retrognathia and CP size) or functional impairments (gravity grades) were not. Thus, all other things being equal, that KIDSCREEN dimension is significantly worse in non-isolated compared to isolated PRS patients, with a difference of 6.3 points between the two groups (95% CI [-11.4, -1.3]).

Among the studied current determinants, i.e., esthetic results, orthodontic state, phonatory sequelae, traumatic life events, socioeconomic status, age, sex, VHI-9i score and COHIP-SF 19 score, only the results of this latter determined QoL for the "physical well-being" dimension. In other words, all other adjustment factors being equal, as oral QoL improved, so did generic QoL in the "physical well-being" dimension.

For the "self-perception" dimension, neither PRS type nor neonatal anatomical data nor functional impairment severity were identified as early risk factors. Poor oral QoL (COHIP), female sex and 15–18 years of age were identified as significant negative current determinants. In other words, and all other things being equal, as COHIP QoL improved, so did generic QoL in the "self-perception" dimension. Self-perception was better in the subjects ages 12–14 years than it was in those aged 15–18 years, with a difference of -5.9 points (15–18 minus 12–14 years; 95% CI [-9.7, -2.2]), and better in males than it was in females, with a difference of more than 5 points (males minus females; 95% CI [1.5, 9.0]).

These calculations were done for six KIDSCREEN dimensions (Table VII). Therein, 2 dimensions “physical well-being” and “parent relations & home life” are affected by PRS type. All six of the dimensions were affected by the COHIP score, which tests some of the same aspects. Female and older adolescents may be more sensitive to differences and thus more susceptible to altered self-perception. To summarize, in the present study, generic QoL in cognitively unimpaired adolescents with PRS was mainly affected by the presence or absence of an associated malformation and by the oral comfort of the adolescents as assessed by the COHIP questionnaire.

**Depression scale (MDI-C).** Multivariate regression analysis considering all factors that may affect depression symptoms (i.e., esthetic result, orthodontic morphology, phonatory difficulties, age group, sex, socioeconomic status, traumatic life events, poor oral or vocal QoL), only the COHIP score was identified as a significant determinant ($p < 0.0001$) and socioeconomic status as a weakly significant

determinant (p 0.05) of that endpoint. In other words, as oral QoL and socioeconomic status fall, depression scores rise.

**Oral-specific QoL (COHIP-SF 19).** Multivariate analysis identified only PRS type as an early risk factor for poor oral QoL (p=0.006). Specifically, the estimated adjusted mean of the non-isolated PRS group was 7.9 points higher (worse status) than that of the isolated PRS group (non-isolated minus isolated; 95% CI [2.4; 13.3]). As expected, among the current determinants, good orthodontic results were correlated with better oral QoL. Thus, all other considered adjustment factors being equal, oral QoL was significantly lower in patients with orthodontically assessed moderate to severe facial abnormalities compared to patients with only minor or no abnormalities (difference of 5.1 points (moderate to severe minus minor or no abnormalities); 95% CI [0.7; 9.5]).

**Vocal-specific QoL (VHI-9).** No considered early factors (i.e., cleft size, initial severity, PRS type, surgery type, secondary pharyngoplasty status) were shown to affect long-term vocal QoL. As expected, vocal QoL was better in adolescents without phonatory difficulties (median=5.0, Q1-Q3=2.0-9.0, n=23) than it was in those with (median=7.0, Q1-Q3=4.0-12.0, n=47) but not to the point of significance for the global score (p=0.098). The "functional" dimension of the VHI-9i did however differ significantly for those two groups (respectively: medians=2.0 and 4.0, Q1-Q3s=1.0-4.0 and 2.0-5.0)

## DISCUSSION

We present here an analysis of the current situation for 91% of the now-adolescents who, at birth, were treated for Pierre Robin sequence in two tertiary hospitals (merged today) in Paris, France. Our study benefits from a high participation rate among the subjects, who were neonates at a time when follow-up was shorter and less strict than it is today.

Overall, our results show that adolescents who were born with PRS but do not suffer from cognitive impairment have, on average, a normal quality of life. We confirm that children with malformations that are not visible have less difficulties regarding their self-esteem and mood than those with visible

craniofacial malformations or scars [14]. Nevertheless, in more detail, the comparison of our series to a pooled series of control patients of the same age showed that the generic QoL of the former is slightly worse than that of the latter in dimensions regarding physical health and relations to others. We showed that having non-isolated PRS was the main factor reducing generic QoL for our adolescents. Dimensions evaluating self-confidence ("self-perception," "autonomy") and social relations ("parent relations & home life," "social support & peers") were affected in adolescents for whom the medical issue remained present (non-isolated PRS). The "self-perception" and "social support & peers" dimensions reflected best what adolescents express in interviews with psychologists, i.e., that they have been and/or are targets of mockery from their fellow students. Also "anxiety" and “self-esteem" were the most frequently affected depression aspects in the MDI-C dimensions.

Contrary to our initial hypothesis, we found that neither facial esthetic nor phonatory sequelae directly affected generic QoL in our adolescents. These findings may reflect the perception of these sequelae as minor by the patients whereas professionals noted them. It may illustrate a good capacity for resilience, surely the result of good medical outcomes and pertinent familial and medical support. That capacity for resilience may also be reflected in the KIDSCREEN "moods & emotions" dimension, in which our adolescents scored higher than the norm.

However, more attention needs to be focused on PRS cases with associated malformations (Stickler or others). This remains true for patients with no cognitive disability or grade retention/schooling delay, as potential suffering in this population may go undetected. We feel that psychological support through childhood and adolescence is important for these patients.

Our results are coherent with those reported by Basart et al. in 2017 [16], the only other team to have evaluated QoL in adolescents with PRS. However, that team's study involved only 17 adolescents who filled in the Pediatric Quality of Life Inventory over the Internet. Because of the lack of a psychologist to guide and deepen responses, those they gathered may not reflect the full breadth of

their patients' perceptions. Parental presence may also have influenced the responses gathered, reducing their value. Those authors also reported a tendency toward lower values in adolescents with non-isolated PRS.

Oral QoL remains an important issue in adolescents with PRS. Indeed, we showed that the generic QoL of our adolescents was well-correlated with their oral QoL, underlining the impact of dental and orthodontic problems on QoL and self confidence in this setting. As in generic QoL, non-isolated PRS was a risk factor for poor oral QoL, even though the objective, professional evaluations of facial morphology, orthodontic state and phonation for the non-isolated PRS patients were not worse than those of isolated PRS patients. Here too, it appears that the simple awareness of having a chronic disease may have a larger impact than do certain objective elements describing current PRS sequelae. The oral QoL results we report here cannot be compared to other series of adolescents with PRS. They can be compared to those of an Australian study [43] on children with various types of clefting, as its authors used the same tool that we did. Their children had poorer oral QoL than ours, but the proportion of subjects with PRS in the Australian study is not known. As we do, those authors underlined the link between oral and generic QoL. This shared observation calls for vigilance as to the management of oral issues in PRS patients.

Although two thirds of the patients in our series retain mild to moderate phonation troubles, their vocal QoL is within the norm, and is higher than those of adults with voice pathologies. It is noteworthy that in our series, children with significant phonatory sequelae had already been operated on. The only determinant for vocal QoL was the intensity of current phonation issues. Our results seem better than but nonetheless go in the same direction as those of authors who specifically investigated effects of velopharyngeal insufficiency (VPI) on QoL with the new VPI Effects on Life Outcomes (VELO) instrument (estimation from the child him/herself and his/her parent(s)) [57, 58]. The VELO is not yet translated nor validated in French. Correlations between VELO results and objective speech assessment by a speech therapist remain controversial [59].

Residual phonation disorders of children with PRS and CP is a major issue, with incidences varying from 13 to 47% across series (interviewer's observations, ages at time of the assessment, specialized examinations by a speech therapist, assessment techniques, voice-correction surgery rate, etc.). Our results confirm this high frequency. Unfortunately, we identified neither early (e.g., PRS type, cleft size, surgery type) nor current (particularly socioeconomic status of the family) risk factors for these phonation disorders. Importantly, the hyperlaxity present in certain patients with Stickler syndrome did not appear to have an effect on velopharyngeal insufficiency. We could not evaluate the quality of any speech therapy our subjects may have had. Interestingly, adolescents who undergo secondary velopharyngeal surgery had final phonation results that were similar to those of adolescents without secondary surgery. We did not collect perioperative data on palatal muscles, the characteristics of which may play a predictive role in later phonation disorders. However, our colleagues from Trousseau hospital did so and found no predictive factors for phonological outcomes [26]. The difficulties we encountered for the prediction of velopharyngeal insufficiency or phonation disorders are shared with other authors. Those who have compared phonatory sequelae in children with PRS to those with isolated cleft palate showed a higher rate of disorders in the former but remained unable to identify determinants therein [23, 26, 60-64]. Recently, Logjes et al. showed that the only determinant for speech sequalae in Robin sequence, as in isolated CP, was the width of the cleft [65]. Differences across these results may be due to variable ways of measuring the type and size of the CP. The standardization of evaluation methods would be of great interest for comparing results from one team to those of another.

Facial growth may be assessed in several ways, including simple clinical observation by an experienced specialist, orthodontic examination or x-rays and angle measurements. In PRS, this aspect is essential for two reasons. The first is a question of pathophysiology. A neonatal retrognathia that finds its origin in bone anatomy should persist more so than one with a functional origin secondary to a defect in fetal oral mobility. The course of mandible growth in these children is thus a retroactive diagnostic element. The second is a question of therapy. If the bone anomaly is the

sequence starting point, early mandibular distraction is more justified than if it is not. In our assessments, 13.5% of adolescents were considered candidates for esthetical surgery. This was particularly the case for male adolescents, as the chin plays a role in the perception of virility. However, we found no correlations between the morphological aspects in adolescence and neonatal retrognathia degree, respiratory impairment severity, or PRS type. Thus, from our findings, we are not able to identify infants who will need genioplasty at adolescence. These results suggest that there is no anatomical justification for early mandibular distraction, and, additionally, genioplasty at adolescence is both a simple surgery and free of side effects on dentition.

The only predictor of better facial morphological results at adolescence was the two-stage protocol. However, intravelar veloplasty with closure of the hard palate resulted in a higher rate of residual fistula compared to uranostaphylorrhaphy. In the literature, the frequency of residual fistulas after surgery varies from several percentage points to 36% [26, 60, 62, 63, 66]. These secondary surgeries are frequent enough to merit early parental information.

## CONCLUSION

Morphological or phonatory impairments remain non-negligibly present in adolescents with Pierre Robin sequence, whether isolated or associated with bone or collagen disorders, but do not appear to be directly responsible for alterations to their quality of life. These adolescents show self-confidence and social-relations fragilities, especially those with non-isolated PRS, who find themselves circumscribed within the status of chronic disease. Building upon the past during which the neurological and cognitive sequelae resulting from neonatal airway obstruction were reduced, the medical community must now turn its attention to bettering long-term functional and psychological results for PRS patients by improving therapy protocols and follow-up, notably those affecting the oral aspects of the disease.

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Legend of figure 1

Pictures of the face of the 10 patients considered as disharmonious

Table I. Neonatal characteristics of the 72 patients of our series : comparison between isolated and non-isolated Pierre Robin Sequence

| | **Total n = 72** | **Isolated PRS n = 59** | **Non-isolated PRS n = 13** | **p-value** |
|---|---|---|---|---|
| Term (weeks) Mean (SD) | 39.1 (1.4) | 39.1 (1.4) | 39.5 (1.7) | |
| Birth weight (g) Mean (SD) | 3303 (532) | 3248 (495) | 3550 (637) | |
| Birth length (cm) Mean (SD) | 49.4 (2.4) | 49.4 (2.1) | 49.7 (3.6) | |
| Head circumference (cm) M (SD) | 34.6 (1.6) | 34.4 (1.4) | 35.7 (2.3) | |
| **Cleft palate size** | | | | 0.6757 |
| Velar cleft | 5 | 4 | 1 | |
| Narrow or incomplete | 6 | 6 | | |
| Large or complete | 61 | 49 | 12 | |
| **Neonatal retrognathia severity** | | | | 0.6800 |
| Minor | 19 | 17 | 2 | |
| Mild | 31 | 25 | 6 | |
| Major | 22 | 17 | 5 | |
| **Functional gravity** | | | | **0.0164** |
| 1 | 26 | 22 | 4 | |
| 2 | 33 | 30 | 3 | |
| 3 | 13 | 7 | 6 | |
| **Tracheostomy** | 9 | 6 | 3 | 0.3487 |
| **Secondary Pharyngoplasty** | 18 | 16 | 2 | |
| **Fistula repair** | 13 | 11 | 2 | |

P-value: Chi-Square or Fisher's Exact Test

Table II. Phonation assessment of the patients of the series, with isolated and non-isolated PRS and with and without secondary pharyngoplasty

| | PRS | | | | |
|---|---|---|---|---|---|
| | **Total n = 70 (%)** | **Isolated n = 59 (%)** | **Non-isolated n = 13 (%)** | **No secondary pharyngoplasty n = 53 (%)** | **With secondary Pharyngoplasty n = 17 (%)** |
| **Nasal air emission** (Glatzer mirror) | 43 (61.4) | 39 (68.4) | 4 (30.8) | 32 (60.4) | 11 (64.7) |
| **Vocal quality** | | | | | |
| Reduced Vocal power | 11 (15.7) | 11 (19.3) | 0 | 5 (9.4) | 6 (35.3) |
| Vocal hoarseness | 6 (8.6) | 3 (5.3) | 3 (23.1) | 5 (9.4) | 1 (5.9) |
| Vocal projection defect | 10 (14.3) | 9 (15.8) | 1 (7.7) | 5 (9.4) | 5 (29.4) |
| **Phonation quality** | | | | | |
| Ph1: normal phonation | 25 (35.7) | 17 (29.8) | 8 (61.5) | 19 (35.8) | 6 (35.3) |
| Ph1/2: occasional NAE | 17 (24.3) | 16 (28.1) | 1 (7.7) | 12 (22.6) | 5 (29.4) |
| Ph2B: constant, non audible NAE | 5 (7.1) | 4 (7.0) | 1 (7.7) | 4 (7.5) | 1 (5.9) |
| Ph2/1: constant, audible NAE, improvement on effort | 15 (21.4) | 14 (24.6) | 1 (7.7) | 12 (22.6) | 3 (17.6) |
| Ph2: constant, audible NAE, no improvement on effort | 8 (11.4) | 6 (10.5) | 2 (15.4) | 6 (11.3) | 2 (11.8) |
| PH2M; Ph2/3; Ph3/2; Ph3 | 0 | 0 | 0 | 0 | 0 |
| **Global phonation outcome** | | | | | |
| Good phonation | 23 (32.9) | 16 (28.1) | 7 (53.8) | 17 (32.1) | 6 (35.3) |
| Mild phonation trouble | 19 (27.1) | 17 (29.8) | 2 (15.4) | 14 (26.4) | 5 (29.4) |
| Moderate phonation trouble | 28 (40.0) | 24 (42.1) | 4 (30.8) | 22 (41.5) | 6 (35.3) |
| Severe phonation trouble | 0 | 0 | 0 | 0 | 0 |

Table III. T- scores in the 10 dimensions of the KIDSCREEN for the 72 patients, with isolated PRS and non-isolated PRS.
P1 value : comparison of the whole patients scores and those of - 1st line to value 50 (One sample t-test / Signed-Rank test) ; - 2nd line: to the weighted values of the controls extracted from Silva's meta-analysis, 2019 (One sample t-test / Signed-Rank test). P2 value : comparison of the patients with isolated PRS scores and those of - 1st line to value 50 (One sample t-test / Signed-Rank test) ; - 2nd line: to the weighted values of the controls extracted from Silva's meta-analysis, 2019 (One sample t-test / Signed-Rank test).

| **KIDSCREEN dimensions** | **Isolated PRS n = 59** | **Non-isolated PRS n = 13** | **Total n = 72** | **Controls n=23845** | **P1** | **P2** |
|---|---|---|---|---|---|---|
| **Physical well being** | | | | | 0.148/0.056 **0.0003/0.0001** | 0.795 / 0.377 **0.016 / 0.008** |
| Mean (SD) | 49.74 (7.73) | 43.56 (7.45) | 48.62 (7.99) | 52.2 | | |
| Median (Min – Max) | 49.63 (34.65-73.20) | 42.53 (34.65-59.36) | 47.08 (34.65-73.20) | | | |
| | | | | | | |
| **Psychological well being** | | | | | 0.790/0.419 0.589/0.419 | 0.747 / 0.794 0.940 / 0.794 |
| Mean (SD) | 50.38 (8.94) | 46.73 (8.51) | 49.72 (8.92) | 50.3 | | |
| Median (Min-Max) | 49.34 (32.80-68.49) | 43.25 35.50-61.55) | 47.12 (32.80-68.49) | | | |
| | | | | | | |
| **Moods and emotions** | | | | | **0.001/0.002 0.001/0.002** | **0.0009 / 0.0007 0.0009 / 0.0007** |
| Mean (SD) | 54.40 (9.71) | 50.46 (6.89) | 53.69 (9.35) | 50 | | |
| Median (Min-Max) | 54.02 (31.42-70.91) | 51.34 (38.86-62.06) | 54.02 (31.42-70.91) | | | |
| | | | | | | |
| **Self perception** | | | | | 0.821/0.435 0.616/0.916 | 0.296 / 0.988 0.198 / 0.402 |
| Mean (SD) | 51.19 (8.67) | 45.88 (7.07) | 50.23 (8.61) | 49.7 | | |
| Median (Min-Max) | 49.76 (34.89-69.78) | 44.58 (31.24-55.38) | 49.76 (31.24-69.78) | | | |
| | | | | | | |
| **Autonomy** | | | | | **0.031/0.013 0.023/0.005** | 0.278/0.115 0.193/0.057 |
| Mean (SD) | 48.63 (9.63) | 42.90 (9.25) | 47.59 (9.76) | 50.3 | | |
| Median (Min-Max) | 46.85 (29.16-68.75) | 40.54 (23.05-60.52) | 46.01(23.05-68.75) | | | |
| | | | | | | |
| **Parents relation and home life** | | | | | 0.241/0.271 0.078/0.078 | 0.728/0.731 0.346/0.301 |
| Mean (SD) | 49.55 (9.97) | (12.25) | 48.56 ((10.53) | 50.8 | | |
| Median (Min-Max) | 49.50 (30.18-65.87) | 41.10 (23.19-65.87) | 46.61 (23.19-65.87) | | | |
| | | | | | | |
| **Financial resources** | | | | | 0.339/0.636 **0.009 / 0.02** | 0.446 / 0.676 **0.021 / 0.047** |
| Mean (SD) | 49.01(9.89) | 48.08 (11.86) | 48.84 (10.19) | 52.1 | | |
| Median (Min-Max) | 49.28 (23.24-62.86) | 49.28 (23.24-62.86) | 49.28 (23.24-62.86) | | | |
| | | | | | | |
| **Social support and peers** | | | | | 0.142/0.056 0.016/**0.006** | 0.579 / 0.28 0.151 / 0.081 |
| Mean (SD) | 49.19(11.19) | 43.07(8.43) | 48.08(10.95) | 51.3 | | |
| Median (Min-Max) | 46.66 [27.22-71.46] | 42.20 (29.19-58.14) | 45.08 [27.22-71.46 | | | |
| | | | | | | |
| **Social acceptance** | | | | | 0.347/0.129 0.057/**0.011** | 0.676/0.41 0.184 /0.076 |
| Mean (SD) | 49.53 (8.56) | 46.66 (10.09) | 49.01 (8.85) | 51 | | |
| Median (Min-Max) | 48.61 (32.25-73.80) | 45.34 (32.25-73.80) | 48.61 (32.25-73.80) | | | |
| | | | | | | |
| **School environment** | | | | 51 | 0.5035/0.181 0.698/0.826 | 0.128 /0.055 0.605/0.508 |
| Mean (SD) | (7.59) | (9.23) | 50.64 (8.07) | | | |
| Median (Min-Max) | 48.07 [31.08-58.85] | 48.07 (27.15-58.85) | 48.07 (27.15-58.85) | | | |

Table IV. Results of the Child Oral Health Impact Profil-short form in the whole group, the isolated PRS and non-isolated PRS, controls and other children with craniofacial conditions

| | Total | Isolated PRS | Non-isolated PRS | Controls | Craniofacial conditions |
|---|---|---|---|---|---|
| n | 72 | 59 | 13 | 1883 (5 series) | 952 (4 series) |
| COHIP-SF 19 global score | 17,5 +/-8,9 | 16,1 +/-7,3 | 24,2 +/-12,5 | 15.4 | 25.7 |
| Oral Health | 5,2 +/-3,1 | 4,8 +/-2,6 | 7 +/-4,2 | 5.3 | 7.5 |
| Functional well-being | 3,2 +/-2,6 | 2,8 +/-2,2 | 4,7 +/-3,7 | 1.9 | 4.3 |
| Socio-emotional well-being | 9,2 +/-5,8 | 8,4 +/-5,2 | 12,5 +/-7,2 | 9.1 | 14.9 |

Table V. Voice Handicap Index -9i of the patients of our series with isolated or non-isolated PRS

| | **Total** n=72 | **Isolated SPR** n=59 | **Non-isolated SPR** n=13 |
|---|---|---|---|
| **Global Score Mean (SD)** | 7.5 (5.4) | 6.8 (5.1) | 10.8 (5.7) |
| Functional subscale M (SD) | 3.8 (2.7) | 3.4 (2.6) | 5.5 (2.7) |
| Physical subscale M (SD) | 2.8 (2.7) | 2.5 (2.7) | 4.0 (2.7) |
| Emotional subscale M (SD) | 0.9 (1.7) | 0.8 (1.6) | 1.2 (2.2) |

Table VI. Voice Handicap Index -9i of patients with other troubles

| VHI-9i | Functional dysphonia | Any voice pathologies | Vocal fold nodules PVU | Vocal fold nodules NPVU | Vocal fold polyps |
|---|---|---|---|---|---|
| | n = 26 | n = 100 | n = 24 | n = 13 | n = 61 |
| Global Score Mean (SD) | 15.6 (6.7) | 13.93 (7.8) | 16 (7) | 17 (8) | 15 (8) |

*PVU professional voice user*
*NPVU non professional voice user*

Table VII. Significant neonatal risk factors and current determinants resulting from the multivariate regression analysis of the Kidscreen in the whole series

| **Kidscreen dimension** | **Neonatal risk factors** | **Current determinants** |
|---|---|---|
| Physical well-being | NON-isolated PRS | Oral quality of life |
| Psychological well-being | None | Oral quality of life |
| Parents relation and home life | NON-isolated PRS | Oral quality of life |
| Self-perception | None | Oral quality of life; female; 14-18 y |
| Autonomy | None | Oral quality of life |
| Social support and peers | None | Oral quality of life |

# Figures

**Figure 1**

Pictures of the face of the 10 patients considered as disharmonious