A novel assessment tool for clinical care of patients with autoinflammatory disease: juvenile autoinflammatory disease multidimensional assessment report

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ABSTRACT

Objective. *To develop and test a new multidimensional questionnaire for assessment of children with auto-inflammatory disease (AID) such as FMF, PFAPA, HIDS, TRAPS in standard clinical care.*

Methods. *The juvenile auto-inflammatory disease multidimensional assessment report (JAIMAR) includes 16 parent or patient-centered measures and four dimensions that assess functional status, pain, therapeutic compliance and health-related quality of life (physical, social, school, emotional status) with disease outcome. It is proposed for use as both a proxy-report and a patient self-report, with the suggested age range of 8–18 years for use as a self-report.*

Results. *250 children with FMF were included in the study. Total of 179 forms were filled up by parents and patients, and 71 forms were filled up by parents having children less than 8 years. Completing and scoring the JAIMAR can be done in 15 minutes. For the JAIMAR's dimensions, the Cronbach's alpha coefficient for internal consistency was between 0.507-0.998. There was a significant and a positive correlation between the test-retest scale scores (ICC=0.607–0.966). Concerning construct validity, all factors loadings were above 0.30. For the criterion validity, the correlation level between each dimension and the related scale ranged from medium (r=0.329, p<0.0001) to large (r=0.894, p<0.0001). The parents' proxy-reported and children's self-reported data were outstandingly concordant (r=0.770–0.989).*

Conclusion. *The development of the JAIMAR introduces a new and multidimensional approach in paediatric rheumatology practice. It is a new tool for children with auto-inflammatory disease and it may help enhance their quality of care.*

Introduction

Auto-inflammatory diseases (AIDs) cover a group of disorders of the innate immune system. These are characterised by unprovoked recurrent inflammation with elevated acute-phase reactants affecting various tissue (1, 2). There are many effects of auto-inflammatory diseases (*e.g.* pain, fatigue, fear of disease attacks, problems at school – absenteeism, loss of performance, difficulty paying attention, having an attack or fear of having attack at school) that have significant impact on the patients' quality of life. These effects have not been measured with currently available outcome instruments (3-6). Assessment of the functional and social skills, school life and psychological status for the child and family members have not been evaluated in daily routine practice (7-10). Patients' individual experiences may represent key domains of illness that differ from clinicians' views. Therefore, it might be important to assess the patient for all dimensions, both clinically and based on the patients' expressions. The information obtained from the parent and the child may contribute significantly to medical decision-making and to the success of patient care (7, 11). Elsewhere in paediatric rheumatology,

the scientific community did successfully develop a scale in which the patient can complete a self-assessment with quantitative results (7-10, 12).

Piram *et al*. developed and validated an instrument called the Auto-inflammatory Diseases Activity Index (AIDAI) (5, 6). Demirkaya *et al*. recently established international severity score for FMF (ISSF) (13). Medication adherence scale (MASIF) is another instrument which aimed to assess and follow up the adherence to treatment in paediatric FMF patients (14). There are many efforts going on in this field such validation of PedsQL, depression, functional ability indexes (1, 15). An important drawback of existing studies is that a different array of instruments have been used in different surveys, which hampers comparability of findings. Furthermore, most studies have focused on single aspects of disease course, such as remission, functional disability, radiographic damage, or health-related quality of life.

These considerations led us to develop a multidimensional questionnaire for the assessment of children with auto-inflammatory diseases in standard clinical care that incorporates parent/patient-reported outcomes. In this report, we describe the development of the new instrument, the Juvenile Auto-inflammatory Disease Multidimensional Assessment Report (JAIMAR), and provide preliminary evidence of its validity in children with FMF.

Materials and methods

Qualitative part for item generation

Items for questionnare were created based on a comprehensive review of the literature, experts opinions (paediatric rheumatologists who were mainly following the patients with AIDs at least ten years), and comprehensive individual interviews. Interviews were performed in children with FMF, TRAPS, HIDS, or PFAPA and their parents using qualitative research methods. The methodology was described in details in the qualitative study and methods paper (9). Briefly the qualitative research was conducted between March and October 2012. 14 mothers whose children have auto-inflammatory diseases (FMF (n=8), PFAPA (n=4), HIDS (n=1) and TRAPS (n=1)) were enrolled in this study. The interviews were conducted both with the children and their parents. The data were collected using both a demographic data form and a semi-structured interview form. The semi-structured interview form were answered both according to attack and non-attack period. Each interview was transcribed as soon as possible after being completed. The data were analysed by grounded theory and the N Vivo 10 software program (9). At the end of this step, the first questionnare was created and named Juvenile Auto-inflammatory Disease Multidimensional Assessment Report (JAIMAR).

Development of the questionnaire

The first version of the questionnare for the JAIMAR which consists of 22 items, was developed based on the recommendations of national expert panel. For the content validity JAIMAR was assessed by the paediatric rheumatologists to get their perspectives and opinions. The first version of questionnare then was discussed with the international experts on this area (MG, IKP, JF, AR). Then all the items of the final version of JAIMAR were re-evaluated in the Paediatric Rheumatology European Society, AID working party in Ljubjiana-Slovenia 25th September, 2013.

Validation procedures

To validate the JAIMAR, the OMERACT filter for outcome measures in rheumatology was applied (16). In the content validity process, relative importance of each item was discussed, and an item was retained only when there was an agreement that it should be kept in the questionnaire. According to the assessment of the expert views and proposals; 5 items that were calculated under 0.49 in the Lawshe Minimum Content Validity Ratios (CVR) at significance level of α=0.05 were removed from the scale, and 17 items remained (Suppl. Table I). The Content Validity Index (CVI) (CVI=Σ CVR / item number) was calculated for the 17 items that remained after the expert assessment in the CVR, and was used for the assessment of content validity (12, 17).

To ensure face validity, the draft questionnaire was further tested by requesting a convenience sample of 27 children with FMF and their parents to complete the questionnaire, and then to criticise or comment about its design, content, and on whether the readability and comprehensibility of the items was appropriate for the education level and background of the respondents. Based on the parents' and childrens' input, one of the question, was deemed to have poor comprehensibility. It was hence removed from both the parents and child form, leaving 16 items in the scale.

Criterion validity

The criterion validity of JAIMARs' dimensions evalulated by following instruments; Physician global assessment of the disease severity, the Wong-Baker FACES Pain Rating Scale (WBS), The Morisky 4-Item Medication Adherence Scale (MMAS), The Childhood Health Assessment Questionnaire (C-HAQ) and the Pediatric Quality of Life Inventory Generic Core scales (PedsQL) physical subscale, the PedsQL social subscale, the PedsQL school subscale and the PedsQL emotional subcsale and the Child Depression Inventory (CDI) (7,18-21).

Reliability

Chronbach alpha coefficients calculated to evaluate internal reliability of each dimensions/sub-dimensions. To evaluate test-retest reliability all forms were completed by 70 parents and 52 patients with FMF who were admitted to clinics at the study visit and 15 days after the first evaluation.

Reduction of form

The questions were removed from the form, whether Chronbach alpha level increased more than 10%. If the factor load of the item is lower than 0.30 it was deleted from the questionnaire.

After all these steps and tests, JAIMAR consists of 16 items including four dimensions such as functional ability, pain, therapeutic compliance, and health-related quality of life (physical, social, school, and emotional status). Items 1-4, 6, 8-12, 15, and 16 were only descriptive in nature (Appendix 1,

Supplementary Table I. JAIMAR Content Validity.

Dimension	After CVR status	Number of questions	Number of questions after CVR
*Functional ability	Reduced	17	10
*Therapeutic compliance	Reduced	10	7
*Pain	Not changed	1	1
*HRQOL physical status	Not changed	6	6
HRQOL social status	Not changed	5	5
HRQOL school status	Not changed	9	9
HRQOL emotional status	Not changed	20	20
**The factors that trigger an attack	Deleted	12	0
**Side effects of the medicine	Deleted	19	0
**Irregularity on medication use	Deleted	16	0
**The experienced problems associated with school/nursery	Deleted	16	0
**Identification of psychological state	Deleted	28	0
***Presence or absence of attacks	Not changed	1	1
***The current status of the disease	Not changed	1	1
***Experienced an attack in the last four weeks	Not changed	1	1
***The most recent time of attack	Not changed	1	1
***Symptoms related to the disease	Reduced	40	25
***Any attacks within the last one year	Not changed	3	3
***The course of disease	Not changed	1	1
***Medicine use status	Not changed	1	1
***Used medicine	Not changed	1	1
***Effective level of medicine therapy on the disease	Not changed	1	1
***The current activity level of disease	Not changed	1	1
***How he/she feels at the moment	Not changed	1	1
***Level of contentment despite disease	Not changed	1	1

*Four dimensions of the scale.
**The items which were removed from scale in the direction of Content Validity Ratios (CVR).
***Descriptive questions of the scale.

2) and these questions aimed at using patient's follow-up without altering the scale score.

When completed the instrument provides no single combined result, but rather a specified score for each dimension. Low scores reflect favourable outcome for the related dimension. The JAIMAR provided information about recent medical history, attack status, and current health status.

Patient selection and completion of the JAIMAR

The study population included patients with clinically diagnosed FMF according to the Tel-Hashomer or paediatric criteria who were genetically confirmed. Patients admitted to the outpatient clinics of the seven participating centers in Turkey between December 2012 and April 2013 were enrolled in the study consecutively. The study protocol was approved by the Institutional Review Board at Gulhane Military Medical Academy. A parent or legal guardian of each patient who was ≤ 18 years and diagnosed with FMF was asked to complete the parent version of the JAIMAR and the children (if older than 7 years) were asked to independently complete the patient version of the JAIMAR. Written informed consents were obtained from all parents/legal guardians, and also from children who were 8 years and older.

Additional clinical assessment

The gender, date of birth, age at first sypmtom, date of diagnosis, genetic mutations, and the characteristics of the attacks were recorded for each patient. At the each visit, the attending physician rated the overall disease severity by assessing the overall disease course with the aid of a 21-numbered circle VAS (0=no severity; 10=maximum severity). The physician also rated the disease activity by assessing the most recent attack of the patient within the last six months on a 21-numbered circle VAS (0=no activity; 10=maximum activity) (21).

Statistics

Item total correlations, Chronbach alpha values if item deleted and the independent sample's *t*-test between lower and upper group were calculated to evaluate item contributions to scale. Paired sample *t*-test and the intraclass correlation coefficient (ICC) between the test and retest total scores was performed to evaluate reproductibility of form. In the validity analysis, CVR and CVI for content validity were calculated. For criterion validity, Pearson's correlation coefficient was calculated between total scores of relevant instruments and specified for the scale dimensions/sub-dimensions of the JAIMAR. In the assessment of construct validity, the principle component analysis from the exploratory/explanatory factor analysis methods were used and varimax rotation (maximum variability) was performed. To determine equivalance of parent and children form Pearson correlation coefficients were calculated. In the assesstment of data and statistical analysis, SPSS for Windows v. 15.00 (SPSS Inc. Chicago, IL, USA) package programme was used. In the statistical analysis, $p<0.05$ was considered statistically significant.

Results

Patients' characteristics

We evaluated a total of 351 visits (included 70 re-test visit) between December 2012 and April 2013. Forms were collected on 250 patients with FMF from seven different paediatric rheumatology centres from Turkey. Total of 179 forms filled up by parents and patients, and 71 forms completed by parents who have children less than 8 years old. 31 patients were excluded from the study, because of incomplete response or refusal to answer questions.

Demographic data were available for 250 patients. Among the patients, 55.2% were female (n=138), while 44.8% were male (n=112). The mean age was 10.64±4.38 years. The mean age of onset of the disease was 4.28±3.34 years, age of diagnosis was 6.99±3.82 years, and disease duration was 3.69±3.35 years.

Item analysis

The item analysis was performed based on corrected item-total correlation coefficients, Cronbach's alpha value if item deleted, and comparison of item

values between lower-upper groups. Following these analyses, it was decided to remove 3 items in the therapeutic compliance dimension and one item from the HRQOL emotional status from the scale.

Internal consistency

To determine reliability, the Cronbach's alpha internal consistency and test-retest reliability were examined (17). The lowest Cronbach's alpha values occurred in the HRQOL social status on child version (0.507), all other values were higher than 0.677 (Table I). Since all Chronbach's alpha levels, except social status, were over 0.60 these were considered to be sufficient (22, 23). In other words, scale items were consistent with one another. As the HRQOL social status parent version had sufficient reliability according to Cronbach alpha (0.677), in the scale implementation – in terms of the concordance of parent and child forms – the social status in the children's form was not changed.

Test-retest reliability

In 70 patients (70 parents, 52 children) the scale was implemented again15 days after the first application. When examining the ICC value that explains the consistency between the retest results for each dimension, except for the quality of life physical status parent form correlation coefficient (0.474), the other ICC values were found to be between 0.607 and 0.966. A statistically significant and positive correlation found between the parents' and children's forms in other dimensions/subdimensions (Table II). Although the correlation coefficient was low (r=0.474; $p<0.001$) in the quality of life physical subdimension of the parents' form, -in terms of the concordance of parent and child forms- this subdimension of the parents' form remained unchanged.

Factor analysis

In order to explore the factorial structure of the JAIMAR, it was given the lowest and highest factor loadings of all dimensions and total explained variance percentage (Table III). When examining the factor loadings of the dimensions/subdimensions in both the parent and children forms, all factor loadings were above 0.30 and total explained variance values were interpreted as an indicator that relevant concept or structure that were measured well were 47.2% and above (Table III). If the variables have high factor load on a factor, then those variables are considered to have a constructive validity. Although there are different opinions regarding what the value of factor loadings should be, it has been stated that this value should be at least 0.30 (24). In the results of the factor analysis; high score in the the obtained factor loadings for each item and the ability of the items to connect in the dimensions show that the scale has a construct validity.

Table I. Internal consistency analysis in the JAIMAR.

JAIMARs' Dimensions	Parent Chronbach's α	Child Chronbach's α
Functional ability	0.886	0.884
Therapeutic compliance	0.689 (0.716)*	0.637 (0.701)*
HRQOL physical status	0.853	0.828
HRQOL social status	0.677	0.507
HRQOL school status	0.998	0.986
HRQOL emotional status	0.810 (0.868)**	0.898 (0.895)**

*Cronbach's alpha after the removal of Therapeutic compliance dimensions of items 3, 4, and 7 in the item analysis.
**Cronbach's alpha after the removal of Health-related quality of life (HRQOL) emotional status subdimension item 9 in the item analysis.

Criterion validity

The correlations between the appropriate scales for each dimensions of the scale range from the mid-range (*e.g.* r=0.329, $p<0.0001$ for the correlation between HRQOL emotional status and CDI score) to a strong level (*e.g.* r=0.894, $p< 0.0001$ for correlation between the Pain dimension and the WBS score) (Table IV). There are significant correlations between dimensions and standard scales in both the children and the parent forms, which provides criterion validity. However, it was determined that there was not a significant correlation between parents form HRQOL social status and PedsQL social subscale (r=-0.099, p=0.142) (Table IV). There was a significant relationship in the children's form between HRQO social status and PedsQL social subscale (r=-0.503, p=0.000) (Table IV) (23-25). Therefore it was decided that the social status remained in this shape in the parents form in terms of the compliance of the parents' and children's forms in the implementation of the scale. The quality of life scores in the JAIMAR were negatively correlated with the PedsQLscores (Table IV). This is due to the fact that higher scores in the PedsQL are indicative of a good quality of life, while in the JAIMAR lower scores are indicative of a good quality of life.

The JAIMAR is available for both parent and child and the same questions are included in both forms. There are strong/very strong positive and a significant correlation between the parents and children forms in all dimensions (correlation coefficeint (r) values were found between 0.77 and 0.99) (Table V).

Discussion

During the last two decades, the requirement to improve quality of life in patients with chronic illness has become an important topic in health policy. Although disease-related measurement tools are difficult to create, their development and utility in autoinflammatory diseases is even more challenging. This is mainly related to the characteristic features of the diseases included under this category, such as being rare (DIRA, DITRA, MWS, etc.) and often localised to a specific geographic region (FMF, HIDS etc.). Moreover, the irregular disease course with attacks and remissions is quite different from the classical chronic, stable or slowly progressing rheumatic illnesses.

Table II. Test-retest reliability for JAIMAR.

Dimensions of scale	Mean ± SS	t	*p*-value	ICC
Parent (n=70)				
Functional ability	19.20 ± 4.77			0.860
Functional ability test-retest	18.84 ± 4.93	1.162	0.249	*p*<0.001
Therapeutic compliance	5.65 ± 1.86			0.819
Therapeutic compliance test-retest	5.44 ± 1.75	1.399	0.168	*p*<0.001
HRQOL physical	8.14 ± 3.39			0.474
HRQOL physical test-retest	8.59 ± 3.39	1.066	0.290	*p*<0.001
HRQOL social	7.76 ± 3.79			0.881
HRQOL social test-retest	7.73 ± 3.62	0.132	0.896	*p*<0.001
HRQOL school	15.86 ± 12.40			0.966
HRQOL school test-retest	19.60 ± 13.49	8.822	0.000	*p*<0.001
HRQOL emotional	37.76 ± 16.93			0.876
HRQOL emotional test-retest	38.01 ± 16.33	0.259	0.796	*p*<0.001
HRQOL general total	74.51 ± 34.41			0.923
HRQOL general total retest	73.93 ± 32.67	0.370	0.712	*p*<0.001
Child (n=52)				
Functional ability	18.59 ± 4.55			0.738
Functional ability test-retest	17.89 ± 3.71	1.661	0.103	*p*<0.001
Therapeutic compliance	5.88 ± 2.05			0.821
Therapeutic compliance test-retest	5.62 ± 1.90	1.631	0.109	*p*<0.001
HRQOL physical	8.31 ± 3.18			0.607
HRQOL physical test-retest	8.29 ± 3.39	0.047	0.962	*p*<0.001
HRQOL social	5.98 ± 1.78			0.676
HRQOL social test-retest	6.04 ± 2.22	0.250	0.803	*p*<0.001
HRQOL school	12.65 ± 4.21			0.761
HRQOL school test-retest	13.92 ± 4.64	2.807	0.007	*p*<0.001
HRQOL emotional	30.50 ± 10.93			0.773
HRQOL emotional test-retest	31.06 ± 10.42	0.558	0.579	*p*<0.001
HRQOL general total	59.38 ± 18.29			0.820
HRQOL general total retest	59.31 ± 17.99	0.051	0.960	*p*<0.001

We have developed the first tool to assess the quality of life with AID patients. This new, multidimensional questionnaire addresses the parent/patient-reported outcome in children with AID, such as the assessment of functional ability, pain, therapeutic compliance, and health-related quality of life. Instead of the assessment of children's state of health in separate scales for each dimension, JAIMAR accomplishes this aim within a single standardised scale. This questionnaire can assess longitudinally the changes in health status of children with AID during routine clinical follow-up. We showed that JAIMAR is a valid and reliable tool for the assessment of patients with FMF with this study.

The assessment of a child's health status by physicians, parents and children can reveal differences. Patients' subjective experiences about the disease may represent key domains of the disease (7, 26). During the follow up of patient with AIDs to apply multidimensional self-assessment instrument are important not only patient but also physician. Overall patient care can be improved with this holistic approach in this manner. The JAIMAR is proposed for use as both a proxy-report and a patient self-report, with a suggested age range of 8–18 years. The questionnaire format has been found easy to understand and readily answered by parents and patients. The questionnaire is completed before the patient is called into an examining room almost in 15 minutes. Each dimension is scored within itself and scoring is easy and fast.

The JAIMAR was found to be feasible and possess face, content, criterion and construct validity. JAIMAR is considered to have good internal consistency. There was a correlation, ranging from a medium level to a high level between the test-retest scale scores. There is excellent concordance between the parent and children forms of JAIMAR in all dimensions/subdimensions. The accordance between children and parents forms, emphasises that the items in the scale are perceived similarly by both parents and children. So, in cases in which children can not complete the form, the form could be completed by the parents. In our study we showed that JAIMAR scale correctly assess the health status in children with AIDs between the age of 8 and 18 years old who were filled out the form by him/herself and whose forms were filled out by their parents for the age of less than 7 years old. In their study Williams *et al*. have determined that there was consistency between the parent and children forms and emphasised the usefulness and importance of this in the evaluation of the child's health status as a screening test (27).

Auto-inflammatory diseases are a group of diseases characterised by attacks. In this regard it is important to identify the severity of the pain experienced and to determine how the functional skills of a child are affected during these episodes. The therapeutic compliance is important for follow-up and replan treatment. Poor medication compliance, which is commonly encountered among children with chronic and autoinflammatory diseases, can result in higher morbidity and mortality with other undesirable conditions (28). To assess medication compliance, a specialised form might be more useful instead of the frequently used Morisky Medication Adherence Scale. Auto-inflammatory diseases affect the quality of the child's and the family's life (1, 29). Deger *et al.,* in their study on a group of adults, stated that the quality of FMF patient's life is negatively affected, and that depression and anxiety were more frequently observed in FMF patients compared to the control group (30). It has been shown that quality of life, mental health, interac-

tion with family members, self-esteem and school life were negatively affected in patients with MKD (31, 32). In addition to medical treatment, physical and psycho-social attempts should be added in the treatment program of these diseases. Our tool provide the researchers and physicians to evaluate their patients with all these dimensions. Our study has some limitations. While scale questions were being prepared, individual interviews were performed with children who had FMF, PFAPA, TRAPS and HIDS and their parents. The questions were created to assess these autoinflammatory diseases. However, the reliability and validity analysis of scale was completed exclusively on children with FMF and their parents in Turkey. After this successful attempt for the validity and reliability of JAIMAR in patients with FMF, we are planning to validate it in other AIDs including MVK, TRAPS and PFAPA with the international collaborative effort. Children and parents were instructed to complete the questionnaire independently. Nevertheless, as we could not observe any difficulties for all parent-child pairs during the completion of questionnaire, some parents may have assisted their children. The sensitivity of the scale to attack was not analyzed during this study. In future studies, this could be investigated with larger study samples.

Conclusions

In conclusion, we developed a disease-oriented health-quality of life scale that consists of four subdimensions intended for children with auto-inflammatory diseases with JAIMAR and was confirmed to be valid and reliable. The performance of the new tool were tested on FMF patients for the first time.

The development of the JAIMAR introduces a new approach in the practice of paediatric rheumatology. It is a valid and reliable tool for Turkish children with FMF and should help to enhance the quality of care in this group of patients. This tool may be useful in clinical practice, as well as in clinical trials for the assessment of functional ability, pain, therapeutic compliance, and health-related quality of life in children with FMF. Cross-cultural adaptation and further validation studies in the other autoinflammatory diseases is planned in the context of the Eurofever project.

Table III. Construct validity principal component analysis for JAIMAR.

Dimensions of scale (Parent)	Lowest factor load	Highest factor load	Total explained variance %
Functional ability	0.458	0.881	63.335
Therapeutic compliance	0.649	0.824	56.784
HRQOL physical status	0.639	0.861	57.961
HRQOL social status	0.636	0.726	47.222
HRQOL school status	0.752	0.923	75.626
HRQOL emotional status	0.518	0.902	65.228
Dimensions of scale (Child)	**Lowest factor load**	**Highest factor load**	**Total explained variance %**
Functional ability	0.547	0.891	62.471
Therapeutic compliance	0.697	0.801	54.425
HRQOL physical status	0.536	0.852	54.520
HRQOL social status	0.601	0.863	60.102
HRQOL school status	0.443	0.829	50.029
HRQOL emotional status	0.385	0.867	58.748

Table IV. Criterion validity for JAIMAR.

Dimensions	Pearson's correlation coefficient	
	Parent	Child
Functional ability dimension with disease severity score given by the physician	0.390*	0.478*
Pain dimension with WBS	0.894*	0.886*
Therapeutic compliance dimension with MMAS	0.435*	0.396*
HRQOL physical status with CHAQ	0.454*	0.485*
HRQOL physical status with PedsQL physical subscale	-0.605*	-0.725*
HRQOL social status with PedsQL social subscale	-0.099**	-0.503*
HRQOL school status with PedsQL school subscale	-0.536*	-0,745*
HRQOL emotional status with PedsQL emotional subcsale	-0.357*	-0.708*
HRQOL emotional status with CDI	0.329*	0.475*
HRQOL general total with PedsQL general total score	-0.620*	-0.809*

*$p<0.0001$ **$p>0.05$

WBS: Wong-Baker FACES Pain Rating Scale; MMAS: Morisky Medication Adherence Scale; CHAQ: Childhood Health Assessment Questionnaire; PedsQL: Pediatric Quality of Life Inventory Generic Core Scale; CDI: Child Depression Inventory.

Table V. Compliance analysis results between JAIMAR parent and child forms scale.

Dimensions	The correlation of children and their parents' scale dimension scores	
Functional ability	r=0.934	$p<0.001$
Pain	r=0.992	$p<0.001$
Therapeutic compliance	r=0.770	$p<0.001$
HRQOL physical status	r= 0.863	$p<0.001$
HRQOL social status	r=0.780	$p<0.001$
HRQOL school status	r= 0.896	$p<0.001$
HRQOL emotional status	r= 0.883	$p<0.001$
HRQOLgeneral total score	r=0.989	$p<0.001$

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