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Research

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**Patient-reported Outcomes in a Chinese Cohort of Osteogenesis Imperfecta Unveil
Psycho-physical Stratifications Associated with Clinical Manifestations**

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Abstract (310 words)

Background: Osteogenesis imperfecta (OI) is a rare congenital disorder that greatly compromises the quality of bones, inflicting debilitating distress both physically and psychologically to patients and caregivers. Over the decades, much efforts have been channeled towards understanding genetic mechanisms and exploring new treatments. Nonetheless, it has recently become more aware that the patient reported outcomes (PRO) and health status during treatment, healing and rehabilitation, are important basis that facilitates smoother communication, refines interventions strategies and achieves higher quality of life. To date, systematic studies and analyses of PRO in OI patients remain scarce.

Results: Here, harnessing the Patient-Reported Outcomes Measurement Information System (PROMIS), we report a cross-sectional and longitudinal study in a cohort of 90 OI patients from southern China, covering both children and adult age-groups. In the young group where both self and parental surveys were obtained, we identified two clusters of comparable sizes showing different outlooks in physical mobility and emotional experiences. One cluster is more positive about themselves than the other. Remarkably, we found a concordance of 84.7% between self and parental assessments, suggesting the stability of the stratification and validity of the PROMIS instruments. We further found that clinical subtyping, deformity, leg length discrepancy and limited joint mobility were significantly associated with this patient stratification, with the cluster with poorer physical functioning and higher psychological depression showing higher percentage of more severe deformity. Analyses of longitudinal data suggested that patients tend to stay in the same psychological state, in both clusters. Adult patients also showed a continuous spectrum of self-evaluation that matches their clinical manifestations.

Conclusion: By probing deep into the subjective quantitation of patient reported outcomes, our study demonstrates the diverse sociopsychological spectrum among OI patients that matches their objective clinical manifestations, which may serve as the basis for evaluating clinical interventions and help achieve better patient-centric medical practices and health maintenance.

Keywords: Osteogenesis imperfecta, rare disease, psycho-physical, PROMIS, genetic testing, patient stratification, cross-sectional, longitudinal, children, adults

Background

Osteogenesis imperfecta (OI) is a heterogeneous group of inherited skeletal dysplasia and connective tissue disorders with a birth prevalence ranging between 0.3-1.5 per 10,000 births (1, 2). Individuals with OI are characterized with low bone mass and high bone fragility, resulting in susceptibility to long bone deformity, fracture and vertebral compression (3). A wide spectrum of secondary features including blue sclerae, dentinogenesis imperfecta, scoliosis, hearing loss, muscle weakness, ligamentous joint laxity and basilar invagination, were present in certain subsets of patients (1, 4). Most OI patients are heterozygous for dominant mutations on *COL1A1* or *COL1A2*, encoding the main components of extracellular matrix in bone and skin, although their prevalence may slightly differ across different populations (5, 6). To date, genetic analysis has identified more than 19 genes associated with OI, which mainly involve in collagen post-translational modification, bone mineralization or osteoblast differentiation (1, 7-10).

The multitude of genes and unlimited mutation possibilities matches the broad spectrum of clinical severities observed in OI, which range from occasional fractures, dwarfism, to perinatal lethality. Based on clinical and hereditary features, Sillence *et al.* classified OI into four major types: type I (mild with bone fragility and blue sclerae), type II (perinatal lethal), type III (progressing deformity) and type IV (short stature, bone deformity and dentinogenesis imperfecta) (10-12). Till lately, much focus has been placed on establishing the genotype-phenotype association (2, 13, 14), in the hope that the mechanistic aspect of the disease can better inform the diagnostic process and improve treatment outcomes. As such, clinical interventions and scientific research have mainly focused on the orthopedic and pharmacological outcomes of OI patients. Nonetheless, the phenotypes and clinical outcomes are still objective observations, which do not reflect the subjective well-being of OI patients suffering from this lifelong debilitating condition. The diverse range of clinical issues inflicted major physical and psychological distress on OI patients (15-18), which greatly compromise their life quality and cause heavy socioeconomic burdens on their family and caregivers (19, 20).

Quality of life (QoL) is a World Health Organization certified concept that measures the overall physical and mental well-being of an individual (15, 19). Several studies have assessed health related QoL in OI patients and caregivers using the generic instruments, including Short Form Health Survey (SF-36) (15, 16), EQ-5D-5 (17) and

WHOQOL questionnaires (18). Such efforts improved the decision-making and communication between clinicians and patients, and increased patient satisfactions overall.

Nevertheless, the various standards used cause difficulty in cross-study comparisons and interpretation, and many of the studies were focused on adults only (15-17, 21). Almost all of these studies are cross-sectional (21). Longitudinal data, which is highly valuable for such chronic conditions, remain scarce. SF-36 is the most frequently used questionnaire, which only has 36 question items. In the past decade, PROMIS® (Patient-Reported Outcomes Measurement Information System) gained traction for its extensive question bank that totals over 20,000 survey items and covers a wide range of mental and physical issues (22). Carrying on from their earlier initiative (23), a pilot study leveraging the power of PROMIS (24) was conducted on 290 OI patients, 198 of which were adults. They showed that the data averted the least desirable characteristics of flooring and ceiling effects commonly infesting survey studies, hence demonstrating the feasibility and potential of PROMIS in OI. Nonetheless, in addition to a number of issues raised by the authors themselves, including gender disparity and insufficient data for non-white ethnicities, more in-depth analyses remain to be shown. For example, patient stratification in terms of PROMIS, and the connections between such stratification and the clinical and genetic features would help gain more insights into the principal factors impacting the patients' QoL, which holds the potential to benefit OI patients for more precise treatments (25). Assessments by parents and children and their concordance, and longitudinal follow-ups are also lacking. Some of the question items are similar, thus proper de-correlation is needed to bring out the principal underlying patient stratifications.

In this study, we presented a PROMIS dataset of children and adults collected from a Southern Chinese OI cohort recruited by our hospital (HKU-SZH). Systematic analyses based on advanced statistical and machine learning approaches were conducted to unravel the patterns, structures and distributions of various self-assessment domains, identifying groups of patients with similar psycho-physical states. We demonstrated the stability of such diversifications from self and parental assessments, and from longitudinal data. We then explored the connections between such PROMIS patient groups, and the objective genetic and clinical features, to identify the most relevant

131 objective factors explaining the subjective feelings. These patient-centric data,
132 methodological developments and novel findings will enrich the toolboxes for OI
133 research, deepen our understanding of the disease, and benefit the life quality of OI
134 community as we are moving towards a more patient-centric diagnostic and therapeutic
135 approach in the future.

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Methods

Subject recruitment and data collection

Ninety OI patients were recruited from our hospital (HKU-SZH) to participate in the current study since July of 2020, with IRB approval and informed consents. A web-based platform was developed based on the RedCap system (26), by which both clinical data and subjective evaluation data were recorded. The young group (age below 18) were invited to fill in a form with 57 items (20 items related to physical capabilities, including mobility and pain; 37 items related to sociopsychological status, including anxiety, depression, and peer relations) (Additional file 1). Their parents or proxies were invited to fill a form with 49 items, including 16 items in physical capabilities and 33 items in sociopsychological states (Additional file 1). The form was adapted from the item banks of PROMIS (22) and translated into Chinese language. A social worker (Y.Q.) was involved in explaining the questions to pre-school children. Most of the items (except overall pain score, ranging from 0 to 10) were scored from 1 to 5, with 5 being the top positive for mobility and peer relations, and most negative for the other items. The surveys were conducted on the first day of inpatient admission to the hospital before surgical and/or drug treatments. Detailed clinical symptoms, including X-ray images, genetic reports, fracture history, heights, bone mineralization density (BMD), sclera and teeth issues, were documented by a panel of clinicians (M.K.T.T., Y.P.Z., S.J.Y., Z.X.D., J.C.X., K.S.L.). The BMD were measured by the Discovery DXA system (Hologic Inc., Massachusetts) in HKU-SZH. The BMDs at the lumbar region of the spine were used.

Targeted amplicon sequencing

The peripheral bloods of the patients were taken and processed before being sent for targeted amplicon sequencing on a panel of 24 genes associated with OI (DynastyGene, Shanghai). The 24 genes are: *COL1A1*, *COL1A2*, *IFITM5*, *SERPINF1*, *CRTAP*, *P3H1*, *PPIB*, *SERPINH1*, *FKBP10*, *PLOD2*, *BMP1*, *SP7*, *TMEM38B*, *WNT1*, *CREB3L1*, *SPARC*, *FAM46A*, *MBTPS2*, *MESD*, *CCDC134*, *P4HB*, *SEC24D*, *PLS3*, and *LRP5*. The samples were sequenced on the NovaSeq 6000 platform (Illumina Inc.). The raw data (150bp paired-end) were aligned to the human reference sequence GRCh37/hg19 by the BWA aligner (version 0.7.17-r1188) (27) with default parameters. The GATK toolkit (version 4.0.4.0) (28) was then used to call the variants from the aligned BAM

files. The results were annotated by SNPeff (29) and ANNOVAR (30), and deposited in VCF (variant calling format) files to be reviewed by our team of clinicians and geneticists.

Data analyses

No missing value was present in our PROMIS data. The data was in integer format ranging from 1 to 5 (for most items except pain scores ranging from 0 to 10). Although the empirical marginal density estimation on the patients or PROMIS items, or their aggregated distributions (Figures 3F, 4C, and 7B) did display certain degrees of skewness, given the narrow dynamic ranges, a Gaussian approximation was considered appropriate. As such the data was directly subject to principal component analyses (PCA), which relies on a Gaussian or quasi-Gaussian assumption. Let $x_i^t \in \mathbb{Z}^m$ be the PROMIS outcome of patient i ($= 1, 2, \dots, n$) at time t ($= 1, 2, 3, 4$), where m is the number of answers per survey, we performed singular value decomposition on the matrix $\mathbf{X}^1 = [x_1^1 \ \dots \ x_n^1]^T \in \mathbb{R}^{n \times m}$, which represents the outcomes from the first PROMIS and has been column-wise zero-meaned (but not unit-varianced to avoid exaggerating less dispersed items), to obtain $\mathbf{X}^1 = \mathbf{U}\mathbf{\Sigma}\mathbf{V}^T$ where $\mathbf{V}^T = [v_1 \ \dots \ v_m]^T \in \mathbb{R}^{m \times m}$, $\mathbf{\Sigma} = \text{diag}(\delta_1, \delta_2, \dots, \delta_m)$ and $\delta_1 \geq \delta_2 \geq \dots \geq \delta_m$. Then, $v_1 \in \mathbb{R}^{m \times 1}$ is the first principal component (PC), v_2 the second, and so on. The percentages of variance explained for PC j is given by $(\delta_j)^2 / \sum_k (\delta_k)^2$. The new projections of the first PROMIS onto PC1 and PC2 are given by: $\mathbf{Y}^1 = \mathbf{X}^1[v_1 \ v_2]$. And the projection of longitudinal PROMIS on the first PROMIS are given by $\mathbf{Y}^2 = \mathbf{X}^2[v_1 \ v_2]$, $\mathbf{Y}^3 = \mathbf{X}^3[v_1 \ v_2]$. and so on.

In correcting heights and BMD for ages, we first performed a linear regression of: $y = \alpha + \beta x + \varepsilon$, where y are heights or BMD, x are the ages, α the intercepts, β the slope, and ε the error term with normal distribution. The coefficients $\hat{\alpha}$ and $\hat{\beta}$ were fitted by maximum likelihood estimation (equivalent to least square under current assumption). We then used the fitted residuals (called ‘partial residuals’) (31): $\hat{\varepsilon} = y - \hat{y}$, where $\hat{y}$ are the fitted values given by $\hat{y} = \hat{\alpha} + \hat{\beta}x$, to compare against other variables (e.g., gender or patient clusters) by Analysis of Variance (ANOVA) (32).

For one- and two-dimensional density estimations, we used the kernel estimation method with default parameter. Heatmap clustering was performed with default

200 parameters using the d3heatmap package of R. Associations between two categorical
201 variables (e.g. patient clusters vs. genotypes) were tested by the Pearson's χ^2 test.
202

Results

Demographic and medical data of patients

A total of 90 OI patients were recruited consecutively and on a come-and-served basis in the current study since July 2020 (Methods). Both objective data (personal, genetics, clinical) and subjective data (PROMIS survey) (22) were collected for analyses, as depicted in a diagram in (Figure 1).

The majority of this cohort were recruited from southern China except for 4 patients from northern China (Supplementary Figure S1A). About 77.8% of the patients completed the questionnaire once, while another 22.2% were involved in longitudinal surveys (Figure 2A). Among the patients with longitudinal survey, the median interval between the first and second surveys was 84 days, while 59 days between the second and third surveys, and 36 days between the third and fourth surveys (Supplementary Figure S1B). Similar intervals were recorded for the parental surveys (70, 61 and 41.5 days respectively) (Supplementary Figure S1C). Gender-wise, 35 (38.9%) of the patients were female and 55 (61.1%) were male (Figure 2B). The ages of the patients ranged from 4 to 43. The majority of the subjects were children and adolescent, with the median age of 10.5 for female and 12 for male (Figure 2C). The peripheral bloods of 59 patients were collected for genetic tests on OI panel genes (Methods). Among the sequencing results, mutations in *COL1A1* and *COL1A2* account for slightly over 50% (Figure 2D), which was slightly lower than the previous reports in western counties (2, 5), but close to a recent Indian study (33). Of note, deleterious mutations in *IFITM5* and *WNT1* were the major non-*COL1A1/2* mutations, occupying 13.6% and 8.5%, respectively (Figure 2D). Most of the patients (~85%) have been treated with surgery (osteotomy) and/or drugs (mainly bisphosphonates) at the first time of PROMIS survey. Fifty patients (58.1%) received both drugs injection and osteotomy at least once (Figure 2E). The financial sources of treatment included charity-supported (38.5%) and self-financed (61.5%) showing better socioeconomic situation as illustrated by annual family income (Figure 2F).

PROMIS by children and adolescents reflected two different psychophysical states

A total of 70 children and adolescents (younger than 18 years old) participated in the current PROMIS survey, among which 46 had both self and parental evaluation, 4 had self-assessment only and 20 were assessed by their parents or proxies only (Figure 3A).

We noticed that some of the question items are similar to each other, which can be addressed by de-correlation methods such principal component analysis (PCA). To extract the main patterns, we first performed a PCA on the 50 self-assessed outcomes (Figure 3B-D). The top 5 principal components (PCs) explained over two thirds (67.2%) of the total variance in the data (Figure 3B). The first PC was the most dominant, explaining almost one third of the variance. A three-dimensional chart showed that the top three PCs in combination distinguished the samples into two major clusters (Figure 3C). A scatter plot with density contours showed two distinct peaks of the subjects with a saddle shape, named “Child C1” (n=27) and “Child2 C2” (n=23) respectively. C1 appeared on the upper left of the chart occupying a more dispersed space, while C2 on the lower right part with a more compact pattern (Figure 3D).

The loading scores (eigenvectors on which the data projected; Methods) for the first two PCs showed different projecting weights and directions for the 57 items surveyed (Figure 3E). In particular, on the first PC, various items measuring the physical capabilities were the most positively weighted domain, while psychological metrics dominated the other negative end (Figure 3E; left). This translated to higher scores of mobility for the patients projected to the C2 cluster, and higher scores for psychological distress towards the negative end of PC1 (Figure 3D). The loading scores for PC2 were less stratified, with a stronger presence of physical metrics (mobility) towards the negative end (Figure 3E; right). The loading scores of PC1 and PC2 suggested that C1 patients suffered from higher disease burden and worse functional mobility.

Using hierarchical clustering, we scored each item with dendrograms showing the sample-sample and item-item correlations respectively (Figure 3F). The horizontal axis of the heatmap, consisting 57 PROMIS items, showed that similar categories were clustered together. We noted that the patients were categorized in a similar topological pattern as shown in the PCA plot. The marginal distributions showed more ‘floor’ and ‘ceiling’ effects (bimodal distributions) from the C2 patients, reflecting their optimism in their physical and psychological states (Figure 3F). The C1 patients tended to have unimodal evaluations, suggesting the overall pessimism in self-evaluations (Figure 3F).

Parental PROMIS reflected similar psychophysical stratification of children

To evaluate the validity of PROMIS questionnaire from the children and adolescents, we also collected the questionnaire from the parents of these young patients. In total,

49 items were evaluated from the parents of 66 patients and similar analyses were conducted as previously. Remarkably, two clusters were also identified, named P1 and P2 including 31 and 33 parents respectively (Figure 4A). The P2 cluster was more compact with denser contours. These two PCs captured over half of the data variance. PC1, the major component that distinguished the two populations, was positively correlated with mobility and peer relations, but negatively correlated with pain, depression and other psychological distress (Figure 4B). As such, P1 was considered as an ‘unhappy/pessimistic’ group, while P2 as a “happier/optimistic” group. Hierarchical clustering simultaneously recapitulated the sample-sample relations in the PCA plot (Figure 4C). The marginal distributions in parental heatmap also displayed highly similar patterns as in the self-assessments of the young patients, with P2 patients showing stronger unimodal distributions, and P1 otherwise (Figure 4C). To delineate the consistency between the parental and self-assessed outcomes, we presented a Venn diagram, showing 84.8% (39 out of 46) concordance between these two datasets (Figure 5A). The remarkable consistency in terms of the overall patterns of clustering between parental and children’s self-assessments further supported the validity of the PROMIS instruments.

Two clusters of patients present with different genetic and phenotypic features

We asked if the subjective evaluations and classification could be related to objective factors such as genetics, clinical and socioeconomic status. We grouped all the unambiguous cases into Cluster 1 (29 patients) and Cluster 2 (34 patients), and referred to as the “unhappy/pessimistic” and “happier/optimistic” clusters respectively (Figure 5A). We found only 36.9% patients in Cluster1 carrying mutations of *COL1A1* or *COL1A2*, whereas 63.7% in Cluster 2 (Figure 5B). This could be explained by the milder symptoms observed in these *COL1A1* and *COL1A2* mutation carriers in this cohort. Similar distribution could also be observed from the PCA plots (Figure 3D and Figure 4A). Interestingly, patients carrying recessive mutations, including *WNT1*, *FKBP10*, *P3H1* and *SERPINF1*, were enriched in the Cluster 1 (Figure 5B), consistent with the more severe skeletal phenotypes in autosomal recessive OI cohort (34). Secondary clinical features, such as blue sclera, hearing loss and dentinogenesis imperfecta, are usually present in OI patients (1). By Pearson’s χ^2 association test, we found that four items were distributed with statistical significance, including clinical subtyping (Sillence scale), deformity, leg length discrepancy (LLD) and limited joint

mobility (Figure 5C). In particular, type IV OI was strongly enriched in Cluster 1, while types I OI was more enriched in Cluster 2. Type I OI is the mildest form of the disease and Type IV ranges from moderate to progressive deforming (1, 10, 35). Deformity and LLD showed a similar trend, with almost doubled positive rates in Cluster 2 comparing to Cluster 1. The positive rate of joint abnormality was increased by 4.6 times, from 6.9% in Cluster 2 to 32.1% in Cluster 1 (Figure 5D), limiting the physical capacity of patients and causing major difficulties in daily life.

We further investigated the correlations between the clustering and other documented medical quantities including height and bone mineral density (BMD). Linear regression was performed between the height and age in a gender and cluster-specific manner. We found that the fitted curve for the female in Cluster 1 was vastly deviating from other three groups, while the BMD of both genders were consistently lower in Cluster 1 as compared with Cluster 2 (Figures 5E and F). To reduce the influence by age, we performed regression of heights and BMD against ages before statistical analyses (Methods). The result showed a significant association between age-corrected heights and gender/clusters (p -value = 0.0148, ANOVA F-testing, degrees of freedom = 3 and 58). Post hoc analyses by Tukey's honestly testing showed the biggest difference between Cluster1F and Cluster2M (p -value = 0.0278), followed by Cluster1F-vs-Cluster1M (p -value = 0.0315) and Cluster1F-vs-Cluster2F (p -value = 0.0519). Comparison of age adjusted BMD between the two clusters indicated that both genders showed lower bone density in Cluster 1 as compared with Cluster 2 (p -value = 0.022, ANOVA F-testing, degrees of freedom = 3 and 60) (Figure 5H). Tukey's honestly testing showed that the adjusted p -value between Clusters 1 and 2 was 0.0018, and no significance for genders (p = 0.54). In brief, the physical characteristics of the patients, including limb deformity, height and BMD, were the most relevant predictors for the two-cluster classification as revealed by the PROMIS data.

Longitudinal data confirms consistency of two-cluster stratification

Both the young patients and their parents were invited to join our longitudinal surveys, with intervals averaging about three months (82.44 and 87.3 days for the children and for the patients, respectively) (Supplementary Figure S1B). We projected these PROMIS data into the loading scores for the top principal components of the first PROMIS dataset (Methods). For the self-assessed data, we observed a much greater

frequency of Cluster 1 patients involved in the longitudinal study, as indicated by the green arrows (Figure 6A). This was consistent with the overall poorer conditions in this population, which may require more frequent hospitalizations. We also observed an overwhelming propensity for these patients prone to stay in the same unhappy state even after clinical interventions (14 out of 15 patients) (Figure 6A). A similar but slightly encouraging trend can be observed from the parental longitudinal data, where the numbers of state-changes from bad to good (n=6) was 3 times more than the other way round (n=2) (Figure 6B). These longitudinal data confirmed the consistency of diversity among young OI patients' subjective evaluation, providing treatment evaluation and disease management recommendations for the clinicians and caregivers.

A spectrum of physical capabilities among adult patients shows

In addition to children and adolescent data, we conducted a relatively small-scale survey on 15 adult patients regarding their physical capabilities only. PCA analyses showed that the adult patients were enriched in one major cluster only (Figure 7A). Heatmap analyses of the original scores and phenotypic features showed continuous spectrums among these patients without clear clustering patterns (Figures 7B and C).

Discussion

Traditionally, medical services and health care primarily focus on the genetics, diagnostics, pharmacologic treatment and orthopedic surgeries, all defined by objective metrics, to address the underlying deformity and fractures of OI patients. It is gradually recognized that for a lifelong condition like this, what ultimately matters most is patients' quality of life (QoL) from their own perspective (the 'subjective' criterion).

The clinical manifestations of OI represent a continuum ranging from mild, moderate, to severe and perinatal lethality. Genetic mutations affecting collagen production, conformation and osteoblast differentiation cause skeletal deformity and joint dysfunction, leading to different levels of functional limitation and physical disability (36). Pain/discomfort and functional mobility have been reported to be the most problematic domains for patients with OI, fibrous dysplasia and other skeletal disorders (17). Knowledge about how chronic diseases affect health related QoL may provide the grounds for improving treatments and support to the needs of these patients. Several studies have leveraged different generic tools to assess health related QoL in children and adults with OI (15, 17, 21). The measures across these studies may differ thus preventing direct comparisons and meta-analyses. On the other hand, using generic tools may not provide information on OI specific aspects affecting patients' QoL, such as pain and social relations (37). Therefore, it is highly recommended that comprehensive assessment of QoL should include both the perspectives from children and their parents as the ground reference for clinical practice and research.

In this study, we probed deep into the subjective quantitation of patient reported outcomes, identified two major clusters of patients with vast distinct outlook for life, one being more optimistic than the other. In addition, we established a connection among the genetics, clinical phenotypes and patient psychological status. We found clinical subtyping, bone deformity, leg length discrepancy and limited joint mobility are most relevant to the patients' PROMIS assessments. Specifically, patients with such issues are much more enriched in the "unhappy" cluster, which couples with QoL meta-analyses suggesting association of pain, scoliosis and participation restriction with low QoL in OI (21). The reliability of this dichotomized clustering was further backed by two additional sources of information: first, the simultaneous survey outcomes of the children and their parents; second, longitudinal data. In the former, a minimum concordance of 84.8% (39 out of 46) was estimated between parental and children

surveys. In the longitudinal data, we found that the ‘unhappy’ individuals tend to stay ‘unhappy’ after multiple surveys, which unfortunately also seems to suggest a grim situation whereby the efficacy of treatments has to yet to be improved or more specific targeting the issues surrounding the limbs. It is also possible that the follow-up intervals (~3 months) are short or insufficient to show the benefits of treatment. Thus, multiple and longer intervals may be needed in future longitudinal study. We note some of the question items are similar to each other, which has been well addressed by applying de-correlation methods (PCA) in this study.

The widely-used PROMIS instrument was validated by a pilot study offer a variety of methods to measure important domains of QoL with established short forms that are suitable for computerized-adaptive testing (24). By leveraging the PROMIS instruments, we presented more systematic, in-depth analyses by overcoming some of their limitations, including gender disparity, insufficient ethnic diversity and lack of self-assessments in the children (24). We conducted both parental and self-assessments, observing a high consistency between them. Longitudinal data further confirmed the clustering analyses, which also helped to evaluate the changes of life quality over time in OI individuals. We integrated the genetics data and patient reported outcomes, and revealed their correlations. The future direction should focus on the development/expansion of disease specific measures in the PROMIS database to detect individual health status and life quality of OI patients as a basis for evaluating clinical management and health maintenance.

Notwithstanding, we are aware that multiple aspects can be improved. The cohort was not randomized. The patients were surveyed consecutively on a first-come-first-served basis. As with most other QoL/PROMIS studies, no control group was unavailable. A control group of non-diseased or of other diseases would be beneficial to compare individual PROMIS items to a baseline background; although it can be projected that the control group would display “floor” and “ceiling” effects for most items. A larger cohort is envisioned to enhance statistical power, especially in light of the multiple clinical features being tested against the stratification results, although sample size is always a big challenge on rare diseases such as OI. The psychological well-being in the adult patients was not comprehensively studied in our study. Supplementing recruitment from OI community, multi-center cooperation, standardized clinical categorization of disease severity and OI-specific questionnaire are advisable next steps.

To sum up, our study obtained analyzable PROMIS data regarding the disease experiences from young OI patients, their parents and longitudinal follow-up to access the physical and psychological health status and responses to clinical interventions. Our data suggest that clinical subtyping and skeletal deformity including leg length discrepancy and limited joint mobility are the major aspects affecting the life quality of OI individuals. Higher level of severity is generally associated with higher psychological depression. High consistence of response from children and their parents further validates the PROMIS questionnaire. Our study demonstrates the merits of patient reported outcomes to understand the diverse spectrum of patient phenotypes and psycho-physical health status, which hopefully will gear us towards building a more patient-centric medical care for OI patients.

Declarations

Ethical approval and consent to participate

Institutional review board (IRB) approvals (ETHICS-2019-010; ETHICS-2020-150; ETHICS-2021-141) were obtained from the Medical Ethical Committee of the University of Hong Kong-Shenzhen Hospital. Informed consents were obtained from the patients or their parents.

Consent for publication

Not applicable.

Availability of data and materials

Some of the custom scripts for data processing were deposited at:
<https://github.com/HKUSZH/OI-PROMIS> . Please contact author for data requests.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

P.K.C. developed the methods, analyzed and interpreted the data, discovered the two clusters of patients, prepared figures and drafted the manuscript. Z.T. coordinated the genetic testing of patients, interpreted the data and revised the manuscript. M.K.T.T., Y.P.Z., S.J.Y., Z.X.D., J.C.X. and K.S.L. (clinicians) provided diagnoses and performed surgery on OI patients. L.N.D. (registered nurse) provided nursing care and documented the clinical data. Y.Q. (social worker) helped explain the questionnaires to the patients and their parents. J.W.L., H.T.S. and Y.P.Z. designed the PROMIS form, translated the questions into Chinese and set up the RedCap system. G.B. coordinated the genetic test and reviewed the genetic reports. E.H.K.Y. (registered physiotherapist)

456 measured the skeletal deformity and joint contracture angles. K.M.C.C. reviewed the
457 diagnoses and interpreted the data. M.K.T.T. secured funding. All authors wrote and
458 approved the manuscript.

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463

Figure legends

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D, Piechart showing the distributions of affected genes among the 59 patients that underwent genetic screening on a panel of 24 genes for targeted sequencing.

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Figure 3. PCA and clustering analyses in the children and adolescent PROMIS.

A, Venn diagram showing the overlap of self and parental assessment cases.

B, Piechart showing the percentages of variance explained by principal component analysis (PCA).

C, A three-dimensional scatter plot showing the projections onto the top three components. Each dot represents one patient.

D, Scatter plot showing the first two PCs, with density contours. Red curves indicated saddle and valley between the two peaks/clusters.

E, Barcharts showing the ordered loading scores for the first and second PC.

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Figure 5. The identification of two PROMIS groups in the children and adolescent patients and their clinical characteristics.

A, A Venn diagram showing the identification of two PROMIS groups in the young patients by their own assessments and their parents' assessments. The numbers correspond to the numbers of patients in each category. The labels C1, C2, P1 and P2 correspond to the [Figure 3D](#) and [Figure 4A](#). The 7 patients with discordance between the patients' own and their parents' assessments are considered "ambiguous".

B, Piecharts showing the distribution of affected genes in the two groups of patients.

C, Bar-charts showing the clinical features in decreasing order of significance, in terms of their associations with the PROMIS groups.

D, Piecharts showing the positive rates for each of the four significantly associated clinical features in the two PROMIS groups.

E, Scatter plot showing the patients' heights versus their ages. The straight lines are regression curve fitted for each of the four patient groups.

F, Scatter plot showing the patients' spine BMD versus their ages. The straight lines are regression curve fitted for each of the four patient groups.

G, Violin plots showing the residuals of heights after fitted against age, with respect to the four groups.

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Figure 6. Projections of later PROMIS outcomes to the PCA of the first PROMIS outcome.

A, Projections of children and adolescent's later PROMIS (second, third or fourth) on the loading scores of the PCA of the first PROMIS.

B, Projections of parents' later PROMIS (second, third or fourth) on the loading scores of the PCA of the first PROMIS.

Arrows point from the PROMIS outcome at one time-point to the next, for each patient. Arrow colors indicate the original states in the first PROMIS. The transition diagrams at the bottoms of (A) and (B) shows the numbers of state changes for each pair of successive PROMIS survey. The numbers on the edges show the numbers of patients or numbers of times a patient changes from one state to another (or the same) state.

Figure 7. PROMIS outcomes of adult patients.

A, PCA of adult patients' PROMIS outcomes.

B, Heatmap showing the individual assessment outcomes. Ridge plots to the right and bottom are the density estimations that show the row-wise or column-wise distributions.

C, Heatmap showing the clinical features of the adult patients.

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546 **Additional file**

547 *Additional file 1. PROMIS form used in this study for children, parents, and adults.*

548

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Figures

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Figure 3

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PCA and clustering analyses in the children and adolescent PROMIS. A, Venn diagram showing the overlap of self and parental assessment cases. B, Piechart showing the percentages of variance

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Figure 7

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