

Health-related Quality of Life in Children With Chronic Myeloid Leukemia in the Chronic Phase

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Abstract

Purpose To explore the health-related quality of life (HRQoL) and associated variables in children with chronic myeloid leukemia in the chronic phase (CML-CP) receiving tyrosine kinase inhibitors (TKIs).

Methods A cross-sectional questionnaire was given to children with CML and their parents, who were <18 years at diagnosis of CML and <19 years at study. The questionnaire consisted of three parts, including demographic information, clinical information, and the Chinese version of Pediatric Quality of Life Inventory™ (PedsQL™) Cancer Module 3.0 as HRQoL questionnaire.

Results 289 questionnaires were collected, and data from 207 (71.6%) respondents were analyzed. Multivariate analysis showed that children with symptoms had worse pain (-10.7; $P<0.001$), nausea(-17.9; $P<0.001$), treatment anxiety(-6.7; $P=0.008$), worse appearance self-assessment (-7.5; $P<0.001$) and communication problems(-3.9; $P=0.028$), and worse HRQoL(-4.1; $P=0.013$). Children whose mothers had low educational qualifications complained worse pain(-8.3; $P=0.005$), worried more about the future (-11.6; $P=0.002$), had poor self-assessment (-5.1; $P=0.045$), and worse HRQoL (-6.5; $P=0.002$). Children at a younger age of study when studied had more procedural anxiety (3.3; $P=0.008$), more cognition problems (3.4; $P=0.001$), and worse HRQoL (1.4; $P=0.040$), while increasing age at diagnosis had worse appearance self-assessment (-2.1; $P=0.015$) and HRQoL (-1.4; $P=0.039$). Other variables significantly associated with worse HRQoL included female sex and rural household registration. Parents reported more gastrointestinal disorders and worry about the future and had less concern about appearance than reported children.

Conclusions This study suggests that female gender, increasing age at diagnosis, younger age at study, lower mother's education level, and TKI-related symptoms reported were significantly-associated with worse HRQoL. Parents and children have different priorities in the HRQoL.

Introduction

Chronic myeloid leukemia (CML) is rare in children contributing only 2–3% of all pediatric leukemia cases. The global incidence rate of CML is 15/1,000,000 per year^[1]. Tyrosine kinase inhibitors (TKIs) have transformed the therapy of CML, and children with CML now have a life expectancy similar to the healthy population^[1, 2]. In addition to leukemia-control, a key goal of therapy is to improve children's health-related quality of life (HRQoL)^[3]. Many studies showed that children with cancer had worse HRQoL when compared with healthy children. Female gender, living alone, severity of the malignant disease, high intensive treatment and poor response to treatment had a negative impact on HRQoL in childhood cancer survivors^[4–14]. Meanwhile, higher education and better communication with parents are related to higher HRQoL^[15–17]. Unlike other cancer patients, children with CML in the chronic phase (CML-CP) mainly receive long-term oral TKIs as outpatients, enabling them to participate normally in family and school life, so their HRQoL and the associated variables may also be different. In addition, since children are actively growing during TKI treatment, they would face unique side effects not seen in adults, such as growth

disturbance^[18]. Thus, the variables associated with HRQoL in adults may be different from CML in children. However, there is a lack of data on HRQoL in those children. Therefore, a cross-sectional study was designed to assess HRQoL in children with CML receiving TKI-therapy and explore its associated variables.

Subjects And Methods

Survey

From July 2018 to December 2019 a cross-sectional study was designed and conducted in 43 hospitals in China. A Chinese-language questionnaire was given to children in CML-CP receiving TKI-therapy and their parents, who were < 18 years at diagnosis of CML and < 19 years when completing the questionnaire. CML diagnosis, disease phase, monitoring, and response to TKIs were based on the European LeukemiaNet 2013 recommendations^[19]. A complete cytogenetic response (CCyR) was defined as 0% Ph + metaphases and > 20 metaphases in a bone marrow sample. A BCR-ABL1 expression of \leq 0.1% was defined as a major molecular response (MMR). The study protocol was approved by the Ethics Committee of Peking University People's Hospital (No. 2019PHB148-01). Patients and/or their caregivers who agreed to participate in the study provided informed consent.

The questionnaire consisted of three parts. The first part collected demographic information, including gender, age at diagnosis, age at study, household registration (urban or rural), and educational qualification of parents. The second part included 16 questions assessing disease- and therapy-related information, including CML data (date of diagnosis, disease phase, etc.), TKI-therapy related data (TKI drugs, date of starting TKI, TKI-therapy duration, patient self-reported discomforts, and response to TKI). The third part was the HRQoL questionnaire. We adopted the Chinese version of Pediatric Quality of Life Inventory™ (PedsQL™) Cancer Module 3.0, which proved to have great reliability and validity in Chinese children^[20]. The HRQoL questionnaire consists of two sections: one section is a child self-report, for children including the age groups 5–7 years, 8–12 years, and 13–18 years, respectively, based on the current age; the other section is a parent proxy-report, for parents on behalf of children including the age groups 2–4 years, 5–7 years, 8–12 years, and 13–18 years, respectively. Each section has eight dimensions: D1 (Pain and hurt), D2 (Nausea), D3 (Procedural anxiety), D4 (Treatment anxiety), D5 (Worry), D6 (Cognition problems), D7 (Perceived physical appearance), and D8 (Communication problems). Each dimension contains 2–5 items. Each item has a five-point scale ranging from 'never' to 'almost always'. Scale scores are computed as the sum of the items divided by the number of items answered, ranging from 0 to 100. The higher the score, the better the HRQoL.

Statistical analyses

Data were represented using mean, mean \pm standard deviation, or median (range) for continuous variables, frequencies and proportions were used for categorical variables. The median was used to

determine the boundary value of continuous variables of the age at diagnosis and TKI-therapy duration. Pearson correlation analyses were performed to assess the correlation of the score of each dimension between child self-report and parent proxy-report. The paired sample t-test was used in the paired analysis of the score of each dimension between child self-report and parent proxy-report. Demographic and clinical variables were included in univariate analysis. Variables associated at a level of $P < 0.2$ in univariate analysis were included in a multivariate linear regression model, where the age at diagnosis, age at study, and TKI-therapy duration were continuous variable. $P < 0.05$ was considered statistically significant. Analyses were conducted with SPSS v19.0 (IBM Corporation, New York, USA).

Results

Subjects

289 questionnaires were collected. Data from 82 respondents (28.4%) were excluded because that they were not in the chronic phase ($N = 6$), had no data of CML diagnosis ($N = 8$) or therapy information ($N = 12$), failed to answer the HRQoL questionnaire ($N = 53$), or had comorbidity(ies) (mental retardation, cardiac insufficiency, or disability) ($N = 3$). Finally, a total of 207 respondents (71.6%) were included in this study. A flowchart of patient enrollment is shown in Fig. 1.

Of the 207 respondents, 128 (61.8%) were male. The median age at diagnosis was 9.0 years (range, 0.2–17.5 years), and the median age at study was 13.0 years (range, 3.0–18.9 years). 148 (71.5%) respondents' mothers had an education level less than a bachelor degree. 194 (93.7%) respondents were receiving imatinib-therapy, 11 (5.3%) dasatinib and 2 (1.0%) nilotinib when completing the questionnaires. The median TKI-therapy duration was 30 months (range, 6–95 months). 120 (58.0%) respondents reported they had TKI-therapy related symptoms (Fig. 2). The other subject-, disease-, and therapy-related characteristics of 207 respondents are presented in Table 1.

HRQoL profile

In the cohort of 207 respondents, six patients were younger than 5 years, thus lacking a child self-report. 48 out of the 201 (23.8%) of the remaining patients in the 5–18 years group did not complete the child self-report part of the questionnaire. Separated into age cohorts, 20 out of 25 (80%) in the 5–7 years group, 18 out of 68 (26.4%) in the 8–12 years group, and 10 out of 108 (9.2%) in the 13–18 years group. All together, data of 153 child self-reports and 207 parent proxy-reports were included in this study (Fig. 1).

Based on the 153 child self-report and 207 parent proxy-report data, the HRQoL scores were 80.6 ± 9.7 and 80.7 ± 10.7 , respectively. The score of the 8th dimension (Communication problems) was the highest, with a mean score of > 96 , while that of the 3rd dimension (Procedural anxiety) was the lowest, with a mean score of < 57 . HRQoL profile is presented in Table 2 and Fig. 3.

In the 153 respondents with both child self-report and parent proxy-report, the scores of child self-report were higher than parent proxy-report in dimensions of nausea and worry ($P < 0.001$). The score of child self-report was higher than parent proxy-report in the dimension of Perceived physical appearance ($P < 0.001$). There was no significant difference in total scores and other dimensions. However, there was an inconsistency of the scores between the child self-report and parent proxy-report (Fig. 4), and there was a high correlation ($r = 0.714 \sim 0.930$, $P < 0.001$) between each dimension and the total score in the 153 respondents.

Variables associated with HRQoL

Variables including demographic (gender, age at diagnosis, age at study, household registration, and education level of parents), disease- and therapy-related (including TKI used, TKI-therapy duration, discomfort reported or not, and treatment response [MMR or not]) were identified if they were associated with the HRQoL. Univariate analysis results are shown in Table 3. In multivariable analysis, children with symptoms had worse pain (-10.7; $P < 0.001$), nausea (-17.9; $P < 0.001$), more treatment anxiety (-6.7; $P = 0.008$), worse appearance self-assessment (-7.5; $P < 0.001$), communication problems (-3.9; $P = 0.028$), and worse HRQoL (-4.1; $P = 0.013$). Children with mothers having low educational qualifications had worse pain (-8.3; $P = 0.005$), worried about the future (-11.6; $P = 0.002$), worse appearance self-assessment (-5.1; $P = 0.045$), and worse HRQoL (-6.5; $P = 0.002$). Children at a younger age at study had more procedural anxiety (3.3; $P = 0.008$), more cognition problem (3.4; $P = 0.001$), and worse HRQoL (1.4; $P = 0.040$), while increasing age at diagnosis had a worse appearance self-assessment (-2.1; $P = 0.015$), and HRQoL (-1.4; $P = 0.039$). In addition, male (4.9; $P = 0.043$) living in urban areas (-9.0; $P = 0.001$) had worse pain, while female had worse appearance self-assessment (-5.0; $P = 0.016$) and worse HRQoL (-3.3; $P = 0.048$). The results of multivariate analyses are shown in Table 4.

Discussion

To our knowledge, this is the first study to assess HRQoL in children with CML-CP and explore the associated variables. Although those children mainly received oral TKIs, which were different from other cancer patients requiring intensive chemotherapy in hospital, we found some variables, including female gender and age, were associated with HRQoL. This is consistent with the previous studies about HRQoL of children with other cancers^[4, 6, 8, 10–12, 14]. Just as adult CML, TKI-related symptoms reported was the variables correlated with impaired HRQoL. In addition, We found that the lower the mother's education level, the worse HRQoL the children had, and parents reported more gastrointestinal disorders and worries about the future and less concerns about the appearance than children's reports.

Our study showed that female children felt more unsatisfied with their appearance, and had worse HRQoL than males, which was consistent with previous findings in other studies^[4, 6, 11]. On the other hand, we found that male, especially living in the village, experienced worse pain, which could be attributed to the more physical activity of male. The discomfort after exercise, coupled with the side effects of TKI drugs,

may cause them to experience worse musculoskeletal pain^[21]; however, further research on this phenomenon would be recommended.

Age at diagnosis was related to the HRQoL of childhood cancer survivors, but the results are different. Speechley et. al. found that the older the children at diagnosis, the lower were physical and psychological scores of survivors^[22]. Fradell's study showed that HRQoL of survivors with acute lymphoblastic leukemia at older age was worse^[11], while Alessi reported that HRQoL of survivors with malignant tumors at older age was better than those diagnosed at a younger age^[23]. In our study, the age at diagnosis was associated with perceived physical appearance; that is, children who were older at diagnosis were more likely to be dissatisfied with their appearance, who often complained about the skin rash and edema, and they had worse HRQoL. In addition, the younger age of the children at study was associated with the worse HRQoL, which was mainly manifested for procedural anxiety and cognitive problems^[24]. It is easy to understand that the frequent hospital visits and the need for invasive procedures (such as blood tests every month in the first 3 months and every 3 months after that, and bone marrow puncture every 3 months before CCyR) may make the younger children feel scared. Moreover, younger children may experience more difficulties in cognitive problems, as Hardy and coworkers reported in their study^[25]. The reasons might be that - although not recommended by medical guidelines - parents of younger children restrict the children's school activities, at least in flu season, to reduce the infectious risk caused by the physical immunity of TKI-therapy. Therefore, younger children were frequently absent from school, which might lead to cognitive problems. Relatively older children might be less detached from school, due to the ability to protect themselves in school and study pressure^[26].

In our study, we found that mother's educational levels also impact their children's HRQoL. Lower educational qualification of mothers was associated with worse HRQoL of their children. This phenomenon may be related to the mother's role in the family^[27, 28]. In China, a mother is more responsible for taking care of the family at home and have a closer relationship with their children, resulting that their feeling could affect children's HRQoL. Mothers with lower education level may have a certain level of cognition whose children are diagnosed with CML, but not comprehensive understanding. Females are delicate, sensitive, and emotional, which usually leads to over-protective behavior. These behaviors of females, in turn, affects their children's HRQoL, especially in the aspects of pain, worry, and self-appearance evaluation^[29].

Many studies found that fatigue was the most common adverse effect in adults with CML receiving TKI-therapy, and fatigue was also the main reason for the worse HRQoL in adult patients^[21, 30-34]. In our study, the first two most common adverse effects reported were gastrointestinal disorders and skeletal muscle pain. These adverse reactions may affect nutrition and sleep quality, thus resulting in fatigue and lack of energy to participate in physical activities^[11, 35]. Furthermore, the children complaining a discomfort of TKI-therapy reported dissatisfaction with appearance, and impaired communication problems. This finding can be explained by the experience of pain, nausea and fatigue, which impaired

their ability to fully participate in physical and social activities^[15, 34, 36]. Moreover, the change in body image caused by TKI-therapy, such as weight gain, skin rash, or skin color, causes children to develop inferiority and then refuse to socialize^[8]. Through these aspects, discomfort reported would affect the HRQoL of children with CML.

Our assessment of HRQoL was mainly based on parent proxy-report, but strong agreement existed between children self-report and parent proxy-report scores on the eight dimensions and total score, so the potential bias between children self-report and parent proxy-report in the results was not likely to be a problem in our study. Parent proxy-report had become an adequate substitute for child self-report, even though large differences can exist in the dimension of nausea, worry, and perceived physical appearance. The difference between child self-report and parent proxy-report reflected the different perspectives of children and parents about the children's HRQoL, consistent with Belson's finding^[8]. Parents reported worse HRQoL than their children in the aspects of gastrointestinal disorders and worried about the future, whereas children reported more significant self-negation of appearance. Parents' view about children's nausea and poor diet may be related to their burden of care-giving and their own well-being^[38]. Moreover, this is communicated with Chinese traditional culture, where parents tend to make diet culture a priority, and exaggerate their children's low appetite. Rama Zilber and Vlachiotti defined the difference of opinion of worry and reported that the basic concern of all parents was the health and future of their children^[17, 23]. They considered disease to have more negative consequences than children themselves. The life experiences and inner lives of children were different from those of the adults, and they may pay more attention to their present conditions and feelings, like appearance, caused by skin rash, change of skin color, short stature produced by TKI-therapy. However, some parents usually have less communication with their children and ignore their children's psychological sensation.

Our study has some limitations. First, respondents needed to be old enough to complete the self-report part independently, and some parents refused their children's wish to answer the questionnaire because of privacy concerns, which significantly reduced the number of child self-report subjects. Second, the patients' self-reported discomfort and degree were subjective feelings with individual differences. Third, parents usually pay different attention to the child's growth, and the mother is more delicate in the relationship, but we did not restrict the selection of father and mother in answering the parent proxy-report^[27].

In conclusion, our findings reflected the HRQoL of children with CML and showed that female gender, increasing age at diagnosis, younger age at study, low mother's educational qualification, and TKI-related symptoms had a negative effect on their HRQoL. In addition, parents paid more attention to poor diet and worried about the future, while children with CML were more dissatisfied with their appearance. This requires pediatrician not only to provide patients with the most appropriate suitable treatment, but also to pay more attention to the patients' psychological and physical needs.

Declarations

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Conflict of Interest

No conflict of interest exists in the submission of this manuscript, and manuscript is approved by all authors for publication.

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Tables

Table 1 Patients' characteristics

| Variable | N (%) |
|---|-----------------|
| Male | 128 (61.8%) |
| Age at diagnosis, median (range), year | 9.0 (0.2-17.5) |
| Age at study, median (range), year | 13.0 (3.0-18.9) |
| 2-4 | 6 (2.9%) |
| 5-7 | 25 (12.1%) |
| 8-12 | 68 (32.9%) |
| 13-18 | 108 (52.1%) |
| Household registration | |
| Urban | 88 (42.5%) |
| Rural | 119 (57.5%) |
| Education level of father | |
| <Bachelor | 149 (72.0%) |
| ≥Bachelor | 58 (28.0%) |
| Education level of mother | |
| <Bachelor | 148 (71.5%) |
| ≥Bachelor | 59 (28.5%) |
| Interval from diagnosis to starting TKI-therapy, median (range), months | 0.2 (0.0-126.0) |
| Current TKI used | |
| Imatinib | 194 (93.7%) |
| Branded Imatinib | 107 (51.7%) |
| Chinese generic Imatinib | 87 (42.0%) |
| Dasatinib | 11 (5.3%) |
| Nilotinib | 2 (1.0%) |
| TKI-therapy duration, median (range), months | 30 (6-95) |
| Patient self-reported discomfort (N) | |
| 0 | 87 (42.0%) |
| 1-2 | 47 (22.7%) |
| 2 | 38 (18.4%) |

| | |
|--|------------|
| ≥3 | 35 (16.9%) |
| Treatment response | |
| MMR | 95 (45.9%) |
| <MMR | 72 (34.8%) |
| Unknown | 40 (19.3%) |
| Interval from diagnosis to MMR, median (range), months | 9.0 (3–48) |

TKI: tyrosine kinase inhibitor; MMR: major molecular remission (= MR3, = <0.1% ratio bcr-abl/control gene)

Table 2 is not available with this version.

Due to technical limitations, table 3 and 4 docx is only available as a download in the Supplemental Files section.

Figures

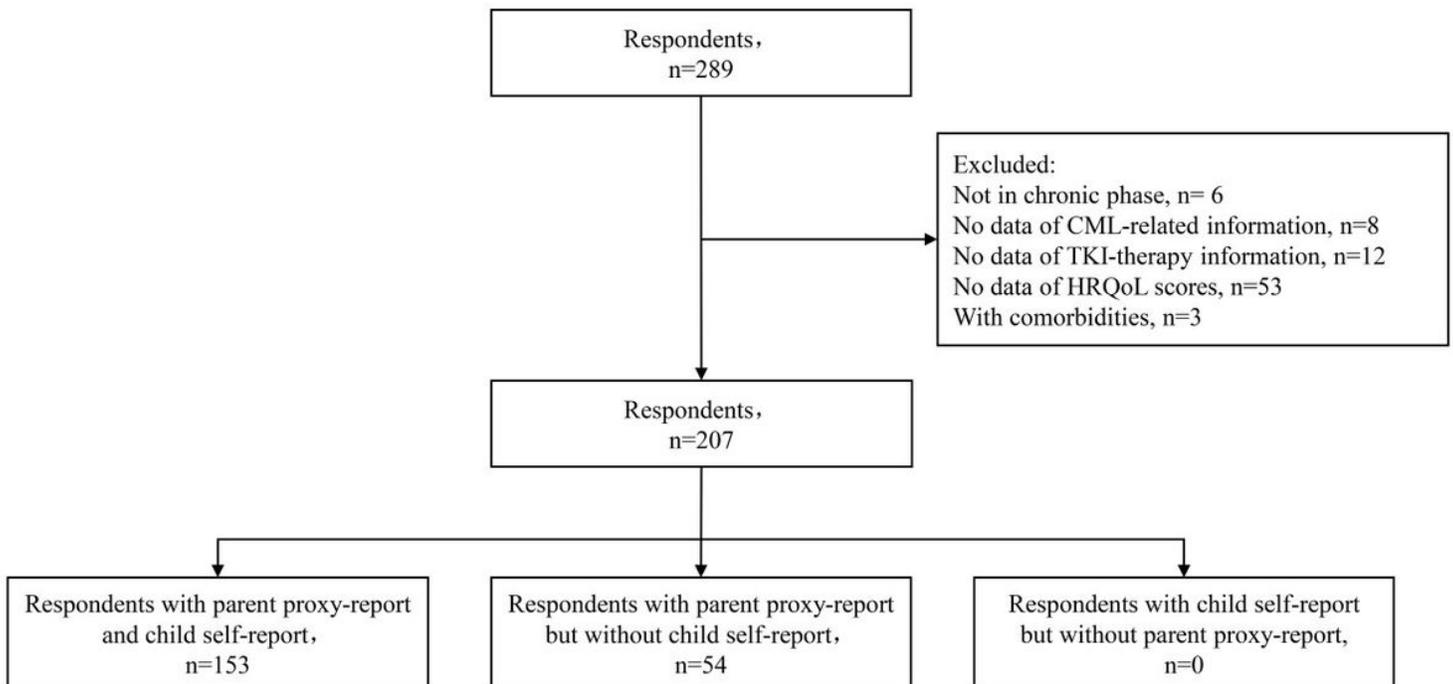


Figure 1

Consort diagram on the different cohort of patients with chronic myeloid leukemia forming the basis for the data analysis. TKI: tyrosine kinase inhibitor

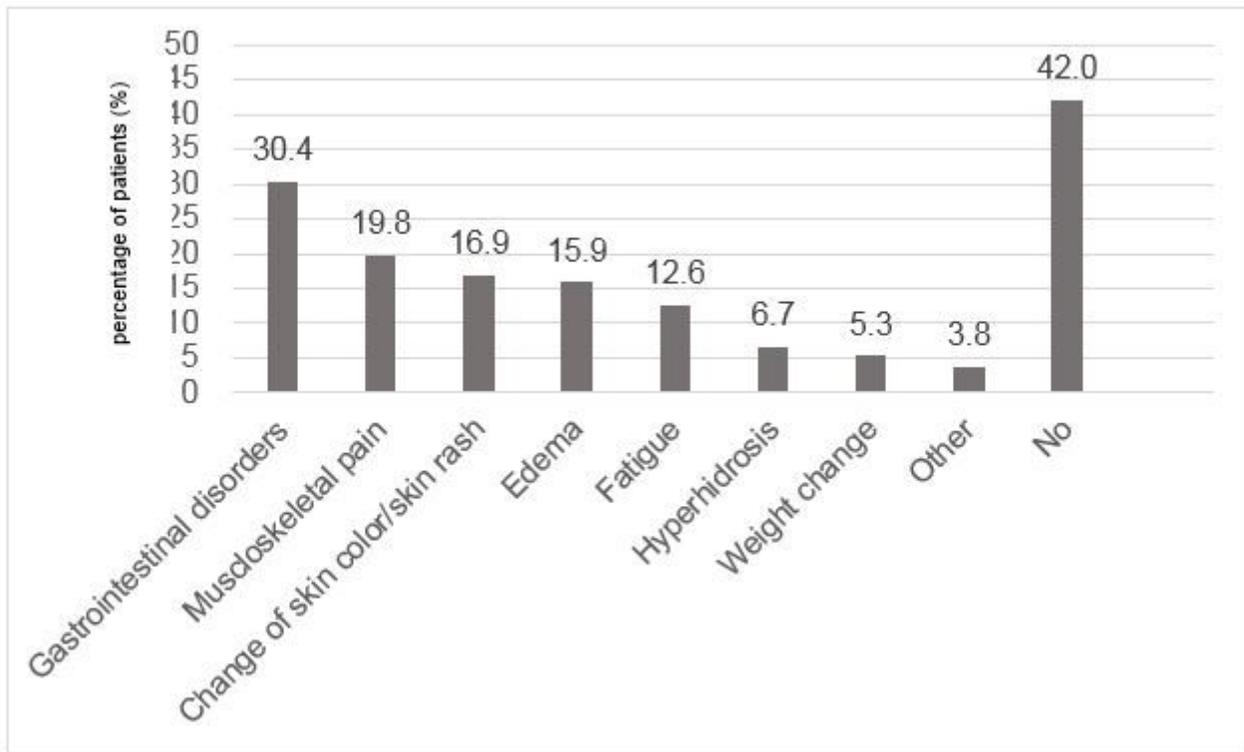


Figure 2

The self-reported discomforts of the patient and the proportion in the 207 respondents

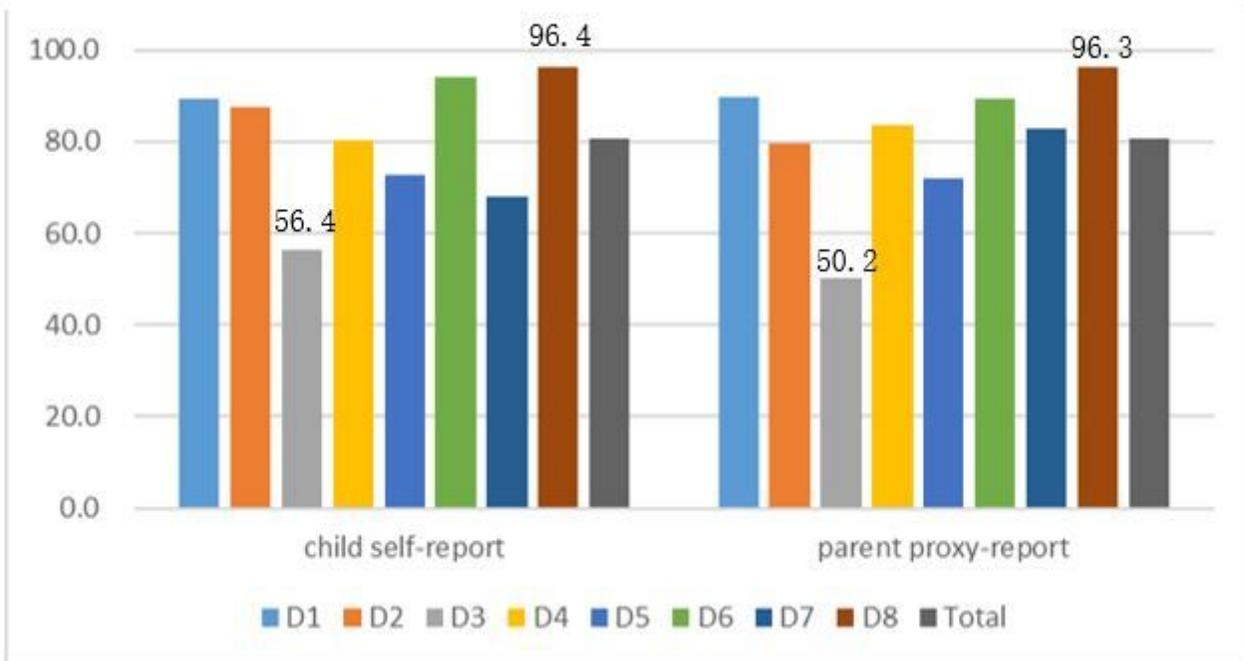


Figure 3

The mean scores of eight dimensions in child self-report (N=153) and parent proxy-report (n=207) D1-D8: dimension 1 to dimension 8. D1: Pain and hurt; D2: Nausea; D3: Procedural anxiety; D4: Treatment anxiety; D5: Worry; D6: Cognition problems; D7: Perceived physical appearance; D8: Communication problems

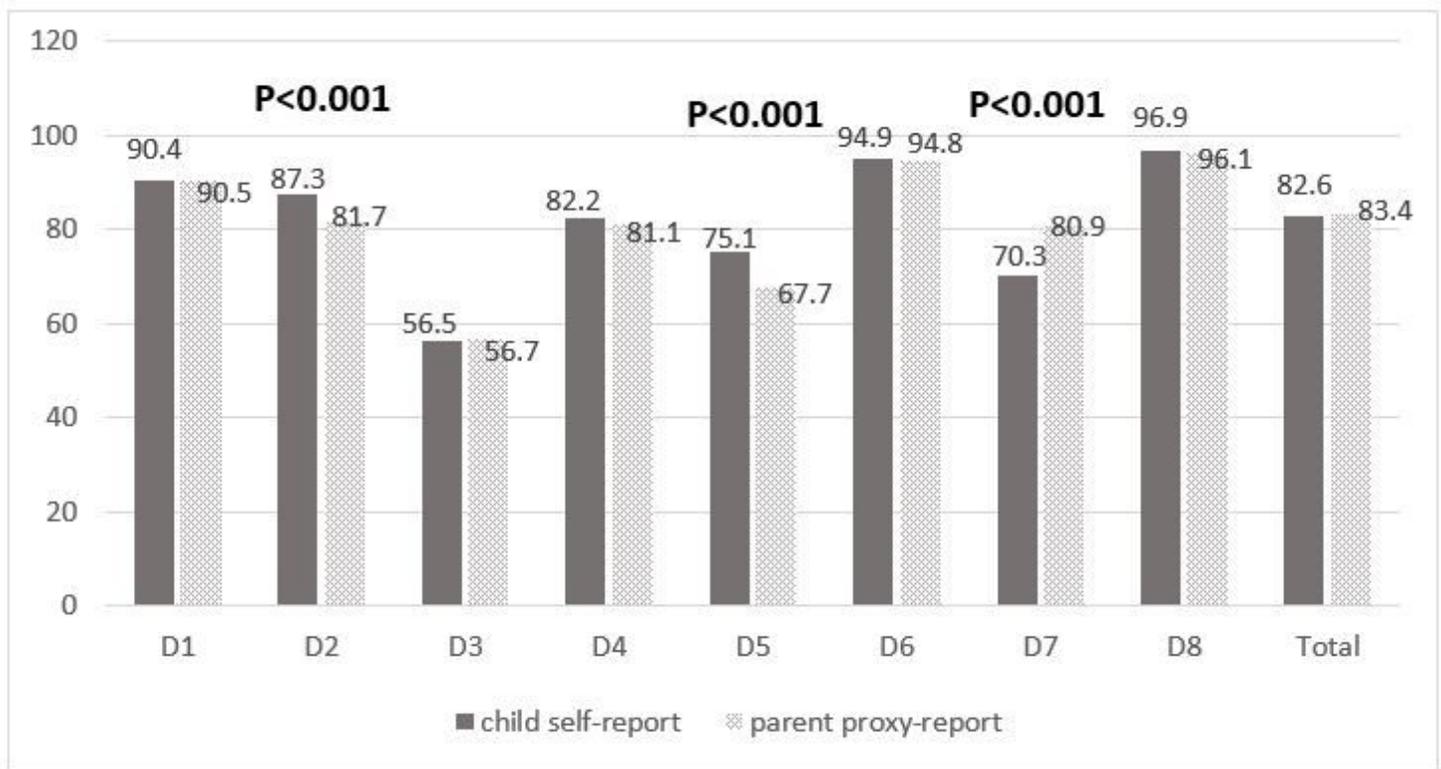


Figure 4

The comparison of HRQoL scores of the eight dimensions and total score between child self-report and parent proxy-report in the 153 respondents with both child self-report and parent proxy-report. D1-D8: dimension 1 to dimension 8. D1: Pain and hurt; D2: Nausea; D3: Procedural anxiety; D4: Treatment anxiety; D5: Worry; D6: Cognition problems; D7: Perceived physical appearance; D8: Communication problems.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table34.docx](#)