Factors Involved in Health-Related Quality of Life in Children with Immune Thrombocytopenia: A Study from the Dallas ITP Cohort

Adolfo Flores BS, Cindy E. Neunert MD, MSCS, Robert J. Klaassen MD,

Leah Adix CCRP, Anna Winborn CCRC, and George R. Buchanan MD

From the Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, Texas, Children's Medical Center Dallas; Department of Pediatrics, Georgia Health Sciences University, Augusta, Georgia; Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Ontario

Abstract:

BACKGROUND: Medication costs and side effects, bleeding severity, and activity restrictions may all play a role in parental/child disease burden in childhood ITP. However, the precise factors involved in health-related quality of life (HRQoL) changes reported by these patients and their families are largely unknown. Our aim was to prospectively explore relationships between clinical/demographic factors that may negatively impact HRQoL in childhood ITP during the first year following diagnosis. *METHODS:* This was a prospective, single-institution study of newly diagnosed children with ITP ages 12 weeks to < 18 years. Serial evaluations of HRQoL were performed using the recently validated Kid's ITP Tools (KIT) at enrollment and 1 week, 6 months and 12 months following diagnosis. All visits included a CBC and bleeding severity grade. Demographic and baseline characteristics were summarized using descriptive statistics, with Kruskal-Wallis and Mann-Whitney tests performed when necessary. Multiple linear regression analysis was used to identify significant associations of patient/parent HRQoL at each study visit.

RESULTS: A total of 163 patients with newly diagnosed ITP were evaluated since study commencement, with 96 patients meeting all eligibility criteria. Mean parental disease burden was higher at enrollment (i.e. lower KIT score) compared to child-self and proxy HRQoL scores. HRQoL improved in parent, child and proxy reports between diagnosis and 12 month follow-up, but only parent and proxy reports were statistically significant, with changes in scores between the 1 week and 6 month visits displaying the greatest degree of improvement. There was a considerably higher disease burden present at enrollment for children and parents of children who received drug therapy at diagnosis compared to those who were managed with close observation. Multiple linear regression analysis failed to identify associations of parental disease burden other than drug treatment at enrollment and sustained skin bleeding at 12 months. Alternatively, fatigue, drug treatment, and activity restrictions remained key variables of diminished HRQoL for child and proxy reports. *CONCLUSIONS:* The findings in this study suggest that in spite of concerns and frustrations with bleeding symptoms, drug treatment, fatigue and activity restrictions, HRQoL in children with ITP is not exceedingly low at diagnosis and shows modest improvement with time.

Introduction

Childhood immune thrombocytopenia (ITP) is a common and generally benign hematologic condition with an annual incidence of approximately 2-5 cases per 100,000 children[1]. The disorder typically presents with a sudden onset of cutaneous and/or mucosal bleeding, with skin manifestations in the form of bruising and petechiae being the most common[2]. Although some patients with extremely low platelet counts ($<20{,}000/mm^3$) exhibit minimal bleeding[3], hemorrhage in childhood ITP may be severe and anxiety provoking, thus negatively impacting the child's health-related quality of life (HRQoL).

In the past, platelet count has often been the primary measure on which treatment decisions were made and outcomes were based. However, platelet count fails to account for relevant clinical and patient related outcomes and may not encompass the entirety of parental/child disease burden in childhood ITP. Additional aspects of childhood ITP including medication cost and side effects, bleeding severity and activity restrictions may all play a role in the child's HRQoL and parental disease burden alike. With this in mind, a disease specific HRQoL measure, the Kids' ITP Tools (KIT), was designed and validated[4,5]. The KIT consists of 3 components: a child self-report that is completed by children $\geq$ 7 years of age; a proxy-report that is completed by parents/primary caregivers on behalf of the child; and a parent self-report all which quantify HRQoL on a continuous scale from 0 (worst) to 100 (best).

The KIT's validation has fostered HRQoL to become an important outcome measure in childhood ITP[6] and it has already been implemented in a prospective clinical trial[7]. Yet, very little is still known about HRQoL in childhood ITP, especially serial evaluations from ITP diagnosis to its resolution. In May 2010, The Dallas ITP Cohort was created to

explore relationships between bleeding severity, drug treatment, platelet count and HRQoL in children with ITP. This report describes factors that negatively impact child and parent HRQoL in childhood ITP throughout the first year following diagnosis.

Methods

Study Design

The Dallas ITP Cohort is a prospective, single-institution study of newly diagnosed children with ITP ages 12 weeks to <18 years seen at Children's Medical Center Dallas. Because the cohort was established in 2010, the diagnosis of primary ITP was made by a pediatric hematologist according to diagnostic criteria outlined in the 1996 American Society of Hematology guidelines[8]. Subjects were enrolled on the cohort within 14 days from the child's initial platelet count. Management was left at the discretion of the treating hematologist. Platelet count at time of diagnosis at Children's Medical Center was ≤ 100,000/mm^3 based on recent IWG diagnostic criteria[9]. Patients with secondary ITP associated with other immunologic or systemic diseases were also eligible. Exclusion of subjects included new patients previously diagnosed as having ITP; seen only for a second opinion; or not anticipating having ongoing management at Children's Medical Center. Approval from The Institutional Review Board at the University of Texas Southwestern Medical Center was obtained prior to commencement, and informed consent was provided by parents/guardians with child assent when appropriate.

Study Visits and Research Assessments

Once enrolled, patients had study-directed scheduled follow-up at 1 week (+/- 5 days), 2 months, 6 months and 12 months (+/- 1 month for each visit); additional visits were scheduled as deemed necessary for clinical purposes. Families were contacted by

telephone and mail if a clinic appointment was missed to re-schedule the appointment. No compensation was offered for study participation, however all clinical and laboratory expenses at the 12 month study visit were covered at no cost to the patient in order to encourage compliance. All visits included a complete blood count (CBC), reticulocyte count, and bleeding severity assessment using the Buchanan and Adix bleeding instrument[10].

HRQoL was assessed in clinic using the Kids ITP Tool (KIT) at all study visits except at 2 months. Children ≥ 7 years of age were asked to complete their own quality of life assessment. Parents of all subjects were asked to evaluate their own quality of life as well as their estimate of quality of life of their child (proxy report). Parents were encouraged not to interact with their child while they completed the questionnaires. Patients and their parents were informed of the results of their current platelet count prior to completing KIT reports. Children were defined as having newly diagnosed ITP if they had resolution of their disease (platelet count ≥ 150,000/mm^3 without treatment in the previous 4 weeks) less than 3 months from diagnosis. Persistent ITP was defined in children with platelet count < 150,000/mm^3 for ≥ 3 months and < 12 months from diagnosis while chronic unresolved ITP was defined as meeting diagnostic criteria ≥ 12 months from diagnosis.

Statistical Analysis

Demographic and baseline characteristics were summarized using descriptive statistics. Mean KIT scores for parent, child and proxy reports were reviewed for each outpatient visit and by treatment (drug treatment vs. expectant management). KIT score analysis from baseline to 12 months was performed with Kruskal-Wallis non-parametric tests using a two-tailed exact method. *Post-hoc* pairwise comparisons between each time point were completed using Mann-Whitney tests with Bonferroni correction for 3 pairwise

comparisons. Mann-Whitney tests were also used to assess differences in HRQoL at 6 and 12 months for children with resolved and persistent/chronic ITP respectively.

Multiple linear regression analysis was used to identify significant associations of patient/parent HRQoL at each study visit. Basic demographic and clinical features included in the model were age, gender, platelet count, bleeding severity (epistaxis, oral and skin) and treatment given at diagnosis. In order to characterize factors that would be sensitive to changes in disease progression, individual responses to questions in the KIT for child and proxy reports were reviewed to isolate questions with the highest incidence of concern. Responses to questions were assigned a numerical value (1 = never, 2 = Seldom, 3 = Sometimes, 4 = Often, 5 = Always) as specified in each report. Median scores for each question at each study visit were obtained and their response was incorporated into the model if a median score of ≥ 3 was observed. Questions thought to contribute to multicollinearity were excluded, in other words, variables perfectly correlated to predictive variables already in use in the model were not included (i.e. platelet count vs. "I worry about my platelet count," or skin bleeding score vs. "My bruises bother me"). If a question was included as a variable, individual responses were recorded as present for review if the child/parent proxy documented ≥ 3 on their singular report. Significance for all tests was set at $P < 0.05$ (Bonferroni correction $P < 0.017$).

Results

Between May 2010 and October 2012, a total of 163 patients with newly diagnosed ITP were evaluated at Children's Medical Center. Of these, 96 subjects met all eligibility criteria and were enrolled in the cohort. Complete 6 month and 12 month follow-up data were analyzed for 60 (63%) and 33 patients (34%) respectively. Figure 1 depicts

completed KIT reports at each clinic visit, including resolved, persistent, and chronic ITP patients. Fifty-five children (57%) were initially identified with ITP by another physician prior to being referred to our clinic. Demographic and clinical characteristics of subjects at enrollment are summarized in Table I. At diagnosis, 69 of the 96 subjects (72%) had a platelet count $\leq 10{,}000/mm^3$, and 80 (83%) had a platelet count $\leq 20{,}000/mm^3$. Forty-four children (46%) received drug treatment at diagnosis [oral steroids: 17 (39%); IVIG: 19 (43%); both: 8 (18%)], whereas 52 were treated without drug therapy.

At diagnosis, 19% of children presented with epistaxis, 35% with oral bleeding, and 83% with bruising and petechiae (Table I). No child initially presented with intracranial hemorrhage (ICH), but one developed ICH 2 weeks later while receiving treatment with oral steroids. Active mucosal bleeding was the leading reason for administration of drug treatment (N = 29). Oral bleeding was the most common (N = 13), followed by epistaxis (N = 8), epistaxis and oral lesions combined (N = 3), hematuria (N = 2), hematochezia (N = 2) and vaginal bleeding (N = 1). Parental anxiety, patient activity level, and a low platelet count (N = 7; N = 5; and N = 3, respectively) were also factors listed by the primary hematologist as influencing the decision for drug treatment.

Parent Impact Report

Mean parental disease burden at enrollment was 30 ± 18.7 and reached 63 ± 29.0 at 12 months ($P < 0.001$; refer to Fig 2). *Post-hoc* univariate analysis did not identify any significant improvement in scores between enrollment and 1 week ($P = 0.092$) or between the 6 month and 12 month visits ($P = 0.077$), but did observe significant progress in scores between the 1 week and 6 month visit ($P = 0.001$). Mean KIT scores at enrollment for parents of children who received drug treatment at diagnosis were lower than scores for

parents of children who were managed with observation alone (26 ± 20.9 and 34 ± 15.8 respectively, P = 0.003). Although KIT scores for parents of children who received treatment continued to be lower in comparison to those who did not receive treatment, these differences were no longer significant at 1 week or beyond. Similarly, although mean scores were lower at 6 and 12 months for parents of children with persistent/chronic ITP compared to scores of children with resolved ITP, no statistical significance was observed (P = 0.323 and P = 0.075 respectively).

Child Self and Proxy Reports

Mean child self-reported KIT scores ranged from 70 ± 16.7 at diagnosis to 84 ± 19.6 at 12 month follow-up (Fig. 2), with no statistical significance being observed between the two time points (P = 0.085). Child self-reported HRQoL was considerably lower at enrollment in patients who received drug treatment at diagnosis (62 ± 15.6 treatment vs. 79 ± 13.4 observation, P = 0.006), and was again lower at 12 month follow-up (54 ± 3.5 treatment vs. 94 ± 5.9 observation, P = 0.036). Although self-reported scores were lower at 1 week and 6 month visits for children who received treatment at diagnosis than those who did not, these differences were not statistically significant (P = 0.071 and P = 0.083 respectively). HRQoL scores were similar at 6 months for both children with resolved and with persistent ITP, but were notably lower at 12 months for children with chronic ITP (resolved 98 ± 1.6; chronic 70 ± 19.5; P = 0.029).

Proxy scores were 68 ± 20.3 at enrollment to 86 ± 14.6 at twelve months (P < 0.001), with statistically significant improvement in scores evident only between the 1 week and 6 month visits (P = 0.001). Proxy scores were significantly lower in children who

received treatment at diagnosis only at enrollment (62 ± 20.5 treatment vs. 74 ± 18.8 observation, P = 0.004). While KIT scores were comparable at 6 months for patients with resolved and persistent ITP, they were distinctly lower at 12 months for children who had chronic disease (90 ± 11.4 resolved; 75 ± 18.2 chronic; P = 0.036).

HRQoL Correlation Models

Parental Disease Burden Model

Age, gender, platelet count, bleeding severity score (epistaxis, oral and skin) and treatment given at diagnosis were used in a stepwise multiple linear regression model to identify significant associations of parental disease burden at enrollment and 1 week, while persistence of disease was included for analysis at 6 and 12 month visits. The correlations of the variables are shown in Table II. At enrollment, drug treatment was the only significant parameter associated with parental disease burden, yet only accounted for approximately 5% of the variance in parental disease burden. No variables were included in the model at 1 week or 6 month visits. A continued manifestation of skin bleeding was the only statistically significant factor of parental disease burden at 12 months and accounted for almost 12% of the variance.

To further account for unknown variables affecting parental disease burden based on the child's age, *post-hoc* analyses using the regression model were run separately for parents whose children were < 7 years and ≥ 7 years old. For parents of children < 7 years, no factors were retained in the model at enrollment or 6 months. However, the child's gender (female) and drug treatment given at diagnosis accounted for approximately 23% of variance in disease burden at 1 week ($R^2 = 0.231$, P = 0.008). Just as in the overall results, skin bleeding with the addition of developing chronic ITP, were negative parameters of

parental disease burden at 12 months (R^2 = 0.466, P = 0.001). Although no associations were observed at enrollment or 1 week for parents of children ≥ 7 years old, drug treatment administered at diagnosis was the only significant variable related to parental disease burden at 6 and 12 months (6 months: R^2 = 0.281, P = 0.035; 12 months: R^2 = 0.576, P = 0.048).

Child HRQoL Model

In addition to the clinical/demographic factors applied for parent impact reports, three questions were included as variables in the model for child self-reported HRQoL based on their incidence: 1) fatigue ("I felt tired"), 2) activity restrictions ("I was bothered because I could not do the activities I like") and 3) venipuncture ("Having blood taken bothered me").

At enrollment, fatigue, venipuncture, and drug treatment given at diagnosis were all associated with a lower child self-reported quality of life. These variables accounted for nearly 72% of the variance in child HRQoL at enrollment, with fatigue present within the past 7 days being the most influential. At the 1 week visit, activity restrictions and treatment given at diagnosis were significant variables, while venipuncture and age were significant at 6 months. Activity restrictions and diagnosis of chronic ITP at 12 months were negative parameters of child self-reported HRQoL and accounted for nearly 99% of the variance in quality of life (P < 0.001).

Proxy HRQoL Model

Baseline and additional variables for proxy reports were obtained and analyzed using the same methodology applied for child self-reports. Just as in child self-reports,

fatigue, activity restrictions and venipuncture were incorporated in the model, with administration of intravenous treatment (IVIG) replacing activity restrictions at enrollment. Fatigue and intravenous treatment were associated with lower proxy KIT scores at enrollment, representing nearly 15% of the variance in quality of life. The presence of oral bleeding, fatigue and activity restrictions were significant at one week, while activity restrictions, fatigue and skin bleeding were noteworthy parameters at 6 months. By twelve months, both activity limitations and fatigue continued to be associated with lower proxy HRQoL.

Post-hoc analyses for proxy scores were also performed based on age (<7 years and ≥ 7 years). No factors were significant at enrollment for patients < 7 years old. However, fatigue continued to be a noteworthy factor from the 1 week to 12 month visit, with activity restrictions also being significant at 6 and 12 months (1 week: $P = 0.026$; 6 month: $P < 0.001$; 12 month: $P < 0.001$). Fatigue, intravenous administration of treatment at diagnosis, and platelet count were associated with lower KIT scores at enrollment for children ≥ 7 years of age ($P = 0.001$). Oral bleeding, treatment at diagnosis, and the patient's current platelet count at one week were significant factors for this patient subgroup ($P < 0.001$), while activity restrictions continued to be associated with a lower HRQoL at 6 and 12 months ($P < 0.001$ and $P = 0.003$ respectively).

Discussion

Health-related quality of life in childhood ITP has recently been recognized as an important outcome measure of disease severity. However, little is known regarding the precise factors involved in HRQoL changes over the course of ITP in both children and their

families. This study was therefore developed with the purpose of prospectively characterizing factors that may impact parental and child disease burden in childhood ITP.

While the current study demonstrated improved HRQoL in all 3 KIT reports between diagnosis and 12 month follow-up, only parent and proxy reports were statistically significant, with changes in scores between the 1 week and 6 month visits displaying the greatest degree of improvement (Fig. 2). This observation is of interest given that proxy scores were comparable to child self scores throughout the natural progression of disease. Although this study did not formally assess child-proxy agreement, moderate concordance has been previously demonstrated between the two reports in the initial study describing the KIT [5]. There are two possible explanations for the absence in statistical significance in child self-reported HRQoL. The first and most likely explanation is the significantly lower sample size of children ≥ 7 years old enrolled in our study who were able to self-complete the measure. This small sample size is to be expected given that the average age of a child presenting with ITP is 5 years[11]. Secondly, child self-reported HRQoL scores were high at diagnosis and consequently, displayed the least overall change in improvement. Whereas both parent and proxy reports had significant improvement in KIT scores between 1 week and 6 month follow-up, child scores were unchanged during that time interval.

At enrollment, KIT scores in our cohort for parent, child, and proxy reports parallel those obtained at diagnosis by Klaassen *et al*. during the initial validation of the KIT[5], and its subsequent international validation[12]. Yet our mean parental scores observed at 6 months are significantly lower compared to those noted at 3 months (53 vs. 71 respectively) during the KIT's validation. This suggests a longer duration of parental disease burden in our study population. Our initial thought was that perhaps a significant

number of children were continuing to have bleeding manifestations at 6 month follow-up, but a review of our data revealed that 72% of children had no bleeding symptoms. Additionally, of the 59 parents with completed KIT reports at 6 months, 16 (27%) still had a score < 30 even though 12 of these parents had children without any visible or spontaneous hemorrhage. Despite our efforts at every clinic visit to remind both parents and children that questions contained in the KIT should be answered with only the prior 7 days in mind, it is plausible that some parents continued to dwell on prior bleeding events/treatment side effects even 6 months after diagnosis. This could influence parent KIT scores and may explain the overall increased parental disease burden observed in our cohort.

A noteworthy finding of this study was the considerably higher disease burden present at enrollment for children and parents of children who received drug therapy at diagnosis. This finding, however, was no longer meaningful in further follow-up for parent and proxy scores but was of importance at the 12 month visit for child self-reports. Treatment was also a significant parameter of lower KIT scores in our multiple regression model, not only at diagnosis, but also 1 week after diagnosis in child self-reports. *Post-hoc* analyses for parental disease burden further established treatment at diagnosis as an early meaningful adverse parameter of HRQoL for parents of children < 7 years. While the leading reason for providing drug therapy to patients in the cohort was to manage bleeding manifestations, one third of patients received pharmacotherapy primarily as a result of parental anxiety, the child's activity level, or thrombocytopenia alone. Although a case can be made that children who received treatment at diagnosis had a higher incidence of hemorrhage and therefore treatment and bleeding are inevitably correlated, our model specifically sought to make a distinction between treatment and site-specific bleeding.

Since site-specific bleeding was not statistically meaningful at diagnosis and treatment continued to be an adverse parameter of child self-reported HRQoL one week post diagnosis, the presence of treatment as a negative parameter of HRQoL might be attributed to variables other than bleeding effects (i.e. side effects of medications, activity limitations, etc).

Pharmacotherapy in childhood ITP has often been argued to negatively impact a child's HRQoL, even prior to the KIT's development, due to its multiple side effects and toxicities[13-16]. Hemorrhage has also been noted by Neunert *et al.* to negatively impact HRQoL in childhood ITP[6], though no statistically significant correlation was observed between bleeding severity and parent/child HRQoL. Our findings support those reported by Neunert *et al*. at diagnosis, though we found that skin bleeding becomes significant for parent and proxy reports at follow-up. A possible explanation for skin manifestations as an adverse parameter of parental disease burden is their perceptibility. Not only do they serve as a constant reminder of their child's ITP, but bruising and petechiae are also visible to others—which may lead to queries by others, possibly resulting in additional parental anxiety. Conversely, the great majority of children in our cohort were not terribly concerned by their bruising or petechiae. On individual analysis to question responses for child self-reports, 56% of children in The Dallas ITP Cohort reported not being bothered by their bruising at diagnosis. Of the 4 children ≥ 7 years of age with chronic ITP at 12 months, only one described being troubled by skin manifestations.

On multivariate analysis, our model failed to identify associations of parental disease burden other than drug treatment at enrollment and sustained skin bleeding at 12 months. These variables alone failed to account for much of the variance in parental disease burden. Alternatively, fatigue, drug treatment, and activity restrictions remained

key variables of diminished HRQoL for child and proxy reports. Of note, fatigue was relevant in child self-reported HRQoL only at enrollment, yet persisted to be statistically significant at all visits for proxy reports.

While we did not formally evaluate fatigue utilizing a symptom-specific measure, fatigue has previously been reported as a common symptom in adults with ITP[17-21], with a prevalence significantly greater than that observed in the normal adult population[17]. The literature is scarce regarding studies in children describing symptoms of fatigue. One particular report from the UK assessed 94 children with primary ITP for bleeding tendency, disease management, recreational activities and social/school performance[22]. In their investigation, 8% of children reported fatigue as a symptom. Our results indicate greater incidence than noted in the previous study, as 70% of children self-reported symptoms of fatigue at diagnosis, with 51% of proxy reports relating the same.

Activity restrictions were also associated with lower HRQoL. Dissatisfaction with activity limitations has previously been reported in UK and Israeli children with ITP [23,24]. Our study observed that 59% of children self-reported frustrations with activity restrictions both 1 week and 6 months post diagnosis, and 3 out of 4 children with chronic ITP also self-reported problems with activity restrictions at 12 months. However, in our model, activity restrictions were significant for child self scores only at 1 week and 12 month follow-up. Proxy scores were comparable to child self-reports in describing frustrations with activity limitations and were statistically significant at all visits likely secondary to a larger sample size of completed reports at each visit.

The main limitation of this study was loss to follow-up, primarily at 12 months, which significantly decreased our sample size for that particular encounter. We had hoped that telephone reminders and covering all medical/visit expenses at 12 months would have

improved patient compliance, but by this study visit the great majority of patients had resolved ITP and/or had no bleeding symptoms. This made it difficult for many of our families, a great majority of whom live 2-3 hours from our institution, to return for a final research evaluation. This smaller sample size at 12 months was mostly of concern when analyzing child self-reports. However, because both proxy and child reports were comparable throughout the course of disease, we believe our data is robust.

Another study limitation is that many of our patients were not enrolled at the time when the first platelet count was obtained but were consented after formal hematologic evaluation confirmed the diagnosis of ITP. The difference in these two events averaged 3-4 days, though was as long as 14 days permissible per study protocol. Although this assured that all patients in the cohort met diagnostic criteria for ITP, it prevented collection of KIT reports and bleeding symptoms at onset. This lapse in time allows both patients and parents the opportunity to search their symptoms/condition on the Internet before formal education by a hematologist has taken place. While some Internet sites contain valid educational resources for ITP, others may have incorrect or outdated information that could increase both parental and child anxiety/disease burden and consequently affect KIT scores at enrollment. Though we did not formally assess whether families had researched their condition on the Internet, many parents in our cohort freely revealed they had searched the interweb prior to hematologic evaluation.

An additional limitation includes the inability to identify variables associated with increased parental disease burden. This observation suggests that variables factoring into parental disease burden in childhood ITP are more complex than once considered and continue to be poorly defined. Although the relationships identified in this study between clinical/demographic factors and HRQoL in childhood ITP will certainly help clinicians

quickly assess a child's/parent's HRQoL, these associations have yet to be validated by a second cohort, which is currently underway in our institution.

Despite these limitations, this is the first study to prospectively evaluate HRQoL changes in children with newly diagnosed ITP throughout the first year following diagnosis. The findings in this study suggest that in spite of concerns and frustrations with bleeding symptoms, treatment, fatigue and activity restrictions, HRQoL in children with ITP is not exceedingly low at diagnosis and shows modest improvement with time. The relationships identified in this report will not only aid clinicians in quickly assessing HRQoL in children with newly diagnosed ITP, but also provide hematologists with foresight of key aspects that negatively impact HRQoL throughout the course of disease.

References

1. Zeller B, Rajantie J, Hedlund-Treutiger I, et al. Childhood idiopathic thrombocytopenic purpura in the Nordic countries: epidemiology and predictors of chronic disease. Acta Paediatr 2005:94(2):178-184.
2. Bolton-Maggs P. Severe bleeding in idiopathic thrombocytopenic purpura. Journal of pediatric hematology/oncology 2003:25 Suppl 1:S47-51.
3. Neunert CE, Buchanan GR, Imbach P, et al. Severe hemorrhage in children with newly diagnosed immune thrombocytopenic purpura. Blood 2008:112(10):4003-4008.
4. Barnard D, Woloski M, Feeny D, et al. Development of disease-specific health-related quality-of-life instruments for children with immune thrombocytopenic purpura and their parents. Journal of pediatric hematology/oncology 2003:25(1):56-62.
5. Klaassen RJ, Blanchette VS, Barnard D, et al. Validity, reliability, and responsiveness of a new measure of health-related quality of life in children with immune thrombocytopenic purpura: the Kids' ITP Tools. J Pediatr 2007:150(5):510-515, 515 e511.
6. Neunert CE, Buchanan GR, Blanchette V, et al. Relationships among bleeding severity, health-related quality of life, and platelet count in children with immune thrombocytopenic purpura. Pediatr Blood Cancer 2009:53(4):652-654.
7. Klaassen RJ, Mathias SD, Buchanan G, et al. Pilot study of the effect of romiplostim on child health-related quality of life (HRQoL) and parental burden in immune thrombocytopenia (ITP). Pediatric blood & cancer 2011.
8. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood 1996:88(1):3-40.
9. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009:113(11):2386-2393.
10. Buchanan GR, Adix L. Grading of hemorrhage in children with idiopathic thrombocytopenic purpura. J Pediatr 2002:141(5):683-688.
11. Kuhne T, Imbach P, Bolton-Maggs PH, et al. Newly diagnosed idiopathic thrombocytopenic purpura in childhood: an observational study. Lancet 2001:358(9299):2122-2125.
12. Klaassen RJ, Blanchette V, Burke TA, et al. Quality of life in childhood immune thrombocytopenia: international validation of the kids' ITP tools. Pediatric blood & cancer 2013:60(1):95-100.
13. Blanchette V, Bolton-Maggs P. Childhood immune thrombocytopenic purpura: diagnosis and management. Hematol Oncol Clin North Am 2010:24(1):249-273.
14. Buchanan GR, de Alarcon PA, Feig SA, et al. Acute idiopathic thrombocytopenic purpura--management in childhood. Blood 1997:89(4):1464-1465; author reply 1466.
15. Bolton-Maggs PH. Acute idiopathic thrombocytopenic purpura--management in childhood. Blood 1997:89(4):1465; author reply 1466.
16. Bolton-Maggs P, Tarantino MD, Buchanan GR, et al. The child with immune thrombocytopenic purpura: is pharmacotherapy or watchful waiting the best initial

management? A panel discussion from the 2002 meeting of the American Society of Pediatric Hematology/Oncology. J Pediatr Hematol Oncol 2004:26(2):146-151.
17. Newton JL, Reese JA, Watson SI, et al. Fatigue in adult patients with primary immune thrombocytopenia. Eur J Haematol 2011:86(5):420-429.
18. Signorovitch J, Brainsky A, Grotzinger KM. Validation of the FACIT-fatigue subscale, selected items from FACT-thrombocytopenia, and the SF-36v2 in patients with chronic immune thrombocytopenia. Qual Life Res 2011:20(10):1737-1744.
19. Mathias SD, Gao SK, Miller KL, et al. Impact of chronic Immune Thrombocytopenic Purpura (ITP) on health-related quality of life: a conceptual model starting with the patient perspective. Health Qual Life Outcomes 2008:6:13.
20. Snyder CF, Mathias SD, Cella D, et al. Health-related quality of life of immune thrombocytopenic purpura patients: results from a web-based survey. Curr Med Res Opin 2008:24(10):2767-2776.
21. McMillan R, Bussel JB, George JN, et al. Self-reported health-related quality of life in adults with chronic immune thrombocytopenic purpura. Am J Hematol 2008:83(2):150-154.
22. Sarpatwari A, Watson S, Erqou S, et al. Health-related lifestyle in adults and children with primary immune thrombocytopenia (ITP). British journal of haematology 2010:151(2):189-191.
23. Butros LJ, Bussel JB. Intracranial hemorrhage in immune thrombocytopenic purpura: a retrospective analysis. Journal of pediatric hematology/oncology 2003:25(8):660-664.
24. Zilber R, Bortz AP, Yacobovich J, et al. Analysis of health-related quality of life in children with immune thrombocytopenia and their parents using the kids' ITP tools. Journal of pediatric hematology/oncology 2012:34(1):2-5.

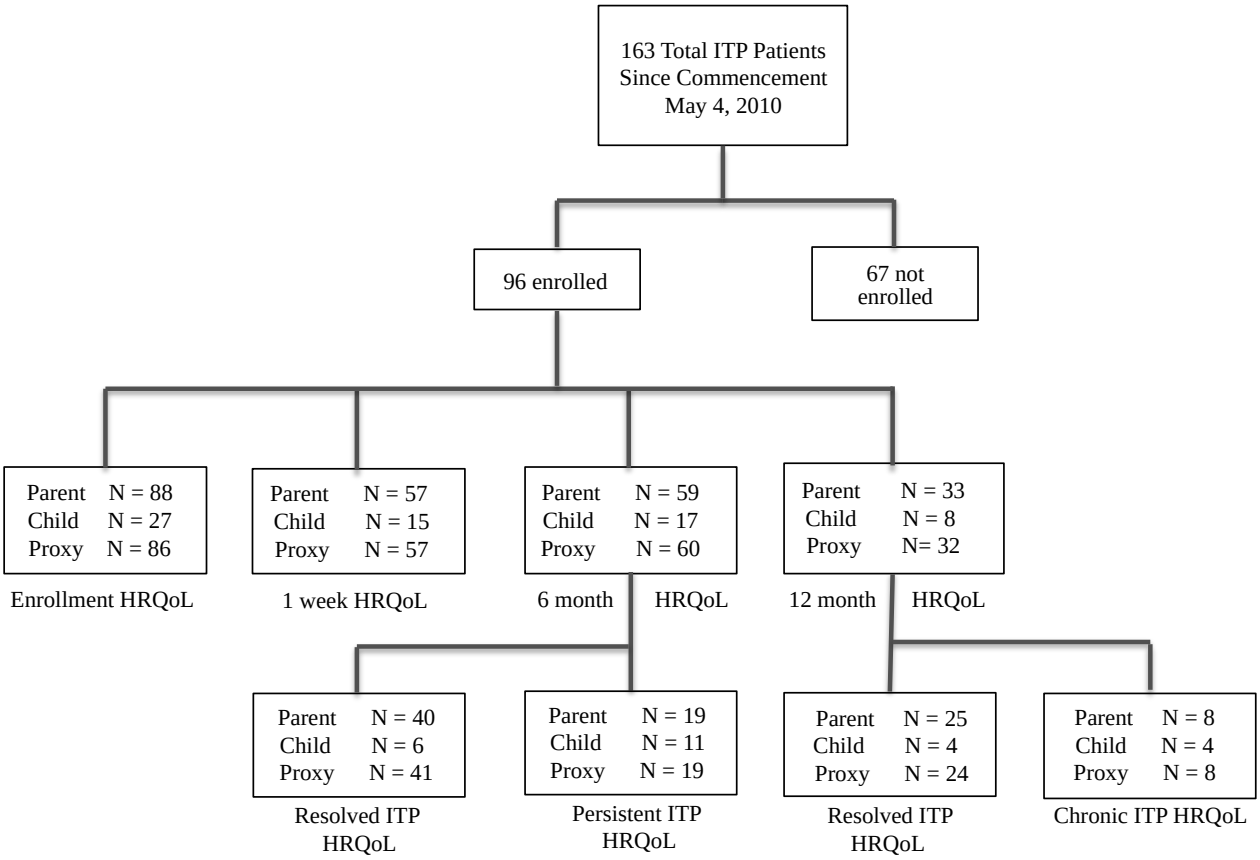

Fig. 1. Flow chart of patient cohort QoL including number of persistent / chronic ITP patients.

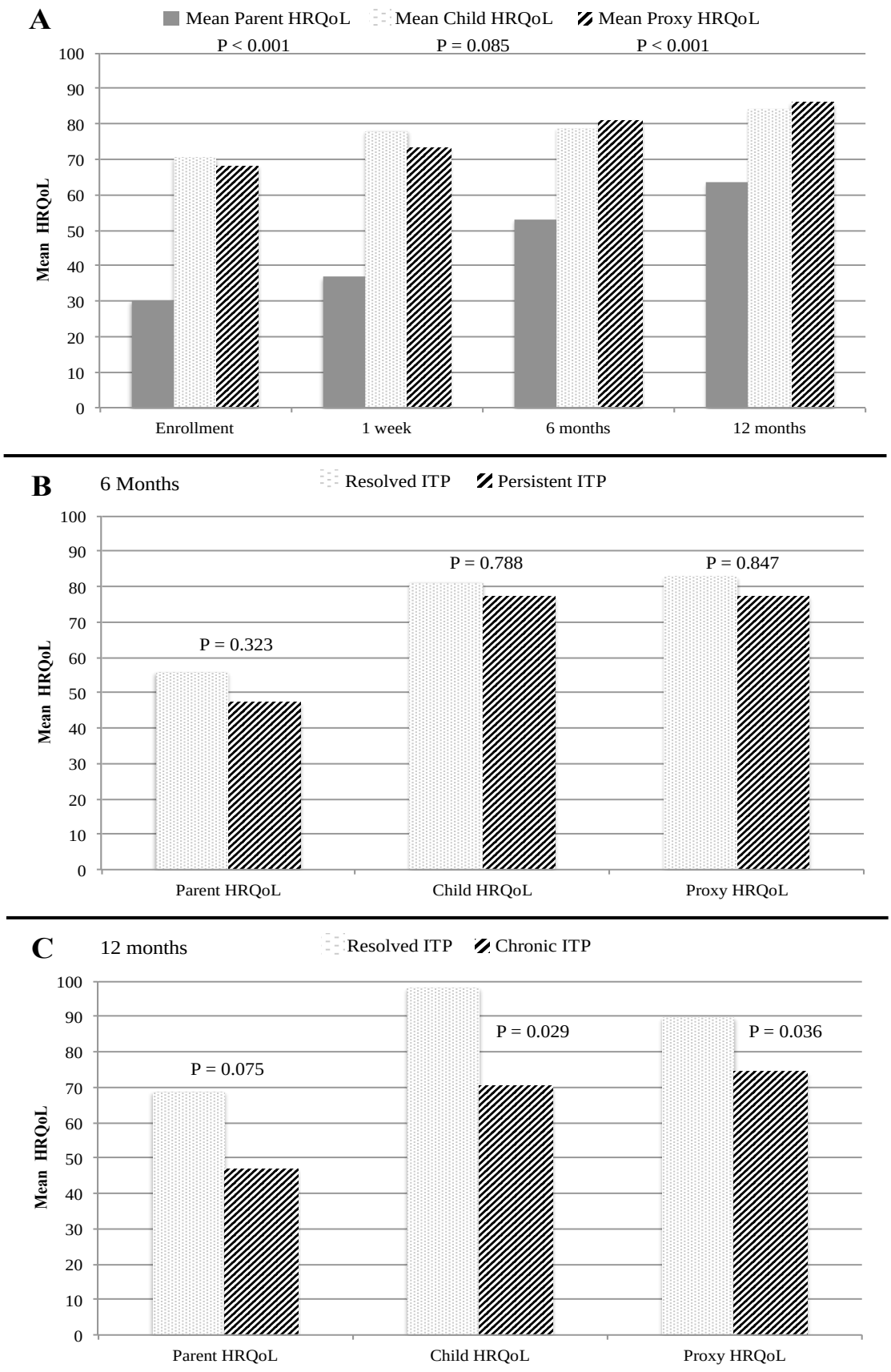

Fig. 2. Mean HRQoL for parent, child and proxy reports. **A.** HRQoL from enrollment through 12 month visit. **B.** Resolved vs. persistent ITP HRQoL at 6 months. **C.** Resolved vs. chronic ITP HRQoL at 12 months.

Table I. Baseline Patient Characteristics

	Total N = 96	Observation N = 52	Drug Treatment N = 44
Mean Age (range)	5 (12 wks -17 yrs)	6 (18 wks -17 yrs)	5 (12 wks -17 yrs)
< 2 years (%)	27 (28)	12 (23)	15 (34)
2 to < 7 years (%)	42 (44)	26 (50)	16 (36)
7 to < 18 years (%)	27 (28)	14 (27)	13 (30)
Gender			
Male (%)	59 (61)	28 (54)	31 (70)
Female (%)	37 (39)	24 (46)	13 (30)
Platelet Count x 10^9/L(range)			
Mean initial plt. count	11 (1-61)	13 (1-61)	8 (1-37)
Mean diagnostic count	12 (0-51)	17 (1-51)	6 (0-46)
Mean no. of days between initial CBC and enrollment	4 (0-14)	3 (0-14)	4 (0-13)
Bleeding Severity at Diagnosis	Epistaxis (%)	Oral (%)	Skin (%)
Grade 0	78 (82)	62 (65)	16 (17)
1	7 (7)	15 (16)	9 (9)
2	5 (5)	16 (17)	36 (38)
3	5 (5)	3 (3)	31 (32)
4	1 (1)	NA	4 (4)
Total	96 (100)	96 (100)	96 (100)

CBC, complete blood count; Bleeding Grade: 0 - none; 1 - minor; 2 - mild; 3 - moderate; 4 - severe

Table II. Clinical and Demographic Factors Correlated with HRQoL

Parent HRQoL Model	Variable(s)[+]	R^2	B	S.B.	*P*
Enrollment	Treatment	0.054	-8.71	-0.233	0.029
1 week	NA				
6 months	NA				
12 months	BS Skin	0.125	-12.82	-0.354	0.043
Child HRQoL Model					
Enrollment	Fatigue	0.724	-15.6	-0.435	< 0.001
	Venipuncture		-15.35	-0.468	
	Treatment		-13.41	-0.409	
1 week	Act. Restr.	0.543	-15	-0.562	0.009
	Treatment		-12.22	-0.476	
6 months	Venipuncture	0.711	-64.65	-0.918	< 0.001
	Age (in years)		-2.13	-0.350	
12 months	Act. Restr.	0.989	-33.5	-0.791	< 0.001
	Chronic ITP		-11	-0.300	
Proxy HRQoL Model					
Enrollment	Fatigue	0.149	-12.24	-0.298	0.002
	IV Tx		-11.1	-0.223	
1 week	BS Oral	0.309	-8.55	-0.279	< 0.001
	Fatigue		-9.5	-0.301	
	Act. Restr.		-7.87	-0.247	
6 months	Act. Restr.	0.557	-21.04	-0.519	< 0.001
	Fatigue		-10.17	-0.273	
	BS Skin		-5.87	-0.250	
12 months	Act. Restr.	0.793	-20.39	-0.612	< 0.001
	Fatigue		-12.52	-0.412	

Results from stepwise multiple linear regression. [+] Variables listed in order of entry; B, beta coefficient; S.B., standardized beta coefficient; NA, no variables were entered into the equation; BS, bleeding severity; Act. Restr., activity restrictions; IV Tx, treatment administered intravenously.