Health-Related Quality of Life and Burden of Fatigue in Chinese Patients with Immune Thrombocytopenia: A Cross-Sectional Study

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Abstract To describe the health-related quality of life (HRQoL) and fatigue burden among adult patients with immune thrombocytopenia (ITP) in China and determine whether they vary with disease phase. This is a cross-sectional, multi-centre observational study of adult ITP patients and the general population. Participants completed the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F). We compared HRQoL and fatigue between ITP patients and the general population, overall and by disease phase (newly diagnosed, persistent, and chronic), using propensity score matching. 203 Patients and 269 members of the general population were recruited. Thirty-six ITP patients (17.7%) were newly diagnosed, 46 (22.7%) were persistent, and 121 (59.6%) were chronic. Compared with the general population, ITP patients had impaired HRQoL and greater fatigue burden. The persistent ITP group showed the largest number of SF-36 scales exceeding the minimally important difference: physical functioning [-10.5 ; 95% confidence interval (CI) -24.5 to 3.5 ; $P < 0.001$], role physical (-16.7 ; 95% CI -36.4 to 3.0 ; $P < 0.001$), social functioning (-15.6 ; 95% CI -34.5 to 3.3 ; $P < 0.001$), and role emotional (-12.1 ; 95% CI -26.0 to 1.8 ; $P < 0.001$). Chronic ITP patients had the worst FACIT-F scores (36.89 ± 5.21). Higher fatigue severity was associated with lower physical and mental HRQoL. The HRQoL and fatigue burden of Chinese adult patients with ITP vary by disease phase.

Persistent ITP patients were the most vulnerable subgroup in terms of HRQoL, while chronic ITP patients bear the heaviest fatigue burden.

Keywords Immune thrombocytopenia · Health-related quality of life · Fatigue · Short form-36 · Functional assessment of chronic illness therapy-fatigue

Introduction

Immune thrombocytopenia (ITP) is a rare autoimmune disease characterized by isolated thrombocytopenia and increased risk of bleeding [1]. ITP affects both children and adults. The annual incidence rate among adults is approximately 50–100 new cases per million population [2]. Thrombocytopenia is caused by pathological anti-platelet antibodies, damaged megakaryocyte production, and T cell-mediated platelet destruction, with the precise roles of these three processes varying by patient [3]. Based on the time since diagnosis, cases can be distinguished as newly diagnosed, persistent, and chronic ITP [2]. Patients within 3 months of their diagnosis were defined as having newly diagnosed ITP. Patients with ITP lasting for 3–12 months were considered to have persistent ITP; this category included patients who did not achieve spontaneous remission and those unable to maintain a response after stopping treatment between 3 and 12 months from diagnosis. Finally, patients with ITP lasting for more than 12 months were considered to have chronic ITP.

Although ITP is the most common haemorrhagic disease in clinical settings, many patients with ITP, even when experiencing severe thrombocytopenia, do not exhibit significant bleeding [1]. Furthermore, life-threatening haemorrhages are rare [4]. Patients with ITP tend to have a

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relatively good prognosis and must live with the disease for a long time. Thus, a good quality of life is necessary [5]. Over the past decade, studies have clearly demonstrated the substantial impact of ITP on health-related quality of life (HRQoL) [6]. In the first such study, adult patients with ITP showed lower HRQoL scores than did the general population in the United States, and even lower scores than those of individuals with other chronic diseases, such as hypertension and arthritis [7]. Fatigue is also a major concern for patients with ITP; indeed, fatigue is one of the most common and distressing symptoms for patients with chronic and autoimmune disorders [8].

Although there is much work evaluating HRQoL and fatigue in adult patients with ITP [9], there is still limited information from real-world settings in Chinese patients. Furthermore, it is unclear whether HRQoL and fatigue vary by disease phase. Therefore, we assessed HRQoL and fatigue burden in Chinese adults with ITP. Our main objective was to compare the HRQoL of ITP patients with that of the general population, overall and by patient group (newly diagnosed, persistent, and chronic). The secondary objective was to describe the level of fatigue burden and analyse its relationship with HRQoL outcomes.

Methods

Study Design and Participants

This was a cross-sectional, multi-centre observational study. From May 2017 to October 2018, 203 adult patients with ITP were recruited from Jiangsu Province Hospital of Traditional Chinese Medicine (TCM), Taizhou Hospital of TCM, and Huaian Second People's Hospital. We recruited adult patients with ITP (≥ 18 years old) with a clear consciousness, who were able to read and understand the questionnaires, who volunteered to participate, and who signed the informed consent form. We excluded those with concomitant participation in other patient-reported outcome (PRO) studies that might interfere with this study, and those with any psychiatric condition or major cognitive impairment hampering a self-reported evaluation. We included patients regardless of whether they were receiving treatment or observation.

We also recruited 269 members of the general population as a control group from the communities of Nanjing. These control participants had no known chronic illness and had signed the informed consent form.

Study Procedures

We trained all investigators using a standardized procedure before the survey. We recruited participants using

convenience sampling. Upon recruitment, we introduced the purpose, content, and significance of the study to them. All those interested gave written informed consent and completed the questionnaires on paper in a quiet, independent room. The questionnaires were checked by the investigators. Participants' personal information was recorded.

HRQoL Evaluation

To assess HRQoL, we used the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36, version 1). This is one of the most widely used generic, self-reported questionnaire on health status. It comprises 36 items in eight scales: physical functioning (PF); role physical (RP); bodily pain (BP); general health (GH); vitality (VT); social functioning (SF); role emotional (RE); and mental health (MH). For each scale, the items are coded, summed, and transformed to range from 0 (worst health) to 100 (best health) [10]. The PF, RP, BP, and GH scales are mainly related to physical health, while the VT, SF, RE, and MH scales are mainly related to mental health [11]. We used the MCS and PCS (the mental and physical component summary scores) in this study.

Fatigue Evaluation

Fatigue was assessed with the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), a validated self-report questionnaire used to assess patients' perceptions of how fatigue affects their cognitive, physical, and psychosocial functioning in the past 7 days. The FACIT-F contains 13 items. The subjects rate how each item is affected by fatigue on a 5-point scale with the following response options: 0 = 'not at all', 1 = 'a little bit', 2 = 'somewhat', 3 = 'quite a bit' and 4 = 'very much'. Except for items An5 and An7 ("An" is the alphanumeric code), which are positive scores, all items are reverse scored. The total score ranges from 0 to 52, with higher scores indicating lighter fatigue [12].

Other Variables

We collected data on the following variables for the analysis: (1) sociodemographic characteristics (i.e. age, gender, education, marital and occupational status) and (2) clinical factors from patients' medical records at last medical visit (i.e. duration of illness, phase of ITP, any comorbidity, current treatment for ITP, the World Health Organization [WHO] Bleeding Scale score, white blood cell count, haemoglobin, platelet count, and neutrophil proportion). We also collected the age, gender, education, and marital status of the general population.

Statistical Analysis

The variables were reported in terms of frequencies and proportions, means and standard deviations, and interquartile ranges. To minimize the bias, we used propensity score matching to compare HRQoL outcomes between the ITP patients (overall and by disease group) and general population. Participants were matched using the optimal nearest-neighbour matching algorithm based on age, gender, education, and marital status. We used the Bonferroni correction for the p values of the adjusted mean difference in SF-36 results between all ITP patients and the corresponding matched control group, to account for multiple comparisons. The effect sizes (ESs) of the adjusted mean differences in SF-36 and FACIT-F scores were also calculated. Based on past literature, the minimally important difference (MID, a measure of clinical relevance) of the SF-36 scale in this study was set to 8 points [13]. According to the quartiles of the FACIT-F scores, we categorized patients as having low, low-medium, medium-high, and high levels of fatigue. We then examined differences in SF-36 scores by fatigue levels. Spearman's correlation coefficient was used to investigate the correlations between patients' clinical factors and FACIT-F scores. All statistical tests were two-tailed, with statistical significance set to $\alpha = 0.05$ (save for when the Bonferroni correction was applied). All analyses were performed using R (v3.5.2).

Results

Of the 230 patients who met the inclusion criteria, 203 (90%) agreed to participate and completed the questionnaire. Their sociodemographic and clinical characteristics are reported in Table 1. The control group comprised 269 members of the general population, as detailed in appendix Table 4.

HRQoL Comparison of Overall ITP Population and General Population

Compared with the general population, ITP patients scored lower on all eight domains of the SF-36 scale. Furthermore, the RP ($\Delta = -10.4$, $P < 0.001$), SF ($\Delta = -13.2$, $P < 0.001$), and RE ($\Delta = -15.6$, $P < 0.001$) all exceeded the MID. The details are depicted in Fig. 1.

HRQoL Comparison by ITP Patient Group with General Population

Adjusted comparisons were made in each patient group with their respective peers in the general population

Table 1 Sociodemographic and clinical characteristics of patients

Variable	N = 203
Gender [n (%)]	
Male	82 (40.39)
Female	121 (59.61)
Age	
Mean (SD)	46.12 (14.20)
Interquartile range	36.00–56.00
Education level [n (%)]	
Primary school and below	46 (22.66)
High school and above	157 (77.34)
Marital status [n (%)]	
Married	166 (81.77)
Single ^a	37 (18.23)
Patient group category [n (%)]	
Newly diagnosed	36 (17.73)
Persistent	46 (22.66)
Chronic	121 (59.61)
Time from diagnosis (months)	
Mean (SD)	42.76 (64.85)
Interquartile range	6.00–47.50
WHO bleeding scale score [n (%)] ^b	
0	157 (77.34)
1	46 (22.66)
Patient currently in treatment [n (%)]	
No	39 (19.21)
Yes	164 (80.79)
Current comorbidity [n (%)]	
No	146 (71.92)
Yes	57 (28.08)
Platelets ($\times 10^9/L$) ^b	
Mean (SD)	61.55 (51.40)
Interquartile range	29.50–80.00
White blood cells ($\times 10^9/L$) ^b	
Mean (SD)	7.60 (3.00)
Interquartile range	5.63–8.83
Haemoglobin (g/L) ^b	
Mean (SD)	136.23 (19.60)
Interquartile range	123.00–151.00
Neutrophil (%) ^b	
Mean (SD)	62.87 (12.28)
Interquartile range	53.95–70.65

SD standard deviation

^aIncluding single, divorced, and widow

^bAt the last medical visit

(Table 2a, b). The persistent group exceeded the MID the most: PF [-10.5 ; 95% confidence interval (CI) -24.5 to 3.5 ; $P < 0.001$], RP (-16.7 ; 95% CI -36.4 to 3.0 ; $P < 0.001$), SF (-15.6 ; 95% CI -34.5 to 3.3 ;

Fig. 1 Adjusted comparisons of the SF-36 scales between ITP patients (overall population) and general population norms

Fig. 2 Health-related quality of life scales by fatigue severity

$P < 0.001$), and RE (-12.1 ; 95% CI -26.0 to 1.8 ; $P < 0.001$). The RP, SF, and RE scales showed the greatest impairments, with all three groups reporting clinically meaningfully worse scores compared to the general population. The RE scale was the worst in the newly diagnosed and chronic groups, while the RP was the worst in the persistent group.

Fatigue Burden by ITP Group and Comparison with the General Population

Table 3(A) shows descriptive comparisons of the mean FACIT-F scores by ITP group. ITP patients showed significantly lower scores than did the general population (37.54 ± 5.56 vs. 44.42 ± 4.49 , $P < 0.001$), with the

Table 2 Adjusted comparisons of SF-36 scales with general population norms by ITP group

ITP group	Physical functioning			Role physical			Bodily pain			General health		
	Mean (95% CI) ^a	P	ES	Mean (95% CI) ^a	P	ES	Mean (95% CI) ^a	P	ES	Mean (95% CI) ^a	P	ES
(A) Physical health scales												
Newly diagnosed	− 1.0 (− 3.0; 1.0)	0.532	− 0.05	− 11* (− 22.3; 0.3)	0.001	− 0.54	− 5.3 (− 11.9; 1.3)	0.053	− 0.27	− 0.3 (− 0.9; 0.3)	0.842	− 0.02
Persistent	− 10.5* (− 24.5; 3.5)	< 0.001	− 0.57	− 16.7** (− 36.4; 3.0)	< 0.001	− 0.82	− 6.2 (− 15.5; 3.1)	0.003	− 0.31	− 6.5 (− 14.8; 1.8)	< 0.001	− 0.43
Chronic	− 4.3 (− 5.8; − 2.8)	0.021	− 0.23	− 8.8* (− 17.9; 0.3)	< 0.001	− 0.43	− 3.3 (− 7.2; 0.6)	0.039	− 0.17	− 5.3 (− 11.7; 1.1)	< 0.001	− 0.35
ITP group	Vitality			Social functioning			Role emotional			Mental health		
	Mean (95% CI) ^a	P	ES	Mean (95% CI) ^a	P	ES	Mean (95% CI) ^a	P	ES	Mean (95% CI) ^a	P	ES
(B) Mental health scales												
Newly diagnosed	− 3.3 (− 7.0; 0.4)	0.189	− 0.21	− 10.6* (− 22.3; 1.1)	< 0.001	− 0.63	− 12.1* (− 26.6; 2.4)	0.001	− 0.51	− 1.7 (− 4.8; 1.4)	0.274	− 0.11
Persistent	− 3.2 (− 8.3; 1.9)	0.045	− 0.21	− 15.6* (− 34.5; 3.3)	< 0.001	− 0.92	− 12.1* (− 26.0; 1.8)	0.001	− 0.51	− 2.7 (− 5.7; 0.3)	0.227	− 0.18
Chronic	− 3.3 (− 7.5; 0.9)	0.017	− 0.21	− 7.9* (− 17.9; 0.7)	< 0.001	− 0.51	− 18.1** (− 40.0; 3.5)	< 0.001	− 0.77	− 8.7* (− 17.2; − 0.2)	< 0.001	− 0.58

ES effect size, computed for each scale as the group-specific adjusted mean difference divided by the standard deviation of the corresponding matched control group

*The score difference exceeds the minimally important difference (MID; 8 points); **the score difference exceeds twice the MID

^aMean difference between patients according to ITP group and the respective matched control subjects, adjusted for age, gender, education, and marital status

Table 3 Burden of fatigue in ITP patients

FACIT-F	All patients	Newly diagnosed	Persistent	Chronic	
(A) Fatigue by ITP group					
Mean (SD)	37.54 (5.56)	37.97 (5.92)	38.91 (5.87)	36.89 (5.21)	
IQ range	33.50–41.50	33.50–43.00	34.00–42.00	33.00–40.00	
ITP group category	Mean (SD)		Δ	ES	P
	ITP patient	General population			
(B) Comparison of fatigue between ITP group and the general population					
Newly diagnosed	37.97 (5.92)	44.42 (4.50)	− 6.1	− 1.35	< 0.001
Persistent	38.91 (5.87)	44.42 (4.50)	− 5.5	− 1.22	< 0.001
Chronic	36.89 (5.21)	44.42 (4.50)	− 7.3	− 1.62	< 0.001

Δ Mean differences adjusted for age, sex, education, and marital status. *ES* effect size, computed for each scale as the group-specific adjusted mean difference divided by the standard deviation of the corresponding matched control group. On this scale, a higher score denotes a lower level of fatigue

ITP immune thrombocytopenia, *FACIT-F* functional assessment of chronic illness therapy-fatigue, *SD* standard deviation, *IQ* interquartile

chronic patients reporting the lowest means (36.89 ± 5.21). Further descriptive comparisons revealed that the chronic ITP group showed the largest mean FACIT-F score differences from the general population ($\Delta = -7.3$, $ES = -1.62$, $P < 0.001$). Specifically, it had the greatest *ES*. The details are reported in Table 3(B).

Relationship Between Fatigue and HRQoL

The 1st, 2nd, and 3rd quartiles in FACIT-F scores among all ITP patients were 33.5, 37, and 41.5, respectively. Figure 2 shows the mean scores of the SF-36 scales by fatigue level. The RE scale was the most compromised by fatigue: Differences in RE scale scores for ITP patients with the highest versus those with the lowest fatigue levels were more than three times the MID ($\Delta = 127.5$). As shown in Fig. 2, higher fatigue severity was associated with lower physical and mental HRQoL.

We also conducted an exploratory analysis investigating the association between fatigue and patients' clinical factors. Fatigue showed strong correlations with platelet count ($\rho = 0.653$, $P < 0.001$), and weak correlations with WHO bleeding scores ($\rho = 0.413$, $P < 0.001$). However, it had almost no correlations with the remaining variables.

Discussion

PROs are meaningful because they offer investigators the opportunity to attain patients' perspectives on illness and help physicians make better-informed treatment decisions [14]. Therefore, we conducted a PRO-based cross-sectional study to examine the HRQoL and fatigue of adult patients with ITP in China.

Patients with ITP showed lower HRQoL on all eight SF-36 dimensions compared with the general population, with the differences in the RP, SF, and RE scales exceeding the MID. These findings indicate that both the physical and mental health of ITP patients are impaired, which aligns with past studies on adults with ITP using the SF-36 in China, the USA, the UK, and Italy [5, 7, 11, 15]. Compared with other patient populations, ITP patients had similar SF-36 scores as patients with diabetes, but lower scores than those of patients with hypertension, arthritis, and cancer. They only had higher scores than those of patients with congestive heart failure or limb loss [7]. The physical and psychological burden of both the disease and its treatment can affect HRQoL. Frequent blood tests, adverse drug reactions, fear of bleeding and haemorrhagic attacks, unreasonable fatigue, non-specific pain, negative emotions, social limitations, and reproductive health problems (e.g. sexual dysfunction and menorrhea) are all considered to be causes of HRQoL in ITP patients [11].

Further analysis revealed that HRQoL varied with ITP patients' disease phase. The greatest HRQoL impairments were found in the persistent ITP group, as they showed the largest number of SF-36 scales exceeding the MID: RF, RP, SF, and RE. There is some previous evidence corroborating this result. Mathias et al. [16] found that patients with ITP at least 1 year after diagnosis ($N = 60$) had lower mental health scores than did patients within 1 year of their diagnosis ($N = 13$). Efficace et al. similarly reported that persistent ITP patients are the most vulnerable subgroup, as they had clinically meaningful impairments in the PF, SF, RP, RE, and MH, in a comparison of patient groups [11]. We speculate that persistent ITP patients are still in a transitional stage, wherein they lack understanding of the disease and feel panicked as a result. They might pay

excessive attention to avoid bleeding events, which can limit their daily activities, leading to impaired physical and psychological health. By contrast, newly diagnosed patients have not yet fully felt the impact of the disease on their life and chronic patients might have already adapted to their situation.

Another key finding was the fatigue burden reported by ITP patients. Compared with the general population, ITP patients had significantly worse outcomes for the FACIT-F. The stratified analysis revealed that the chronic group had the largest mean differences in the FACIT-F scores compared to the general population. Fatigue in ITP patients is often dismissed by clinicians as unrelated to their disease, even though it is an important symptom that has been reported in numerous ITP studies [8]. A large joint study using the Fatigue Impact Scale (FIS) to assess 585 British and 93 American ITP patients found that the incidence of significant fatigue ($FIS \geq 40$) was markedly higher in these patients than in the general population (39% and 22%, respectively, vs. 2.5%) [17]. Similarly, an extended study of eltrombopag showed that the average FACIT-F score of patients with ITP ($n = 197$) was lower than that of healthy people [12].

Fatigue is known to be an important aspect of HRQoL, so we explored the connection between them. As expected, we found that higher levels of fatigue corresponded to impairments in most physical and psychological HRQoL dimensions. Furthermore, the difference in HRQoL between patients with high fatigue and those with low fatigue was significant. A relationship between fatigue and HRQoL has also been found in patients with other chronic haematological diseases [18].

To our knowledge, this is the first study to simultaneously evaluate HRQoL and fatigue burden of ITP patients in China, while also stratifying them by disease phase. Our results overall suggest that the HRQoL of ITP patients in China has obvious deficiencies that need to be addressed. Physicians should pay greater attention to the persistent and chronic groups, as they might benefit most from targeted supportive care programs.

This study has several limitations. First, as a cross-sectional design, it is impossible for us to establish causation regarding HRQoL and fatigue changes with disease progress. For example, the effects of treatment on patients' HRQoL and fatigue may reflect both positive effects of disease remission and negative effects of adverse drug reactions. Because of the lack of longitudinal studies, the relationship between therapeutic factors and fatigue is difficult to clarify. Second, we used a generic HRQoL measure (the SF-36), which might not capture specific

aspects of HRQoL affected by ITP or detect subtle differences between patient groups. However, there is currently no Chinese version of a disease-specific instrument (e.g. the Immune Thrombocytopenic Purpura Patient Assessment Questionnaire). Lastly and quite notably, our study only included patients who gave informed consent; it is possible that only some patients with symptoms agreed to take part in the study and many of the relatively well patients chose not to participate. In addition, the control group was drawn from local communities in Nanjing and might not be representative of the general population. All of these factors may have led to selection bias. Thus, future research should take these limitations into account.

Conclusion

This study showed that (1) HRQoL and fatigue burden in adult ITP patients vary by disease phase, and (2) persistent ITP patients were the most vulnerable subgroup in terms of HRQoL, while the chronic group bore the heaviest fatigue burden when compared with their peers from the general population. In the future, more practical scales for Chinese ITP patients should be developed and longitudinal studies are needed to explore the causal relationship and trends over time in HRQoL and fatigue.

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Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Appendix

See Table 4.

Table 4 Sociodemographic characteristics of general population

Variable	N = 269
Gender [n (%)]	
Male	114 (42.38)
Female	155 (57.62)
Age	
Mean (SD)	45.11 (12.97)
Interquartile range	35.00–56.00
Education level [n (%)]	
Primary school and below	50 (18.59)
High school and above	219 (81.41)
Marital status [n (%)]	
Married	217 (80.67)
Single (including single, divorced, and widow)	52 (19.33)

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