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Possible Targets to Reduce Fatigue in Chronic Immune Thrombocytopenia Patients – An Explorative Study

Wobke E.M. van Dijk[1] Merel M. Nap-van der Vlist[2] Hans Knoop[3] Roger E.G. Schutgens[1]

[1] Center for Benign Hematology, Thrombosis and Hemostasis, Van Creveldkliniek, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
[2] Department of Social Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
[3] Department of Medical Psychology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam Public health research institute, Amsterdam, The Netherlands

Address for correspondence Roger E.G. Schutgens, MD, Van Creveldkliniek, University Medical Centre Utrecht, University Utrecht, Office C.01.428, Postbox 85500, 3508 GA Utrecht, The Netherlands (e-mail: r.schutgens@umcutrecht.nl).

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Abstract

Background Fatigue in immune thrombocytopenia (ITP) is frequent and burdensome, but we lack the knowledge to help these patients.

Aim The aim of the study is to explore the role of disease activity and other potentially modifiable factors in fatigue.

Method This cross-sectional study included adult chronic ITP patients ($n = 59$). Univariable linear regression (corrected for confounders) was used to determine the relationship between disease activity (platelet count $<30 \times 10^9$/L or treatment), disease-specific factors (bleeding symptoms, ferritin), and transdiagnostic factors (FACT-G physical/functional/emotional/social well-being subscales, physical activity level, and vitamin D) and fatigue (Checklist Individual Strength fatigue subscale). Several multivariable models with clustered sets of variables were used to compare the proportion of explained variance of fatigue (adjusted R^2).

Results Significant relations with moderate effect sizes (>0.50) were found for physical and functional well-being and fatigue, and physical activity and fatigue. Other significant relations with fatigue (effect size 0.30–0.47) included skin and organ bleeding, emotional and social well-being, vitamin D, and disease activity. Notably, the models with disease activity and disease-specific factors explained $<20\%$ of the variance in fatigue, while the models with transdiagnostic factors (functioning and physical activity) explained $>50\%$. Vitamin D alone explained 12% of the variance in fatigue.

Conclusion Transdiagnostic (non-disease-specific) rather than disease-specific factors explained a large part of the variance in ITP-related fatigue. Many factors related to fatigue are potentially modifiable and should be investigated as targets for interventions.

Keywords
- fatigue
- immune thrombocytopenia
- modifiable factors
- disease activity
- transdiagnostic

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Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Introduction

Fatigue is a complaint that has been underestimated for a long time in patients with immune thrombocytopenia (ITP). Historically, the care for ITP patients focused on preventing severe bleeding manifestations, which occur mainly when platelet counts are below 30×10^9/L.[1] However, almost half of the patients report fatigue as the top symptom they would like to have resolved.[2] Severe fatigue is present in 22% up to 58% of the ITP patients and was found to remain prevalent and debilitating throughout the course of the disease.[2–4] Subsequently, the burden of fatigue for ITP patients has become an important topic for clinicians and researchers worldwide.

Many clinicians acknowledge that improving quality of life, including fatigue, is an important treatment goal for patients with ITP. An intuitive approach to achieve this is to treat the ITP with any of the known ITP-specific treatment options.[5–7] However, these treatments may also cause side effects and adverse events and may actually increase rather than reduce fatigue.[8] To date, there is no convincing evidence of a beneficial effect on fatigue for any of the existing ITP treatments.[6–9] Some patients do tend to report more fatigue when their platelet count is low, which suggests a relationship between fatigue and disease activity or signs and symptoms of ITP.[4] However, the existing literature about the relationship between fatigue and platelet count or bleeding is ambiguous.[4,8] In fact, fatigue is known to persist even after treatment and in patients with low disease activity.[2,4,7–12] Overall, it may be that we need to broaden our horizon beyond the ITP-specific approach to solve fatigue, particularly in patients who do not have an indication for treatment based on bleeding symptoms and platelet count.

As fatigue remains present in patients with low disease activity, other, non-disease-specific, factors are likely to contribute to persistent fatigue in ITP.[2,4,7–12] An extensive review has identified many potentially relevant factors contributing to fatigue in ITP, including sleep disturbances, pre-morbid lack of activity or psychological symptoms, work and career responsibilities, illness beliefs, perceived stress, and mood.[8] The relevance of these factors has been demonstrated in many other chronic diseases, where fatigue also often persists in the absence of disease activity.[13,14] In fact, in chronically ill patients, non-disease-specific factors seem to explain fatigue much better than the specific diagnosis and its symptoms.[8,15–18] Behavioral interventions, such as exercise programs or cognitive behavioral therapy, can successfully target many of these non-disease-specific "transdiagnostic" factors.[19,20] Indeed, cognitive behavioral therapy has proven to be beneficial for fatigue in patients with diabetes mellitus type 1 and multiple sclerosis patients, among other chronic diseases.[21,22] As such, a transdiagnostic approach to modify fatigue might be a valuable addition to the ITP-specific approach.

This cross-sectional study aimed to assess the relationship between several disease-specific and transdiagnostic factors and fatigue. As many of these factors are potentially modifiable, this study aimed to generate hypotheses for potential targets for interventions for fatigue in chronic ITP patients. First, we assessed the relationship between disease activity and fatigue to investigate the role of a disease-specific approach. Second, we assessed the individual relationships between other disease-specific factors, transdiagnostic factors and fatigue. The factors were selected beforehand based on clinical reasoning and, if available, on previous research in ITP or other diseases. Third, we assessed which cluster of factors contributed most to explaining the variance in fatigue by comparing the adjusted R^2 of different multivariable models.

Methods

This cross-sectional cohort study (the PICI study[23]) was performed at the University Medical Center Utrecht, The Netherlands. The study comprised a single visit including blood withdrawal and the completion of several questionnaires, as explained below. This study was approved by the local Medical Ethical Committee and is in accordance with the Good Clinical Practice guidelines.

Subjects

The inclusion period ran from April 01, 2019 to July 01, 2021. We included patients with primary chronic ITP who had active disease at the time of study participation. Primary chronic ITP was defined according to the criteria of the American Society of Hematology: a current platelet count $\leq 100 \times 10^9$/L, a disease duration of $\geq$1 year, and no indication of an underlying condition.[24] Furthermore, patients with a current platelet count $>100 \times 10^9$/L because of current ITP treatment were also included, as they were also considered to have active disease. Patients were eligible if they were in care of the outpatient clinic of our tertiary center in the past or at the time of study participation, were $\geq$16 years of age, and willing and able to both understand the study information and give written informed consent. No additional exclusion criteria were applied.

Measurements

Demographics and disease specifics were extracted from the patient's medical record, and included age, sex, disease duration, comorbidities, and current ITP treatment.

The outcome, fatigue, was assessed by the fatigue severity subscale of the Checklist Individual Strength (CIS-fatigue). The CIS-fatigue is a self-reported questionnaire about the prior 14 days, that comprises eight items with a 7-point Likert scale scoring.[25–27] The score ranges from 8 to 56. A cut-off score of 35 or more is used to define severe fatigue.[27] The CIS-fatigue has been extensively validated in many chronically ill populations.[15,28,29] Recently, we have validated the CIS-fatigue in ITP.[23]

To assess the role of disease activity, we categorized patients into high and low disease activity.[4,8,30] In the high disease activity group, we aimed to include patients with a more active autoimmune reaction. Therefore, this group included both patients with a platelet count $<30 \times 10^9$/L or

ITP therapy at the time of study participation. The low disease activity group included patients with a platelet count $\geq 30 \times 10^9$/L without treatment.

We assessed several potentially modifiable factors. The assessed disease-specific factors were ferritin and bleeding symptoms measured by the ITP-Bleeding Assessment Tool (ITP-BAT).[31,32] Hemoglobin was not assessed as a potentially modifiable factor, because none of the patients in our sample were anemic. The ITP-BAT is a questionnaire that comprises several items regarding specific bleeding symptoms and is scored by a physician or trained researcher. It generates three separate scores, one for the skin domain (four items, e.g., petechiae, hematomas), one for the mucosal domain (five items, e.g., epistaxis, gum bleeding), and one for the organ domain (nine items, e.g., menorrhagia, gastrointestinal bleeding, hemoptysis). The highest item score within each domain reflects the final score for the respective domain. Each item is scored on severity, based on the worst incident in the prior 2 weeks. The severity score ranges from zero (not at all severe) to three or four (most severe) depending on the potential severity of the symptom. The non-disease-specific factors we assessed included level of physical activity, physical, functional, social, and emotional well-being, and vitamin D. The level of physical activity was measured by a subscale of the CIS, with three items on a 7-point Likert scale and a score range of 3 to 21; a higher score indicates more complaints.[25–27] Similar to the CIS-fatigue, this subscale has been validated in the current study population.[23] Functioning was measured with the Functional Assessment of Cancer Therapy-General (FACT-G), which is a questionnaire from the Functional Assessment of Chronic Illness Therapy (FACIT) measures.[33] Although originally developed for patients with cancer, the scale has been used and validated in many other chronically ill populations, including human immunodeficiency virus and multiple sclerosis, as well as the healthy population.[33] It comprises 27 items on quality of life that are divided into four subscales: physical well-being, functional well-being, social well-being, and emotional well-being. The five response options range from "Not at all" to "Very much." Vitamin D was assessed by the 25-OH-vitamin D levels, using a routine laboratory test.

Statistical Analysis

Descriptive statistics were used to summarize the patient characteristics.

All subsequent analyses were done by linear regression. Each of the presented models were corrected for confounders, i.e., non-modifiable factors that are known to be related to fatigue: age, sex, the presence of comorbidity (dichotomous), and ITP duration in years.[4,8] The assumptions of all linear regression models were tested for linearity between the dependent and independent variable, homoscedasticity, and normality of the residuals. Multicollinearity among the dependent variables and confounders in each model (defined as correlations stronger than 0.7) were ruled out. We did not strictly adhere to the rule of thumb of a maximum of one predictor per ten patients, as this study was primarily aimed to generate hypotheses.

First, the relationship between disease activity and fatigue was assessed. Second, separate models were made for each potentially modifiable factor, with the respective factor as the predictor and fatigue severity as the dependent variable. To compare the effects of the different models the effect sizes (standardized β's) were reported. An effect size of $\geq|0.2|$, $\geq|0.5|$, and $\geq|0.8|$ was considered small, moderate, and large, respectively. For simplicity, we will refer to these models as univariable, even though they are corrected for confounders. Finally, we assessed how much of the variance of fatigue was explained by different sets of the factors. For this, we made several multivariable models with clustered sets of factors, i.e., one model with disease activity variable(s), one model with variables of the signs and symptoms of ITP, one model with the functioning variables, one model with physical activity level, and one model with vitamin D, respectively. The proportion of the variance of fatigue that was explained by each model was expressed by the adjusted R^2.

We performed two sensitivity analyses. The first assessed the relationship between the specific FACT-G items and fatigue. This was done by four multivariable models, one for each of the four subscales, where every model contained the items of the respective subscale as separate variables. This way, we were able to assess the contribution of the specific items to fatigue to further explore specific potential targets for intervention. The second analysis assessed the relative contribution of each significant ($p < 0{,}20$) predictor if they are all combined into one multivariable model. Because our sample size is much too small for a model with so many predictors, it should be interpreted with caution, therefore we do not report p-values for this analysis.

For the analyses with the FACT-G, two questions were removed from the original questionnaire: "I have a lack of energy" was removed from the physical well-being subscale because of its close resemblance to the outcome, fatigue; and "I am content with the quality of my life right now" from the functional well-being subscale because a reduced quality of life is a known consequence from fatigue that does not directly offer any potential for intervention. We do report the analyses using the full FACT-G scales (without removal of questions) in ►**Supplementary Table S1**.

Software

All analyses were performed in RStudio, version 2021.09.0 + 351.

Sample Size

We aimed at a sample size of 60 patients, which makes the study sufficiently powered to detect correlations of ≥ 0.355 ($\alpha = 0.05$, $\beta = 0.20$), and thus assess internal consistency and convergent validity.

Results

In total, 59 patients were included, of whom 33 patients (56%) were severely fatigued. The baseline characteristics are depicted in ►**Table 1**. One patient (2%) was younger than 18, all others were 18 years or older.

Table 1 Baseline characteristics

Total	59
Female *n* (%)	36 (61)
Mean age, years ± SD	45 ± 18.4
Any comorbidity *n* (%)	26 (44)
Medication use, not ITP-related *n* (%)	24 (41)
Median ITP duration years (IQR)	7 (3–17)
Median platelet count at visit $\times 10^9$/L (IQR)	61 (39–92)
Platelet count $<30 \times 10^9$/L *n* (%)	12 (20)
Median hemoglobin level at visit mmol/L (IQR)	9,1 (8.6–9.6)
Median ferritin level at visit µg/L (IQR)	62 (34–106)
Ferritin <20 µg/L *n* (%)	6 (10)
Current ITP treatment *n* (%)	
None	45 (76)
TPO-RA	11 (19)
Sirolimus	1 (2)
Combined treatment	2 (3)[a]
Number of previous therapies[c] *n* (%)	
0	18 (31)
1	5 (12)
2	11 (27)
3	3 (7)
≥4	22 (54)
History of splenectomy *n* (%)	7 (12)
ITP-BAT skin score	
0	13 (22)
1	17 (29)
2	25 (42)
3	4 (7)
ITP-BAT mucosal score	
0	27 (46)
1	22 (37)
2	10 (17)
ITP-BAT organ score	
0	39 (66)
1	7 (12)
2	12 (22)

Abbreviations: IQR, interquartile range; ITP, immune thrombocytopenia; *n*, number; SD, standard deviation; TPO-RA, thrombopoietin-receptor agonist.
[a]Prednisone, eltrombopag, and sirolimus.
[b]Prednisone and mycophenolate mofetil.
[c]Including the current therapy.

Disease Activity and Fatigue

Severe fatigue was present in 16/34 (47%) patients with low disease activity and 17/25 (68%) patients with high disease activity. In the patients with high disease activity, severe fatigue occurred in 9/13 (69%) with a platelet count of $\geq 30 \times 10^9$/L and treatment, and 8/12 (67%) with a platelet count of $<30 \times 10^9$/L.

Linear regression showed that patients with high disease activity were significantly more fatigued (►**Table 2**, β 8.83, $p = 0.02$, ES 0.30). When we split the high disease activity group into patients with a platelet count of $\geq 30 \times 10^9$/L and treatment and patients with a platelet count of $<30 \times 10^9$/L, both groups were still more fatigued than patients with low disease activity, although the confidence interval was too wide to reach statistical significance in the latter group (β 7.29, 95% CI −2.18 to 16.76, and β 10.72, 95% CI 0.47–20.97, respectively).

Potentially Modifiable Factors

Signs and Symptoms of ITP and Fatigue

Bleeding symptoms and ferritin levels were considered signs and symptoms of ITP. Of these variables, both skin and organ bleeding were significantly related to fatigue (►**Table 3**, β 5.73, $p = 0.01$, ES 0.35 (small) and β 6.42, $p = 0.01$, ES 0.36, respectively). High skin scores were the result of many petechiae or large subcutaneous hematomas, while high organ scores were mainly due to menorrhagia (►**Supplementary Table S2**). Ferritin was unrelated to fatigue, also when assessed as a continuous variable (data not shown).

Transdiagnostic Factors and Fatigue

All non-disease-specific factors were significantly related to fatigue, with at least a small effect size (►**Table 3**). Moderate effect sizes were found for physical and functional well-being (β −2.99, $p = 0.00$, ES −0.67 and β −2.74, $p = 0.00$, ES −0.70, respectively), level of physical activity (β 1.83, $p = 0.00$, ES 0.72), and vitamin D (β −10.42 for a level of ≥50 vs. <50 nmol/L, $p = 0.01$, ES −0.36). The direction of the relationships was as expected: fatigue was worse in patients with a worse (i.e., lower) well-being score, a worse (i.e., higher) physical activity score, or a vitamin D level below 50 nmol/L.

The Explained Proportion of Fatigue

Overall, disease activity and signs and symptoms of ITP explained 16 to 17% of the variance in fatigue (►**Table 4**). In contrast, a much higher proportion of the variance was explained by functioning and level of physical activity (54–56%). Notably, the model with vitamin D deficiency alone also explained 12%.

Sensitivity Analysis: Exploring the Specific FACT-G Items

In the analysis assessing which specific items of each FACT-G subscale were related to fatigue, we found significant relationships for the patients' ability to meet the needs of the family (β −7,48, $p < 0.01$, ES −0,62), sadness (β −7.33, $p < 0.01$, ES −0.56), receiving emotional support from the family (β −7.99, $p = 0.04$, ES −0.48), the ability to work (β −5.58, $p < 0.01$, ES −0.42), the quality of sleep (β −3.94,

Table 2 The relation between fatigue and disease activity

	Unstandardized β (95% CI)	*p*-Value	Effect size
High disease activity vs. low disease activity	8.83 (1.20–16.46)	0.02	−0.30
Platelet count $\geq 30 \times 10^9$/L without treatment[a]	Ref		
Platelet count $< 30 \times 10^9$/L[b]	7.29 (−2.18–16.76)	0.13	0.21
Platelet count $\geq 30 \times 10^9$/L with treatment[c]	10.72 (0.47–20.97)	0.04	0.29

Abbreviations: CI, confidence interval; *n*, number.
Note: All models are correct for age, sex, comorbidities, and immune thrombocytopenia duration.
[a]$n = 34$.
[b]$n = 12$, of whom one received current treatment.
[c]$n = 13$.

Table 3 Univariable linear analyses (corrected for confounders) for each of potentially modifiable factors with fatigue as dependent variable

	Unstandardized β (95% CI)	*p*-Value	Effect size
Disease-specific factors			
Signs and symptoms of ITP			
ITP-BAT skin score	5.73 (1.46–10.01)	0.01	0.35
ITP-BAT mucosal score	3.60 (−1.87–9.08)	0.19	0.18
ITP-BAT organ score	6.42 (1.50–11.33)	0.01	0.36
Ferritin level of ≥20 vs. <20 μg/L	−4.30 (−17.64–9.03)	0.52	−0.09
Transdiagnostic factors			
Functioning (FACT-G subscales)			
Physical well-being	−2.99 (−3.94– − 2.04)	0.00	−0.67
Functional well-being	−2.74 (−3.54– − 1.93)	0.00	−0.70
Emotional well-being	−1.61 (−2.46– − 0.75)	0.00	−0.47
Social well-being	−1.19 (−2.05– − 0.34)	0.01	−0.35
Activity (CIS subscale)			
Level of activity	1.83 (1.37–2.29)	0.00	0.72
Vitamin D			
25-OH-vitamin D level of ≥50 vs. <50 nmol/L	−10.42 (−17,98– − 2.85)	0.01	−0.36

Abbreviations: CI, confidence interval; CIS, Checklist Individual Strength; FACT-G, Functional Assessment of Cancer Therapy-General; ITP, immune thrombocytopenia; ITP-BAT, immune thrombocytopenia-Bleeding Assessment Tool.
Note: All models are correct for age, sex, comorbidities, and immune thrombocytopenia duration.

Table 4 Multivariate models comparing the explained proportion of fatigue for clustered sets of variables

	Adjusted R^2
Model 1 ITP disease activity	17%
Model 2 ITP signs and symptoms	16%
Model 3 Functioning (FACT-G subscales)	56%
Model 4 Activity (CIS subscale)	54%
Model 5 Vitamin D	12%

Abbreviations: CIS, Checklist Individual Strength; FACT-G, Functional Assessment of Cancer Therapy-General; ITP, immune thrombocytopenia.
Note: All models are correct for age, sex, comorbidities, and immune thrombocytopenia duration.

$p = 0.01$, ES −0.29), and the satisfaction with their sex life (β −4.76, $p = 0.03$, ES −0.38) (►**Supplementary Table S3**).

The analysis that combined all significant predictors into one model showed that the level of physical activity and physical well-being remained the most relevant (ES >0.20). The effect sizes of the other well-being subscales, disease activity, vitamin D, and bleeding scores dropped below 0.20 (►**Supplementary Table S4**).

Discussion

This study suggests that high disease activity is associated with more fatigue. However, severe fatigue seemed also highly prevalent in ITP patients with low disease activity. We have identified many factors that may be related to

fatigue, including skin and organ bleeding, physical and functional well-being, physical activity, and vitamin D. Many of these factors are potentially modifiable. Notably, transdiagnostic factors seemed to explain more of the variance in fatigue than disease activity or signs and symptoms of ITP.

Strengths and Weaknesses

This is the first study to explicitly search for transdiagnostic and potentially modifiable factors in ITP-related fatigue and to assess how much variance is explained by different sets of factors. This study design ensured clinical relevance by indicating which research direction is promising to help fatigued patients. The most important weakness of the study is the relatively small sample size, which makes this study primarily explorative and not fit for drawing firm conclusions. Furthermore, this study has partly taken place during the SARS-CoV-2 pandemic. This may have influenced our study results to some extent, particularly because the pandemic may have contributed to fatigue through personal or societal (transdiagnostic) factors. However, none of our patients had SARS-CoV-2-related complaints during study participation. Overall, we believe that the results are largely generalizable, although future research should confirm this. The other weaknesses of this study are due to its cross-sectional nature. First, there may be an overrepresentation of patients with a long duration of fatigue; the results may therefore mainly apply to patients with chronic fatigue. Furthermore, the causality of the factors that were related to fatigue cannot be demonstrated. However, fatigue is often not solely a cause or consequence. Instead, fatigue often has bi-directional interactions with factors such as depression, anxiety, social support, and ability to work.[34] Previous research shows that interventions targeting such factors successfully reduced fatigue in other chronic diseases.[22,35–38] The last limitation of this study is the, intentional, lack of correction for multiple testing. We found this strategy appropriate, as the aim of this study was to explore plausible hypotheses rather than prove significance. The findings of this study should be confirmed in larger studies.

Fatigue and Transdiagnostic Factors

We found that all transdiagnostic factors were significantly related to fatigue and explained by far the largest part of the variance. This is supported by the full multivariable model where only transdiagnostic factors kept a relevant effect size. This is not surprising, as previous research also found that the specific diagnosis or disease-specific factors were only accountable for a small part of the variance in fatigue.[8,15–18] Indeed, all identified factors in our study are well-known in the pathogenesis of fatigue in other chronic diseases.[15] Many have also been identified before in ITP-related fatigue, including vitality, social functioning, and emotional functioning.[3,4,9] Furthermore, anxiety and depressive symptoms are known to be frequently present in ITP and related to quality of life, although the relation with fatigue has not been directly assessed in ITP patients before.[39–42]

Transdiagnostic factors offer potential targets for interventions. Although causality between transdiagnostic factors and fatigue could not be demonstrated in this study, fatigue is often perpetuated by a complex interplay of bidirectional relationships between different factors, as shown by the biopsychological model and the International Classification of Functioning, Disability and Health (ICF-model) from the World Health Organization.[16,43] Targeting one of the factors involved can improve the entire interplay, which can result in less fatigue. A good example is physical activity: a reduced activity is a normal response to short-term fatigue, but in the long term it may actually perpetuate fatigue by causing sleep disturbances and dysregulation of the sleep–wake cycle. Specific transdiagnostic factors that could be targeted with, for example, behavioral interventions could be sleep disturbances, physical inactivity, or experiencing a lack of emotional support from others. Indeed, behavioral interventions (e.g., cognitive-behavioral therapy, exercise therapy, and self-management programs) were all effective in reducing fatigue in several other chronic diseases.[22,35–38] Two specific findings were the quality of sleep, that was also associated with ITP-related fatigue in our sensitivity analysis, and the relative importance of vitamin D in explaining variance in fatigue. Sleep disturbances may be caused by a delayed melatonin secretion onset, in which case supplementation of melatonin may be effective. In other chronic diseases, melatonin supplementation was found to effectively reduce fatigue, although not in all trials.[44–46] It may be worthwhile to explore this therapeutic option further. Vitamin D deficiency was highly prevalent in our study population (49%). Interestingly, reduced vitamin D levels have been found previously in ITP, as well as in other autoimmune cytopenias, and systemic lupus erythematosus (SLE), among others.[47–49] In fact, vitamin D supplementation was found to reduce fatigue in (juvenile-onset) SLE.[50] Although vitamin D supplementation in deficit patients will not solve all fatigue, further investigating the effect of this easy and cheap treatment option may also be worthwhile.

Of note, the specific factors playing a role may be very different between individuals, which urges for an individualized approach in management decisions. Overall, however, our study suggests that interventions regarding sleep, social, and emotional functioning, mood, and physical activity may successfully reduce fatigue in ITP.

Fatigue and Signs and Symptoms of ITP

We found that skin and organ bleeding were related to fatigue. Previous literature shows that bleeding symptoms are related to a lower quality of life and possibly fatigue, partly due to worries about physical appearance and suspicions about domestic abuse.[4,7,8,39,41] Of note, high organ bleeding scores comprised mainly patients with menorrhagia, which is known to independently affect the quality of life in many different domains.[51,52] Bleeding symptoms may be a relevant target for interventions in fatigued patients. Depending on the type of bleeding, symptoms may be targeted symptomatically (for example with tranexamic acid or hormonal therapy in case of menorrhagia) or by increasing the platelet count with ITP-specific treatments. However, the benefits of ITP-specific treatment may not

outweigh the side effects, particularly in patients with a platelet count $\geq 30 \times 10^9$/L. It may therefore be interesting to study whether it is preferable to target cognitions regarding bleeding rather than the bleeding symptoms themselves. Importantly, signs and symptoms seem to explain only a limited part of the variance in fatigue. Resolution of bleeding symptoms is, therefore, unlikely to completely resolve fatigue.

Fatigue and Disease Activity

We found more fatigue in patients with high disease activity. The high disease activity group comprised both patients with a current platelet count below 30×10^9/L and patients with current treatment. In both these subgroups, we assume that the fatigue is due to high disease activity. However, of course, both platelet count and treatment have their limitations as a proxy for disease activity. Instead, fatigue may be related to the thrombocytopenia in the first group and to treatment side effects in the second group.[4,8,53] Unfortunately, we cannot distinguish between disease activity, thrombocytopenia, and treatment side effects in our study. It would, therefore, be insightful to use inflammation parameters in future research to measure the relation between fatigue and disease activity.[8] This has not been done before in ITP. The overall literature is ambiguous about the relationship between both platelet count and ITP-treatment and fatigue. For example, one previous study confirmed an independent association between a platelet count below 30×10^9/L and fatigue,[4] but other studies contradicted it.[30,54] This is in line with our results, as disease activity did explain a small part of the variance in fatigue, but other factors seem to play a more important role. Similarly, some studies found that ITP-treatment reduced fatigue, while others found no beneficial effect.[6–9] Of course, our definition of low and high disease activity is somewhat arbitrary. More specific subgroups, such as patients with no response, partial response, and complete response with medication and without medication could provide additional information on the role of disease activity. Unfortunately, our sample size is too small for so many subgroups. However, it is important to realize that the disease activity accounted for only a limited part of the variance in fatigue. This is also illustrated by the presence of severe fatigue in patients with low disease activity, in both our study and other chronic diseases.[13,14,17] Possibly, inflammation is mainly involved in the initial phase of fatigue, while transdiagnostic factors, such as cognition and activity, play a larger role in the perpetuation of fatigue.[2,4,8,9] More research is necessary to identify the different processes that lead to the occurrence and perpetuation of fatigue in ITP. However, based on this study, transdiagnostic symptoms seem a more promising target for ameliorating fatigue than disease activity.

Implications for Clinicians and Future Research

Clinicians may want to realize that disease activity, signs, and symptoms only partly explain fatigue. Treating the ITP will, thus, often not solve the fatigue. Although this study is only explorative, it may be advised to address transdiagnostic factors in the doctor's office, for example by providing adequate verbal and written information and discussing topics such as anxiety, fear, physical activity, and the acceptance of family and friends. Furthermore, this study generated many promising hypotheses: including the potential benefit of interventions targeting psychosocial factors, physical activity, quality of sleep, and vitamin D levels. Further research should investigate whether modifying these factors will indeed reduce ITP-related fatigue. Specific interventions that could be further explored are self-management programs, exercise therapy, cognitive behavioral therapy, and/or vitamin D supplementation. Furthermore, further research should explore a more personalized approach, so that counselling and interventions can be tailored to the individual.

Conclusion

This hypothesis-generating study suggests that fatigue in ITP is partly explained by disease activity, but for a much larger part by transdiagnostic factors. Many of these factors are potentially modifiable, including physical and functional well-being, physical activity, and vitamin D. As such, they may be promising targets for interventions such as self-management programs, exercise therapy, cognitive behavioral therapy, sleep interventions, and/or vitamin D supplementation.

What Is Known on This Topic?

- Fatigue is considered one of the top symptoms that patients with immune thrombocytopenia would like to have resolved.
- In many other chronic diseases, disease activity or the specific diagnosis only explains the variance in fatigue for a small part.

What Does This Paper Add?

- This hypothesis generating study suggests that fatigue in chronic immune thrombocytopenia is only partly explained by disease activity, but for a much larger part by transdiagnostic factors.
- Transdiagnostic factors that were associated with fatigue included physical and functional well-being, activity, and vitamin D.

Supporting Information

Additional supporting information can be found online in the Supporting Information section at the end of the article.

Supplementary Tables

- ►**Supplementary Table S1**. All models assessing the relation between complete (without removal of questions) physical and functional well-being subscale and fatigue

- ►**Supplementary Table S2**. Immune thrombocytopenia Bleeding Assessment Tool (ITP-BAT) scores per domain and item in all patients
- ►**Supplementary Table S3**. Multivariable models assessing the relative contribution of the questions within the respective subscales of the Functional Assessment of Cancer Therapy-General (FACT-G)
- ►**Supplementary Table S4**. Full model with all significant predictors ($p < 0.20$)

Authors' Contributions

The research was designed and performed by W.E.M.v.D. and REGS. The analyses were performed by W.E.M.v.D. W. E.M.v.D. wrote the manuscript, which was critically revised by M.M.N.V., H.K., and R.E.G.S..

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Conflict of Interest

None declared.

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