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Original Article

Assessment of Fatigue in Patients with Chronic Myeloid Leukemia Receiving Targeted Therapy: A Cross-Sectional Study

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Abstract

Background: Fatigue is a common side effect of tyrosine kinase inhibitor (TKI) therapy in patients with chronic myeloid leukemia (CML), leading to reduced health-related quality of life (HRQoL) and decreased treatment adherence.

Aim: To evaluate the severity of fatigue and the factors influencing it, including vitamin D deficiency, in CML patients undergoing TKI therapy.

Methods: This cross-sectional observational study included 60 CML patients on TKI therapy. Fatigue severity was assessed using the 13-item Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale, with severe fatigue defined as a score of ≤30. HRQoL was evaluated using the Functional Assessment of Cancer Therapy-General (FACT-G). Vitamin D levels were measured, and sociodemographic, clinical, and laboratory data were collected from patient records.

Results: The mean age of participants was 44.6 years, with 34 (57%) being female. The median duration of treatment was 82.3 months. Severe fatigue was reported by 29 (48%) participants. Univariate analysis showed significant associations between severe fatigue and factors such as TKI dose, adherence to treatment, time to first complete cytogenetic response, and vitamin D deficiency ($p = 0.009$, 0.006, 0.021 and <0.001; respectively). Multivariate analysis confirmed a significant association between severe fatigue and vitamin D deficiency. Additionally, severe fatigue and vitamin D deficiency were both significantly linked to poorer overall HRQoL.

Conclusion: Healthcare providers should address factors influencing fatigue, particularly vitamin D deficiency, in the management of CML patients receiving TKI therapy.

Keywords: Chronic myeloid leukemia, Fatigue, Quality of life, Tyrosine kinase inhibitors, Vitamin D
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Introduction

Tyrosine kinase inhibitors (TKIs) have significantly improved the prognosis of chronic myeloid leukemia (CML), increasing the 8-year relative survival rate from below 15% to over 85% [1]. As a result, patients successfully treated with TKIs now have a life expectancy comparable to the general population. However, TKI therapy requires long-term, often indefinite, daily treatment, and it can lead to side effects that negatively impact patients' health-related quality of life (HRQoL), potentially affecting treatment adherence [2].

Fatigue is a common side effect experienced by patients with CML undergoing TKI therapy. Previous studies have shown that 68% of CML patients on TKIs experience moderate to severe

fatigue, which is associated with poorer HRQoL and decreased adherence to treatment [3]. Identifying the psychological, biological, and social factors contributing to fatigue in these patients could help develop targeted interventions to support those at risk of significant fatigue [4].

Earlier research has examined factors linked to the severity of fatigue in CML patients receiving TKI therapy, identifying associations with younger age, female sex, use of medications known to cause fatigue, medical comorbidities, and physical inactivity. These findings align with the broader cancer survivorship literature, which also highlights age, gender, and comorbid conditions as risk factors for increased cancer-related fatigue [5]. However, the relationship between fatigue and vitamin D deficiency has not been thoroughly explored.

One biological factor linked to fatigue is vitamin D deficiency [6]. Vitamin D is a group of fat-soluble secosteroid hormones derived from various dietary sources. Sunlight exposure activates vitamin D, which supports overall health and immune function [7]. Vitamin D deficiency is common, especially among individuals experiencing muscle pain, headaches, weakness, osteomalacia, and other age-related issues [8].

This analysis aimed to explore sociodemographic factors, clinical aspects (including vitamin D deficiency) and health behaviors associated with fatigue severity and its relationship with HRQoL in a sample of patients with CML undergoing TKI therapy.

Methods

This cross-sectional observational study was conducted at the Clinical Oncology Department of Menoufia University Hospital and the Medical Oncology Department of the National Cancer Institute, Cairo University, Egypt, from June to December 2023.

Participants

The participants were recruited during their regular visits to the hematology outpatient clinics at the two study sites. The study included adults who met the following inclusion criteria: age 18 years or older, diagnosed with chronic phase CML, and received TKI for at least three months. Patients who had progressed to the accelerated or blast phases were excluded.

Fatigue and Health-Related Quality of Life Assessment and Other Data Collected

Participants completed a questionnaire to evaluate fatigue severity and its predictors using the 13-item Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-Fatigue), which assessed fatigue experienced over the past week. Each item was rated on a 5-point Likert scale, from 0 (not at all) to 4 (very much). The FACIT-Fatigue score was calculated by summing the item responses, with possible scores ranging from 0 to 52; lower scores reflected greater fatigue. A FACIT-Fatigue score of 30 or below was considered indicative of severe fatigue [9].

To assess HRQoL, the 27-item Functional Assessment of Cancer Therapy-General (FACT-G) was used, which includes four subscales measuring physical, social/family, emotional, and functional well-being over the past week. Responses were also recorded on a 5-point Likert scale, from 0 (not at all) to 4 (very much). The the total HRQoL and subscale scores were obtained by summing the responses, with the total FACIT-G score ranging from 0 to 108; higher scores signified better HRQoL.

Patient records were reviewed to collect sociodemographic data (age, gender, marital status, smoking status, and body mass index [BMI]), details of treatment with TKIs and its outcomes, as well as information on other medications received. All patients underwent a thorough clinical examination.

Measurement of Serum 25-Hydroxy Vitamin D Levels

Two milliliters of venous blood were drawn from each patient using clean venipuncture from the cubital vein. The blood was collected in a plain vacutainer tube and allowed to clot at 37°C for 30 minutes. The serum was then separated by centrifugation at 2000-3000 rpm. The aliquot was stored at -20°C for the assay of serum 25-hydroxy vitamin D (25OHVD). The level of serum human 25OHVD (catalog 201-12-5419) was estimated using sandwich-based ELISA kits (SunRed, China) according to the manufacturer's instructions. The level of vitamin D was classified into deficient (<30 nmol/L), insufficient (30 to <50 nmol/L), and sufficient (≥50 nmol/L) [10].

Sample size and statistical Analysis

Based on a review of past literature that found greater fatigue was correlated with higher BMI (r =

-0.36, p = 0.018) [2], the minimal sample size calculated is 60 participants at 80% power and 95% confidence interval (CI). Therefore, the total sample size was 60 participants.

The normality of the data was assessed using the Shapiro-Wilk test. Variables were expressed as number (No), percentage (%), mean ($\bar{x}$), median, and standard deviation (SD).

For normally distributed data, Student's t-test was applied, while the Mann-Whitney test was used for non-normally distributed data. The Chi-square test (χ^2) was employed to examine associations between qualitative variables, with the Z test used to compare column proportions. When expected cell counts were fewer than five, Fisher's Exact test was utilized.

Univariate and multivariate logistic regression analyses were conducted to evaluate risk factors for severe fatigue, and linear regression was used to assess factors associated with overall HRQoL. A two-sided p-value was considered statistically significant. Data were analyzed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY).

Results

Of the 60 participants, 26 (43.3%) were male and 34 (56.7%) were female. The average age was 44.26 ± 12.1 years. Twenty-nine (48.3%) participants experienced severe fatigue, while 31 (51.6%) did not. No significant differences were found between those with and without severe fatigue regarding age, sex, marital status, comorbidities, smoking status, or BMI categories. More details can be found in Table 1.

There was no statistically significant difference in the prevalence of severe fatigue among patients using different types of tyrosine kinase inhibitors (TKIs). However, regarding TKI dosage, Nilotinib 600 mg was associated with the absence of severe fatigue, while Nilotinib 800 mg was linked to an increased occurrence of severe fatigue (p = 0.009). A delayed time to first complete cytogenetic response (CCyR) was significantly more common in patients experiencing severe fatigue (p = 0.021). Additionally, patients with normal vitamin D levels were more frequently found among those without severe fatigue, while vitamin D deficiency (<30 nmol/L) was more common in those with severe fatigue (p < 0.001). None of the patients with sufficient vitamin D levels experienced severe fatigue, whereas 17% of patients with insufficient vitamin D and 83% with deficient vitamin D had severe fatigue (Figure 1). Furthermore, patients who consistently adhered to their treatment regimen were significantly more likely to avoid severe fatigue (p = 0.006). For further details, please refer to Table 2.

Table 1: Characteristics of severely fatigued patients and those without severe fatigue (n = 60)

Characteristic			**Severely fatigued** (n=29)	**Not severely fatigued** (n=31)	p **value**
Age (years)		Mean (SD)	46.89 ± 12.40	41.80 ± 11.48	0.104
Sex	Male	*n* (%)	10 (34.5)	16 (51.6)	0.181
	Female	*n* (%)	19 (65.5)	15 (48.4)	
Marital status	Single	*n* (%)	5 (17.2)	7 (22.6)	0.605
	Married	*n* (%)	24 (82.8)	24 (77.4)	
Comorbidities	Hypertensive	*n* (%)	1 (3.4)	1 (3.2)	0.501
	Diabetic	*n* (%)	3 (10.3)	2 (6.5)	0.937
	Cardiac	*n* (%)	1(3.4)	2 (6.5)	0.952
	Hepatic	*n* (%)	1 (3.4)	0 (0.0)	0.973
Smoker	Yes	*n* (%)	5 (1.2)	7 (22.6)	0.605
Body mass index	Normal	*n* (%)	11 (37.9)	18 (58.1)	0.284
	Overweight	*n* (%)	12 (41.4)	8 (25.8)	
	Obese	*n* (%)	6 (20.7)	5 (16.1)	

Table 2: Disease characteristics between patients with severe and mild fatigue

			Severely fatigued (*n*=29)	**Not severely fatigued** (*n*=31)	*p* **value**
Eutos score	Low <87	*n* (%)	14 (48.3)	15 (48.4)	0.993
	High >87	*n* (%)	15 (51.7)	16 (51.6)	
TKI type	Imatinib	*n* (%)	10 (34.5)	13 (41.9)	0.816
	Nilotinib	*n* (%)	15 (51.7)	15 (51.7)	
	Dasatinib	*n* (%)	4 (13.8)	3 (9.7)	
TKI dose	Imatinib 400	*n* (%)	11 (37.9)	13 (41.9)	0.009
	Nilotinib 600	*n* (%)	0 (0)	8 (25.8)	
	Nilotinib 800	*n* (%)	14 (48.3)	7 (22.6)	
	Dasatinib 100	*n* (%)	4 (13.8)	3 (9.7)	
TKI line	1st	*n* (%)	10 (34.5)	19 (61.3)	0.124
	2nd	*n* (%)	16 (55.2)	10 (32.3)	
	3rd	*n* (%)	3 (10.3)	2 (6.5)	
TKI toxicity	Muscle cramp	*n* (%)	2 (6.9)	3 (9.7)	0.937
	Nausea	*n* (%)	1 (3.4)	3 (9.7)	0.653
	Abdominal pain	*n* (%)	4 (13.8)	1 (3.2)	0.311
	Thrombocytopenia	*n* (%)	2 (6.9)	0 (0)	0.442
	Neuropathy	*n* (%)	1 (3.4)	0 (0)	0.973
	Headache	*n* (%)	1 (3.4)	0 (0)	0.973
	Pleural effusion	*n* (%)	0 (0)	1 (3.2)	0.973
Regular on treatment	No	*n* (%)	13 (44.8)	4 (12.9)	0.006
	Yes	*n* (%)	16 (55.2)	27 (87.1)	
Treatment duration		Mean ± SD	94.06 ± 46.99	71.38 ± 45.19	0.068
Disease control	No	*n* (%)	1 (3.4)	0 (0)	0.483
	Yes	*n* (%)	28 (96.6)	31 (100)	
Time to first CCyR	Early (<1 y)	*n* (%)	11 (37.9)	21 (67.7)	0.021
	Late (>1 y)	*n* (%)	18 (62.1)	10 (32.3)	
Co-medication	B-blockers	*n* (%)	2 (6.9)	1 (3.2)	0.952
	Oral antidiabetics	*n* (%)	1 (3.4)	2 (6.5)	0.953
	Gabapentin	*n* (%)	1 (3.4)	0 (0)	0.973
	Liver support	*n* (%)	1 (3.4)	0 (0)	0.973
	Insulin	*n* (%)	1 (3.4)	0 (0)	0.973
Vitamin D	Sufficient (≥50 nmol/L)	*n* (%)	0 (0)	15 (48.4)	<0.001
	Insufficient (30- <50 nmol/L)	*n* (%)	5 (17.2)	9 (29)	
	Deficient (<30 nmol/L)	*n* (%)	24 (82.8)	7 (22.6)	

TKI: Tyrosine kinase inhibitor, **SD**: Standard deviaion, **CCyR**: Complete cytogenetic response

Patients with severe fatigue had significantly lower HRQoL scores including all domains as shown in Table 3. Univariate binary logistic regression analysis revealed that a delayed time to first CCyR was associated with an increased risk of severe fatigue (p = 0.023, OR [95% CI] 3.436 [1.187–9.947]). Conversely, vitamin D insufficiency (30–<50 nmol/L) was protective compared to deficiency (<30 nmol/L) (p = 0.01, OR [95% CI]: 0.162 [0.041–0.644]), and treatment adherence also demonstrated a protective effect (p = 0.09, OR [95% CI]: 0.182 [0.051–0.656]). In the multivariate regression analysis, none of the variables showed a significant association with severe fatigue; however, vitamin D insufficiency (30–<50 nmol/L) remained protective compared to deficiency (<30 nmol/L) (p = 0.01, OR [95% CI]: 0.162 [0.041–0.644]). For detailed results, refer to Table 4.

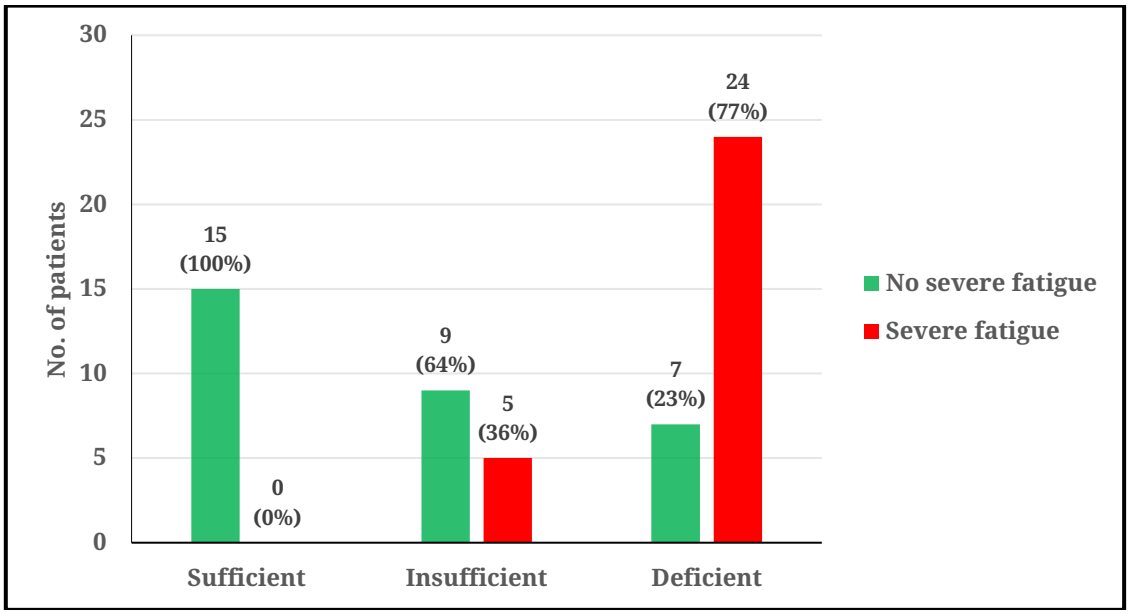

Fig 1: Severe fatigue status according to vitamin D level

Table 3: Comparing quality of life scores between patients with severe fatigue and those without

Domain		Severely fatigued (n=29)	Not severely fatigued (n=31)	*p* value
FACIT-G total	Mean ± SD	50.41 ± 10.21	83.67 ± 13.13	<0.001
Physical wellbeing subscale	Mean ± SD	11.96 ± 4.46	20.83 ± 3.89	<0.001
Social wellbeing subscale	Mean ± SD	13.86 ± 3.66	20.77 ± 3.85	<0.001
Emotional wellbeing subscale	Mean ± SD	11.31 ± 3.53	19.67 ± 4.06	<0.001
Functional wellbeing subscale	Mean ± SD	13.27± 5.17	22.32 ± 5.25	<0.001

FACIT-G: Functional Assessment of Cancer Therapy-General

Table 4: Regression analysis of potential predictors of severe fatigue

Variable		Univariate		Multivariate	
		OR (95% CI)	***p* value**	**OR (95% CI)**	***p* value**
TKI type	Imatinib	Ref			
	Nilotinib	1.300 (0.436 - 3.874)	0.638	----	----
	Dasatinib	1.733 (0.314 - 9.573)	0.528	----	----
TKI dose	Imatinib 400	Ref			
	Nilotinib 600	0.00	0.999	----	----
	Nilotinib 800	2.364 (0.704 - 7.939)	0.164	----	----
	Dasatinib 100	1.576 (0.288 - 8.614)	0.6	----	----
Time to first CCyR	Early	Ref		Ref	
	Late	3.436 (1.187 - 9.947)	0.023	2.634 (0.630 - 11.089)	0.184
Vitamin D	Deficient	Ref		Ref	
	Sufficient	0.00	0.998	0.00	0.998
	Insufficient	0.162 (0.041 - 0.644)	0.010	0.168 (0.039 - 0.728)	0.017
Regular on treatment	No	Ref		Ref	
	Yes	0.182 (0.051 - 0.656)	0.009	0.423 (0.086 - 2.083)	0.290

TKI: Tyrosine kinase inhibitor, **CCyR**: Complete cytogenetic response

The linear regression analysis revealed that overall HRQoL was significantly impacted by severe fatigue (p = 0.001) and vitamin D deficiency (p < 0.001)

Discussion

Fatigue is a common side effect experienced by patients undergoing TKI treatment for CML [3]. Severe fatigue is particularly concerning, as it is linked to a decline in HRQoL, which remains a key therapeutic goal for CML patients [11]. Despite the significant impact of fatigue, the factors that predict its onset and severity, particularly those related to biological factors like vitamin D deficiency, are not well understood. In this study, we explored the sociodemographic, clinical, and health behavior-related factors associated with fatigue severity and its effect on HRQoL in a cohort of CML patients receiving TKI therapy.

In a study conducted to assess the prevalence and predictors of severe fatigue in this population Janssen et al. identified five major factors that predict severe fatigue: younger age, female gender, a higher Charlson Comorbidity Index (CCI), the use of medications known to induce fatigue, and physical inactivity [12]. In line with the results reported by Oswald et al., we did not find that younger age, female gender, or a higher number of medical comorbidities were significant correlates of fatigue severity [2]. Oswald's study also found that a higher BMI was associated with worse fatigue, but we did not observe a significant difference in BMI categories between patients with severe fatigue and those with mild fatigue.

Our results indicated that a delayed time to CCyR and a higher TKI dose were associated with more severe fatigue in univariate analysis. However, these factors lost significance in the multivariate model. Consistent with recent studies, we found that severe fatigue was not independently associated with treatment-related factors, such as the dose and duration of TKI therapy, nor with disease control [6]. Additionally, we observed no difference in fatigue prevalence among patients using different TKIs, which aligns with the results of large clinical trials [13-16].

Vitamin D deficiency has emerged as one of the biological factors potentially linked to fatigue [6]. Vitamin D plays a critical role in various biological processes, particularly in the metabolism of bone and skeletal muscle. As such, vitamin D deficiency has been associated with musculoskeletal pain, chronic pain, lower back pain, bone disorders, and myopathy [17]. Studies suggest that vitamin D deficiency may also contribute to the onset of various diseases, including pulmonary disorders, tonsillar hypertrophy, and metabolic syndrome. Furthermore, vitamin D deficiency may be related to immune dysregulation, which could manifest as excessive daytime sleepiness [18].

Growing evidence points to a potential role for vitamin D in fatigue across different patient groups. A recent study investigating the impact of vitamin D deficiency on HRQoL and fatigue among patients with multiple sclerosis found that 90% of 149 patients were vitamin D deficient. After receiving vitamin D supplementation, there were significant improvements in both HRQoL and fatigue levels [19]. Another study in older adults found that vitamin D deficiency was associated with both mental and physical fatigue, suggesting that vitamin D supplementation could help reduce the risk of fatigue in this population [20]. While these studies highlight the potential benefits of addressing vitamin D deficiency, strong evidence establishing vitamin D as a causal factor in the development of fatigue in CML patients is still lacking.

Our study is the first to examine the relationship between vitamin D deficiency and fatigue in CML patients, yielding intriguing results. We found that normal vitamin D levels were significantly more common among patients with mild fatigue, while levels below 30 were more prevalent among those with severe fatigue (p < 0.001). In multivariate regression analysis, vitamin D deficiency was significantly associated with severe fatigue. Furthermore, linear regression analysis demonstrated that both severe fatigue (p = 0.001) and vitamin D deficiency (p < 0.001) had a significant negative impact on HRQoL. These findings suggest that vitamin D deficiency may play a crucial role in fatigue severity and highlight the need for further research to explore vitamin D as a potential therapeutic target for improving fatigue and enhancing HRQoL in CML patients.

Our study underscores the importance of considering vitamin D deficiency as a potential modifiable factor in the management of fatigue among CML patients. Future studies should focus on determining whether vitamin D supplementation could alleviate fatigue and

improve the overall quality of life in this patient population.

Limitations

Our study has several limitations. First, the sample size of included patients was relatively small, and larger studies are needed to validate our findings. Second, the observational design of our study allows for the identification of associations but does not establish causation. Further research, particularly prospective studies, is required to evaluate the impact of vitamin D levels and the potential benefits of vitamin D correction on fatigue and related outcomes.

Conclusions

Our findings highlight vitamin D deficiency as a significant predictor of severe fatigue in most CML patients receiving TKI therapy, with severe fatigue being associated with a notable decline in HRQoL. Future studies should aim to explore additional factors contributing to fatigue severity and incorporate longer follow-up periods to enable a more comprehensive analysis.

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Authors' contribution

Conception & Design: Hebesh EH, Alhassanin S; Acquisition, analysis, or interpretation of data: Hebesh EH, Basiouny AM, Soliman SS; Drafting / revising the manuscript: All authors; Approval of the final version of the manuscript: All authors; Agreement to be accountable for all aspects of the work: All authors.

Conflict of interest

The authors declare that they have no conflict of interest to disclose.

Data availability

De-identified data from patients included in this study are available upon reasonable request from the corresponding author.

Ethical considerations

The study was approved by the Research Ethics Committee of the Faculty of Medicine - Menoufia University (reference: 6/2023 ONCO 1). All participants signed a written informed consent.

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Study registration

Not applicable.

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