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Prevalence of fatigue among pediatric cancer patients in Egypt

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Abstract

Background Cancer-related fatigue (CRF) is a common side effect of cancer and cancer treatment that impacts quality of life. To our knowledge, statistics on its prevalence in children are lacking in Egypt. This study aims to record the prevalence and key dimensions of fatigue in pediatric oncology patients undergoing chemotherapy in Egypt and identify its predictors to inform management strategies.

Methods This study was conducted between October and December 2022 at Dar El Salam Oncology Hospital, Cairo, Egypt. Interviewed participants were children aged 8–18 years with cancer, prescribed chemotherapy, and not in severe distress. The children personally filled out 2 questionnaires relating to fatigue (PROMIS Pediatric Short Forms of Fatigue (PROMIS fatigue), pedsQL multidimensional fatigue (PedsQL fatigue)), and 3 symptoms-related questionnaires.

Results A total of forty-two children (47.6% female) (mean age 12.1 years (SD 3.3 years)) participated. Reported moderate to severe fatigue in children is between half to a third of the children depending on the measurement tool used. The mean T-score for PROMIS fatigue was 53.76 (SD 12.5), and for PedsQL fatigue was 74.27 (SD 21.79). Stepwise standardized multivariant linear regression showed that fatigue following PROMIS fatigue could be predicted by depressive symptoms (β= 0.47, $p < 0.001$) and mobility (β= -0.39, $p < 0.01$) while following PedsQL fatigue, it could be predicted by upper extremity function (β = 0.34, p 0.005), depressive symptoms (β =-0.49, $p < 0.001$) and treatment status (β=-0.25, $p < 0.05$).

Conclusion Cancer-related fatigue of oncology children patients in Egypt is multifactorial and prevalent in more than 52% of the patients. Moreover, significant predicting factors included depression, mobility especially upper extremity function, and treatment status. Fatigue screening and controlling these factors in pediatric oncology patients is advisable to improve their medical care plan.

Keywords PedsQL, Quality of life, PROMIS, Pediatric short form-fatigue, Arabic, Oncology

1 Introduction

The National Comprehensive Cancer Network (NCCN) defined cancer-related fatigue (CRF) as "a distressing persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional

to recent activity and interferes with usual functioning" [1]. The official definition of CRF is resilient to practice and research as it is rare to find significant fatigue indications over consecutive checkpoints. To overcome this issue in the absence of a universal tool measuring fatigue, researchers divided fatigue into mild, moderate, and severe depending on cutoff scores focusing on moderate to severe fatigue in their work [2]. Based on a recent review, the prevalence in pediatrics ranges from 36–93% of cases with a greater level in cases receiving chemotherapy ranging from 70–100% of the cases [3, 4]. A report from Jordan estimated fatigue prevalence among cancer patients to be around 82% [5].To our knowledge, these statistics for pediatrics are lacking in Egypt.

Multiple risk factors have been linked with CRF. They are classified into modulating (gender and age), maintaining (lifestyle factors, demographic, and current health), triggering (disease and treatment-related factors), and pre-disposing (genetic disposition) [2]. Under this general classification, there are multiple subclasses. To illustrate, cancer and its treatment can lead to complications such as anemia and gastrointestinal symptoms, which contribute to fatigue during each treatment cycle [4]. Furthermore, fatigue is closely related to both psychological and physical limitations in this group of patients. For instance, a study published in BMC Psychology found that 70% and 30% of brain tumor survivors and leukemia survivors respectively experienced cognitive fatigue. Furthermore, fatigue was commonly misdiagnosed as depression due to the overlapping presentation [6]. When investigated, depression often correlated with fatigue in cancer patients [4] and was found to be a predictor of fatigue [6, 7]. This could highlight the complex interplay between psychological well-being and fatigue in pediatric oncology patients. Additionally, physical activity is limited by fatigue. Children receiving intensive cancer treatment that affects their ability to engage in daily activities and reduces overall mobility reported deconditioning that exacerbates fatigue [4, 8]. Recent studies found that physical activity intervention significantly reduces fatigue in children with cancer [9–11]. Other factors related to severe fatigue were reported such as cancer stage and elevated body mass index (BMI) [2].

Consequently, assessing CRF requires considering a variety of factors, Multiple instruments have been developed ranging from single-item questions to multidimensional assessment tools. The former assesses multiple fatigue dimensions, allowing for the most accurate measurement and precise results. One of the largest Quality of life (QoL) questionnaire databases is the patient-reported outcomes measurement information system (PROMIS), It evaluates the social, physical, and psychological health of patients and can be used in clinical practice and research [12]. The Pediatric Short Form v2.0 - Fatigue 10a was developed by The National Institution of Health (NIH) [13, 14] and then used in multiple studies, including studies about pediatric chronic pain [15], cancer [4, 15–17] and sickle cell disease [18]. The questionnaire has been proven valid and sensitive to change [19–21]. Another promising measure is the Pediatric Quality of Life Inventory (PedsQL) measurement model, which measures health-related quality of life (HRQoL) [22]. It is a multidimensional fatigue measurement tool that has been used and verified in studies regarding pediatric rheumatology [23], pediatric obesity [24], multiple sclerosis [25] and cancer patients [26–28]. It also has an Arabic translation that was validated in native Arabic-speaking cancer patients [29] In this research, we used both questionnaires because they measure distinct aspects of fatigue.

Severe fatigue has a significant effect on children with cancer as it interferes with the disease, treatment, function, and every aspect of quality of life (QoL) [4]. In some cases, it might even lead to discontinuation of treatment [30]. Parents have reported that cancer-related fatigue in adolescents disrupts normal life more than the cancer treatment itself, leading to both physical and cognitive challenges that impede the return to regular activities post-treatment [31]. Therefore, parental involvement in the management of fatigue, such as in exercise and dietary programs, is pivotal and enhances the outcomes of the management programs [32]. Early recognition of fatigue in children with cancer is expected to improve their prognosis and quality of life. Children and adolescents depend on their parents for support and access to healthcare [33]. As this close relationship impacts the positive progression of the management when the parents are actively involved and aware of the condition it may also negatively impact the child's quality of life when the parents are experiencing stress resulting from the burden of their child's symptoms [33–35]. Therefore, parental awareness is essential for early intervention in CRF.

Despite the burden of CRF on children, it is yet to be explored in Egypt. Our current aim is to determine the prevalence and key dimensions of fatigue in pediatric cancer patients undergoing chemotherapy in Egypt and identify clinical, functional, and emotional predictors of fatigue to inform clinical management strategies. These predictors include sociodemographic characteristics, type of cancer and chemotherapy treatment, patient-reported symptoms (e.g. depression), functionality e.g.(upper extremity, mobility), and clinical data (e.g. leucocytic counts). Shedding light on children's CRF and their risk factors will provide grounds for addressing this chronic symptom and support the efforts to find a channel that predicts and manages cancer-related fatigue.

2 Methodology

2.1 Study design

This is a cross-sectional study to assess fatigue prevalence and its associated risk factors in children and adolescents suffering from cancer in Egypt. Convenience sampling was used to recruit participants from Dar El Salam Oncology Hospital (Harmil). Every patient showing up in the day-care clinic or admitted to the inpatient department who was not previously interviewed in the day-care clinic was approached to participate in the study. The recruitment process continued until there were no new patients to interview.

2.2 Participants

Inclusion criteria were: (1) Age 8- <18 years at the time of the study, (2) Diagnosed with any type of cancer, (3) Ability to speak, read (alone or with supervision) and understand Arabic, (4) Not in severe distress, (5) prescribed chemotherapy. The employed questionnaires were validated in children 8 years and above hindering the application to any younger age without the need for further validation and possible modifications.

Exclusion criteria were children suffering from sensory or cognitive deficits that prevent understanding or answering the questionnaire.

2.3 Measurements

Five questionnaires: *PROMIS pediatric short form v2.0 Fatigue 10a* (PROMIS fatigue), *PedsQL multidimensional fatigue score acute version 3.0* (PedsQL fatigue), *PROMIS Pediatric Item Bank v2.0 – Depressive Symptoms – Short Form 8a*, *PROMIS Pediatric Item Bank v2.0 – Mobility– Short Form 8a and PROMIS Pediatric Item Bank v2.0 – Upper Extremity – Short Form 8a.* They are self-filled questionnaires by the child. Licensed validated Arabic translations have been obtained from the main distributor of the questionnaires. They are listed in the appendix [1–5].

PROMIS pediatric short form v2.0 Fatigue 10a (PROMIS fatigue): It has 10 items with a 7-day recall period that measures the degree of fatigue generally from mild to severe. Each item is measured by a 5-point Likert response scale ranging from "never" to "almost always". PROMIS scores are reported as T-scores with a mean of 50 and a standard deviation (SD) of 10. A higher T-score means a higher degree of fatigue. The questionnaire has been proven valid and sensitive to change [19–21] and has been used and validated in oncology patients [17].

PedsQL multidimensional fatigue score acute version 3.0 (PedsQL fatigue): It has eighteen items with a 7-day recall period that measures 3 dimensions of fatigue; sleep/rest fatigue (6 items), general fatigue (6 items), and cognitive fatigue (6 items). A 5-point Likert scale from 0 "Never" to 4 "Almost always" is used to scale each of the items, Then the scores are reversed and linearly transformed to a 0-100 scale. It has been proven to have strong internal consistency, reliability, and validity in cancer patients [26]. and has an Arabic-validated translation [29].

Co-occurring symptoms (depressive symptoms) and function (mobility and upper extremity) were measured using the Arabic versions of the PROMIS Pediatric Short Forms of depressive symptoms, mobility, and upper extremity measures. These instruments follow the same measurement technique as PROMIS Fatigue except having eight items. Except for the depressive symptoms, a higher score means a higher experience of the symptoms.

Other data recorded were demographics (age, gender, height, weight, caregiver relationship, nationality (ethnicity), province and education level), disease and treatment information (type of cancer, time since diagnosis, treatment protocol, and other chronic health conditions) and relative clinical data (most recent test results of hemoglobin and white blood cell count).

2.4 Data collection

The data collection process was performed every day the clinics were held from October to November 2022. The guardian was approached by the investigator who introduced herself and explained the concept of the survey. If they accepted participation in the study or wanted further information, the couple was directed to a quiet location. Then the investigator explained the research aims to the guardian and the child and asked for their consent. Once written consent was gained from the guardian and a verbal agreement from the child, the investigator asked the guardian not to interrupt the child while filling out the questionnaires, and any inquiries from the child were directed to the investigator. The questionnaires were printed, and the child read the questions and filled in the questionnaire without interference. The questionnaires were expected to take about 15 min. The other data were gathered from the guardian and patient files. Given

the difference in cognitive level between the age groups, the younger age groups received extra support in reading the questions and understanding the structure of the questionnaires. From the principal investigator. Moreover, the pilot study accommodated participants from both age groups and their feedback was taken into consideration to ensure a complete independent response as much as possible.

2.5 Pilot study

The questionnaires were the first run in a pilot study to standardize interviewing, ensure clarity of translation, and confirm the average completion duration. The first stage was run on healthy children, they commented on some expressions that they were unfamiliar such as (shirt – in Arabic) in item 5 of PROMIS fatigue, which was explained to be a (T-Shirt). The average completion time was 12 min. Cancer children were recruited in the following stage, confirming the viability of the culturally adapted explanation examples from the first stage with delicate refinements in the approach and interview. The average duration for this stage was 14 min. A full description of the sample in both stages is in Appendix 6.

2.6 Ethical consideration

Ethical approval was obtained from the Ethics Research Committee at the School of Pharmacy Newgiza University and the IRB committees at the participating hospital. Written consent was obtained from the child's guardian. A verbal consent was obtained from the child. They were assured that participation was voluntary. All personal information was kept with the principal investigator.

2.7 Statistical analysis

For the descriptive analysis, means (SD) were calculated for continuous variables and frequencies (%) for categorical and ordinal variables. Subgroups' characteristics and measures were compared using Mann Whitney U, Fischer exact, and chi-square tests to reveal possible significant differences. Correlation analysis between fatigue from both fatigue measurement tools and patient characteristics was run using the Spearman correlation test. A strong correlation was identified as a significant correlation with a correlation coefficient of 0.7–0.9, a moderate correlation had a coefficient of 0.4–0.69 and a weak one was 0.1–0.39 using a conventional approach to interpretation [36] The characteristics that showed a correlation probability value of < 0.1 were used in the multivariant regression analysis. The regression was refined through stepwise regressions which are iterative repetitive regressions where there is a contentious selection of significant independent variables and the exclusion of insignificant variables to reach a final optimized model. The coefficients were further standardized to unify the scales and ease the interpretation of the results. To ensure an acceptable error level in the regression analysis, a minimum of six participants per variable in the regression model + 1 must be available [37].

3 Results

A total of 46 patients were approached between October and December 2022, 42 (91.3%) of them agreed to participate while 4 opted out of participating. After the consent process, all 42 children completed the questionnaires taking an average time of 14.61 min (SD: 4.18).

3.1 Characteristics of participants

About half of the children were female (20, 47.6%) with a mean age of 12.1 years (SD 3.3). According to their body mass index (BMI), a substantial number of children were normal weight (31, 73.8%) - only 7 (16.7%) were obese or overweight- and had a mean body surface area (BSA) of 1.27 m^2 (SD: 0.31). Most of the participants had a hematological tumor while only 5 (11.9%) had a solid tumor. All children received chemotherapy but were at different stages: most were actively receiving chemotherapy treatment; others were between cycles of chemotherapy or had finished chemotherapy treatment and one hadn't started chemotherapy yet. The average blood hemoglobin level was 11.03 g/dl (SD 1.86) and the average total leukocytic count was 4.17×10^3 cells/ml (SD 3.89). The vast majority did not have any other chronic health conditions (39, 92.8%) except for two (4.8%) with a heart condition and one (2.4%) with diabetes. Further sample characteristics are summarized in Table 1.

The sample could be stratified into 2 distinct subgroups, inpatients, and outpatients. The inpatient group (13, 30.9%) were patients who received care and stayed in the admission unit, while the outpatient group (29, 69.1%) were patients treated in a day-care setting. The two groups were significantly different in terms of type of cancer ($p < 0.01$), time since diagnosis ($p < 0.01$), type of treatment ($p < 0.01$), current treatment status ($p < 0.01$) and hemoglobin ($p < 0.01$) as well as showing a significant difference in the mean score of the PROMIS mobility questionnaire ($p < 0.05$).

3.2 Fatigue questionnaires' scores

The mean fatigue score measured by PROMIS fatigue of all participants was 53.76 (SD: 12.5), interpreted as mild fatigue, while PedsQL fatigue was 74.27 (SD: 21.79). The participants had variant answers in the two questionnaires, only 33.3% of the participants had matching scores in the two questionnaires (appendix 7). For PROMIS fatigue almost half showed no fatigue (20, 47.6%) and for pedsQL fatigue two fifth scored mild fatigue (17, 40.5%). Further details are presented in Table 2.

The inpatient and outpatient groups showed no significant difference in the average scores of PROMIS fatigue ($p = 0.65$) and PedsQL fatigue ($p = 0.80$). However, the inpatient group showed a slightly higher result. In the inpatient group, the two questionnaires were the same in describing the absence of fatigue or mild fatigue but showed differences in moderate and severe fatigue. As for the outpatient group, the score distribution was completely different between the two tools. For instance, PedsQL fatigue valued about half (15, 51.7%) with mild fatigue while only one (3.4%) was mild in PROMIS fatigue.

3.3 Correlations between fatigue score and characteristics

Mobility and depressive symptoms showed a significant correlation with both fatigue questionnaires, for PROMIS fatigue, mobility showed a strong correlation in all

Table 1 Sample characteristics (*N* = 42)

Characteristic	All participants *N* = 42 *N* (%)	In-patients *n* = 13 *n* (%)	Out-patients *n* = 29 *n* (%)	*p* value
Age				
8–12 years	22 (52.4)	6 (46.2)	16 (55.2)	0.861
13–18 years	20 (47.6)	7 (53.8)	13 (44.8)	
Mean (SD)	12.1 (3.3)	12.3 (3.4)	12.1 (3.3)	
Gender				
Female	20 (47.6)	5 (38.5)	15 (51.7)	0.514
BMI (Kg/m^2)				
Underweight	4 (9.5)	3 (23.1)	1 (3.4)	0.185
Normal weight	31 (73.8)	9 (69.2)	22 (75.9)	
Obese	6 (14.3	1 (7.7)	5 (17.2)	
Overweight	1 (2.4)	0	1 (3.4)	
BSA (m^2)				
Mean (SD)	1.27 (0.31)	1.21 (0.35)	1.30 (0.29)	0.414
Province				
North Upper Egypt	20 (47.6)	5 (38.5)	15 (51.7)	0.832
Cairo province	14 (33.3)	5 (38.5)	9 (31)	
Canal province	4 (9.5)	1 (7.7)	3 (10.3)	
Other[A]	4 (9.5)	2 (15.4%)	2 (6.9%)	
Caregiver relationship				
Parents	35 (83.3	9 (69.2%)	26 (89.7%)	0.203
Siblings	4 (9.5)	2 (15.4%)	2 (6.9%)	
Other [B]	3 (7.2)	2 (15.4)	1 (3.4%)	
Education level				
Primary school	21 (50)	6 (46.2	15 (51.7)	0.619
Preparatory school	8 (19)	2 (15.4)	6 (20.7)	
Secondary school	10 (23.8)	3 (23.1)	7 (24.1)	
Other [C]	3 (7.2)	2 (15.4)	1 (3.4)	
Type of cancer				
Hematological tumors				0.005
ALL	26 (61.9)	4 (30.8)	22 (75.9)	
AML	7 (16.7)	5 (38.5	2 (6.9)	
Lymphoma	2 (4.8)	1 (7.7)	1 (3.4)	
Solid tumors				
Sarcoma	4 (9.5)	3 (23.1)	1 (3.4)	
Colon cancer	1 (2.4)	0	1 (3.4)	
Missing	2 (4.8)	0	2 (6.9	
Other chronic health conditions				
No other conditions	39 (92.8)	12 (92.3)	27 (93.1)	0.681
Heart disease	2 (4.8)	1 (7.7)	1 (3.4)	
Diabetes	1 (2.4)	0	1 (3.4)	
Time since diagnosis				
Less than 6 months	17 (40.5)	10 (76.9)	7 (24.1)	0.0038
6–12 months	12 (28.5)	2 (15.4)	10 (34.5)	
Over 12 months	13 (30.5)	1 (7.7)	12 (41.3)	
Type of treatment				
Total 15 protocol	27 (64.3)	4 (30.8)	23 (79.3)	0.004
AML protocol	7 (16.7)	5 (38.5)	2 (6.9)	
t-10 protocol	2 (4.8)	2 (15.4)	0	
Other[D]	5 (12)	2 (15.4)	3 (10.3)	
Missing	1 (2.4)	0	1 (3.4)	
Current treatment status				

Table 1 (continued)

Characteristic	All participants *N* = 42 *N* (%)	In-patients *n* = 13 *n* (%)	Out-patients *n* = 29 *n* (%)	*p* value
Active chemotherapy treatment	36 (85.7)	9 (69.2)	27 (93.1)	0.007
Between cycles of chemotherapy	4 (9.5)	4 (30.8)	0	
Finished treatment	1 (2.4)	0	1 (3.4)	
Didn't start treatment yet	1 (2.4)	0	1 (3.4)	
Number of cycles received				
Over 8 cycles	31 (73.8)	7 (53.8)	24 (82.7)	0.078
3–4 cycles	4 (9.5)	3 (23.1)	1 (3.4)	
1–2 cycles	6 (14.3)	3 (23.1)	3 (10.3)	
Didn't receive chemotherapy	1 (2.4)	0	1 (3.4)	
Hemoglobin (g/dl)				
Mean (SD)	11.03 (1.86)	10.07 (1.59)	11.46 (1.84)	0.009
Total leukocytic count (10^3 cell/ml)				
Mean (SD)	4.17 (3.89)	3.12 (1.86)	4.65 (4.47)	0.149
PROMIS upper extremity				
Mean (SD)	37.04 (4.98)	36.46 (5.12)	37.31 (4.98)	0.280
PROMIS mobility				
Mean (SD)	32.02 (8.89)	26.92 (10.3)	34.31 (7.26)	0.026
PROMIS depressive symptoms				
Mean (SD)	15.38 (7.80)	16.07 (7.72)	15.06 (7.95)	0.974

[A] Other provinces: Alexandria province, South upper Egypt, Delta province and Outside Egypt

[B] Other caregiver relationship: grandparents and uncle/aunt

[C] Other education level: uneducated and commercial secondary school

[D] Other types of treatment: ICE (ifosfamide, carboplatin, and etoposide phosphate), VAC (Vincristine, actinomycin D and cyclophosphamide), COPDAC protocol (cyclophosphamide, vincristine sulfate, prednisone and dacarbazine), FOLFOX (leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin), LMB protocol (Vincristine, cyclophosphamide, methotrexate, Adriamycin). ALL: acute lymphoblastic leukemia

AML acute myeloid leukemia, *BSA* body surface area (Mosteller formula), *BMI* body mass index

Table 2 Score of fatigue questionnaires

	All participants *N* = 42 *N* (%)		In-patient *n* = 13 *n* (%)		Out-patient *n* = 29 *n* (%)	
	PROMIS fatigue	**PedsQL fatigue**	**PROMIS fatigue**	**pedsQL fatigue**	**PROMIS fatigue**	**pedsQL fatigue**
Normal	20 (47.6%)	13(30.9%)	5 (38.5%)	5 (38.5%)	15 (51.7%)	8 (27.6%)
Mild	3 (7.1%)	17 (40.5%)	2 (15.4%)	2 (15.4%)	1 (3.4%)	15 (51.7%)
Moderate	12 (28.6%)	10 (23.8%)	2 (15.4%)	6 (46.1%)	10 (34.5%)	4 (13.8%)
Severe	7 (16.6%)	2 (4.8%)	4 (30.8%)	0	3 (10.3%)	2 (6.9%)
Mean (SD)	**53.76 (12.5)**	**74.27 (21.79)**	**55.07 (23.7)**	**72.5 (23.7)**	**53.17 (11.8)**	**75.1 (21.2)**

PROMIS T-score: <50 is no fatigue (Normal), 50–55 is mild, 55–65 is moderate, >65 is severe pedsQL: >90 is no fatigue (Normal), 61–90 is mild, 60 – 31 is moderate, =<30 is severe

participants (r= −0.702, $p < 0.001$) while depressive symptoms moderately correlated with all participants ($r = 0.669$, $p < 0.001$). This correlation remained consistent after subgrouping as mobility showed a strong correlation in in-patients (r= −0.752, $p < 0.001$) and a moderate correlation in outpatients (r= −0.620, $p < 0.001$), while depressive symptoms showed a moderate correlation in in-patients ($r = 0.688$, $p < 0.001$) and outpatients ($r = 0.672$, $p < 0.001$).

This pattern also presented in PedsQL fatigue as mobility showed a moderate correlation in all participants ($r = 0.667$, $p < 0.001$), inpatients ($r = 0.654$, $p = 0.015$), and outpatients ($r = 0.659$, $p < 0.001$). Depressive symptoms showed a moderate correlation with PedsQL fatigue in all participants ($r = -0.597$, $p < 0.001$) and outpatients ($r = -0.484$, $p < 0.001$) and a strong correlation in inpatients ($r = -0.730$, $p < 0.001$). Additionally, upper extremity mobility moderately correlated with PedsQL fatigue in all participants ($r = 0.524$, $p < 0.001$), inpatients ($r = 0.611$, $p = 0.026$), and outpatients ($r = 0.496$, $p < 0.001$) which is a pattern that wasn't present in PROMIS fatigue.

It's worth noting that correlation patterns differed in the inpatient group and outpatient group. In the inpatient group, time since diagnosis showed a moderate correlation with PROMIS fatigue ($r = 0.608$, $p = 0.027$) and PedsQL fatigue ($r = -0.514$, $p = 0.072$). In the outpatient group, BSA showed a moderate correlation with PedsQL fatigue ($r = -0.428$, $p = 0.021$) and a weak correlation with PROMIS fatigue ($r = 0.379$, p value = 0.042) (Table 3).

3.4 Regression (factors)

According to the available sample of 42 participants and the role of 6 participants per independent variable in the regression as stated in the methodology, the maximum number of independent variables included in the regression before saturation was 7 variables to be investigated in the regression model.

Table 4 contains the results for the stepwise regression of PROMIS fatigue where two variables were significant predictors: PROMIS mobility (β −0.39, $p = 0.002$) and PROMIS depressive symptoms ($\beta = 0.47$, $p < 0.001$). Regarding PedsQL fatigue, stepwise regression results showed three significant predictors: PROMIS upper extremity ($\beta = 0.34$, $p = 0.005$), PROMIS depressive symptoms ($\beta = -0.49$, $p < 0.001$), treatment status ($\beta = -0.25$, $p = 0.013$) (Table 5).

4 Discussion

This study evaluated the prevalence and factors predicting fatigue in children with cancer prescribed chemotherapy at various stages of treatment. Results supported the global finding that CRF in children undergoing chemotherapy treatment was prevalent as one in two or three of these children reported moderate to severe fatigue. Findings confirmed the convoluted nature of CRF and added to previous research on the significant roles of depressive symptoms, mobility, upper extremity function, and treatment status on fatigue in oncology children undergoing chemotherapy, especially in Egypt.

PROMIS fatigue showed that over half of the children had a fatigue score higher than the public (T score = 50). The mean T score for all children was 53.76 which is less than 1 point above their U.S. counterparts (T score 52.9) [38] and five points above their Chinese counterparts (T score 48.52) [4]. The minimal significant difference is 3 points [39], making our sample equivalent to their U.S. counterparts and more fatigued than their Chinese counterparts. Suggested reasons could be cultural or sample differences. Culturally, the Chinese might view "enduring" fatigue as "tolerating hardship" and thus must bear it and refuse to report it. Looking further into the study sample, half of them were suffering from solid and brain tumors and those diagnosed with solid tumors were on average approaching the end of their active treatment [4]., which is expected to have less fatigue overall.

Table 3 Correlation between fatigue score and measured patients' characteristics

	All participants				In- patients				Out-patients			
	PROMIS fatigue		PedsQL fatigue		PROMIS fatigue		PedsQL fatigue		PROMIS fatigue		PedsQL fatigue	
	r	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value
Age	0.157	0.318	−0.227	0.148	0.342	0.252	−0.153	0.616	0.167	0.384	−0.285	0.133
Gender	0.029	0.852	0.001	0.990	0.170	0.577	−0.169	0.581	−0.182	0.343	0.078	0.685
BMI	0.124	0.432	−0.202	0.197	0.306	0.308	−0.346	0.245	0.072	0.708	−0.163	0.396
BSA	**0.297**	**0.056**[b]	**−0.360**	**0.019**[b]	0.341	0.254	−0.274	0.363	**0.379**	**0.042**[b]	**−0.428**	**0.021**[b]
Province	0.178	0.259	0.081	0.607	0.379	0.201	−0.189	0.535	0.075	0.698	0.254	0.182
Caregiver relationship	−0.027	0.862	0.043	0.782	0.169	0.579	−0.003	0.991	−0.178	0.354	0.107	0.578
Education level	0.252	0.107	**−0.272**	**0.081**[A]	0.299	0.319	−0.090	0.768	0.296	0.118	**−0.376**	**0.04**[b]
Cancer type	0.142	0.369	−0.054	0.733	0.417	0.155	−0.201	0.508	0.028	0.883	0.051	0.702
Other chronic health conditions	0.198	0.208	−0.087	0.582	−0.077	0.801	0	1	0.298	0.116	−0.131	0.498
Time since diagnosis	−0.074	0.641	−0.058	0.714	**0.608**	**0.027**[b]	**−0.514**	**0.072**[A]	−0.270	0.155	0.074	0.702
Type of treatment	0.198	0.206	−0.052	0.739	0.319	0.287	−0.178	0.559	0.129	0.504	0.062	0.747
Current treatment status	0.056	0.724	**−0.275**	**0.077**[A]	0.247	0.415	−0.356	0.232	−0.077	0.691	−0.231	0.228
Number of chemotherapy cycles	0.045	0.773	0.074	0.639	−0.413	0.159	0.171	0.575	0.177	0.356	0.054	0.779
Hemoglobin	0.128	0.418	−0.044	0.777	−0.168	0.583	0.331	0.269	**0.321**	**0.089**[A]	−0.181	0.345
Total leucocytic count	−0.126	0.426	0.164	0.296	−0.427	0.145	**0.605**	**0.028**[b]	0.024	0.899	−0.042	0.826
PROMIS upper extremity	**−0.545**	**<0.001**[b]	**0.524**	**<0.001**[b]	−0.440	0.132	**0.611**	**0.026**[b]	**−0.551**	**<0.001**[b]	**0.496**	**<0.001**[b]
PROMIS mobility	**−0.702**	**<0.001**[b]	**0.667**	**<0.001**[b]	**−0.752**	**<0.001**[b]	**0.654**	**0.015**[b]	**−0.620**	**<0.001**[b]	**0.659**	**<0.001**[b]
PROMIS depressive symptoms	**0.669**	**<0.001**[b]	**−0.597**	**<0.001**[b]	**0.688**	**<0.001**[b]	**−0.730**	**<0.001**[b]	**0.672**	**<0.001**[b]	**−0.484**	**<0.001**[b]

[A] Significant at 0.1 level (two-tailed)

[b] Significant at 0.05 level (two-tailed)

Bold numbers are significant correlations

As for the PedsQL fatigue, around half (47.6%) of children reported more fatigue than the mean score of healthy children from a sample in the United States (score = 80.49) [28]. The mean score of the sample (mean score of 70.98) was around 3.5 points higher than their U.S. counterparts (mean score of 70.98) [28], even after stratification of the sample, the trend for both strata remained the same [40]. An explanation behind our participants showing less fatigue than their U.S. counterparts could be traced back to sample differences. Their sample was more diverse including brain tumors, recent remissions, and long-term off-treatment which could influence the results as long-term off-treatment patients are more fatigued than cancer patients on active treatment [41].

Our sample showed different results for the measured level of fatigue in the two questionnaires. That could be attributed to differences between the dimensions measured by the two questionnaires. PROMIS fatigue was focused on general fatigue a child might experience in their day-to-day life while PedsQL fatigue had one section for general fatigue and two other sections for sleep/rest fatigue and cognitive fatigue making it more sensitive to detecting fatigue and determining the source of it. That is reflected in our sample by PedsQL fatigue detecting fatigue in more participants than PROMIS fatigue in our overall sample and the outpatients group.

Subgroup comparison between inpatients and outpatients showed no statistical difference in fatigue in both questionnaires. It was anticipated that the inpatient group would show more fatigue than the outpatient group as observed by previous research [40]. Our sample followed that observation despite the difference not being significant, which could be due to the lack of statistical power in our sample. However, it revealed interesting observations. At first, although the perceived reason for admission was low TLC and hemoglobin, the two subgroups were equivalent regarding these two clinical indicators. This might be due to other admission reasons that were not properly recorded like the start of treatment or complaining of fever [40]. Additionally, the subgroups were significantly different in terms of mobility as inpatients had much lower mobility (26.92, 10.3) than outpatients (34.31, 7.26) which is constant with research stating that patients exposed to intensive treatment have lower mobility [4, 8] and intern higher fatigue.

The predictors of PedsQL fatigue and PROMIS fatigue scores were not the same, For PROMIS fatigue they were PROMIS mobility and PROMIS depressive symptoms, while for PedsQL fatigue predictors were PROMIS upper extremity, PROMIS depressive symptoms, and treatment status. Depressive symptoms have been recognized as a part of a symptoms cluster made of fatigue and were found to be a significant predictor of fatigue in other studies [8, 42]. Looking at the standardized coefficients, PROMIS depressive symptoms are the highest predicting factor of fatigue in both PROMIS fatigue and PedsQL fatigue emphasizing the importance of mental health in fatigue management. PROMIS mobility and PROMIS upper extremity, being significant predictors also comply with previous research as it was found that inactivity contributes to the development and persistence of fatigue [8]. As for treatment status being a significant predictor, chemotherapy leads to an increase in the level of specific inflammatory markers and is associated with an increase in fatigue prevalence [8].

Despite the inability to run a regression for the inpatients and outpatients due to the small sample size, correlation analysis on the two groups could be used to have a better understanding of the factors impacting fatigue in them. For instance, mobility and depressive symptoms showed a strong to moderate correlation with the two fatigue

Table 4 Results of Stepwise regression predicting PROMIS SF fatigue scores

	Unstandardized β coefficients	Standardized β coefficients	*p* value	Standard error	Lower limit	Upper limit
PROMIS mobility	−0.56	−0.39	0.002	0.122	−0.645	−0.150
PROMIS depressive symptoms	0.75	0.47	< 0.001	0.122	0.222	0.717

Table 5 Results of Stepwise regression predicting PedsQL fatigue scores

	Unstandardized β coefficients	Standardized β coefficient	*p* value	Standard error	Lower limit	Upper limit
PROMIS upper extremity	1.51	0.34	0.005	0.117	0.107	0.584
PROMIS depressive symptoms	−1.38	−0.49	< 0.001	0.117	−0.734	−0.260
Treatment status	−15.44	−0.25	0.013	0.096	−0.447	−0.054

measures in both groups which is consistent with the predicting factors of the overall sample and previous research. In the inpatient group, time since diagnosis correlated moderately with fatigue scores in both questionnaires. The correlation was interpreted as the longer the time since diagnosis is the higher the fatigue. Previous research on breast cancer found that fatigue increases in the first 6 months of treatment followed by a gradual decrease over time [43]. It's believed that time since diagnosis showed this pattern of correlation because most of the inpatients (10, 76.9%) were diagnosed less than six months at the time of the study. In the outpatient group, BSA showed a weak to moderate correlation to fatigue scores in both questionnaires. The correlation is interpreted as the higher the BSA the higher the fatigue. This correlation pattern was shown only in the overall sample and in the outpatient group. A possible explanation as to why it didn't show in the inpatient group is that inpatients had a lower BSA (mean of 1.21 (0.35)) and research showed that obesity is one of the factors associated with severe fatigue [2].

Despite fatigue's magnitude in children in Egypt, it is not being screened for regularly, which could be for multiple reasons, for example, there is no agreed-upon measure to be used in screening [2]. The current study introduced two of the common measurements and explored the potential use of each of them. In addition, healthcare professionals have limited knowledge about fatigue and its management [44]. This warrants multiple educational campaigns to healthcare providers and patients about the condition and approaches to manage it. Also, patients perceive fatigue as a normal thing to experience because of their diagnosis and not as something they should seek medical attention for [45]. These factors collectively lead to overlooking fatigue and not including it in the medical care plan.

An initial step to resolve fatigue in pediatric oncology patients after admitting the problem is implementing a regular measurement of fatigue. Clinically, routine screening should be performed with a validated tool [46]. The next step would be to adopt an intervention to manage the condition. Up to this point, only a few interventions have been explored and developed to reduce fatigue in cancer patients. NCCN developed an algorithm for pediatrics made of screening, primary evaluation, intervention, and re-evaluation. Their intervention plan is based on eliminating the factors causing fatigue and if the fatigue is unresolved, there is a spectrum of recommendations ranging from nonpharmacological approaches like exercise and psychological programs to pharmacological

approaches like antidepressants [1]. it's also recommended that physical activity, relaxation, and mindfulness be used as interventions to reduce fatigue in pediatric oncology patients while pharmacologic intervention is not advised for routine use [46].

This study has limitations. The relatively small sample size affects the power of differentiation and prediction of some factors as stated earlier. This study could be viewed as an opportunity to raise the problem of fatigue in cancer patients and open the door for future larger studies. Our data was only collected from one site. Despite that the location was a tertiary hospital and our sample comes from different provinces of Egypt, it does not cover the whole population. Moreover, the guardians and children sat at the same location during the interviews. Although we tried to eliminate the guardian's influence on the child, the simple presence of the guardian could affect the independence of children's answers to the questionnaires. Moreover, guardians' characteristics, such as educational level, might influence the fatigue level of the children because they are highly dependent on them. The focus of this study was mainly on factors related to the patients themselves, and exploring these external factors could be accounted for in future studies. Finally, the potential impact of treatment delays, (e.g. caused by sepsis) on fatigue was not reported. These delays are expected to exacerbate fatigue via different mechanisms such as prolonged systemic inflammation and physical deconditioning. However, proper documentation of these incidents was not recorded. Future research is advised to document and account for these independent factors and measure their impact on fatigue levels to generate a more comprehensive understanding of the condition.

In conclusion, children with cancer in Egypt experience fatigue during their chemotherapy treatment which is underreported and undermanaged, this was evident by moderate to severe fatigue in third to half of the participants. Significant factors predicting fatigue were depression and mobility. Especially upper extremity mobility and treatment status. This means that patients during active chemotherapy treatment with upper mobility issues and depressive symptoms are in most need of fatigue management. PedsQL Fatigue might represent more detailed information about the nature of fatigue which allows for a better holistic care plan design. In contrast, PROMIS fatigue measures fatigue in general which fits longer surveys or research questionnaires. Future studies are warranted on a wider spectrum of children with cancer post/pre-treatment to quantify the extent of fatigue and start implementing its prevention in the care plan.

Supplementary Information

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Supplementary material 1.

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Author contributions

A.O. was responsible for conceptualization and project administration, A.O. and N.A. ran the formal analysis and developed the methodology, A.O. and A.Z. overviewed and supervised the study as well as validated the results, N.A. and S.L. were responsible for data acquisition and curation, N.A. wrote the first draft, A.O. and A.Z reviewed & edited the first draft. All authors reviewed the final manuscript.

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Data availability
The data that support the findings of this study are not openly available due to sensitivity reasons and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Newgiza University.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the the 1964 Declaration of Helsinki and its later amendments. Ethical approval was obtained from the Ethics Research Committee at the School of Pharmacy Newgiza University and the IRB committees at the participating hospital. Written consent was obtained from the child's guardian. Verbal consent was obtained from the child. They were assured that participation was voluntary. All personal information was kept with the principal investigator.

Consent for publication
Participants and/or their legal guardians were informed about the intent to publish the findings of this research, and consent for publication was obtained. By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

Competing interests
The authors declare no competing interests.

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