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ORIGINAL ARTICLE

Fatigue in survivors of Childhood Acute Lymphoblastic Leukemia

Elhamy Rifky Abd El-khalek [1], Laila M Sherief [1], Eman Roshdy El Safy [2], Marwa Mohamed Elsayed Azab [3]

1. Professor of pediatric Faculty of Medicine - Zagazig University, Egypt
2. Professor of Psychiatry Faculty of Medicine - Zagazig University, Egypt
3. MBBCH, Faculty of Medicine, Zagazig University

Corresponding author:

Marwa Mohamed Elsayed Azab

Email:
m.azab2025@gmail.com

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ABSTRACT

Background: The impact of therapy on psychosocial well-being is becoming more and more important as the survival rate for childhood Acute Lymphoblastic Leukemia (ALL) increases. There is a need for extensive research on fatigue throughout therapy. However, little information about this subject is known after treatment of ALL. The present work aims to assess fatigue experienced by adolescents and children after successful management for childhood ALL and its effect on the Quality of Life (QoL).

Methods: This cross-sectional comparative study included 30 children survivors of ALL and their parents. Another 30 healthy sex and age-matched children were recruited to serve as a control group. All survivors were conducted to complete history taking, full clinical examination, fatigue and QoL questionnaires.

Results: There was a remarkable variation between self-reported and parent-proxy fatigue scales including general, cognitive, and total fatigue scores among the survivors group (All parent-proxy domains were remarkably higher than self-reported) ($P<0.001$). There was a substantial adverse relationship between survivor-reported QoL and survivor-reported total fatigue score ($p<0.001$). There was a remarkable adverse association between parent proxy QoL of survivors and parent proxy fatigue ($p<0.001$).

Conclusion: This study suggests that adolescents and children survivors of ALL experience higher levels of fatigue compared to their healthy counterparts.

Keywords: fatigue, survivors, QOL, childhood, acute lymphoblastic leukemia.

INTRODUCTION

In recent years, the long-term survival percentage of children with acute lymphoblastic leukemia (ALL) has significantly increased and surpass 90% in several developed nations, particularly for those with good prognoses [1].

Despite this, one of the most prevalent and serious side effects that pediatric oncology cases encounter during therapy is fatigue [2], The frequency of fatigue and its effects on ALL survivors' quality of life (QoL) are quite poorly understood [3].

Its incidence, causes, conceptual and operational definitions, and successful interventions for survivors are all poorly understood. There is no quantitative research on fatigue among pediatric cancer cases [4].

The present work aims to assess fatigue experienced by adolescents and children after successful therapy for childhood ALL and its impact on QoL.

METHODS

Patients:

This cross-sectional study included 30 ALL survivor children and their parents recruited from the Pediatric Oncology Clinic at Zagazig University Hospital in the period between March 2022 to April 2024 aiming to describe fatigue experienced by children and adolescents after successful therapy for childhood ALL and its impact on QOL. Another 30 healthy age and sex-matched children were recruited to serve as a control group. Their parents assented to participate in the study or had a parent who consented to the study. The research was conducted under the World Medical Association's Code of Ethics (Helsinki Declaration) for human research. Approval was taken from the Institutional review board (IRB) of the Faculty of Medicine Zagazig University (ZU-IRB#6133/17-5-2020).

Survivors with the following characteristics were included; survivors with age 5-15 years of both sexes. Survivors of ALL that have been successfully treated according to total-XV ALL protocol at the Pediatric Oncology Department of Zagazig University Hospital 1- 10 years ago.

Survivors with the following characteristics were excluded; cases affected by any disease other than cancer. Children receiving concomitant radiation. Children who received bone marrow transplantation. If they were received corticosteroids outside of chemotherapy (CTX) regimen. Children who already have a communication difficulty, mental health condition, or cognitive impairment. Children whose health care team determines that they have an unstable physical state that would prevent them from participating in the study.

Sample size:

Assuming that the mean physical fatigue score among survivors from ALL is 3.5±0.8 and among the matched control group is 4.2±1.1. So, the sample size is determined by the open Epi program to be 60 cases. 30 cases in each group. With a confidence level of 95%. And the power of the test is 80%.

All study group were subjected to complete history taking (Demographic, cancer-related variables and full psychiatric history taking to exclude any psychiatric disorder) and full clinical examination.

Fatigue/QoL:

The Pediatric Quality of Life Inventory (PedQL) multidimensional fatigue and the PedsQL 3.0 Cancer Module were used to evaluate the fatigue and QoL of our series (Copyright c 1998 JW Varni,Ph.D. All rights reserved). English was used for their initial design and testing. Validated Arabic translated version was used as per Al-Gamal and Long [5].

The PedsQL Multidimensional Fatigue scale [5] formed of 3 categories, including general, sleep/rest, and cognitive, each subscale includes six items.

The purpose of the PedsQL 3.0 Cancer Module is to assess Health-Related Quality of Life (HRQOL) factors that are especially relevant to pediatric cancer in children ages 2 to 18. The Dimensions of QOL scales: include Physical (8 items), emotional (5 items), social well-being (5 items), and cognitive/school functioning (5 items). The Total scale scores (23 items) include a Physical Health summary score (8 items) and a Psychosocial Health summary score (15 items).

All items used a five-point response set, ranging from 0= 'not at all' to 4= 'Almost always. These scales' validity and reliability were examined. Rise in fatigue was reflected by higher scores.

Statistical Analysis:

Data analyses were carried out with SPSS version 26. The acquired data are statistically analyzed utilizing the simple classification approach based on two markers and the Fischer factorial test, which allows the independence hypothesis to be verified even at low frequencies.

A comparison score between different demographic characteristics and diagnosis is assessed by employing the Independent-Sample T-test. P-values <0.05 are considered significant.

RESULTS

There was a remarkable variation between the groups regarding weight, height, and body mass index (All were remarkably elevated among the control group) (p<0.01). There was a substantial variation between self-reported and parent-proxy QoL including health and activity domain, emotional, social activity, and school performance domains, and total QoL scores among the survivor group (All parent-proxy domains were notably reduced than self-reported) (p<0.001). (Table 1)

In addition to substantial variance between self-reported and parent-proxy fatigue scales including general, cognitive, and total fatigue scores among the survivors group (All parent-proxy domains were remarkably higher than self-reported) (P<0.001). (Table 2)

Additionally, there was a remarkable adverse relationship between the age of the survivor and total QoL (p=0.006). There was a remarkable positive relation between the age of the survivor and parent- proxy total fatigue scores (p=0.029). There was a non-substantial relationship between age at diagnosis and duration since chemotherapy and either survivor-reported or parent-proxy QoL, fatigue scores. (Table3)

There was a non-significant relation between sex of cases and risk of ALL and either survivor-reported or parent-proxy QoL and fatigue scores. (Table 4)

Moreover, the significant adverse relationship between survivor-reported QoL and survivor-reported total fatigue score (p<0.001). There was a substantial adverse association between parent proxy QoL of survivor and parent proxy fatigue. (Table 5)

Table (1): Comparison between the studied groups regarding demographic data and survivors and parent reported QoL:

	Survivors group	Control group	χ^2	P
	N=30(%)	**N=30(%)**		
Gender: Female Male	 17 (56.7%) 13 (43.3%)	 21 (70%) 9 (30%)	1.148	0.284
Family income Moderate Poor	 21 (70%) 9 (30%)	 25 (83.3%) 5 (16.7%)	1.491	0.222
Residence: Rural Urban	 22 (73.3%) 8 (26.7%)	 21 (70%) 9 (30%)	0.082	0.774
Birth order: First Second Third	 7 (23.3%) 23 (76.7%) 0 (0%)	 15 (50%) 10 (33.3%) 5 (16.7%)	0.399	0.528
	Mean ± SD	Mean ± SD	T	P
Age (year)	11.03 ± 2.14	11.43 ± 2.78	-0.625	0.534
Weight (kg)	39.47 ± 8.99	43.5 ± 11.78	-6.668	<0.001**
Height (cm)	138.5 ± 14.29	144.37 ± 11.69	-2.927	0.005*
BMI (kg/m2)	18.25 ± 4.25	20.46 ± 2.72	-6.734	<0.001**
Health and activity domain	77.29 ± 8.99	82.29 ± 12.1	-1.817	0.074
Emotional domain	70.33 ± 14.74	71.33 ± 18.89	-0.229	0.82
Social activity	85.83 ± 12.25	85.5 ± 14.58	0.096	0.924
School performance	64.17 ± 12.04	69.5 ± 12.22	-1.505	0.138
Total	74.41 ± 8.06	77.16 ± 9.6	-1.202	0.234

	Survivors group	Control group	χ^2	P
	Survivors	Parents	T	P
Health and activity domain	77.29 ± 8.99	64.9 ± 21.13	4.124	<0.001**
Emotional domain	70.33 ± 14.74	48.67 ± 26.42	5.758	<0.001**
Social activity	85.83 ± 12.25	70.33 ± 16.5	5.204	<0.001**
School performance	64.17 ± 12.04	47.17 ± 19.46	4.922	<0.001**
Total	74.41 ± 8.06	57.76 ± 13.25	9.969	<0.001**

χ^2Chi square test, t independent sample t-test, **p≤0.001 is statistically highly significant

Table (2): Comparison between the studied groups regarding the survivor- and parent-reported fatigue questionnaire:

	Survivors group	Control group	Z	P
	Median (IQR)	Median (IQR)		
General Fatigue	6(4 – 10.5)	4(2 – 6)	-2.311	0.021*
Feeling tired	1(0 – 2)	1(1 – 2)	-0.838	0.402
Feeling weak	1.5(0 – 2)	1(0 – 1)	-2.786	0.005*
Feeling too tired to do things he likes	1(0 – 2)	1(0- 1)	-0.987	0.324
Feeling too tired to spend time with friends	1(0 – 2)	1(0 – 1)	-1.489	0.137
Trouble finishing things	1(0 – 2)	1(0 – 1)	-2.435	0.015*
Trouble finishing new things	1.5(0 – 2)	1(0 – 1)	-2.668	0.008*
cognitive Fatigue	8.5(4 – 11.25)	5.5(2 – 6)	-2.683	0.007*
Hard to keep attention	2(0 – 2)	1(0 – 1)	-1.438	0.15
Hard to remember what people tell him	2(0 – 2)	1(0 – 1)	-2.25	0.024*
Hard to remember what just heard	1(0 – 2)	0.5(0 – 1)	-2.133	0.033*
Hard to think quickly	1.5(0 – 2)	1(0 – 1)	-2.33	0.02*
Hard to remember what just he thinks	2(0 – 2)	0.5(0 – 1)	-3.017	0.003*
Hard to remember more than one thing at a time	2(1 – 2)	2(0 – 2)	-2.344	0.019*
Total	20.5(15.25 – 30.25)	14(9.75 – 18)	-3.312	0.001**
	Survivors	Parent	Wx	P
General fatigue	6(4 – 10.5)	10.5(4 – 12.5)	-3.533	<0.001**
Cognitive fatigue	8.5(4 – 11.25)	12(5.75 – 13.25)	-3.753	<0.001**
Total	20.5(15.25 – 30.25)	31(24.5 – 46)	-4.708	<0.001**

Z: Mann Whitney test, Wx: Wilcoxon signed rank test, *p<0.05 is statistically significant, **p≤0.001 is statistically highly significant

Table (3): Correlation between age of survivors, age at diagnosis, and duration after chemotherapy and QOL and fatigue questionnaires:

	Survivors		Parent	
	R	P	R	P
Between Age				
Total QoL	-0.489	0.006*	-0.346	0.061
Total fatigue	0.238	0.205	0.398	0.029*
Age at diagnosis				
Total QoL	-0.104	0.583	-0.157	0.408
Total fatigue	-0.005	0.979	0.081	0.672
Duration after chemotherapy				
Total QoL	-0.254	0.176	-0.076	0.688
Total fatigue	0.176	0.352	0.348	0.06
r Pearson correlation coefficient *p<0.05 is statistically significant				

Table (4) :Relation between gender, family income, and risk and Survivors QoL and fatigue scores

Sex	Male (n=13)	Female (17)	T	P
	Mean ± SD	Mean ± SD		
Total survivors QoL	74.28 ± 5.92	74.5 ± 9.56	-0.074	0.941
Total parent QoL	56.88 ± 12.88	58.45 ± 13.89	-0.317	0.754
Total survivors fatigue	22.31 ± 9.29	21.76 ± 9.03	0.161	0.873
Total parent fatigue	35.46 ± 12.77	33.06 ± 13.01	0.505	0.617
Family income	Poor (n=7)	Moderate (21)	T	P
Total survivor QoL	72.81 ± 8.02	75.09 ± 8.17	-0.703	0.488
Total parent QoL	53.28 ± 13.9	59.69 ± 12.83	-1.223	0.231
Totalsurvivor fatigue	24.11 ± 11.8	21.1 ± 7.65	0.838	0.409
Total parent fatigue	36.89 ± 16.21	32.9 ± 11.19	0.672	0.515
Risk	Standard (n=13)	High (n=17)	T	P
Total survivor QoL	76.01 ± 7.53	73.18 ± 8.45	0.952	0.349
Total parent QoL	59.58 ± 11.86	56.58 ± 14.47	0.553	0.585
Totalsurvivor fatigue	20.08 ± 9.06	23.47 ± 8.92	-1.026	0.314
Tota lparent fatigue	31.38 ± 13.51	36.18 ± 12.11	-1.022	0.316
t: independent sample t test, *p<0.05 is statistically significant				

Table (5): Correlation between both survivor-reported QOL and parent-reported QOL with fatigue scores of both survivors and parents of survivors

	R	P
survivor reported QoL		
Total fatigue reported survivors	-0.685	<0.001**
Parent proxy QoL		
Total fatigue reported by parents of survivors	-0.754	<0.001**

r: Pearson correlation coefficient, **p≤0.001 is statistically highly significant, *p<0.05 is statistically significant

DISCUSSION

The increased survival rates of ALL have drawn attention to other outcomes, including as QoL and tiredness. In the clinical setting, it appears that these difficulties are not infrequent throughout ALL therapies; nonetheless, investigations on this subject are scarce [6].

This cross-sectional study aimed to evaluate fatigue experienced by adolescents and children after successful treatment for childhood ALL and its effect on QOL.

In this study, there was a remarkable variation between self-reported and parent-proxy QoL including health and activity domain, emotional, social activity, and school performance domains, and total QoL scores among survivors group (All parent-proxy domains were remarkably reduced than self-reported)

This is in accordance with Gordijn et al. [7] who demonstrated that parents evaluated the ALL survivors as experiencing a lower physical QoL. All survivors indicated improved psychosocial well-being.

In the present study, there was a substantial variation between the groups concerning self-general fatigue, Cognitive fatigue and total fatigue scores (All are significantly higher among the survivors group)

In accordance with Steur et al., [8] Fatigue related to cancer was more prevalent in the general group, except for cognitive cancer-related fatigue. The lack of cognitive cancer-related fatigue may be attributed to the reduced cognitive requirements and expectations in the initial stages of treatment.

In present study, there was a remarkable variation between self-reported and parent-proxy fatigue scales including general, cognitive, and total fatigue scores among the survivors group (All parent-proxy domains were significantly higher than self-reported).

Gordijn et al. [7] showed that Parents assessed ALL survivors to be more fatigued than the Dutch mean, but fatigue experienced by survivors did not vary.

Our self-report findings correspond with Mulroony et al., [9] as they reported that ALL survivors had no higher levels of self-reported fatigue than their siblings or the general population.

Parents of children with cancer face extra strain along with the usual responsibilities of everyday life, which can be aggravated by fatigue. This significantly elevated fatigue puts them at risk for several unfavorable health consequences, including depression and anxiety, and could lead to a lower subjective QoL, as previously found in parents of children with cancer [10].

In present study, there was a non-remarkable relationship between duration since chemotherapy and either survivor-reported or parent-proxy QoL and fatigue scores

The current work demonstrated that results are not consistent with Gordijn, et al., [7] which found that pediatric survivors of childhood ALL approximately three years post treatment did not report significantly poorer fatigue than population norms.

Further, literature evaluating fatigue in adult survivors of childhood ALL suggests no differences exist in long-term survivorship, either [9].

In this study, there was a statistically non-remarkable relation between the sex of cases and either survivor-reported or parent-proxy QoL and fatigue questionnaire.

Sex disparities in fatigue and neurocognitive assessments were a bit astonishing and may be attributable to more widespread self-reported symptoms of fatigue in female survivors [11].

Prior research has established the gender-specificity of late consequences of cancer therapy, specifically in neurocognitive abilities in cancer survivors [12].

Because fatigue and sleep are highly changeable health outcomes, addressing gender-specific pathophysiology may have a substantial effect on neurocognitive ability in this population. In this regard, female survivors who demonstrate sleep disorders may require additional preventive efforts, including cognitive and psychological behavioral treatment, in addition to information or education interventions to enhance sleep hygiene [13].

In the present study, there was a remarkable adverse association between survivor-reported QoL and survivor-reported total fatigue scores.

This agrees with Gordijn et al. [7] who indicated that proxy-reported fatigue inversely correlated with QoL.

Van Litsenburg et al. [14] reported that QoL was adversely linked with numerous items. Most associations were moderate, with Spearman's rho ranging from 0.5 to 0.8.

Additionally, we verified a previously documented link between greater cancer-related weariness and reduced levels of physical activity [15]. These findings emphasize the importance of addressing and managing fatigue in pediatric ALL survivors to optimize their post-treatment QoL and overall health.

Conclusion

This study suggests that children and adolescents who have successfully undergone childhood treatment of ALL experience higher levels of fatigue compared to their healthy counterparts. While overall QoL did not significantly differ between the two groups, there was a notable disconnect between self-reported and parent-proxy QoL scores, with parents consistently rating their child's QoL lower. Additionally, survivor-reported QoL was negatively correlated with total fatigue, highlighting the potential impact of these symptoms on the well-being of ALL survivors.

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