

Research Article

A Comparative Study of Sleep Parameters in Adult Survivors of Childhood Acute Lymphoblastic Leukemia and Healthy Peers: Insights from Accelerometer Data

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Background. Sleep problems are among the common late side effects of treatment that can occur in survivors of childhood acute lymphoblastic leukemia. At present, the objective evaluation of sleep in the natural environment using actigraphy rather than self-assessment of research participants or the more demanding polysomnography is increasingly coming to the forefront in population epidemiological studies. The main objective of this cross-sectional study is to objectively characterize selected sleep parameters with respect to gender in adult survivors of childhood acute lymphoblastic leukemia (ALS) in their natural environment and to compare them with a control group (CG) sampled from a healthy population. Another partial aim of the study is to determine the fulfillment of recommendations in the areas of sleep (SL) and sleep efficiency (SE). **Methods.** 20 ALS and 20 CGs aged 18–30 years participated in the survey. The ALS were diagnosed on average 15.5 years ago. Selected sleep parameters were measured instrumentally by means of an Axivity AX3 accelerometer worn on the wrist for seven days in a natural environment. **Results.** No significant differences were found between the ALS and CG groups for the selected sleep parameters. The total time in bed for the ALS was 405.5 min/day compared to 428.2 min/day for the CG ($p = 0.37$), sleep for the ALS was 372.7 min/day compared to 382.9 min/day for the CG ($p = 0.34$), and SE for the ALS was 88.0% compared to 88.5% for the CG ($p = 0.99$). No significant gender differences were found. The sleep recommendation of >420 min/day was met by 15% for the ALS and 19% for the CG; SE > 85% was achieved by 80% for the ALS and 80% for the CG. **Conclusion.** The results of our study suggest that ALS may achieve the same values as the healthy population in selected sleep parameters.

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common type of malignant tumor in children [1, 2]. In developed countries, the five-year survival rate now exceeds 90% [3]. However, in this specific population, survival may be complicated by impaired quality of life [4–6] and by the large number of late treatment-related adverse sequelae [7, 8]. Very often, sleep problems are among them in survivors of childhood cancer [9–11].

Sleep and sleep problems in long-term survivors of childhood ALL may be key factors that can negatively affect mental health [9, 12], lead to problems with health behaviors [13], and may also be significantly related to fatigue [14, 15].

These sleep problems may occur months to years after the treatment has been completed [16]. Poor sleep quality has been confirmed not only in children [17] but also in adolescent survivors of childhood ALL [18]. Survivors of childhood ALL may also very often fail to meet the sleep recommendations [19].

Sleep problems have been addressed in research studies both during treatment (in children) and after the end of treatment, e.g., in the first period after diagnosis [20], during the first year of treatment [21], three years after the end of treatment [17], after two to seven years [19], and with an average number of years after diagnosis of 7.4 years [18]. Measuring selected sleep parameters using actigraphy [22] is coming to the forefront in population epidemiological

studies compared with self-reported methods. Actigraphy is a feasible alternative to polysomnography, and its huge advantage is its application to a natural environment [23]. Instrumentally measured sleep parameters should play a major role in future studies [24], and sleep assessment should become a part of annual patient care [25].

In our study, we are interested in whether sleep problems can persist in other stages of life and what sleep parameters in the areas of time in bed (TIB), sleep (SL), and sleep efficiency (SE), which are one of the important indicators of sleep quality [26], are achieved by adults who became ill in childhood. We have not been able to find studies that characterize (using the method of actigraphy) sleep with such a long-term (>ten years) distance from the completion of treatment or from diagnosis in this target group. Given that research studies in the healthy population also point to sex-related differences in sleep parameters—women achieve longer sleep times and higher SE compared to men [27, 28]—we are interested in whether these differences also occur in adult survivors of childhood acute lymphoblastic leukemia (ALS).

The main objective of the study is to characterize the selected sleep parameters (TIB, SL, and SE) within a normal week in ALS with regard to gender and to compare these characteristics with the characteristics of their healthy peers. Another partial aim of the study is to determine the fulfillment of recommendations in the areas of SL and SE.

2. Methods

This cross-sectional study involved a total of 40 participants. 20 participants formed the group ALS, where the criterion for inclusion in the research was an age of 18–30 years, having undergone active treatment for ALL in childhood at departments of pediatric hematology and hemato-oncology in the Czech Republic, and with the minimum time since their diagnosis being more than ten years. The exclusion criterion was disability or medical condition not related to the treatment. The control group (CG) consisted of 20 healthy participants who had not experienced any cancer and had no disability or health impact. All the members of both groups (ALS and CG) had their permanent residence in the Czech Republic.

2.1. Recruitment of Participants. At present, addressing potential research participants with such a long time since the completion of treatment is very demanding organizationally. One of the main ways to reach this target group is to reach out through patient organizations. However, these organizations only register patients who are interested. For the purposes of our research, this target group was addressed through the patient organizations—Šance Association and Společně s úsměvem (together with smile). Out of a total of 31 ALS addressed who met the criteria for inclusion in the research, 21 ALS showed interest in participating. As part of

the research survey, each ALS had the opportunity to involve a CG sampled from a healthy population in the research. In this way, 21 participants forming the CG were recruited. Because of the failure to meet the minimum wear time of the sleep monitoring device, the data of one ALS and one CG were excluded from the study. The total number of participants meeting the research criteria is 20 ALS and 20 CG. The recruitment of the participants is shown in Figure 1.

2.2. Data Collection. Those interested in participating in the research survey contacted the principal investigator of the research, who provided them with all the necessary information. Their informed consent to the research was required for them to participate in the research survey. The study was approved by the Ethics Committee of the Faculty of Physical Culture of Palacký University in Olomouc under no. 20/2021. The monitoring equipment was handed over to both research groups in person one or two days before the scheduled start of the research. This period was chosen to reduce the risk of battery discharge and thus not meeting the specified number of days of measurement. The actual data collection took place for seven days and was carried out from June 14 to 20, 2021. After the end of the data collection, the device was sent back by post at the expense of the project investigator for evaluation. Information regarding treatment (in the ALS) and current characteristics such as age, height, and weight (in both the ALS and CG) were obtained by a questionnaire survey.

2.3. Sleep Monitoring. The Axivity AX3 accelerometer (Axivity Ltd., Newcastle upon Tyne, UK), a small waterproof device (23 × 32.5 × 7.6 mm; 11 g), was used to measure sleep quantity and quality. The Axivity AX3 was used in the UK Biobank study [29] and has been previously used in cancer survivors [30–32]. The participants were instructed to wear the device on their nondominant wrist for seven consecutive days, except while swimming. The device was initialized to measure data at 100 Hz with an 8G bandwidth using the OmGui software (version 1.0.0.43, Newcastle University, UK). The raw accelerometer data were processed using the R package GGIR (v2.1–0, <https://cran.r-project.org/web/packages/GGIR/>) [33]. The default sleep algorithm [34] was used to identify periods of sleep (sustained periods of inactivity with no change greater than 5° over at least five min), the onset of sleep, and waking time.

2.4. Sleep Parameters. The indicators for assessing sleep quantity and quality were determined as time in bed (TIB), sleep (SL), and sleep efficiency (SE). TIB was defined as the difference between the onset of sleep and the time of waking, SL was defined as the sum of all the recorded periods of sleep during the night, and SE was defined as the percentage of time spent sleeping within the TIB [34]. The optimal SL for this study was determined to be 420 min/day [35]. SE can

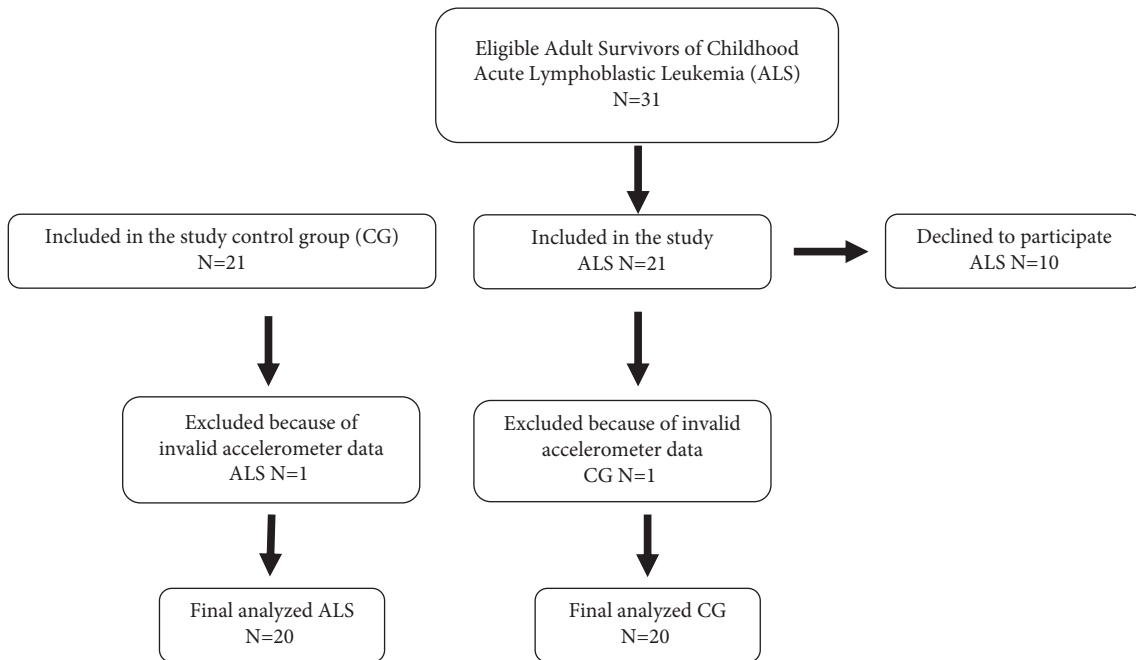


FIGURE 1: Flowchart of the study.

provide essential information about the health status of an individual [36]; the threshold of $\geq 85\%$ was used as an indicator of good sleep quality [37].

2.5. Statistical Data Processing. Descriptive statistics (median and interquartile range) were used to provide the basic characteristics of the study sample. To compare the groups (gender and treatment), the nonparametric Mann–Whitney U test was used. The significance level was set to $\alpha = 0.05$. The coefficients of the effect size were evaluated as follows: $0.2 \leq d < 0.5$: small effect size, $0.5 \leq d < 0.8$: medium effect size, and $d \geq 0.8$: large effect size. The IBM SPSS Statistics 25 statistical software (IBM SPSS, Inc. Chicago, IL, USA) was used. A chi-squared test as recommended by Campbell [38] was used for the comparison of proportions.

3. Results

In terms of descriptive characteristics of the study participants (Table 1), there is homogeneity between the groups (ALS versus CG) among men (age, $p = 0.86$; body height, $p = 0.33$; body weight, $p = 0.79$; and BMI $p = 0.72$) and among women (age, $p = 0.95$; body height, $p = 0.70$; body weight, $p = 0.95$; and BMI $p = 0.56$).

Concerning gender (male \times female), in the ALS, a significant difference was found in the category of body height, $p = 0.04$ (age, $p = 0.94$; body weight, $p = 0.14$; and BMI, $p = 0.35$). Similar results were obtained for the CG (body height, $p = 0.01$; age, $p = 0.88$; body weight, $p = 0.08$; and BMI, $p = 0.20$).

In the ALS group, the median age at the time of the disease was 7.5 (IQR: 8.0), the median duration of treatment was 18.0 months (IQR: 13.0), and the median time from diagnosis was 15.5 years (IQR: 8.9).

The overall results (Table 2) showed no significant differences between the ALS and CG groups. For the TIB parameter, the instrumentally measured resulting values were 405.5 min/day for the ALS (CG: 428.2 min/day), SL 372.7 min/day for the ALS (CG: 382.9 min/day), and SE 88.0% for the ALS (CG: 88.5%).

An overview of the selected sleep parameters evaluated on the basis of gender is shown in Table 3. Again, there were no significant differences between the ALS and CG. No significant differences were found even when the gender of the participants was taken into account (TIB ALS male vs. female, $p = 0.71$; TIB CG male vs. female, $p = 0.70$; SL ALS male vs. female, $p = 0.88$; SL CG male vs. female, $p = 0.94$; SE ALS male vs. female, $p = 0.37$; SE CG male vs. female, $p = 0.06$).

In terms of established sleep recommendations (Table 4), >420 min/day was achieved by 15% of the ALS and 19% of the CG. SE $> 85\%$ was achieved by 80% of the ALS and 80% of the CG.

No gender differences were found in terms of meeting the sleep recommendations (SL ALS male \times female, $p = 0.42$; SL CG male \times female, $p = 0.60$; SE ALS male \times female, $p = 0.83$; SE CG male \times female, $p = 0.12$).

4. Discussion

The main finding of this study was that the results for the ALS and CG did not differ for the sleep parameters that were selected. It can be assumed that ALS may achieve the same values in individual sleep parameters as the healthy population.

When comparing the selected sleep parameters measured using an actigraph in the ALS, we could not find a study where it would be possible to compare these parameters objectively. A study of the pediatric population with acute lymphoblastic leukemia [20] achieved significantly higher values for TIB

TABLE 1: Descriptive characteristics of the study sample ($n = 40$).

	N	Age (years)		Body height (cm)		Body weight (kg)		BMI (kg/m ²)	
		Mdn	IQR	Mdn	IQR	Mdn	IQR	Mdn	IQR
<i>Adult survivors of childhood acute lymphoblastic leukemia</i>									
Male	11	23.0	5.5	176.0	8.0	81.0	16.0	25.0	5.8
Female	9	23.7	6.4	171.0	15.0	68.0	21.0	22.2	6.5
<i>Control group</i>									
Male	7	24.2	7.6	185.0	19.0	75.0	50.0	23.4	9.5
Female	13	24.8	5.9	168.0	8.0	62.0	16.0	23.6	5.2
Total	40	23.9	5.4	172.5	15.0	68.0	22.0	23.3	5.5

N, number of participants; Mdn, median; IQR, interquartile range.

TABLE 2: Overall overview of the selected sleep parameters.

	ALS (N = 20)		Control groups (N = 20)		Difference	
	Mdn	IQR	Mdn	IQR	p value	d
Time in bed (min/day)	405.5	32.5	428.2	85.7	0.37	0.29
Sleep (min/day)	372.7	30.4	382.9	43.9	0.34	0.31
Sleep efficiency (%)	88.0	4.25	88.5	3.15	0.99	0.01

Mdn, median; IQR, interquartile range; d, effect size coefficient.

TABLE 3: Overview of the selected sleep parameters by gender.

	ALS		CG		Difference	
	Mdn	IQR	Mdn	IQR	p value	d
<i>Gender</i>						
Male	(N = 11)		(N = 7)			
Time in bed (min/day)	425	52.1	433	87.1	0.60	0.28
Sleep (min/day)	378	33.7	405	81.6	0.54	0.32
Sleep efficiency (%)	89	4.91	90	3.03	0.38	0.45
Female	(N = 9)		(N = 13)			
Time in bed (min/day)	389	121.5	423	87.1	0.43	0.36
Sleep (min/day)	364	117.0	382	53.9	0.51	0.30
Sleep efficiency (%)	87	5.97	88	6.65	0.79	0.13

Mdn, median; IQR, interquartile range; d, effect size coefficient; ALS, adult survivors of childhood acute lymphoblastic leukemia; CG, control group.

TABLE 4: Overview of meeting recommendations for sleep and sleep efficiency.

	ALS		CG		Difference p value
	N	%	N	%	
<i>Sleep >420 min/day</i>					
Male	1	9	1	13	0.55
Female	2	22	3	23	0.96
Total	3	15	4	19	0.74
<i>Sleep efficiency >85%</i>					
Male	9	82	7	100	0.25
Female	7	78	9	69	0.65
Total	16	80	16	80	1.00

N, number of participants; ALS, adult survivors of childhood acute lymphoblastic leukemia; CG, control group.

(663.6 min/day vs. 405.5 min/day) and SL (506.7 min/day vs. 372.8) compared to our results (adult population min/day) although the overall SE was lower (76.6% vs. 88.0%). It should be noted that although the sleep parameters were measured at home, they were measured at the time of treatment. Pediatric cancer patients with a greater post-treatment interval (two to

seven years) experienced decreases in SL (451.5 min/day) and increases in SE (84.3%) [19]. With regard to our study, it seems that with the passage of treatment, SE may increase. Since this is one of the important indicators of sleep quality, it would be appropriate to carry out more instrumentally measured studies on this topic.

In terms of gender, the sleep parameters did not differ between the ALS and CG. These results do not correspond with the findings of other studies dealing with healthy populations [28, 39], which suggest that men sleep less on average than women across age categories.

The recommended sleep duration >7 h/day (420 min/day) [35] showed almost no difference between the groups (ALS and CG). However, only a small number of probands met this sleep recommendation in both groups. Since sleep lasting between seven and eight hours per day is associated with health benefits [35], it is necessary to place much greater emphasis on this recommendation.

One of the limitations of our study is the sample size, which may not be large enough to conduct robust associative analyses between sleep quality and various demographic, social, and psychological parameters. Exploring these relationships could provide a more comprehensive understanding of sleep functioning in childhood cancer survivors, and we acknowledge that this is an important area for future research.

Other limitation of our study stems from the inability to collect data on the reasons why some childhood cancer survivors chose not to participate. While we were able to engage with those who expressed interest in the study, we did not have a mechanism in place to gather information from those who did not respond to our invitation. This is a significant limitation as it leaves unanswered questions about whether the nonparticipants experienced sleep problems or other mental health difficulties, which could have potentially biased our findings.

In addition, we did not collect data on the use of medications affecting sleep and anxiety levels by the participants. These substances could potentially influence sleep duration and quality, and having information on their use could have added valuable insights to our findings. We can speculate that the use of these substances might be present in both our study and control groups, and thus their impact on our findings might be mitigated to some extent. We recognize that this is a speculative assumption and that concrete data would have strengthened our study.

Nevertheless, we believe that the ALS target group with a long time lag (in our study, an average of >15 years) since the established diagnosis is a strength of the study since this target group is not the subject of current research studies. Also, instrumental measurement in the natural environment provides a greater advantage over polysomnography.

Adopting a longitudinal approach to assess sleep problems in patients undergoing therapy and patients after treatment is crucial, with objective, regular sleep assessments in natural settings being paramount. These assessments may not only facilitate a comprehensive understanding of sleep patterns and potential disruptions but also enable the implementation of preventive measures aimed at mitigating or resolving sleep-related issues. The integration of instrumentally measured sleep parameters should be considered an essential component of long-term patient follow-up post-treatment. Already, a minimal 2 week intervention using actigraphy-based sleep feedback can yield positive effects on sleep quality and overall well-being [40]. This highlights the potential of regular sleep assessments and feedback in positively influencing patients' outcomes. In

addition, combining objective sleep monitoring with ecological momentary assessment [41] may offer a promising approach. Incorporating these methodologies into future research could significantly enhance our understanding of sleep problems in patients undergoing therapy and after treatment and contribute to the development of tailored interventions to improve sleep quality and overall well-being.

5. Conclusion

The evidence of our study suggests that adult survivors of childhood acute lymphoblastic leukemia may achieve the same values as the healthy population for the selected sleep parameters. No significant gender differences were found. Only a small number of the ALS and CG probands met the recommended total length of sleep time. For the SE parameter, the recommendation was met to a much greater extent in both groups.

Data Availability

The datasets used to support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Palacký University Olomouc (no. 20/2021).

Consent

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

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation and data collection and analysis were performed by Vyhlidal T. The first draft of the manuscript was written by Vyhlidal T, and all authors commented on previous versions of the manuscript. All the authors have read and approved the final manuscript.

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