



# A Report of Pediatric Langerhans Cell Histiocytosis in a Hospital-Based Study

Javad Sabery Nejad<sup>1</sup>, Ali Ebrahim Ahmadi<sup>1</sup>, Maryam Tashvighi<sup>1</sup>, Narjes Mehrvar <sup>2,\*</sup>, Azim Mehrvar <sup>1</sup>

<sup>1</sup> AjA University of Medical Sciences, Tehran, Iran

<sup>2</sup> Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

\*Corresponding author: Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: narjes.mehrvar@gmail.com

Received 2024 February 27; Accepted 2024 March 16.

## Abstract

**Background:** The reports of Iranian Pediatric Langerhans Cell Histiocytosis (LCH) are rare and there is no specific survival rate for those cases.

**Objectives:** This study was designed as a hospital-based project for evaluating the epidemiological data and survival rates of the mentioned patients.

**Methods:** This was a cross-sectional descriptive study that enrolled patients younger than 15 years old with approved LCH malignancy. Data was gathered based on a unique questionnaire and analyzed by SPSS Software version 25.

**Results:** There were 32 cases (male/female ratio = 0.88) who were categorized as high risk (n = 18), moderate (n = 9) and low risk (n = 5), respectively. The mean age of patients was 5.1 years and the common chief complaint in them was bone pain, with the skeleton site of involvement. The 5-years overall and event-free survival rates were 93.3% and 72.9%, respectively.

**Conclusions:** The suggestion is to provide a national registry for pediatric LCH followed by designing future projects around affective genes on the treatment response of the mentioned patients. In that way, we can improve the survival rate of these patients and decrease mortality.

**Keywords:** Langerhans Cell Histiocytosis, Pediatric, Survival Rate

## 1. Background

The accumulation of antigen-presenting dendritic cells in granulomatous lesions can lead to single system langerhans cell histiocytosis (SS-LCH) or multi-system LCH (MS-LCH) (1) which are rare malignancies that can affect any age ranges of children (1, 2). The age-specific rate (ASR) of LCH in patients younger than 15 years old is 4 to 9 per 1 000 000 children (3, 4).

As a result of being heterogenous, this malignancy can have multiple clinical symptoms, which lead to various prognoses and outcomes (4). A report in 2016 revealed that severe types of LCH are mainly diagnosed in cases less than 2 years old which can result in poor prognosis (5). Routinely, the main treatment modality in pediatric LCH is chemotherapy which differs based on the new cases or recurrent LCH patients (3). In 2015, a study was published that confirmed hematopoietic

stem cell transplantation in patients with recurrent LCH (6) which could access 70% of overall survival in that patients.

Iran as a low-middle-income country has a noticeable rate of pediatric malignancies in where the prevalence of childhood LCH could be worthwhile for further clinical research. By designing the clinical trials through these cases and evaluating the modern therapies, the cure rate could increase and as a result, mortality, poor outcomes, and prognoses will decrease. By the way, there could be some limitations beyond this idea, that relate to the rare reports of Iranian pediatric patients with LCH. The majority of published papers from Iran are review articles, which considered childhood LCH and scare reports around epidemiology from Iranian pediatric malignancies' single centers. Finally, these limitations turned on the light of designing the current project for considering the care and management of Iranian childhood LCH in a referral pediatric cancer

center. Regarding this idea, the survival rates of these cases were evaluated too.

## 2. Methods

### 2.1. Study Design and Patients

The study was conducted as a cross-sectional retrospective hospital-based study which included all of the patients younger than 15 years old who had been diagnosed as new cases with LCH from 2007 to 2019. The exclusion criteria were defined for those patients who lost the therapy during the courses and left their treatment for unknown reasons. The follow-up of enrolled patients was done in 2022 to estimate the survival rates.

### 2.2. Data Gathering

The ethical committee of the hospital approved the designed unique questionnaire for gathering patients' data based on demographic information, pathology reports, treatment modalities, and status updates. The gathered data was entered into SPSS software version 23 for further analysis.

### 2.3. Patients' Risk Stratification

Patients were categorized into 3 risk groups based on below criteria (7, 8):

- Multisystem high-risk patients: Who had involvement of one or more risk organs like the hematopoietic system, liver, spleen, or lungs
- Multisystem low-risk patients: With multiple organs involved but without involvement of risk organs
- Single system multifocal bone disease (moderate risk): Or localized special site involvement which included patients with multifocal bone disease (lesions in two or more different bones) or with localized special site involvement (lesions with intracranial soft-tissue extension or vertebral lesions with intra-spinal soft-tissue extension)

### 2.4. Patients' Systemic Chemotherapy

The initial phase of systemic chemotherapy for all of the risk groups started with (9):

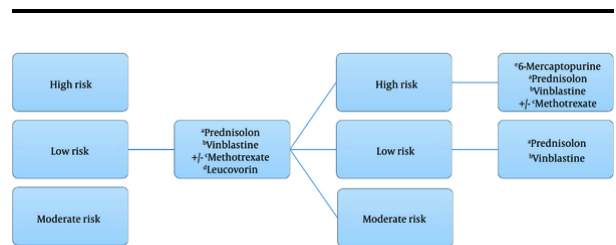
- Prednisolone (Pred) for 14 days in 2 weeks followed by taper for 2 weeks.
- Vinblastine (VBL) on the first day of the week for 6 weeks.

- Methotrexate (MTX) on the first day of weeks 1, 3, and 5.

- Leucovorin (Leuc) for 3 days started on the second day of weeks 1, 3 and 5.

At the end of the initial phase, the patient was evaluated and the next phase was continued based on their risk groups as below: (1) Group 1: Received the course of VBL, 6-Mercaptopurine (6-MP), Pred (for 5 days), and MTX (weekly). Patients of this group were administered 16 courses, which were repeated every 21 days; (2) Groups 2 and 3: Received the course Pred (for 3 days) and VBL per week, which continued for 6 weeks.

Figure 1 shows the schematic view of treatment in considered cases and the dosage of chemotherapy agents.



**Figure 1.** Schematic view of systemic chemotherapy in pediatric patients with langerhans cell histiocytosis based on different risk groups. A, 40 mg/m<sup>2</sup>/day; B, 6 mg/m<sup>2</sup>/day; C, 500 mg/m<sup>2</sup>/day; D, 12 mg/m<sup>2</sup>; E, 50 mg/m<sup>2</sup>/day; F, 20 mg/m<sup>2</sup>/day.

### 2.5. Data Analysis

Analyses were done by SPSS software version 25 for parametric and non-parametric data. Kolmogorov-Smirnov was used for evaluating the normality of variables also, Fisher test and chi-square tests were used for the relation between variables, in addition, ANOVA was used for parametric variables.

The overall survival rate was defined as the duration of the time between the date of diagnosis and the date of last status in patients. The last status was confirmed as last visit, last phone call, or date of death. The relapse and death were considered as events and also the event-free survival was estimated based on the time duration from diagnosis to the first event in patients. These rates were calculated by Kaplan-Meier analysis.

### 2.6. Ethical Committee

The ethical committee of AJA University of Medical Sciences, Tehran, Iran with the ethical committee code IR. AJAUMS.REC1401.063 approved the designed project

## 3. Results

### 3.1. Patients

During 12 years of evaluation, 32 new cases with approved pediatric LCH (patients younger than 15 years old) were administered who were 17 (53.1%) and 15 (46.9%) female and male, respectively (male to female ratio: 0.88). Out of those cases, 18 children were treated as high risk and the others were related to moderate (n = 9) and low (n = 5) risk groups.

The frequency of males to females was higher only in the high-risk group (M/F: 10/8) while it was vice versa in low and moderate-risk groups (M/F of low-risk patients: 2/3; M/F of moderate-risk group: 3/6). The mean age of total patients was  $5.1 \pm 0.7$  years old (age range 1 - 14 years old), and there was not any significant relation between the risk groups and patients' age ( $P$ -value > 0.05).

The chief complaints or symptoms of patients that were the cause of referee to the clinic were bone pain (in 62.5% of cases) and eyelid swelling (28.1% of patients). Analyses of data based on the site of disease revealed that the most common involvement was in the skeleton (87.5% of total cases) followed by skin (21.9% total), in addition, the rate of hematopoietic system involvement was the same in lymph nodes, and the less site related to central nervous system (Table 1). Clinical manifestations showed that only 5 patients had hepato-splenomegaly.

**Table 1.** Patients' Characteristics at the Time of Diagnosis

Variables	High Risk		Low Risk		Moderate Risk	
	Male (n = 10)	Female (n = 8)	Male (n = 2)	Female (n = 3)	Male (n = 3)	Female (n = 6)
Mean age (y) (Min-Max)	6.3 ± 1.4 (2-14)	5.2 ± 1.5 (1-13)	5.5 ± 3.5 (2-9)	5 ± 3.1 (1-11)	2 ± 1 (1-4)	4.5 ± 1.5 (1-9)
<b>Site of disease (n)</b>						
Skeleton	9	7	1	2	3	6
Skin	1	2	1	2	0	1
Hematopoietic system	0	0	0	2	2	0
Lymph nodes	0	1	0	1	0	2
Central nervous system	0	0	0	0	0	3
<b>Chief complaint (n)</b>						
Mouth mucositis	1	0	1	0	0	0
Bone pain	6	5	1	3	2	3
Eyelid swelling	4	4	0	0	0	1
Ptosis	2	1	1	0	0	1
Hepato and splenomegaly	0	0	2	2	1	0

### 3.2. Patients' Treatment Modalities

All of the patients had chemotherapy protocol according to the risk groups (Figure 1). The type of surgery based on diagnostic biopsy, total or partial resection are categorized in Table 2. There was only one female low-risk case who did not have any surgery.

**Table 2.** Patients' Treatment Modalities

Variables	High Risk		Low Risk		Moderate Risk	
	Male (n = 10)	Female (n = 8)	Male (n = 2)	Female (n = 3)	Male (n = 3)	Female (n = 6)
<b>Surgery (n)</b>						
Biopsy	3	4	1	2	2	1
Total resection	6	4	1	-	1	5
Partial resection	1	-	-	-	-	-
<b>Radiotherapy</b>	0	1	0	0	2	0
<b>Relapse</b>	2	2	0	0	0	1

Only 3 cases had radiotherapy:

- (1) A 15-year-old male from a moderate risk group with skeleton and hematopoietic system involvement who referred with bone pain.
- (2) A 15-year-old male from a moderate risk group with skeleton involvement and had hepato and splenomegaly at the time of diagnosis.
- (3) A 13-year-old female from high-risk group with skin involvement and referred with eyelid swelling.

All of those three cases were alive at the time of writing this paper, and unfortunately, there was not enough data about the dose and site of radiotherapy for them.

Based on the data in Table 2, only 5 cases had relapse and the mean time of recurrence (from diagnosis to the first relapse) was  $2.6 \pm 0.8$  years (range 1 to 5 years).

### 3.3. Survival Rates

Unfortunately, only 2 cases died who were:

- (1) A 7-year-old male from low-risk group who had mouth mucositis and hepatosplenomegaly with skin involvement (dead after 30 months following diagnosis).
- (2) An 11-year-old female from the low-risk group who referred with bone pain and hepatosplenomegaly and had skin involvement (dead after 3 months following diagnosis).

The survival rate from diagnosis to the last update of patients was from 3 months to 11 years (mean time  $4.5 \pm 0.5$  years). The 5-year overall survival rate in enrolled patients was  $93.3\% \pm 0.05$  (Figure 2). The event-free time was from 3 months to 11 years with the meantime of  $4 \pm$

0.5 years, and also the 5-year event-free survival rate was  $72.9\% \pm 0.09$  (Figure 3).

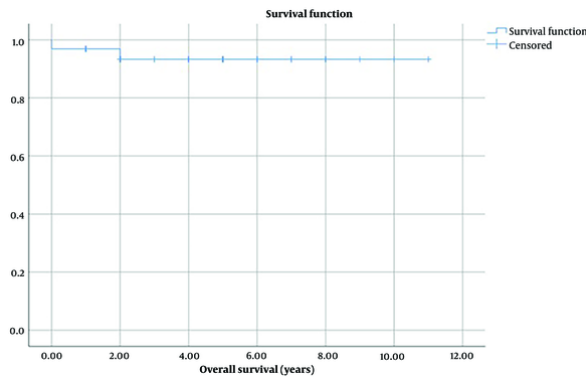


Figure 2. Overall survival rate in enrolled patients

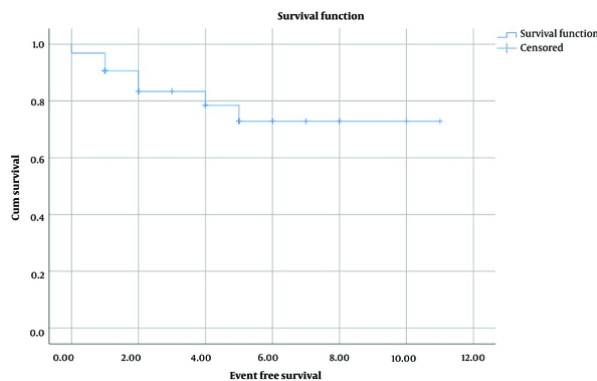


Figure 3. Event Free Survival rate in considered patients

#### 4. Discussion

Langerhans cell histiocytosis (LCH) is due to the accumulation of pathologic Langerhans cells in the bones, skin, bone marrow, brain, etc. Furthermore, heterogeneous presentations can present both in children and adults (2). In 2020, a review study confirmed that the incidence rate of LCH in children younger than 15 years old ranged from 2.6 to 8.9 cases per million children (the median age at diagnosis: 3 years old) (10). The incidence rate of this malignancy is similar to pediatric Hodgkin Lymphoma (11).

According to the design of this study, the demographic characteristics and survival rates of Iranian pediatric patients with LCH were considered.

The main idea of conducting this project was related to the rarity of published data about the mentioned patients. The gathered data from 32 patients with LCH revealed a slight increase in female patients with a mean age of 5 years old. At that time, the majority of patients were high risk, otherwise, there was not any death in that risk group, while there were only 2 deaths from low-risk group patients. The chief complaint of bone pain and the skeleton site involvement was common throughout the patients, and finally, the 5-year overall survival and event-free survival rates (93.3% and 72.9%) were reasonable based on patients' therapy.

In 2023, based on literature reviews, Kemps announced that the severe forms of LCH relate to patients younger than 2 years old who have involvements of the hematopoietic system, liver, and spleen (12). The results of this study confirmed this point, as two cases who died had involvement of liver and spleen, but there were not any patients younger than 2 years old with LCH. Moreover, that study (12) highlighted the low mortality rate in pediatric patients with LCH alongside a significant rate of relapse. Our present study findings corroborate these observations, as we also noted a low rate of deaths and nearly 16% of patients experiencing relapses.

Between 2000 and 2004 in France, 258 cases with LCH younger than 15 years were evaluated. The male-to-female ratio was 1.2 and the most involved organs were bone and skin. That scientific group confirmed the 2-year overall survival rate of 99% in considered patients (13). In comparison with our data, the female ratio of enrolled patients in the presented study was more than France's study, and according to figure 2, the 2-year survival rate of cases was the same as 5-years survival rate (93.3%) that is lower than France's study.

In 2022, a report was published from 6 years of evaluation (from 2013 to 2019) of registered patients with LCH in London. In total, 658 patients enrolled in that study of which 49% of them were children (younger than 15 years old) (14). Other information from that study relates to the incidence and prevalence of cases that could be on behalf of our limitations through the registry of pediatric cancers in Iran. In this regard, all of the reports from Iranian pediatric LCH are from hospital-based studies with a limited considered case.

Another study that considered 91 pediatric patients with multifocal LCH reported a 5-year survival rate of 100% for their single-system multisite patients ( $n = 32$  cases) and 94% for multisystem patients ( $n = 59$  patients) (15). That study was designed and performed in 2006 in Japan, which that means currently improving in their survival rate is inevitable.

Literature reviews have confirmed that one of the most critical considerations in pediatric patients with LCH is the role of genetic factors, particularly those associated with treatment response.

The worst comment is that setting up molecular evaluations in Iran is a hardship because of sanctions, and in this regard, the current research around these cases already relate to epidemiological data and survival rates of these cases. Another effective point is that there is no national pediatric cancer registry in Iran, in that way all of the reports are hospital-based studies that contain a limited number of cases. Finally, the treatment protocols in Iran improve gradually, and administrating modern chemical agents is complicated. All of the above-mentioned factors can negatively effect on the data and results of this study, however, the most important point is that this 5-year survival rate is desirable for considered cases.

#### 4.1. Conclusions

In summary and based on the results, the suggestion is to provide a national registry for pediatric LCH followed by designing future projects around affective genes on the treatment response of mentioned patients. In that way, we can improve the survival rate of these patients and decrease mortality.

#### Acknowledgements

The authors are thankful to all of the staff and patients who collaborated in this study.

#### Footnotes

**Authors' Contribution:** Study concept and design: J.S. and A.M., acquisition of data: A.E.A., analysis and interpretation of data: A.E.A. and N.M., drafting of the manuscript: N.M., critical revision of the manuscript for important intellectual content: N.M., statistical analysis: N.M., administrative, technical, and material support: J.S. and M.T. and A.M., study supervision: A.M.

**Conflict of Interests Statement:** Dr. J. Saberynejad, Dr. M. Tashvighi, Dr. N. Mehrvar and Dr. A. Mehrvar have not conflict of interest because of Unpaid advisory position. Dr. A. Ebrahim Ahmadi has not conflict of interest because of unpaid membership in AJA University of Medical Sciences.

**Data Availability:** It was not declared by the authors.

**Ethical Approval:** The ethical committee of AJA University of Medical Sciences, Tehran, Iran with the

ethical committee code IR. AJAUMS.REC1401.063 approved the designed project.

**Funding/Support:** This study was supported by the authors in regard of scientific management.

**Informed Consent:** It was not declared by the authors.

#### References

- Stalemark H, Laurencikas E, Karis J, Gavhed D, Fadeel B, Henter JI. Incidence of Langerhans cell histiocytosis in children: a population-based study. *Pediatr Blood Cancer*. 2008;**51**(1):76-81. [PubMed ID: 18266220]. <https://doi.org/10.1002/pbc.21504>.
- Thacker NH, Ablu O. Pediatric Langerhans cell histiocytosis: state of the science and future directions. *Clin Adv Hematol Oncol*. 2019;**17**(2):122-31.
- Whitlock JA, Georger B, Dunkel IJ, Roughton M, Choi J, Osterloh L, et al. Dabrafenib, alone or in combination with trametinib, in BRAF V600-mutated pediatric Langerhans cell histiocytosis. *Blood Adv*. 2023;**7**(15):3806-15. [PubMed ID: 36884302]. [PubMed Central ID: PMC10393756]. <https://doi.org/10.1182/bloodadvances.2022008414>.
- Sterlich K, Minkov M. Childhood Langerhans Cell Histiocytosis: Epidemiology, Clinical Presentations, Prognostic Factors, and Therapeutic Approaches. *Rare Diseases - Diagnostic and Therapeutic Odyssey*. 2021. <https://doi.org/10.5772/intechopen.96543>.
- Heritier S, Emile JF, Barkaoui MA, Thomas C, Fraitag S, Boudjemaa S, et al. BRAF Mutation Correlates With High-Risk Langerhans Cell Histiocytosis and Increased Resistance to First-Line Therapy. *J Clin Oncol*. 2016;**34**(25):3023-30. [PubMed ID: 27382093]. [PubMed Central ID: PMC5321082]. <https://doi.org/10.1200/JCO.2015.65.9508>.
- Veys PA, Nanduri V, Baker KS, He W, Bandini G, Biondi A, et al. Haematopoietic stem cell transplantation for refractory Langerhans cell histiocytosis: outcome by intensity of conditioning. *Br J Haematol*. 2015;**169**(5):711-8. [PubMed ID: 25817915]. [PubMed Central ID: PMC4433436]. <https://doi.org/10.1111/bjh.13347>.
- Jeziarska M, Stefanowicz J, Romanowicz G, Kosiak W, Lange M. Langerhans cell histiocytosis in children - a disease with many faces. Recent advances in pathogenesis, diagnostic examinations and treatment. *Postepy Dermatol Alergol*. 2018;**35**(1):6-17. [PubMed ID: 29599667]. [PubMed Central ID: PMC5872238]. <https://doi.org/10.5114/pdia.2017.67095>.
- Haupt R, Minkov M, Astigarraga I, Schafer E, Nanduri V, Jubran R, et al. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. *Pediatr Blood Cancer*. 2013;**60**(2):175-84. [PubMed ID: 23109216]. [PubMed Central ID: PMC4557042]. <https://doi.org/10.1002/pbc.24367>.
- Lanzkowsky P, Lipton J, Fish JD. Lanzkowsky's manual of pediatric hematology and oncology. *Elsevier*. 2016.
- Rodriguez-Galindo C, Allen CE. Langerhans cell histiocytosis. *Blood*. 2020;**135**(16):1319-31. [PubMed ID: 32106306]. <https://doi.org/10.1182/blood.2019000934>.
- Allen CE, Merad M, McClain KL. Langerhans-Cell Histiocytosis. *N Engl J Med*. 2018;**379**(9):856-68. [PubMed ID: 30157397]. [PubMed Central ID: PMC6334777]. <https://doi.org/10.1056/NEJMra1607548>.
- Kemps PG, Zondag TCE, Arnardottir HB, Solleveld-Westerink N, Borst J, Steenwijk EC, et al. Clinicogenomic associations in childhood Langerhans cell histiocytosis: an international cohort study. *Blood Adv*. 2023;**7**(4):664-79. [PubMed ID: 36083130]. [PubMed Central ID: PMC9979766]. <https://doi.org/10.1182/bloodadvances.2022007947>.
- Guyot-Goubin A, Donadieu J, Barkaoui M, Bellec S, Thomas C, Clavel J. Descriptive epidemiology of childhood Langerhans cell histiocytosis



- in France, 2000-2004. *Pediatr Blood Cancer*. 2008;**51**(1):71-5. [PubMed ID: [18260117](#)], <https://doi.org/10.1002/pbc.21498>.
14. Liu H, Stiller CA, Crooks CJ, Rous B, Bythell M, Broggio J, et al. Incidence, prevalence and survival in patients with Langerhans cell histiocytosis: A national registry study from England, 2013-2019. *Br J Haematol*. 2022;**199**(5):728-38. [PubMed ID: [36122574](#)]. [PubMed Central ID: [PMC9826274](#)]. <https://doi.org/10.1111/bjh.18459>.
15. Morimoto A, Ikushima S, Kinugawa N, Ishii E, Kohdera U, Sako M, et al. Improved outcome in the treatment of pediatric multifocal Langerhans cell histiocytosis: Results from the Japan Langerhans Cell Histiocytosis Study Group-96 protocol study. *Cancer*. 2006;**107**(3):613-9. [PubMed ID: [16804933](#)]. <https://doi.org/10.1002/cncr.21985>.