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Comparison of Survival Rates of Syrian Refugee Versus Turkish Pediatric Patients with Leukemia

Özlem Terzi, Cengiz Bayram, Ali Ayçiçek, Ezgi Uysalol, Şadan Hacısalihoğlu, Hüseyin Avni Solgun, Tuba Nur Tahtakesen, Esra Arslantaş, Gül Nihal Özdemir, Sibel Tekgündüz

Pediatric Hematology and Oncology, Basaksehir Cam and Sakura Training and Research Hospital Istanbul, Health Science University, Turkey.
*Email: doktorozlem2020@hotmail.com

Abstract: Although survival rates are increasing in acute leukaemias today, this rate is lower in developing countries; there are very few studies conducted on this matter in refugee patients. This research aims to evaluate the survival rate in pediatric Syrian refugee patients with acute leukaemia and compare it with Turkish pediatric leukaemia patients. A total of 144 patients diagnosed with acute leukaemia were included in the study, and their files were reviewed retrospectively. Nineteen 144 patients (13%) were Syrian refugees, and 125 (87%) were Turkish patients. The median age of the Syrian refugees and Turkish patients was 6.9 years (range 1-18 years) and 7.2 years (range 2-18 years), respectively, and gender distribution was similar for both groups (p:0.32). The relapse rate and rate of patients in the high-risk leukaemia group were higher in the Syrian refugee patient group (p=0.05). The survival rates of the Syrian refugee patients at the 11th month and 23nd month of the follow-up were 87.5% and 70%, respectively. The survival rates of the Turkish patients in the 23rd month and 44th month of the follow-up were 96.6% and 85%, respectively. The survival rates of the Turkish patients were significantly higher (p<0,001). The odds ratio of mortality adjusted for being a Syrian refugee was 5.3 (with a 95% confidence interval, 1.5 to 18.3). No difference was observed between the groups regarding compliance with treatment. Survival rates of the Syrian refugee leukaemia patients were lower, and the rate of patients in the high-risk leukaemia group and the relapse rate was higher in Syrian refugee patients compared to Turkish patients.
Keywords: Childhood leukaemias; refugee; survival rates; treatment-related mortality.

INTRODUCTION

Leukaemia is one of the children's most common malign diseases and accounts for 30% of all childhood cancers. While the survival rate for pediatric leukaemias is over 80% in developed countries, this rate is lower in developing countries[1]. Although the situation in Syrian refugee pediatric patients is not well known, considering the behavioural and environmental factors, including difficulty in accessing pediatric oncology centres, language barrier, difficulties in nutrition and accommodation, pollution, possible chemical exposure, viral infections, sedentary lifestyle, and other

Corresponding Author: Özlem Terzi
Pediatric Hematology and Oncology, Basaksehir Cam and Sakura Training and Research Hospital Istanbul, Health Science University, Turkey.
Email: doktorozlem2020@hotmail.com

adverse factors caused by the war, the survival rates in Syrian refugee children is probably lower than the rest of the world[2].

Since the beginning of the conflict in Syria in March 2011, more than 3 million registered Syrian refugees have been accepted by Turkey[3]. Of the 182 patients diagnosed with leukaemia in our Pediatric Hematology Clinic between January 2018 and September 2021, 25 are Syrian refugees. The adverse factors brought by being a Syrian refugee can cause delays in cancer diagnosis and challenges in treatment administration. Some studies have reported that low socioeconomic status is associated with low awareness of cancer symptoms in patients[2,4], and the lack of insurance and funds to cover treatment costs has been particularly emphasized[2]. All current study's patients have been living in cities, not at the camps and the healthcare services and treatments of Syrian refugees have been provided free of charge in our country since the beginning of the crisis in 2011; daily bare essentials, education facilities, and health services. Syrian refugees have been supported by The Disaster and Emergency Management Presidency of Turkey[5,6]. In April 2013, Turkey passed its first asylum law—the "Law on Foreigners and International Protection", which regulates all proceedings for Syrian refugees living in Turkey[5,6,7]. According to this law, people who have registered as Syrian refugees, including children, have been provided with free medical treatment as Turkish citizens, including cancer treatment and care at tertiary government and university hospitals. Due to the Turkish government's legislation, almost all standard and new chemotherapeutics, including many targeted agents and transplantation facilities, are available to Syrian refugees[8,9].

In Turkey, the 7-year survival rate in children with cancer, including leukaemias and solid tumours, is reported as 65%[8,10]. Higher 7-year survival rates of 74% for children with cancer are reported in specific cancer centres in Turkey[11]. Very few publications about diseases, especially cancer, are seen in Syrian refugees[12-15]. This study examined treatment compliance and survival rates of Syrian refugee pediatric leukaemia patients diagnosed and treated in our centre, and the results were compared with Turkish pediatric leukaemia patients.

MATERIALS AND METHODS

A total of 182 patients diagnosed with leukaemia between January 2018 and September 2021 at the Pediatric Hematology and Oncology Clinic of Health Sciences University, Istanbul Kanuni Sultan Süleyman Training and Research Hospital and Basaksehir Cam and Sakura City Hospital, were retrospectively evaluated, and 144 patients were included in the study. Patient data, including clinical findings, age, gender, leukaemia type, leukaemia risk group, chemotherapy protocol, treatment compliance, treatment-related mortality, and survival rates, were reviewed from the patients' files. Of the 144 patients, 119 patients diagnosed with acute lymphoblastic leukaemia (ALL) were treated according to ALL IC BFM 2009 and ALL IC REL BFM 2016 protocols, and 25 patients diagnosed with acute myeloblastic leukaemia (AML) were treated according to AML BFM 2019 protocol.

ALL IC BFM 2009 standard risk group (SRG): Patients aged ≥1 to <6 years at the time of diagnosis, an initial leukocyte count of < 20,000/mm3, patients with <1000/mm3 blasts in the peripheral blood on day 8, M1/M2 bone marrow in bone marrow aspiration on day 15, MRD level <0.1% (complete remission) on day 15, without

Ph 1 + (BCR/ABL+), or t(4;11) (MLL/AF4+) were classified into the standard risk group. ALL IC BFM 2009 high-risk group (HRG): Patients with absolute blast count of ≥1,000/mm3 in the peripheral blood on day 8, or M3 bone marrow with ≥25% blasts on day 15, or FC MRD level >10% on day 15, or those with M2/M3 bone marrow on day 33, and, irrespective of treatment response, patients with Ph 1 + (BCR/ABL+), or t(4;11) (MLL/AF4+) or hypodiploidy (<45 chromosomes) classified into the high-risk group. ALL IC BFM 2009 medium risk group (MRG): All patients not stratified to standard or high-risk group were classified into intermediate-risk patients.

Relapse Criteria: More than 25% blasts in the bone marrow after the achievement of remission with initial leukaemia treatment or extramedullary leukaemia involvement in any site were considered as relapse. Relapse can be isolated in bone marrow, CNS and testicular, or ≥2 sites of involvement defined as combined relapse. Relapse in 18 months after initial diagnosis or <6 months after completion of initial treatment is defined as very early relapse; defined as an early relapse if relapse occurred ≥ 18 months after initial diagnosis or <6 months after completion of initial treatment, and defined as a late relapse if relapse occurred ≥6 months after completion of initial treatment. AML BFM 2019 risk criteria: Initial risk stratification was based on the biological characteristics of leukaemia (cyto and molecular genetics). Children and adolescents with AML with t(8;21), inv(16), t(15;17), t(1;11) and who had received adequate therapy were identified as favourable prognostic subgroups of AML. In addition, therapy response (evaluated via morphology and immunophenotyping) after the 1st (day 28) and second (day 56) induction was used for a subsequent re-stratification. Re-stratification into the intermediate or high-risk group was based on nonresponse (≥10% blasts after 1st or ≥5% after the second induction). Patients with nonresponse after the second induction were re-stratified into the high-risk group.

All AML patients with the following genetic evidence were stratified in the high-risk group: abnormalities in chromosome 12p/ t(2;12), monosomy 5/5q-, WT1mut and FLT3-ITD, monosomy 7 (not in combination with favourable/MLL- aberrations), t(4;11)(q21;q23); MLL/AF4, t(5;11)(q35.3;p15); NUP98/NSD1, t(6;11)(q27;q23)); MLL/AF6, t(10;11)(p12;q23); MLL/AF10, t(6;9)(p23;q34), t(7;12)(q36;p13), t(9;22)(q34;q11), complex karyotype (three or more aberrations, including at least one structural aberration, without favourable genetics and MLL-rearrangement.), inv(3)(q21q26.2)/t(3;3)(q21;q26.2), t(16;21)(p11;q22); FUS/ERG, Inv(16)(p13.3q24.3) CBFA2T3-GLIS2.

All patients with de-novo AML who do not belong to the standard-risk group (favourable prognosis) or the high-risk group (unfavourable prognosis) were stratified into the intermediate-risk group. Overall survival (OS) was defined as the time from diagnosis to death from any cause or last follow-up time. Event-free survival (EFS) was defined as the time from remission until the failure date (induction failure, relapse or death) or the last follow-up time. The odds ratio defines the event in which death and recurrence are evaluated together. Poor compliance to treatment was defined as non-attendance to a scheduled hospital appointment and leading to > seven days of chemotherapy treatment delays for at least one time on separate occasions. Language differences were another essential barrier to treatment that needed to be overcome.

A total of 38 patients were excluded from the study; thirty-four patients did not reach maintenance treatment and their follow-up periods were short; 2 patients moved

to another city, and two returned to their country. The hospital ethics committee approved this study of Başakşehir Çam and Sakura City Hospital Ethical Committee. Specific statistical application was used for statistical analysis. The Chi-square test was used to compare categorical measures, Mann-Whitney U and Student T-Tests were used to compare the two groups, the Kaplan-Meier method was used for survival analysis, and Cox Regression Analysis was used to compare survival between the groups. A P-value of <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Table 1. Classification According to Risk Groups of Syrian and Turkish Patients with Leukemia

	Risk Group	Age of Diagnosis	Gender	ALL		AML		Relapse		Death	
				%	n	%	n	%	n	%	n
Syrian Refugee Patients	Middle	5,6 ±4,1	9/6	63	12	16	3	13,3	2	5,2	1
	High	11±2	4/0	21	4	0	0	0	0	10,5	2
	Total		13/6	84	16	16	3	13,3	2	15,7	3
Turkish Patients	Low	5,1 ±3,2	8/9	9	12	4	5	0	0	0	0
	Middle	5,0±4,0	48/45	62	77	13	16	4,7	5	0,8	1
	High	7,2 ±5,0	11/	11	14	1	1	0	0	0,8	1
	Total		67/58	82	103	18	22	4,7	5	1,6	2

ALL: Acute Lymphoblastic Leukemia. AML: Acute Myeloblastic Leukemia.

Data from 182 pediatric leukaemia patients were evaluated, and 144 of 182 patients were included in the study. Of the 144 patients, 19 (13%) were Syrian refugees, and 125 (87%) were Turkish patients. The median age of the Syrian refugees and Turkish patients was 6.9 years (range 1-18 years) and 7.2 years (range 2-18 years), respectively (p:0.32), and gender distribution for both groups was similar (Table1). In the Syrian refugee patient group, 15 patients (79%) were in the intermediate-risk group, four patients (21%) were in the high-risk group, and there were no patients in the standard-risk group. In the Turkish patient group, 93 patients (74.4%) were in the intermediate-risk group, 15 patients (12%) were in the high-risk group, and 17 (13.6%) patients were in the standard-risk group (Table1).

Table 2. Relapse and Death Rates of Syrian and Turkish Patients with Leukemia

	Refugee Patients n (%)	Turkish Patients n (%)	P
No Relapse	17 %86,7	120 %95,3	0,05
Relapse	2 %13,3	5 %4,7	
Alive	16 %84,3	123 %88,4	
Death	3 %15,7	2 %1,6	

The relapse rate of the Syrian refugee patients (n=2, 13.3%) was higher than Turkish patients (n=5, 4.7%). (p=0.05). The mortality rate was also found to be higher (p=0.05) in the Syrian refugee group (n=3, 15.7%) compared to the Turkish group (n=2, 1.6%) (Table 2).

Table 3. Demographic Characteristics of Syrian and Turkish Patients with Leukemia

Event	Patients	Age of Diagnosis	Gender	Diagnosis	Risk Group	Event Occurrence Time
Relapse	Syrian Refugee	8	Female	B ALL	Middle	Maintenance therapy
		2	Male	AML	Middle	Maintenance therapy
	Turkish	2	Female	B ALL	Middle	Maintenance therapy
		6	Female	B ALL	Middle	Maintenance therapy
		6	Male	B ALL	Middle	Maintenance therapy
		13	Female	B ALL	Middle	Maintenance therapy
		14	Female	AML	Middle	Maintenance therapy
Death	Syrian Refugee	8	Male	B ALL	Middle	Maintenance therapy
		10	Male	T ALL	High	Maintenance therapy
		17	Male	B ALL	High	Maintenance therapy
	Turkish	6	Male	AML	Middle	Maintenance therapy
		1	Male	AML	High	Maintenance therapy

B ALL: B cell Acute Lymphoblastic Leukemia. T ALL: T cell Acute Lymphoblastic Leukemia. AML: Acute Myeloblastic Leukemia.

The odds ratio of mortality adjusted for being a Syrian refugee was 5.3 (with a 95% confidence interval, 1.5 to 18.3). All relapsed patients in both Syrian refugee (n=2) and Turkish (n=5) groups were noted to be in a moderate-risk group and at maintenance treatment at the time of relapse. There was 1 ALL patient and 1 AML patient in relapsed Syrian refugee group, whereas all five relapsed Turkish patients were ALL. It was determined that all deceased patients were also in maintenance treatment and male. While the deceased Syrian refugee patients were diagnosed with ALL, two of the patients in the Turkish group were diagnosed with AML (Table 3).

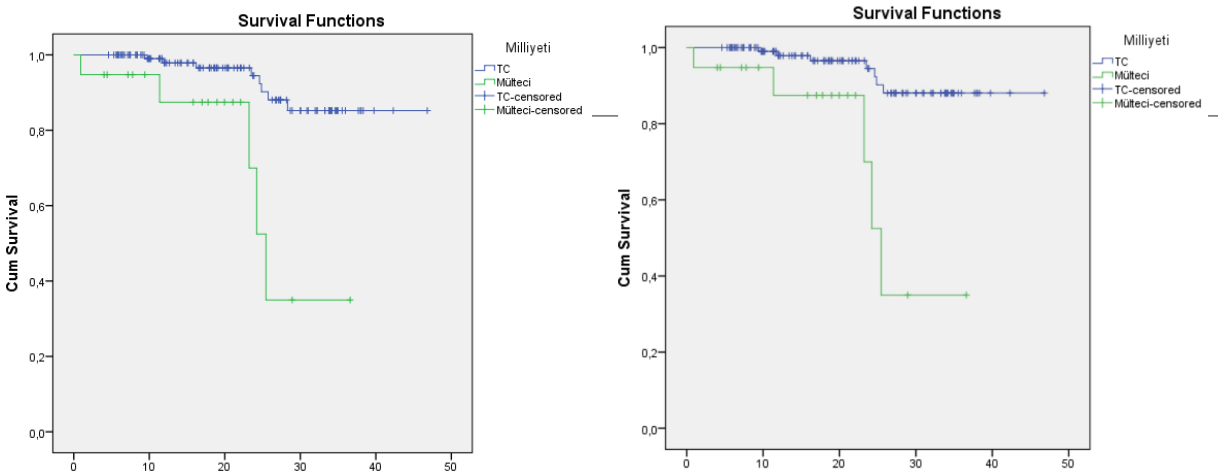

Figure1-2. The survival rates of Syrian and Turkish Patients with Leukemia.

A significant difference was found in examining the survival rates ($p<0.001$). The follow-up period range of the patients was 1-35 months and 4-44 months in the Syrian refugee and Turkish patient groups, respectively. The survival rates of the Syrian refugee patients in the 11th month of the follow-up were 87.5%. The survival rates of the Turkish patients in the 44th month of the follow-up were 85%. The survival rates of the Syrian refugee and Turkish patients in the 23rd month of the follow-up were 70% and 96.6%, respectively (Figure1-2). No difference was found between the groups concerning hospitalization time, diagnosis and initiation of treatment at the time of leukaemia suspicion (mean: 1 day). There was no difference between the groups regarding treatment administration and subsequent treatment starting after discharge during treatment intervals. There was no significant disruption in the treatment of patients due to Covid 19. Only 1 of the Syrian refugee patients had poor compliance with treatment and interrupted the treatment to use alternative medicine without informing the doctors. He came back with a progressive disease. In the Turkish patient group, only one patient also had a problem with treatment compliance.

Many people had to find asylum in neighbouring countries due to the war. The poor prognosis of the patients may result from the reasons related to the war environment, in addition to the biological properties of the tumour. Their countries' limited healthcare services may have contributed to this situation. Ten of the nineteen Syrian refugee patients in our study were born before they migrated: all of the three deceased patients, 1 of the two relapsed patients, and 1 of the two patients in the high-risk group migrated after they were born in their country. Studies must examine environmental factors such as barriers to basic needs, stress and nutritional deficiencies, and clean water from the war environment. In our study, the high-risk group rate in the Syrian refugee patient group compared to Turkish patients might be due to these unidentified factors (Table 1). The time to start treatment for Syrian Refugee patients after diagnosis and the treatment and time to start the subsequent treatment after discharge was similar to that of Turkish patients. The results did not appear to be due to the conditions mentioned. There is also no difference between Syrian refugees and Turkish patients in terms of accessing the drugs required for treating the patients in our hospital. Health services are provided free of charge to the victims of war in our country. All deaths and relapses occurred during the maintenance treatment of patients (Table 3). This may be due to the patient's compliance with the treatment and the fact that they received it without interruption.

While deceased patients in the Syrian refugee group were diagnosed with ALL, all deceased patients in the Turkish group were AML (Table 1). Although the total number of deaths in the study was low, considering the higher survival rates in ALL compared to AML, it can be thought that the risk of death in Syrian refugee patients was higher. Preliminary outcomes of Syrian refugee children with cancer were similar to those of Turkish children. In a study by Kebudi et al., the survival rate of Syrian refugee children with cancer was similar compared to native Turkish patients. In a median 20-month follow-up (IQR 1-40 months), 75% of Syrian refugee patients were alive, 15% died, and 10% missed follow-up[13]. However, in another study from Turkey, although the follow-up period was shorter in Syrian refugee pediatric patients with malignancy compared to Turkish patients, the OS rate was 55.7% and 69.7%, and EFS was 28.9% and 55.7% in Syrian and Turkish patients, respectively. Overall survival

(OS) and event-free survival (EFS) rates were lower in Syrian refugees compared to Turkish patients (p=0.01, p<0.001, respectively). The metastatic or advanced-stage disease was significantly more frequent in Syrian refugees (p=0.002). Relapse or progression and poor compliance to treatment were more common in Syrian refugees (p=0.01, p<0.001, respectively)[12]. In our study, the advanced-stage disease was more frequent in Syrian refugees (Table 1), and the relapse and mortality rates of Syrian refugee patients were higher than Turkish patients (p=0.05) (Table 2).

The problem of adherence to treatment in Syrian refugee patients was seen in only one patient. Language differences were another essential barrier to treatment that needed to be overcome. Medical staff or Turkish patients who spoke Arabic helped voluntarily, so there were no problems. There are some limitations in the current study. First, the current study included several cases in the Syrian refugee group. Second, the follow-up period was short. Third, environmental factors due to being a Syrian refugee could not be examined.

CONCLUSION

In the present study, the rate of patients in the high-risk leukaemia group and relapse rates were higher in Syrian refugee leukaemia patients, and the survival rates were lower in Syrian refugee children with leukaemia compared to Turkish children with leukaemia.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

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