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ABSTRACT

Background Childhood lymphoma is the second leading cause of cancer in children under 15 years of age in Iran. The aim of this study was to investigate the spatial and time variations in lymphoma incidence as well as the children's survival time in Iran.

Method This cross-sectional study was conducted using lymphoma cases (children under 14 years of age) from 2005 to 2015, and the data were obtained from the National Cancer Registry Center. The frequency, age-standardised incidence rate (ASIR), spatial clustering in national level and the survival rate (1 year and 5 years) using Kaplan-Meier method were evaluated. We used Spatial and Temporal Scan statistics software in order to detect statistically significant clusters in spatial analysis.

Results A total number of 746 girls and 1610 boys were diagnosed with lymphoma during a 10-year period. ASIRs (per 100 000 people) for girls ranged from 0 in Ilam to 3.47 in Yasuj, and it ranged from 0.19 in Ilam to 5.91 in Yazd for boys from 2005 to 2015. Spatial analysis result showed a large statistically significant cluster (the most likely cluster) for both boys (relative risk (RR)=2.37) and girls (RR=2.49) located in the northwest of Iran. Fortunately, survival rate for both boys and girls was over 95.5%.

Conclusion Lymphoma incidence rates had heterogeneous geographical distribution, and some significant clusters were identified which strengthens the role of possible aetiological factors, and further studies are needed to clarify this ambiguity. Fortunately, the survival rate of this cancer in Iran was good and it was similar to the high-income countries.

INTRODUCTION

Lymphomas contain different subtypes that originate in the lymphatic system and have two main types: Hodgkin’s lymphoma (HL) and non-Hodgkin’s lymphoma (NHL).1 According to the report of the WHO, lymphoma is the third most common type of cancer in the world,2 and it is the second leading cause of cancer in children under 15 years of age in Iran.3-4 Between Asian countries, Singapore (15.9), Turkey (14.4) and the Republic of Korea (12.6) had the highest incidence rate of NHL; while Kuwait (16.2), Saudi Arabia (14.6) and Turkey (10.6) had the highest incidence rate of HL from 2003 to 2007, respectively. In Portugal, HL has increased and in the USA, NHL has also increased in the last decades.5-7

Cause of cancer in children is still unclear, but some studies have mentioned that environmental factors (exposure to certain chemicals and radiation), infections and autoimmune diseases, genetic factors, and socioeconomic status are risk factors and possible causes of some childhood cancers.8-10

Cluster analysis is a popular method that is used in various fields as well as in public health research. The spatial and temporal patterns of the disease and its variations help identify
the risk factors and high-risk groups. They also allow for better planning to control the disease and increase the quality of healthcare services.\textsuperscript{11,12} It is noticeable that the incidence of cancer in children is low compared with adults, but more than 80% of them can be treated.\textsuperscript{13} Also, a uniform upward trend of cancer has been reported in Iran.\textsuperscript{14} With regard to heterogeneous ethnic groups in Iran, they show a high grade of genetic diversity.\textsuperscript{15} The aim of this study was to investigate the spatial and time variations in lymphoma incidence as well as the children’s (0–14 years) survival rate in Iran from 2005 to 2015.

METHODS

Data variables

In this cross-sectional study, cancer data were retrieved from the Iran National Cancer Registry (INCR). Data included personal information (gender, date of birth, age, place of residence) and tumour information (pathological stage of the tumour, date of cancer diagnosis, method of diagnosis and histology of the primary tumour based on International Classification of Childhood Cancer-third edition (ICCC-3). The methods of diagnosis were pathology/cytology, clinical and patients’ death certificate. Approximately 60\% of diagnostic methods were performed by pathology and cytology, 8\% by clinical evaluation, 1\% by death certificate and the rest (31\%) was unclear.

Study population

Population data were obtained from the National Statistics Center in 2005 and 2010 from census data, and the uncounted years were calculated based on the annual growth rate. Histology and topography codes of data were recorded based on the ICCC-3 classification of lymphoma subtypes. The city of residence (the place where the patient lives) must be specified in the spatial analysis. This variable was not recorded for about 100 people. Based on the relative frequency of cities, these missing values were imputed.

Missing values in observational study are one of the common problems. It can be due to the lack of measurement of the considered factor, or due to unavailability, or due to registry problems. This problem influences the estimation of models and study results. A common approach to solve this problem is to remove the missing data. It has been mentioned in various studies that if the missing data are less than 5\%–10\%, they can be ignored. But this reduces the sample size of the study and reduces the statistical power of the study. Another approach to managing missing data is to replace missing values using methods such as single imputation (mean, median and mode), maximum likelihood and multiple imputation.

The missing values in our study were less than 5\%; instead of removing the values, we replaced these values using the single method. In this way, we first calculated the percentage of patients in each city and multiplied these numbers by the missing value. Due to the results obtained, the contribution of each city to be replaced with missing values was determined.

The frequency of cases was present by gender and city. The crude incidence rate (CIR) (100 000) is:

$$CIR = 10^5 \left( \frac{\sum d_i}{\sum y_i} \right)$$

Then, age groups were indicated by the subscript \(i\), the number of cases is indexed by \(d_i\) in age group \(i\), \(y_i\) is the population at risk in age group \(i\).

Age-standardised incidence rates (ASIRs) (per 100 000 population) were calculated using the WHO world standard population (2000–2025):

$$ASIR = 10^5 \sum d_i w_i / y_i$$

It must be noted that \(w_i\) is the number of individuals in (weight) age group \(i\) in the WHO standard population.\textsuperscript{16}

ASIRs were calculated by geographical area (entire 30 province centres), gender and cancer subtypes. Since the annual number of cases was low, the rates were estimated using 5-year intervals.

Spatial analysis

Spatial and Temporal Scan statistics (SaTScan) was used to investigate the geographical distribution of lymphoma in children. SaTScan is software designed for purposes such as geographical surveillance of disease, identification of significant statistical clusters and faster diagnosis of outbreaks. This software uses the scan statistic to detect the clusters. Identification of clusters was done by moving circular scan windows between predefined areas. The radius of the circle shows the spatial distribution of the scan window, and its value varies from zero to the maximum value set by the user and height of the circle indicates the temporal distribution of the scan window.\textsuperscript{17} We performed purely spatial analysis to identify geographical clusters of lymphoma cancer. In this study, the radius of the circle was 50\% of the population census, and the centres of 30 provinces were used as geographical coordinates in software.

In discrete scan statistics, the locations of the observation are non-random and fixed, but in the continuous type, the geographical location is random and can occur in any predefined geographical area by user.

In our study, data type was counted, and distribution of observations in geographical location was through Poisson distribution.\textsuperscript{18} The approach of this study was to identify geographical high-risk areas of the disease.

Let us assume that the probability of the patient located within the window is equal to \(p\), and the probability of the patient being outside the window is equal to \(q\). The spatial scan statistic tests each window for null hypothesis, that is, \(H_0: p = q\), and risk of cancer within the cluster is equal to the outside, or distribution of disease is random. The alternative hypothesis is \(H_1: p > q\), that is, the risk of cancer inside the window is more than outside the window.\textsuperscript{12}
Survival analysis
There was no patient follow-up in INCR dataset. Therefore, 35% (787 persons) of the patients were randomly selected from all over the country, and their parents were interviewed by telephone. In this telephone interview, the type of cancer recorded in the data was checked and verified. Besides, their survival status, death status due to lymphoma and patient's death date were recorded. One-year and 5-year probability survival rates of patients were calculated by Kaplan-Meier method.

RESULTS
Descriptive statistics
Totally, 746 girls and 1610 boys were diagnosed with lymphoma during a 10-year period. The percentage of cancer for girls during 2005–2010 and 2010–2015 ranged...
from 0.00% in Ilam to 15.26% in Tehran. There was an increasing trend in 11 cities, stable trend in 1 city and a decreasing trend in 19 cities. Shiraz and Tehran indicated the greatest increase and decrease, respectively. For boys, the percentage of cancer ranged from 0.12% in Qom to 19.02% in Tehran. There was an increasing cancer trend in 16 regions and a decreasing cancer trend in 14 regions. The greatest increase and decrease of cancer were in Tehran and Orumieh, respectively (see online supplemental table S1).

**Cancer incidence**

ASIRs (per 100 000 people) for girls ranged from 0 in Ilam to 3.47 in Yasuj from 2005 to 2015. There was an increased incidence rate in 14 cities and a decreasing rate in 16 cities. ASIR (per 100 000 people) for boys ranged from 0.19 in Ilam to 5.91 in Yazd from 2005 to 2015. There was an increasing incidence rate in 15 cities and a decreasing rate in 16 cities. Among all cities, Yazd showed a significant increase of lymphoma incidence, while Semnan and Bushehr indicated a significant decrease for boys and girls, respectively (see table 1).

Age-standardised HL incidence rate was high among the other subtypes of lymphoma in boys (0.49) and girls (0.25) from 2005 to 2010. In the second time interval, NHL with 0.43 and 0.24 in boys and girls, respectively, was at the top of the incidence rate. Miscellaneous lymphoreticular neoplasm (MLN) lymphoma had lower rates in boys and girls from 2005 to 2015. An upward trend for NHL as opposed to HL and a growing trend in other subtypes were observed. Generally, the entire types of cancer, except for MLN lymphomas, were significantly higher in boys than girls (see table 2).

**Purely spatial clusters**

The identified clusters were ranked based on their likelihood ratio test statistic. The probability of the most likely cluster (primary), which has the largest likelihood ratio happening by chance, is very low. Clusters were identified besides the most likely clusters that are known as secondary clusters. However, we had better not report the secondary clusters that have overlapped with most likely clusters because they have little extra information, and their interpretation should be done with more caution.

### Table 2

Frequency (percentage) and ASIR (per 100 000 population) of cases with lymphoma by the main groups of the ICCC-3 among children in Iran: 2005–2015

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>ASIR</td>
<td>N</td>
<td>ASIR</td>
</tr>
<tr>
<td>Hodgkin's lymphoma</td>
<td>172</td>
<td>0.25</td>
<td>127</td>
<td>0.19</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma (except Burkitt lymphoma)</td>
<td>117</td>
<td>0.18</td>
<td>156</td>
<td>0.24</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>27</td>
<td>0.04</td>
<td>33</td>
<td>0.05</td>
</tr>
<tr>
<td>Miscellaneous lymphoreticular neoplasm</td>
<td>7</td>
<td>0.01</td>
<td>7</td>
<td>0.01</td>
</tr>
<tr>
<td>Unspecified lymphomas</td>
<td>44</td>
<td>0.07</td>
<td>56</td>
<td>0.09</td>
</tr>
</tbody>
</table>

ASIRs per 100 000 population were calculated using the 2000–2025 WHO world standard population.

ASIR, age-standardised incidence rate; ICCC-3, International Classification of Childhood Cancer-third edition; N, frequency.

### Table 3

Purely spatial cluster analysis based on ASIRs (per 100 000 population): 2005–2015

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Observed cases</th>
<th>Expected cases</th>
<th>RR</th>
<th>Log likelihood ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most likely</td>
<td>393</td>
<td>193.30</td>
<td>2.37</td>
<td>99.42</td>
<td>10^{-12}</td>
</tr>
<tr>
<td>Secondary 1</td>
<td>542</td>
<td>365.89</td>
<td>1.73</td>
<td>49.96</td>
<td>10^{-12}</td>
</tr>
<tr>
<td>Secondary 2</td>
<td>426</td>
<td>285.02</td>
<td>1.67</td>
<td>23.96</td>
<td>10^{-9}</td>
</tr>
<tr>
<td>Secondary 3</td>
<td>106</td>
<td>46.48</td>
<td>2.37</td>
<td>2.06</td>
<td>10^{-6}</td>
</tr>
<tr>
<td>Secondary 4</td>
<td>9</td>
<td>1.98</td>
<td>4.57</td>
<td>4.56</td>
<td>10^{-2}</td>
</tr>
<tr>
<td>Girls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most likely</td>
<td>193</td>
<td>91.77</td>
<td>2.49</td>
<td>50.51</td>
<td>10^{-12}</td>
</tr>
<tr>
<td>Secondary 1</td>
<td>263</td>
<td>182.59</td>
<td>1.68</td>
<td>21.59</td>
<td>10^{-9}</td>
</tr>
<tr>
<td>Secondary 2</td>
<td>7</td>
<td>1.55</td>
<td>4.55</td>
<td>5.12</td>
<td>0.042</td>
</tr>
</tbody>
</table>

ASIRs, age-standardised incidence rates; RR, relative risk.
caution. However, it is recommended to report these clusters because they may be of remarkable interest to researchers.\(^\text{12}\)

In purely spatial analysis, five geographically significant clusters for boys and three significant clusters for girls were identified (see table 3). The most likely male cluster revealed 13 cities (Ardabil, Ilam, Orumieh, Zanjan, Semnan, Qazvin, Qom, Sanandaj, Kermanshah, Rasht, Khorramabad, Arak, Hamedan) with 393 observed cases and 193.30 expected cases. In this cluster, the relative risk (RR) was 2.37 \((p=10^{-12})\) which means that the risk of lymphoma in boys of 0–14 years of age within the cluster is 2.37 times higher than elsewhere. Similar areas were identified for the most likely female cluster with 193 observed cases and 91.77 expected cases. The RR in this cluster was 2.49 \((p=10^{-12})\) (see figure 1).

The first secondary male and female clusters had analogous cities (Isfahan, Shahrekord, Semnan, Shiraz, Bushehr, Yazd, Kerman, Zahedan and Birjand). There were 542 observed cases and 365.89 expected cases among boys with RR 1.73 \((p=10^{-12})\) and 263 observed cases and 182.59 expected cases among girls with RR 1.68 \((p=10^{-9})\) (see figure 2).

The second secondary male cluster \((RR=1.67, p=10^{-9})\) overlapped with the previous cluster (Shiraz, Bushehr, Yazd, Kerman, Birjand, Yasuj, Bandar Abbas, Qazvin). Two small (third and fourth secondary clusters) male clusters were detected in north of Iran (Semnan, Gorgan,
Sari and Bojnourd) and their RRs were 2.37 (p=10^{-6}) and 4.57 (p=10^{-5}). There was one small cluster for girls in Bojnourd with an RR of 4.55 (p=0.042) (see figure 2).

**Survival analysis**

One-year and 5-year survival rates of lymphoma in 0–4 years age group for boys (97.4%) and girls (95.8%) were similar. For other age-specific groups, 5-year survival rate was slightly lower than 1-year survival rate, and it was better in boys than girls (see table 4).

The Cox proportional hazards model indicated that cancer subtypes of patients were not associated with survival time after adjustment for gender and age (sig>0.05) (see table 5).

**DISCUSSION**

The aim of the present study was to investigate the temporal and spatial variations of lymphoma in Iranian children and their survival rate over a 10-year period. Our results showed the varied relative frequency of cancer in different cities. Some cities, such as Tehran, Shiraz, Ahvaz and Mashhad, had a higher relative frequency.

Our study showed a heterogeneous geographical distribution of lymphoma incidence in two time intervals. Ilam and Qom had very low ASIRs, while Yasuj and Yazd had high ASIRs.

Although the main cause of cancer in children is unknown, previous studies revealed that socioeconomic
status, along with some risk factors during pregnancy (ionising radiation, diethylstilbestrol), the parents’ occupation and their contact with environmental risk factors (hydrocarbons, insecticides and pesticides in jobs such as farming, painting and working with hydrocarbons) and infectious diseases (HIV, Epstein-Barr virus and malaria), are possible reasons of lymphoma geographical disparity. Zhang et al showed that genetic factors were the cause of almost 10% of all cancers in children. Shabani et al assessed trend of incidence of childhood cancer from 1990 to 2016 in Iran and reported Yazd had the highest and Ilam and Qom had the lowest incidence rate of paediatric cancer in Iran.

In our study, the ASIR of NHL has an upward trend compared to HL from 2005 to 2015. The same trend can be observed in the USA and some European countries. Although, they have not mentioned the reason for this reverse trend, it may be attributed to environmental risk factors, improved diagnosis and access to medical care over time.

In our finding, the ASIR for lymphoma was higher for boys as compared with girls, which is in accordance with the results of other studies in Iran. In Canada, boys had higher incidence rates than girls in the entire lymphoma subtypes from 1984 to 2013.

The spatial analysis result showed similar large and statistically significant most likely cluster for boys (RR=2.37, p=10−12) and girls (RR=2.49, p=10 −12) in the northwest of the country. Also, there were several similar significant secondary clusters in the southwest, central and northeast cities for boys and girls.

We detected some significant clusters of lymphoma similar to the study of Goujon et al in which they reported some spatial heterogeneity and large cluster of lymphoma in France with SaTScan and FleXScan. A cluster of lymphomas was reported to be located in the centre and centre-east of France. In another study, Ye et al investigated time and spatial trends of lymphoid leukaemia and childhood lymphoma incidence in Canada. Their results showed that there were spatial clusters for all three cancers in southern parts of Manitoba.

The 1-year and 5-year lymphoma survival rate was over 95.5%, and there was a slight difference between the levels of age groups and gender. A previous study on childhood HL in Iran had shown that overall survival rates of 2 and 5 years were 98.9% and 93.8 in patients younger than 19 years of age. In high-income countries such as the USA and Canada, survival rate was reported at 97.5%–100% for HL, 97% for NHL and 85%–87.4% for Burkitt lymphoma. Additionally, boys had better survival than girls. Various factors including age, race/ethnicity, gender, insurance, histology, stage of disease and access to appropriate medical diagnostic services affected the successful treatment of cancer and patient survival.

Table 4 One-year and 5-year relative survival rates of childhood lymphoma in Iran: 2005–2015

<table>
<thead>
<tr>
<th>Classification</th>
<th>Gender</th>
<th>1 year</th>
<th>Survival rate</th>
<th>5 years</th>
<th>Survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4 years</td>
<td>Boys</td>
<td>115</td>
<td>97.4</td>
<td>114</td>
<td>97.4</td>
</tr>
<tr>
<td></td>
<td>Girls</td>
<td>70</td>
<td>95.8</td>
<td>71</td>
<td>95.8</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>186</td>
<td>96.8</td>
<td>184</td>
<td>96.8</td>
</tr>
<tr>
<td>5–9 years</td>
<td>Boys</td>
<td>206</td>
<td>99.5</td>
<td>195</td>
<td>97.5</td>
</tr>
<tr>
<td></td>
<td>Girls</td>
<td>71</td>
<td>98.5</td>
<td>68</td>
<td>97.1</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>277</td>
<td>99.6</td>
<td>195</td>
<td>97.5</td>
</tr>
<tr>
<td>10–14 years</td>
<td>Boys</td>
<td>218</td>
<td>98.6</td>
<td>210</td>
<td>97.7</td>
</tr>
<tr>
<td></td>
<td>Girls</td>
<td>106</td>
<td>98.1</td>
<td>101</td>
<td>97.2</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>324</td>
<td>98.7</td>
<td>311</td>
<td>97.5</td>
</tr>
</tbody>
</table>

N, number

Table 5 The results of Cox proportional hazards model on patients with lymphoma

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR</th>
<th>SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer types—Hodgkin’s lymphoma*</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma (except Burkitt lymphoma)</td>
<td>0.75</td>
<td>0.41</td>
<td>0.60</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>0.66</td>
<td>0.52</td>
<td>0.60</td>
</tr>
<tr>
<td>Unspecified lymphomas</td>
<td>1.52</td>
<td>0.87</td>
<td>0.46</td>
</tr>
<tr>
<td>Gender—girls</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>boys</td>
<td>0.70</td>
<td>0.30</td>
<td>0.42</td>
</tr>
<tr>
<td>Age—0–4 years</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5–9 years</td>
<td>0.62</td>
<td>0.34</td>
<td>0.40</td>
</tr>
<tr>
<td>10–14 years</td>
<td>0.60</td>
<td>0.32</td>
<td>0.34</td>
</tr>
</tbody>
</table>

*Because of rare frequency in patients with miscellaneous lymphoreticular neoplasms, they were removed in Cox proportional hazards model.
addition, long-term cure complications such as cardiovascular and lung diseases, breast cancer and secondary cancers by lower-dose chemoradiation treatment have raised survival time.\textsuperscript{26, 33}

The Cox regression model showed no significant difference among gender, age and cancer subtypes. Mukhtar et al\textsuperscript{36} showed that survival rates of Burkitt lymphoma did not vary among different ages, genders and races of children in the USA.\textsuperscript{36}

However, this study was faced with some limitations. A major limitation was that the survival data were based on the phone calls to about 30\% of all cases, although we observed slight differences between the distribution of age category and gender in the cases who participated in telephone interviews and others. Furthermore, some information in our dataset was not listed, including tumour size, stage, grade and type of treatment. In addition, the validity and accuracy of different cancer diagnoses in the National Cancer Registry including pathology, clinical and death certificate were not similar. The diagnosis method of disease for 31\% of patients in our data was not registered. We could not evaluate smaller geographical areas or shorter time intervals due to the rarity of the disease.

**CONCLUSION**

Lymphoma incidence rates had heterogeneous geographical distribution, and some significant clusters were identified in Iran from 2005 to 2015. This evidence strengthens the role of possible aetiological factors such as environmental and genetic factors, and further studies are required to clarify this ambiguity. The survival rate in Iran was over 95\%, which is a significant result in contrast with some Asian countries because of the use of novel treatment approaches that promote survival and well-being of these patients.

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**Contributors** MEA, MAL and FR—data collection. SZ and SK—conception or design of the work. MAL—data cleaning. SZ—data analysis and interpretation. SZ, MAL and FR—drafting the manuscript. MAL, SK, FR, MEA and SZ—review and editing the manuscript. All authors are responsible for the overall content of this manuscript as guarantor.

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**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

**Ethics approval** This study involves human participants and was approved by the ethical committee of School of Medicine, Shiraz University of Medical Sciences (approval ID: IR.SUMS.MED.REC.1400.424, 30 October 2021). Participants gave informed consent to participate in the study before taking part.

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**Data availability statement** Data are available upon reasonable request. The datasets used during the current study are available from the corresponding author on reasonable request.

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