https://doi.org/10.32394/pe.75.51

Ayda Hasanpour Dehkordi[1], Hasan Askarpour[2], Farshid Karami Pordanjani[3], Zaher Khazaei[4], Sajjad Rahimi Pordanjani[5,6]*

CRUDE INCIDENCE, AGE-SPECIFIC INCIDENCE, AND STANDARDIZED INCIDENCE RATES OF LEUKEMIA IN CHILDREN UNDER 14 YEARS OF AGE IN IRAN: A META-ANALYSIS

[1]Departments of Psychiatric, Faculty of Medical Sciences, Islamic Azad University of Khomein, Khomein Iran
[2]Department of Disease Management, Deputy of Health,
Yasuj University of Medical Sciences, Yasuj, Iran
[3]Department of Psychology, Yasuj Branch, Islamic Azad University, Yasuj, Iran
[4]Nahavand Paramedical Faculty, Hamadan University of Medical Sciences, Hamadan, Iran
[5]Social Determinants of Health Research Center, Semnan University of Medical Sciences, Semnan, Iran
[6]School of Medicine, Department of Epidemiology and Biostatistics,
Semnan University of Medical Sciences, Semnan, Iran,
*Corresponding Author

ABSTRACT

BACKGROUND. Cancer is the second leading cause of death in children aged 0-14 years and leukemia is the most prevalent of them among children in the world and Iran. Estimating cancer incidence is a vital tool in epidemiology and subsequent cancer control programs. The aim is to evaluate the crude incidence, age-specific incidence and standardized incidence rates of leukemia in these children in Iran through a meta-analysis.
METHODS. This is a systematic review and meta-analysis between 1950 and 2019. We searched national (Iran Medex, Mag Iran and Scientific Information Database) and international (Google Scholar, PubMed, Science Direct, Scopus, and the Web of Sciences) databases for this purpose. The quality of articles was evaluated using the guidelines checklist for critically appraising studies of the incidence of a health problem. After the quality assessment the random effect meta-analysis was used to estimate the incidence rates in overall and based on sex.
RESULTS. A total of 382 articles were identified in the search phase and finally, 15 studies were included. The crude incidence rate in the total population using the Random effect model was estimated at 29.29 (CI %95, 25.74-32.84) per one million children aged 0-14 years. This rate was 34.72 (CI %95, 28.85-40.59) in boys and 24.89 (CI %95, 20.28-29.5) in girls. According to the results, three provinces of Fars (51.48), Golestan (40.86) and Qazvin (35.82) had the highest prevalence, respectively.
CONCLUSION. Given that the incidence of leukemia in boys is higher than in girls and it is more drastic in some Iranian provinces, further attention should be dedicated to risk factors in boys and high risk locations in Iran to help prevent of incidence of this disease.

Keywords: *leukemia, incidence, children, cancer, Iran, meta-analysis*

INTRODUCTION

Today, cancer is one of the major health-related issues and its high mortality, disability and the exorbitant costs of treatment impose a heavy burden on human resources and the national economy (1, 2). Cancer is the third leading cause of death in Iran after cardiovascular diseases and car accidents and its incidence and prevalence is on rise annually in Iran and the world (3-6). The World Health Organization estimates that the average incidence of cancer in all children worldwide is 100 cases per million children (7) and the annual incidence of cancer in the United States is estimated at 186.1 cases per million children (8). The most common type of cancer in children is leukemia or blood cancer, which accounts for about

41% of malignancies in children under the age of 5 (9, 10). Among different types of cancers in Iran, leukemia is one of the most prevalent in Iran and the age-specific incidence rate of leukemia in men and women is 7.7 and 4.4, in 100,000 people, respectively (11, 12). Based on cell origin (lymphoid or myeloid) and course of disease (acute or chronic), leukemia is classified into four groups: acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloblastic leukemia (AML) and chronic myeloblastic leukemia (CML). ALL is the most common and AML is the second most common type of childhood leukemia (13). ALL accounts for about 77% of all cases of childhood leukemia, with a significant incidence peak in 2 to 5-year-olds. It is slightly more frequent in boys than in girls (14, 15). AML accounts for 5% of total cases of childhood leukemia (14).

The United States is estimated to spend $10.4 million annually on treating acute childhood leukemia (16). The 2016 study of Ehsani in Iran revealed that the total direct medical costs per patient of leukemia after completion of treatment course was $15,026, the total non-medical direct cost per patient was $1,688, and the total indirect costs including diminished productivity were estimated at $932 (17). These figures represent the enormous economic burden inflicted on patients and their families. Accordingly, the Ministry of Health and Medical Education of Iran should adopt an efficient strategy to reduce these costs.

Currently, cancer control is one of the top priorities in the healthcare systems (18). Estimation of incidence rates, monitoring of temporal trends, and identifying high-risk cancer regions are critical tools in the epidemiology, etiology, and cancer surveillance system of children (19-21).

There have been various studies on leukemia in different regions of Iran but so far, no study has reviewed the findings of these studies in form of a meta-analysis and there are no reliable statistics on leukemia incidence in Iran. Thus, the present study was undertaken to provide an overview of the epidemiology of this disease in Iran by presenting accurate, and reliable estimates of the crude incidence rate, age-specific incidence and standardized incidence ratio of leukemia in Iranian children. By doing so, it not only allows international comparisons of disease incidence in children based on standardized incidence ratio, but also contributes to more effective planning, and interventions to prevent of incidence and reduce of prevalence in the national health system of Iran.

METHOD AND MATERIAL

Study design. This is a systematic review and meta-analysis on the incidence of leukemia in Iranian children aged 0-14 years, during which all studies about leukemia in different parts of Iran published between 1950 and 2019 were reviewed and evaluated. Subsequently, studies that met the inclusion criteria and were of high quality were subjected to the meta-analysis.

Search Strategy. The articles published in Iranian and international databases were used to identify relevant studies. Iranian databases comprised articles indexed in Iran Biomedical Journals (Iran Medex), Country Magazines Database (Mag Iran), and Scientific Information Database (SID). International databases also consisted of articles indexed in Google Scholar, PubMed, Science Direct, Scopus, and the Web of Sciences. In the review of sources, in addition to searching papers, other types of documents including theses, abstracts of papers published at Iranian and international conferences and congresses, and reports from the National Cancer Registry Program were also used. Articles were searched based on keywords such as Epidemiology, Age Specific Incidence Rate, Age Standardized Incidence Rates, Crude Incidence Rate, Leukemia, Acute Lymphoblastic Leukemia, Acute Myeloblastic Leukemia, Cancer, Malignancy, Tumor, Carcinoma, Children, Childhood, Iran, Pediatric or a combination of these terms with Boolean operators. The articles that contained the above key words or a combination of them in their titles or abstracts in the period of 1950 to 2019 were searched by two members of the research team independently.

Study selection and eligibility criteria. At the end of the search phase, the preliminary screening was conducted to select relevant articles that met criteria for quality assessment process. At this stage, inclusion criteria were evaluated against a researcher-made checklist: 1) Studies investigating leukemia incidence in the target population of children with 0-14 years for each gender, 2) Studies reporting the incidence of one type of leukemia (crude, age-specific and standardized) or their data allowed calculation of the above measures, 3) Relevant studies published between 1950 and 2018, 4) Studies and reports published in Persian or English with full text access, 5) Studies that allowed generalization of the results to the target population, and 6) Original research studies (non-research studies such as letters, comments, and editorials were excluded).

Two independent researchers applied inclusion criteria to the identified studies, and papers that did not meet the inclusion criteria were excluded. Following evaluations by these researchers, the titles of articles

and related reports that met the eligibility criteria were examined and duplicate or similar studies were omitted. The flowchart of the various stages of the study is illustrated in Figure 1.

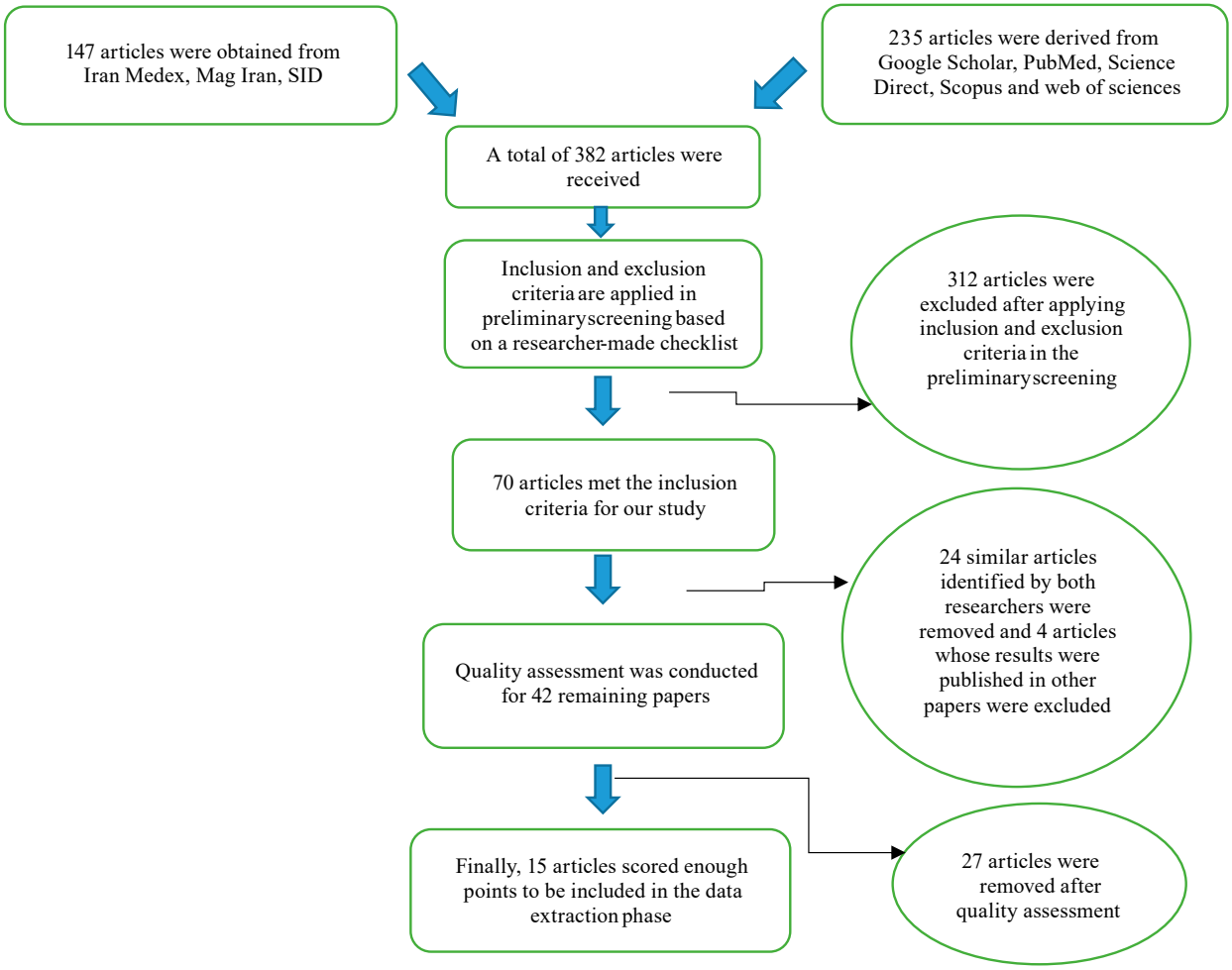


Figure 1. Flowchart of different research stages

Quality assessment. After selecting the relevant studies and reports, the quality assessment was conducted. At this stage, each study was evaluated based on the guidelines for critically appreciating studies of the prevalence or incidence of a health problem developed by Loney et al. (22). This checklist reviews eight important parts of articles including study design and sampling method adequate, sampling frame adequate, sample size adequate, objective health outcome measurement, health outcome measurement unbiased, response rate adequate, and confidence intervals reported, study subjects and settings described. For the purpose of scoring, 1 point is assigned to each question, so the total score ranged from 0 to 8. Articles with a score of 0 to 4 are classified as low quality, articles with a score of 5 to 6 are classified as medium quality, and papers with a score of 7 to 8 are classified as high quality (23). Subsequently, high quality articles are included in the data extraction phase.

Data extraction. Data extraction, which was performed by two members of the research team, comprised of two parts: 1) data on the biography and methodology of studies and reports whose characteristics are shown in Table 1, and 2) data on the incidence of leukemia. Incidence rates were calculated and reported in three forms of crude incidence rate, age-specific rate and standardized age ratio. The World Health Organization and several other studies have estimated the incidence of cancer in children per one million children. Hence, in the present study, we calculated the incidence rate per one million children as follows (7, 24, 25):

1) Crude incidence rate: The total number of the new cases of leukemia divided by the entire at-risk population multiplied by 1 million children. This rate is influenced by age composition of the population and therefore not suitable for comparisons between communities with different age composition.

2) Age-specific incidence rate: The total number of new leukemia cases in a given age group divided

by the population in the same age group in 1 million children. This value is calculated to estimate the incidence rate in a specific age group. In this study, leukemia incidence rate was computed in three age groups of 0-4 years, 5-9 years and 10-14 years.

3) Age-standardized incidence ratio: The crude rate is influenced by the population composition and gender and therefore gives an inaccurate estimation of the incidence and distribution of cancer. Thus, the direct adjustment method is used to remove confounding factors of age and sex compositions. In this method, it is necessary to consider a population as the reference or standard population. Here, the standard population introduced by the World Health Organization was utilized to allow for international comparisons.

Statistical analysis. Random effects model meta-analysis was used to estimate the overall incidence and corresponding 95% confidence interval (CI). In order to check heterogeneity, two statistics, I^2 and Tau^2, were used. In addition, in order to identify the source of heterogeneity, subgroup analysis was performed based on gender. All analyses were done using Stata version 14 software. Statistical significance was considered at < 0.05.

Table 1. Biographical and methodological data of studies included in meta-analysis

First Author Year of publishing (Reference Number)	Time interval	Geographical Location of the Study Area	Type of study design	Method of Cancer Registry
Seyed Mohsen Mousavi 2010 (7)	2005–2006	Ardebil Province Golestan Province Isfahan Province Kerman Province Lorestan Province	Review study	Population based
Fatemeh Koohi 2016 (37)	2003–2009	Iran	Cross-sectional study	Population based
Gholamreza Roshandel 2018 (38)	2014	Iran	National Cancer Registry Program	Population based
Mahin Farahmand 2011 (39)	2001–2008	Fars Province	Fars Province Cancer Registry	Population based
Babaei Masoud 2009 (40)	2004–2006	Ardebil Province	Ardabil Province cancer registry	Population based
Mohammad-Ali Mohagheghi 2009 (41)	1998–2001	Tehran Province	Tehran Population-Based Cancer Registry (TPCR)	Population based
Abdolvahab Moradi 2010 (27)	2004–2006	Golestan Province	Golestan population based cancer registry (GPCR)	Population based
Parviz Haghighi 1974 (42)	1963–1971	Fars Province	Cross-sectional study	Pathologic base
Mohammad H Somi 2008 (43)	2006–2007	East Azerbaijan	Population-Based Cancer Survey	Population based
Saeed Dastgiri 2011 (44)	2003–2006	Tabriz and Ardebil Provinces	Cross-sectional study	Pathologic base
Ali Akbar Sayari 2002 (45)	1997	Iran (Nine provinces)	National Cancer Registry Program	Pathologic base
Shahryar Semnani 2008 (46)	2006	Golestan Province	Golestan population based cancer registry (GPCR)	Population based
Alireza Sadjadi 2007 (47)	1996–2000	Kerman Province	Population-Based Cancer Survey	Population based
Tahere Dargahi 2016 (48)	2006–2016	Qazvin province	Cross-sectional study	Pathologic base
Maryam Parvareh 2015 (49)	1998–2009	Kerman Province	Cohort study	Population based

RESULTS

A total of 382 articles were identified in the search phase, of which 367 were excluded in the quality assessment process for inclusion criteria. Finally, 15 studies conducted in different regions of Iran were reviewed and incorporated in the meta-analysis. The results of extracting crude incidence rate, age-specific incidence, and standardized incidence ratio in children aged 0 to 14 years are outlined for each age, sex, and geographic location in Table 2.

The crude incidence rate using Random Effect model in the entire population was estimated at 29.29 (95% CI: 25.74-32.84) per one million children aged 0-14 years, but heterogeneity tests in pooled analysis were statistically significant. The results of meta-regression revealed that a major cause of heterogeneity is the gender of children. Hence, we decided to perform a subgroup analysis by gender.

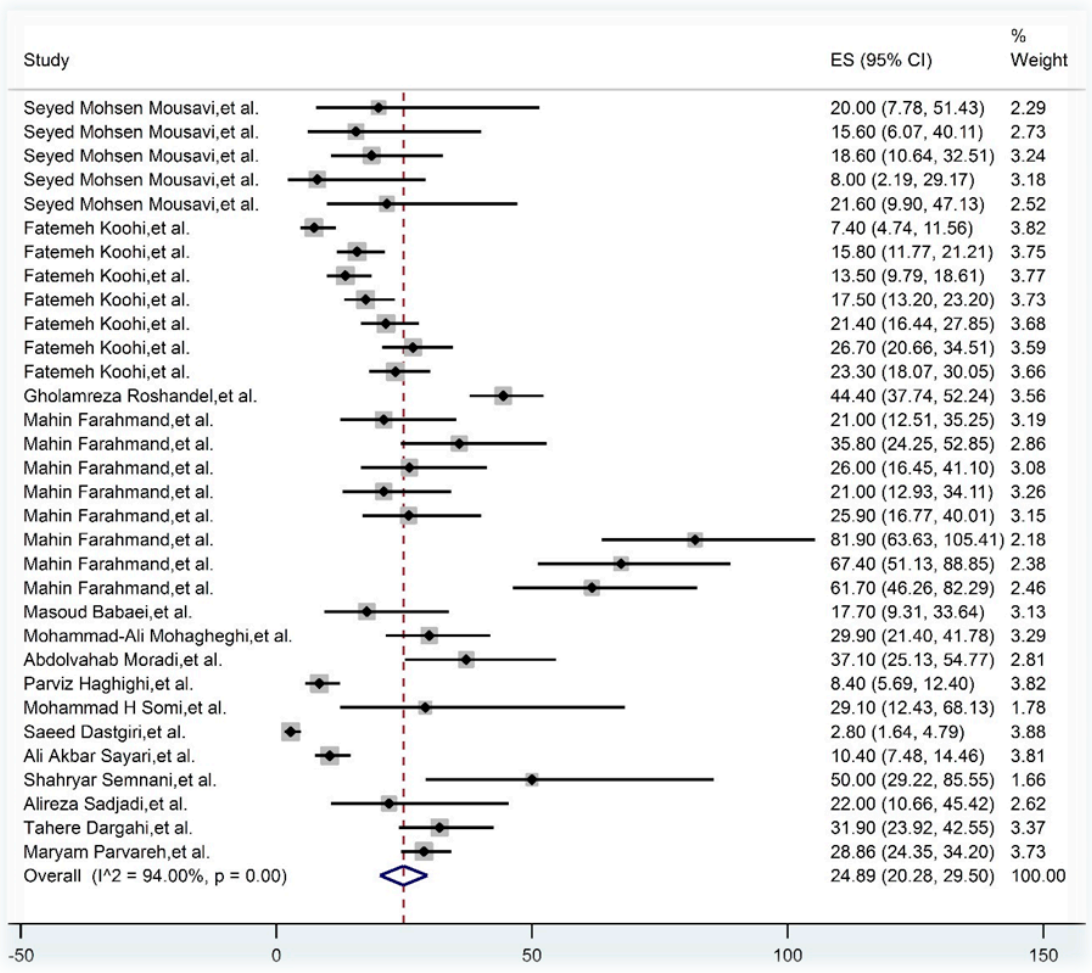
After subgroup analysis, the crude incidence rate was estimated at 34.72 (95% CI: 28.85-40.59) for boys and 24.89 for girls (95% CI: 20.28-29.5) in children aged 0-14 years. These results demonstrate that the

Table 2. Crude incidence rate, age specific incidence rate and standardized incidence ratio in 0-14-year-old children by age, sex and geographical location (per million)

Variable types		Male					Female				
		Age Specific Incidence Rate			0-14 year		Age Specific Incidence Rate			0-14 year	
Geographical Settings		0-4	5-9	10-14	Age Standardized Incidence Rates	Crude Incidence Rate (Number)	0-4	5-9	10-14	Age Standardized Incidence Rates	Crude Incidence Rate (Number)
National Cancer Registry Program	Ardebil	18.4	14.2	0.0	11.7	9.3 (2)	20.1	0.0	36.0	18.2	20.0 (4)
	Golestan	71.5	77.2	34.0	62.5	57.5 (16)	15.6	0.0	28.0	14.2	15.6 (4)
	Isfahan	15.7	12.1	9.3	12.7	11.8 (8)	22.9	17.2	17.1	19.4	18.6 (12)
	Kerman	39.1	7.5	17.4	22.6	19.6 (7)	10.7	8.0	6.4	8.6	8.0 (2)
	Lorestan	13.2	20.4	23.6	18.5	19.9 (6)	28.8	21.6	17.3	23.1	21.6 (6)
IRAN	2003	8.2	5.7	10.4	8.3	7.9(24)	7.7	5.8	9.3	7.8	7.4(19)
	2004	19.2	23.4	16.8	20.2	19.3(79)	19.4	15.4	13.7	16.5	15.8(44)
	2005	18.7	13.7	14.5	15.9	15.3(40)	16.8	13.7	11.1	14.1	13.5(37)
	2006	34.6	31.8	18.6	28.8	27.6(61)	23.8	16.2	14.0	18.4	17.5(48)
	2007	43	32.1	17.6	31.5	30.2(74)	34.1	19.5	12.3	22.3	21.4(55)
	2008	39.3	34.2	24.8	33.3	32.1(95)	39.6	27.2	15.1	27.8	26.7(58)
	2009	37.8	36.9	22.9	33.1	31.7 (79)	30.3	25.3	16.3	24.4	23.3(59)
Annual report of Iranian national population – base cancer registry	2014	73.3	65.1	41.8	61.6	56.7(152)	54.7	54.6	26.9	46.2	44.4(145)
Fars	2001	59	53	26	36	31.7(23)	35	35	22	22.6	21(14)
	2002	137	59	86	74.5	66.5(49)	48	41	53	35.1	35.8(25)
	2003	39	13	55	26.4	27.1(20)	47	34	31	29.61	26(18)
	2004	50	87	44	45.2	43.6(34)	39	39	15	24.6	21(16)
	2005	50	62	39	38.4	36(28)	59	20	36	30.6	25.9(20)
	2006	112	74	135	79.5	81.7(63)	91	58	91	76.2	81.9(60)
	2007	184	165	109	119.7	107.3(83)	96	122	65	72.5	67.4(50)
	2008	133	235	131	128	117.5(92)	114	89	59	68.5	61.7(46)
Ardebil		14	31	22	21.7	22.4 (12)	15	0.0	32	15.1	17.7 (9)
Tehran		47	50	25	41.5	38.7(45)	31	34	26	30.5	29.9(34)
Golestan		78.2	66	30.6	47.2	49.9(33)	26.3	38.6	42.7	35.3	37.1(25)
Southern of Iran		9	23	22	19.3	18.8(59)	7	8	12	9.2	8.4(25)
East Azerbaijan		60	44.9	31.2	46.2	44.4(7)	47.6	23.7	19.8	30.8	29.1(5)
Northwest of Iran		NC*	NC*	NC*	NC*	3.47(16)	NC*	NC*	NC*	NC*	2.83(13)
Nine provinces		NC*	NC*	NC*	NC*	13.5 (49)	NC*	NC*	NC*	NC*	10.4 (35)
Golestan		NC*	NC*	NC*	NC*	48(13)	NC*	NC*	NC*	NC*	50(13)
Kerman		NC*	NC*	NC*	NC*	41.0 (13)	NC*	NC*	NC*	NC*	22.0 (7)
Qazvin		NC*	NC*	NC*	NC*	40.49(62)	NC*	NC*	NC*	NC*	31.95(46)
Kerman		NC*	NC*	NC*	NC*	17.85(86)	NC*	NC*	NC*	NC*	28.86(133)

*Not Calculable

Figure 2. Forest plot of the crude incidence rate of leukemia in Iranian girls aged 0-14 years



incidence of leukemia in Iranian boys is higher than in girls.

The results of the meta-analysis of crude incidence of leukemia in Iranian girls aged 0-14 years are shown in Table 3 and Figure 2 for each study.

The results of the meta-analysis of the crude incidence rate of leukemia in Iranian boys aged 0-14 year are shown in Table 4 and Figure 3 for each study.

Moreover, we investigated the crude incidence rate of leukemia in children aged 0-14 years in different geographical areas of Iran with the results suggesting that three provinces of Fars (51.48), Golestan (40.86) and Qazvin (35.82) had the highest incidence of leukemia. The findings of this analysis are shown in Table 5.

As can be seen from the results of Table 5, the incidence rates obtained from surveys in all regions of Iran closely resemble those estimated in our meta-analysis, and the updated estimate of random pooled incidence rate is at 95% confidence interval for surveys carried out in all regions of Iran, which indicates the accuracy and reliability of that meta-analysis.

Table 3. Meta-analysis of crude incidence rate of leukemia in Iranian girls aged 0-14 years in each study

Study	ES	[95% Conf.	Interval]	% Weight
Seyed Mohsen Mousavi	20.00	7.78	51.43	2.29
Seyed Mohsen Mousavi	15.60	6.07	40.11	2.73
Seyed Mohsen Mousavi	18.60	10.64	32.51	3.24
Seyed Mohsen Mousavi	8.00	2.19	29.17	3.18
Seyed Mohsen Mousavi	21.60	9.90	47.13	2.52
Fatemeh Koohi,et al.	7.40	4.74	11.56	3.82
Fatemeh Koohi,et al.	15.80	11.77	21.21	3.75
Fatemeh Koohi,et al.	13.50	9.79	18.61	3.77
Fatemeh Koohi,et al.	17.50	13.20	23.20	3.73
Fatemeh Koohi,et al.	21.40	16.44	27.85	3.68
Fatemeh Koohi,et al.	26.70	20.66	34.51	3.59
Fatemeh Koohi,et al.	23.30	18.07	30.05	3.66
Gholamreza Roshandel	44.40	37.74	52.24	3.56
Mahin Farahmand,et a	21.00	12.51	35.25	3.19
Mahin Farahmand,et a	35.80	24.25	52.85	2.86
Mahin Farahmand,et a	26.00	16.45	41.10	3.08
Mahin Farahmand,et a	21.00	12.93	34.11	3.26
Mahin Farahmand,et a	25.90	16.77	40.01	3.15
Mahin Farahmand,et a	81.90	63.63	105.41	2.18
Mahin Farahmand,et a	67.40	51.13	88.85	2.38
Mahin Farahmand,et a	61.70	46.26	82.29	2.46
Masoud Babaei,et al.	17.70	9.31	33.64	3.13
Mohammad-Ali Mohaghe	29.90	21.40	41.78	3.29
Abdolvahab Moradi,et	37.10	25.13	54.77	2.81
Parviz Haghighi,et a	8.40	5.69	12.40	3.82
Mohammad H Somi,et a	29.10	12.43	68.13	1.78
Saeed Dastgiri,et al	2.80	1.64	4.79	3.88
Ali Akbar Sayari,et	10.40	7.48	14.46	3.81
Shahryar Semnani,et	50.00	29.22	85.55	1.66
Alireza Sadjadi,et a	22.00	10.66	45.42	2.62
Tahere Dargahi,et al	31.90	23.92	42.55	3.37
Maryam Parvareh,et a	28.86	24.35	34.20	3.73
Random pooled ES	24.89	20.28	29.50	100.00

Table 4. Meta-analysis of the crude incidence rate of leukemia in Iranian boys aged 0-14 years for each study

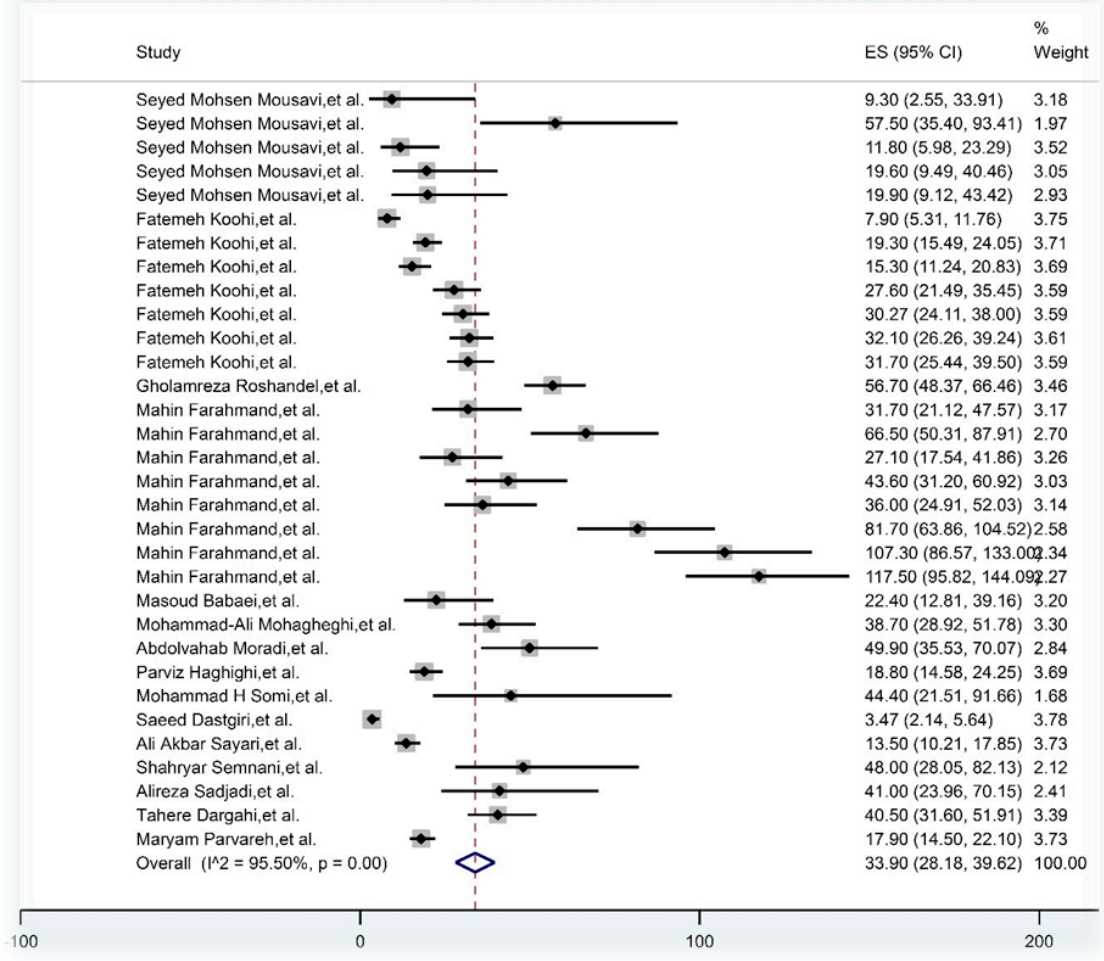
Study	ES	[95% Conf. Interval]		% Weight
Seyed Mohsen Mousavi	9.30	2.55	33.91	3.18
Seyed Mohsen Mousavi	57.50	35.40	93.41	1.97
Seyed Mohsen Mousavi	11.80	5.98	23.29	3.52
Seyed Mohsen Mousavi	19.60	9.49	40.46	3.05
Seyed Mohsen Mousavi	19.90	9.12	43.42	2.93
Fatemeh Koohi,et al.	7.90	5.31	11.76	3.75
Fatemeh Koohi,et al.	19.30	15.49	24.05	3.71
Fatemeh Koohi,et al.	15.30	11.24	20.83	3.69
Fatemeh Koohi,et al.	27.60	21.49	35.45	3.59
Fatemeh Koohi,et al.	30.27	24.11	38.00	3.59
Fatemeh Koohi,et al.	32.10	26.26	39.24	3.61
Fatemeh Koohi,et al.	31.70	25.44	39.50	3.59
Gholamreza Roshandel	56.70	48.37	66.46	3.46
Mahin Farahmand,et a	31.70	21.12	47.57	3.17
Mahin Farahmand,et a	66.50	50.31	87.91	2.70
Mahin Farahmand,et a	27.10	17.54	41.86	3.26
Mahin Farahmand,et a	43.60	31.20	60.92	3.03
Mahin Farahmand,et a	36.00	24.91	52.03	3.14
Mahin Farahmand,et a	81.70	63.86	104.52	2.58
Mahin Farahmand,et a	107.30	86.57	133.00	2.34
Mahin Farahmand,et a	117.50	95.82	144.09	2.27
Masoud Babaei,et al.	22.40	12.81	39.16	3.20
Mohammad-Ali Mohaghe	38.70	28.92	51.78	3.30
Abdolvahab Moradi,et	49.90	35.53	70.07	2.84
Parviz Haghighi,et a	18.80	14.58	24.25	3.69
Mohammad H Somi,et a	44.40	21.51	91.66	1.68
Saeed Dastgiri,et al	3.47	2.14	5.64	3.78
Ali Akbar Sayari,et	13.50	10.21	17.85	3.73
Shahryar Semnani,et	48.00	28.05	82.13	2.12
Alireza Sadjadi,et a	41.00	23.96	70.15	2.41
Tahere Dargahi,et al	40.50	31.60	51.91	3.39
Maryam Parvareh,et a	17.90	14.50	22.10	3.73
Random pooled ES	33.90	28.18	39.62	100.00

Table 5. Crude and standardized incidence ratios of leukemia in different geographical areas of Iran

Region or Province	Crude Incidence Rate	CI %95
Isfahan	14.36	7.91 – 20.85
Lorestan	20.68	8.76 – 32.91
Ardebil	19.76	4.52 – 38.54
Tehran	33.78	26.34 – 41.21
Golestan	40.86	27.49 – 54.23
Southern of Iran	11.73	9.42 – 14.57
Fars	51.48	39.12 – 63.86
East Azerbaijan	34.85	14.64 – 55.41
Northwest of Iran	3.10	1.96 – 4.23
Qazvin	35.82	29.27 – 42.64
Kerman	21.43	14.33 – 28.17
IRAN*	23.98	18.51 – 30.45
Random pooled incidence rate	29.29	25.74 – 32.74

* Surveys conducted throughout of Iran

Figure 3. Forest plot of the crude incidence rate of leukemia in Iranian boys aged 0-14 years



DISCUSSION

Leukemia is the most common childhood cancer that poses enormous challenges not only to children but also to their families and society, and its prevalence is on rise in Iran and the world (26). According to global estimates, its incidence has spiked from 35 cases per million people in Israel to 60 cases per million people a year in Italy and Malta (27). The most common cancer among children in the world and Iran is leukemia (28). In 2012, 1,514,027 cases of cancer were recorded in Southeast Asia, of which 480,267 (32%) were related to leukemia (12). The highest incidence rate of leukemia in children under 14 years of age in South Asian countries has been recorded in Iran (3.6 per 100,000), Kazakhstan (3.2 per 100,000), Sri Lanka and Uzbekistan (3 per 100,000). The lowest incidence rate has been reported in Bangladesh (0.8 per 100,000 population) and Bhutan (0.9 per 100,000 population) (12).

The average annual incidence rate of acute lymphoblastic leukemia (ALL) has been reported 2.25 in Iranian children during the years 2006 to 2014 and the cumulative incidence rate (CIR) was 21.31 per 100,000 under-15 children (29). Seems that the incidence of leukemia in Iranian children has been lower than in developed countries and similar to developing countries (30).

In a study in 2021 conducted by Rahimi et al. on the data of the National Cancer Registry of Iran during 2006-2014, the incidence of leukemia was 57.9% in boys and 42.1% in girls and sex ratio of boys to girls was 1.37 (30, 31). Also changes in the time trend of ALL incidence in Iran was showed that leukemia increased by an average of 7.1% between 2006 and 2014 (30).

The results of the analysis of the spatial pattern of the disease showed that ALL in Iran tends to have high spatial autocorrelation and has created spatial clustering (29-31). All hot spots and high risk clusters were located in the north and west of Iran and all cold spots and low risk clusters were located in the south and east of Iran (29-31).

The most probable high-risk cluster with LLR = 327.47 is located in the southwestern part of Iran with a radius of 294.93 km and a center of 30.77 N & 50.83 E, udes Fars, Bushehr, Kohgiluyeh, Boyer-Ahmad and Khuzestan provinces. On the other hand, the most probable low-risk cluster with 517 cases of patients, relative risk of 0.49 and LLR = 227.03 was discovered in the northwestern part of Iran with a radius of 270.38 km and a center of 37.25 N & 49.49 E, including Zanjan, Qazvin, Gilan and East Azarbaijan, Ardabil, Alborz and Tehran provinces (31).

The occurrence of leukemia may be the result of an interaction between environmental, infectious, geographical and genetic risk factors (28, 31). A study conducted in Iran on spatial analysis and geographical pathology of leukemia, was provided evidence on the influence of solar UV radiation, low latitude and high longitude, high concentrations of benzene and other petroleum hydrocarbons and intervention of viruses (HBV, HCV, HCG, HTLV-1) in the disease cycle (30, 31). A 2021 study found that Max Temperature of Warmest Month (MTWM) and Direct Normal Irradiation (DNI) played a risk factor, and Precipitation of the Coldest Quarter (PCQ) and Altitude (AL) played a protective factor in the development of leukemia (28).

Genetic differences may be involved in the incidence of ALL, with higher incidence reported in Hispanic and Latin American breeds (31). 3-4% of leukemia cases are attributed to hereditary genetic predisposition (30, 31).

Different types of leukemia also conform to diverse patterns and geographical distribution. ALL is the most common type of leukemia in children under 14 years of age in Europe, accounting for 80% of childhood leukemia (1). The prevalence of ALL is approximately five times higher than that of AML, affecting approximately 380 children annually (12, 15). Its incidence is estimated to be around 40 cases per year in industrialized countries in Western Europe, 30 to 35 cases in Eastern European countries and less than 20 cases per million children in sub-Saharan Africa (26). The highest incidence of ALL in children under 14 years of age in Iran was reported in Fars province (32.6%). The incidence of leukemia in boys (57.5%) is higher than in girls (42.5%) (12). The second most prevalent type of childhood leukemia is AML, which accounts for 20% of childhood leukemia in Europe with a relatively stable prevalence worldwide (5-9 cases per million children per year) (32).

In most cases, the causes of childhood leukemia are unknown. Various studies have mentioned some causes and risk factors of leukemia, including genetic factors (2-3% of cases suffer from Down Syndrome) and exposure to ionizing radiation in the uterus and after birth (15, 33). Other factors may include infectious diseases, birth weight, maternal age at birth, insecticide use, metronidazole use during pregnancy, maternal education, birth rate, number of family members and previous history of hospitalization with allergic diseases (34). A number of environmental studies have also exhibited a positive association between leukemia, especially ALL, with improved economic and social status (35, 36). Other epidemiological studies have reported significant risk factors associated with acute childhood leukemia, including father's occupation, maternal smoking during pregnancy, father's smoking

(more than ten cigarettes per day, for more than ten years) (13, 36). However, some studies have declared that the only important environmental risk factor associated with ALL or AML is ionizing radiation (15).

CONCLUSION

In light of the results of the study according to which the incidence of childhood leukemia varies in different provinces of Iran, greater attention should be allocated to risk factors in these areas, especially among boys, to reduce the incidence of this cancer in children. In this regard, the results of this study can be used for fundamental and clinical studies and interdisciplinary research to shed further light on the pathophysiology and development of more effective and cheaper prevention methods and early detection and treatment of leukemia in children.

REFERENCES

1. Yomralioglu T, Colak EH, Aydinoglu AC. Geo-relationship between cancer cases and the environment by GIS: A case study of Trabzon in Turkey. Int J Environ Res Public Health. 2009;6(12):3190-204.
2. Goodarzi E, Beiranvand R, Mosavi-Jarrahi A, et al. Epidemiology Incidence and Mortality Worldwide Common cancers in males and Their Relationship with the Human Development Index (HDI): An Ecological Study Updated in the World.
3. J Contemp Med Sci. 2019;5(6).
4. Roshandel G, Sadjadi A, Aarabi M, et al. Cancer incidence in Golestan Province: report of an ongoing population-based cancer registry in Iran between 2004 and 2008. 2012.
5. Aminzadeh A, Ramzanpoor M, Molaarazi A, et al. Relationship between rainfall and temperature with the incidence of cancer in Golestan Province, northern Iran. J Gorgan Univ Med Sci. 2017;19(3):80-5.
6. Curado M-P, Edwards B, Shin HR, et al. Cancer incidence in five continents, Volume IX: IARC Press, International Agency for Research on Cancer; 2007.
7. Rasaf MR, Ramezani R, Mehrazma M, et al. Inequalities in cancer distribution in tehran; a disaggregated estimation of 2007 incidencea by 22 districts. Int J Prev Med. 2012;3(7):483.
8. Mousavi SM, Pourfeizi A, Dastgiri S. Childhood cancer in Iran. J Pediatr Hematol Oncol . 2010;32(5):376-82.
9. Ward E, DeSantis C, Robbins A, et al. Childhood and adolescent cancer statistics, 2014. CA: Cancer J Clin. 2014;64(2):83-103.
10. Lankowsky P. Leukemia: In: Lankowsky P. Manual ped: Hematology and oncology. Amsterdam: Elsevier Academic Press; 2005.
11. Hashemi A, Besharati A, Taghipour S, et al. Frequency of Various Malignant Diseases in Children Younger Than 10 Years Old in Yazd. JSSU. 2007;14(4):9-14.
12. Rajabli N, Naeimi-Tabeie M, Jahangirrad A, et al. Epidemiology of leukemia and multiple myeloma in Golestan, Iran. Asian Pac J Cancer Prev. 2013;14(4):2333-6.
13. Khazaei Z, Goodarzi E, Adineh HA, et al. Epidemiology, incidence, and mortality of leukemia in children early infancy to 14 years old of age in south-central Asia: A global ecological study. J Compr Ped. 2019(In Press).
14. Malcol S, Lym N. Childhood cancer: In: Pizzo PA, Poplack DG, editors. Principles and practice of ped oncology 4th ed Philadelphia: LWW Co. 2002:1-556.
15. Nikpour S, Rahimian S, Shokrabi S, et al. Relationship between breast-feeding duration and childhood acute leukemia. Iran J Endocrinol Metab. 2010;11(2):185-90.
16. Belson M, Kingsley B, Holmes A. Risk factors for acute leukemia in children: a review. Environ Health Perspect. 2007;115(1):138-45.
17. Guise J-M, Austin D, Morris CD. Review of case-control studies related to breastfeeding and reduced risk of childhood leukemia. Pediatrics. 2005;116(5):e724-e31.
18. Ehsani M, Shahgholi E, Hayati H, et al. Cost-analysis of treatment of pediatrics acute lymphoblastic leukemia based on ALL-BFM protocol. Pediatr Blood Cancer. 2018;65:S113-S.
19. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127(12):2893-917.
20. Pagano M, Gauvreau K. Principles of biostatistics: Chapman and Hall/CRC; 2018.
21. Kaatsch P. Epidemiology of childhood cancer. Cancer Treat Rev. 2010;36(4):277-85.
22. Bhakta N, Force LM, Allemani C, et al. Childhood cancer burden: a review of global estimates. Lancet Oncol. 2019;20(1):e42-e53.
23. Loney PL, Chambers LW, Bennett KJ, et al. Critical appraisal of the health research literature: prevalence or incidence of a health problem. Chronic Dis Can. 1998;19(4):170-6.
24. Lang J, Yao Y. Prevalence of nonsuicidal self-injury in Chinese middle school and high school students: A meta-analysis. Medicine. 2018;97(42).
25. Stiller CA, Bayne AM, Chakrabarty A, et al. Incidence of childhood CNS tumours in Britain and variation in rates by definition of malignant behaviour: population-based study. BMC Cancer. 2019;19(1):139.

26. Rivas-Vilela S, Rubió-Casadevall J, Fàbrega-Ribas A, et al. Incidence and survival of central nervous system tumors in childhood and adolescence in Girona (Spain) 1990–2013: national and international comparisons. Clin Transl Oncol. 2019;21(9):1177-85.
27. Ivanov V, Tsyb A, Khait S, et al. Leukemia incidence in the Russian cohort of Chernobyl emergency workers. Radiat Environ Biophys. 2012;51(2):143-9.
28. Moradi A, Semnani S, Roshandel G, et al. Incidence of childhood cancers in golestan province of Iran. Iran J Pediatr. 2010;20(3):335.
29. Pordanjani SR, Kavousi A, Mirbagheri B, et al. Spatial analysis and geoclimatic factors associated with the incidence of acute lymphoblastic leukemia in Iran during 2006-2014: An environmental epidemiological study. Environ Res. 2021;202:111662.
30. Pordanjani SR, Kavousi A, Mirbagheri B, et al. Temporal trend and spatial distribution of acute lymphoblastic leukemia in Iranian children during 2006-2014: a mixed ecological study. Epidemiology Health. 2020;42:e2020057.
31. Pordanjani SR, Kavousi A, Mirbagheri B, et al. Geographical Pathology of Acute Lymphoblastic Leukemia in Iran with Evaluation of Incidence Trends of This Disease Using Joinpoint Regression Analysis. Arch Iran Med. 2021;24(3):224-32.
32. Pordanjani SR, Kavousi A, Mirbagheri B, et al. Identification of high-risk and low-risk clusters and estimation of the relative risk of acute lymphoblastic leukemia in provinces of Iran during 2006-2014 period: A geo-epidemiological study. J Res Med Sci 2021;26:18.
33. Wu M, Hsu L, Zhang B, et al. The experiences of cancer-related fatigue among Chinese children with leukaemia: a phenomenological study. Int J Nurs Stud. 2010;47(1):49-59.
34. Hassanzade J, Mohammadi R, Rajaeefard A. Risk factors in childhood lymphoblastic leukemia in Shiraz-Iran (2009): an epidemilogical study. J Gorgan Univ Med Sci. 2012;14(4):119-24.
35. Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood. 2010;116(19):3724-34.
36. WHO. Hazardous chemicals: main risks to children's health. Fact Sheet EURO/02/04 Copenhagen: WHO. 2004.
37. Fürstová J, Valenta Z. Statistical analysis of competing risks: overall survival in a group of chronic myeloid leukemia patients. Eur J Biomed Inform. 2011;7(1).
38. Koohi F, Ghoncheh M, Salehiniya H. Epidemiology and trend of incidence of the Leukemia in Iran. J Isfahan Med Sch. 2016;33(361):2055-61.
39. Roshandel G, Ghanbari-Motlagh A, Partovipour E, et al. Cancer incidence in Iran in 2014: results of the Iranian National Population-based Cancer Registry. Cancer Epidemiol. 2019;61:50-8.
40. Farahmand M, Almasi-Hashiani A, Mohammad Beigi A, et al. The epidemiology of childhood hematopoietic and reticuloendothelial cancer based on Fars province cancer registry data system from 2001 to 2008. Daneshvar. 2011;18(94):27-34.
41. Babaei M, Jaafarzadeh H, Sadjadi A, et al. Cancer incidence and mortality in Ardabil: Report of an ongoing population-based cancer registry in Iran, 2004-2006. Iran J Public Health. 2009:35-45.
42. Mohagheghi S, Mousavi JS, Malekzadeh R, et al. Cancer incidence in Tehran metropolis: the first report from the Tehran Population-based Cancer Registry, 1998–2001. 2009.
43. Haghighi P, Mohallatee E, Nasr K, et al. Childhood cancer in southern Iran. Cancer. 1974;34(5):1842-8.
44. Somi MH, Farhang S, Mirinezhad SK, et al. Cancer in East Azerbaijan, Iran: results of a population-based cancer registry. Asian Pac J Cancer Prev. 2008;9(2):327-30.
45. Dastgiri S, Fozounkhah S, Shokrgozar S, et al. Incidence of Leukemia in the Northwest of Iran. Health Promot Perspect. 2011;1(1):50.
46. Sayyari A, Zadeh I, Esfandyar A, et al. Epidemiology of pediatric cancers in Iran. Iran J Pediatr. 2002;12(3):9-12.
47. Semnani S, Roshandel G, Keshtkar A, et al. Golestan population-based cancer registry. Golestan Research Center of Gastroenterology and Hepatology, Golestan University of Medical Sciences. 2008:84-95.
48. Sajadi A, Zahedi M, Darvish MS, et al. The first population-based cancer survey in Kerman Province of Iran. 2007.
49. Dargahi T, Goudarzi M, Mobarra N, et al. Investigation of Leukemia Frequency in Children of Qazvin Province and its Correlation with Gender, Age, and Blood Groups between 2006-2016. Novelty in Biomedicine. 2016;4(4):135-41.
50. Parvareh M, Khanjani N, Frahmandinia Z, et al. The Survival rate of childhood leukemia and its related factors in Kerman, Iran. Iran J Health Sci. 2015;3(4):24-32.

Received: 06.09.2021
Accepted for publication: 20.12.2021

Address for correspondence:
Sajjad Rahimi Pordanjani, PhD
Department of Epidemiology and Biostatistics,
Semnan University of Medical Sciences, Semnan, Iran
Email: sajadrahimip@gmail.com
Tel:+98-9133809081