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Five-Year Survival, Mortality, and Relapse Rate of Childhood Leukemia in Iran: A Systematic Review and Meta-Analysis

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Abstract

Background: Childhood leukemia (CL) is a cancer that occurs mostly in children and adolescents**.** A comprehensive image of the survival, mortality, and relapse rate in leukemia in Iran is less visible. Therefore, the current study aimed to estimate the five-year survival, mortality, and relapse rates of CL in Iran.

Materials and Methods: The current systematic review and meta-analysis examined all observational studies in English and Persian that were published from January 2000 to July 2024 in different international databases, including Google Scholar, Web of Science, PubMed, Scopus, and local databases such as SID, IranDoc, Magiran, and IranMedex. The statistical heterogeneity was assessed using the I^2 index, Tau^2, and the Q test. Due to high heterogeneity ($I^2 > 50\%$), a random-effect model was used for pooled estimation. The Beggs and Eggers test served to assess the publication bias. Sensitivity analysis was performed to determine the influence of individual studies on the pooled estimate.

Results: A total of 22 relevant manuscripts that reported the mortality, survival, and relapse rate of Childhood leukemia were reviewed and analyzed in this study. The 5-year survival rate of childhood leukemia in Iran was 63% (95% CI: 57%- 70%, I^2: 94.57, $P < 0.001$). The survival rate in ALL and AML cases were 66% (95% CI: 58%- 74%, I^2: 95.80, $P < 0.001$) and 58% (95% CI: 48%- 68%, I^2: 83.13, $P < 0.001$), respectively. The 5-year mortality and relapse rates in childhood leukemia were also 26% (95% CI: 21%-31%, I^2: 89.76, $P < 0.001$) and 24% (95% CI: 18%-30%, I^2: 90.09, $P < 0.001$), respectively**.**

Conclusion: The 5-year survival rate in Iranian children with leukemia is not very high, and the death and recurrence rates caused by the disease are remarkable. Therefore, developing health and treatment infrastructure to reduce morbidity and improve patient survival is inevitable.

Keywords: Childhood, Leukemia, Mortality, Relapse, Survival

Introduction

Childhood leukemia (CL) is a cancer that occurs mostly in children and adolescents (1). This cancer is diagnosed by the abnormal growth and proliferation of immature white blood cells in the bone marrow (2). The process of uncontrolled growth in the bone marrow disrupts the production of healthy blood cells, and the result is a weakening of the immune system and the appearance of various symptoms (3)as well as a profound impact on the quality of life of young patients and their families (4, 5). Nowadays, CL is a main concern worldwide, accounting for a significant amount of cancer incidence and deaths in children aged 0 to 14 years. According to reports, approximately 33% of all new cancer cases and 31% of cancer-related deaths have occurred in this age group (1, 6). The incidence of childhood cancers is not uniform in all parts of the world; in general, the incidence of these cancers is higher in developed countries (6, 7). Despite the increase in the incidence of the disease in these countries, the mortality rate is decreasing. However, in low-income countries, due to the lack of access or difficult access to diagnostic and treatment facilities, the mortality rates of these cancers in children are increasing (8,

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9). Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) are two main types of childhood leukemia, which account for 80% and 15% of CL cases, respectively (10). More than one-third of all leukemia cases occur in children under 15 years of age. (11). According to GLOBOCAN 2020 reports, 2.5% of new cases and 3.1% of cancer-related deaths in all age groups in 185 countries were related to leukemia (12). In leukemia, patients may experience complete remission, relapse, and death (13). Despite various treatment options, such as radiotherapy and chemotherapy, relapse of the disease remains common and can lead to an increased death rate (14, 15). Even though the results of various studies indicate improvements in the survival and mortality rates of leukemia in many countries (10, 11), especially developed countries (16, 17), the treatment of the disease and the improved survival of patients can be a main challenge of health care systems in low and middle-income countries. While Iran's upper-middle-income status enables advanced care in urban centers (e.g., Tehran), rural regions face diagnostic delays and fragmented follow-ups (9). Several studies have been conducted on the rate of survival, mortality, and relapse of Iranian children with leukemia, but they have yielded different results. One of the reasons for these differences is the conduction of studies in various regions of Iran with varying treatment facilities. Therefore, a comprehensive image of the survival, mortality, and relapse rate in leukemia in Iran is less visible. To feel part of the gap, the current study was done to estimate the five-year survival, mortality, and relapse rate of childhood leukemia in Iran.

Materials and methods

Search strategy

The present systematic review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Different international databases, including Google Scholar, Web of Science, PubMed, Scopus, and local databases such as SID, IranDoc, Magiran, and IranMedex, were used for searches. The keywords to try included ("Childhood Leukemia" OR "Pediatric Leukemia" OR "Leukemia, Child*" OR "Acute Lymphoblastic Leukemia" OR "ALL" OR "Acute Myeloid Leukemia" OR "AML"), ("Child*" OR "Pediatric" OR "Infant" OR "Adolescent" OR "Teenager"), ("Five-Year Survival" OR "5-Year Survival" OR "Survival Rate" OR "Survival Analysis" OR "Long-Term Survival"), ("Mortality" OR "Death Rate" OR "Fatality" OR "Cause of Death"), ("Relapse Rate" OR "Recurrence Rate" OR "Disease-Free Survival" OR "Treatment Failure"), and ("Iran" OR "Iranian" OR "Persian" OR "Iran, Islamic Republic of" [Mesh] OR "Iran" [Mesh]). Furthermore, to increase the sensitivity of the search, two independent reviewers checked the data. Childhood leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, survival, survival rate, mortality, relapse, children, Iran, and Iranian children were searched for through Boolean operators 'AND' and 'OR'.

Inclusion criteria

All cohort studies (retrospective and prospective) and cross-sectional studies in English and Persian languages were included. They were published from January 2000 to July 2024.

Exclusion criteria

The studies performed in other countries and those that did not report the survival, mortality, or relapse rates of childhood leukemia were excluded.

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Data extraction

The data extracted included the author's name, city, publication year, type of leukemia, age, sample size, survival rate, mortality rate, relapse rate, and risk of bias score.

Quality assessment

The assessment of the risk of bias was performed using the Newcastle-Ottawa Scale (18). This scale consists of three domains, which include the selection of study groups, comparability of groups, and description of exposure and outcome. The range of scores is 0 to 10. Using this scale, studies can be classified as high (7-10), medium (5-6), or low-quality (< 4) stars. The quality assessment was done by two reviewers independently; in cases of disagreement, a third review was involved.

Ethical considerations

The current study is a systematic review, and the ethical considerations are not applicable.

Statistical analysis

The statistical heterogeneity among the included studies was assessed using the I2 index, Tau2, and Q test. Due to high heterogeneity (I2 > 50%), the random-effect model was used for pooled estimation. The Beggs and Eggers test served to assess publication bias in this study. Sensitivity analysis was performed to assess the influence of individual studies on the pooled estimate. Analysis was also done by the Stata software Version 17 at a significance level of 5%.

Results

Description of the included studies

A total of 1451 manuscripts were retrieved through an electronic database search. Possibly relevant articles were identified after removing 943 articles due to duplication, 857 articles were excluded due to irrelevant titles and abstracts, and 64 articles were excluded due to a lack of required information. Finally, 22 relevant manuscripts that reported the mortality, survival, and relapse rate of childhood leukemia were included. The published studies were from different cities in Iran. Ten manuscripts were about the ALL, five were about the AML, and seven manuscripts studied both ALL and AML in Iranian children (Table I and Figure 1).

Five-year survival rate

The 5-year survival rate in the ALL cases was 66% (95% CI: 58%-74%, I2: 95.80, P < 0.001). The 5-year survival rate in the AML cases was 58% (95% CI: 48%-68%, I2: 83.13, P < 0.001). The overall survival rate in childhood leukemia was 63% (95% CI: 57%-70%, I2: 94.57, P < 0.001) (Figure 2 and Table II).

Five-year mortality rate

The 5-year mortality rate in the ALL cases was 24% (95% CI: 19%-29%, I2: 88.82, P < 0.001). The 5-year mortality rate in the AML cases was 30% (95% CI: 17%-44%, I2: 91.73, P < 0.001). The overall mortality rate in childhood leukemia was 26% (95% CI: 21%-31%, I2: 89.76, P < 0.001) (Figure 5 and Table II).

Five-year recurrent rate

The 5-year recurrent rate in the ALL cases was 19% (95% CI: 12%-26%, I2: 92.47, P < 0.001). The 5-year recurrent rate in the AML cases was 31% (95% CI: 24%-38%, I2: 54.81, P < 0.001). The overall recurrent rate in childhood leukemia was 24% (95% CI: 18%-30%, I2: 90.09, P < 0.001) (Figure 8 and Table II).

Publication bias

According to the results of Begg's test, there was a significant publication bias regarding the survival (P = 0.009) and mortality estimation (P = 0.01), but regarding the Eggers test, the publication bias was seen in relapse rate (P = 0.001) (Figures 3, 6, and 9).

Heterogeneity

According to the results of univariate Meta-regression, the sample size had no significant effect on the heterogeneity among the studies. The Galbraith plot showed some heterogeneity among them (Figures 4, 7, and 10).

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Sensitivity analysis

Sensitivity analysis discovered that no study changed the results of the meta-analysis. A trim-and-fill analysis was conducted to assess the effect of publication bias. To assess any potential publication bias, the trim and fill method was applied. The analysis suggested that some studies were potentially missing due to the existence of asymmetry in the funnel plot. After adjusting for these missing studies, the overall survival, as well as mortality and relapse, decreased slightly but remained statistically significant, indicating that the findings are likely robust despite possible publication bias.

Table I: The studies included in the current meta-analysis

First author	City	Year	Study type	Leukemia type	Age	Sample size	Risk of bias score
Karimi (28)	Shiraz	2002	Retrospective	ALL*	<15	76	6
Akramipour(43)	Ahvaz	2007	Retrospective	ALL	<15	40	5
Hashemi (44)	Yazd	2009	Observational Study	ALL	<15	56	6
Teshnizi(45)	Isfahan	2013	Retrospective	ALL	<15	197	7
Mousavinasab(46)	Mazandaran	2015	Historical Cohort	ALL-AML**	<15	97	6
Ansari (47)	Tehran	2009	Historical Cohort	AML	<15	83	7
Parvareh(48)	Kermanshah	2015	Cohort Study	ALL-AML	<15	218	8
Almasi-Hashiani(29)	Shiraz	2012	Retrospective	ALL-AML	<15	243	7
Moshfeghi(49)	Arak	2015	Cohort Study	ALL	<15	59	6
Teshnizi(50)	Bandar Abbas	2017	Retrospective Cohort	ALL	<15	164	8
Sadat Hosseini-Baharanchi(51)	Mashhad	2021	Retrospective Cohort	ALL	<15	424	8
Noroozi(52)	Urmia	2022	Retrospective Study	ALL	<15	176	7
Mehrbakhsh(53)	Golestan	2024	Retrospective Cohort Study	ALL-AML	<15	187	7
Ayatollahi(54)	Mashhad	2020	Retrospective Cohort Study	AML	<15	5	5
Mehrvar(55)	Tehran	2015	Retrospective Cohort Study	AML	<15	104	6
Bordbar(56)	Shiraz	2022	Retrospective Cohort Study	ALL-AML	<18	780	7
Heidary Sadegh (57)	Tehran	2023	Retrospective Cross-Sectional	AML	<15	45	5
Moradi (58)	Kurdistan	2018	Retrospective Study	ALL-AML	<15	109	6
Mehrbakhsh(59)	Golestan	2024	Retrospective Cohort	ALL	<16	161	6
Teshnizi(60)	Isfahan	2011	Retrospective Study	ALL	<15	197	6
Soheila Zareifar(61)	Shiraz	2012	Retrospective Study	ALL-AML	<15	243	7
Ghanavat(62)	Ahvaz	2024	Retrospective Study	AML	<15	98	6

* Acute Lymphoblastic Leukemia
** Acute Myeloid Leukemia

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Table II: Pooled estimation of 5-year survival, mortality, and relapse rate according to leukemia type

Survival	Pooled estimation	LCL	UCL	df	Q	P > Q	tau2	% I^2	H2	Beggs	Egger
ALL	0.66	0.58	0.74	16.00	381.04	0.00	0.03	95.80	23.81	0.009	0.33
Study year											
2015 and before	0.59	0.50	0.68	9	81.91	0.00	0.01	89.8	9.76		
After 2015	0.75	0.65	0.85	6	130.98	0.00	0.01	96.24	26.59		
Region											
South	0.67	0.51	0.84	5	155.74	0.00	0.04	97.6	43.04		
Center	0.58	0.46	0.70	2	8.47	0.00	0.009	79.9	4.98		
North	0.71	0.63	0.80	3	14.71	0.00	0.006	83.7	6.14		
West	0.63	0.45	0.81	3	80.89	0.00	0.03	95.3	21.30		
AML	0.58	0.48	0.68	8.00	47.43	0.00	0.02	83.13	5.93		
Study year											
2015 and before	0.58	0.44	0.72	4	41.58	0.00	0.02	87.66	8.10		
After 2015	0.57	0.48	0.67	3	4.83	0.18	0.04	37.17	1.59		
Region											
South	0.52	0.40	0.64	2	7.91	0.02	0.00	72.9	3.69		
North	0.60	0.43	0.77	3	28.95	0.00	0.02	88.3	8.60		
West	0.61	0.47	0.76	1	0.28	0.60	0.00	0.00	1.00		
Overall	0.63	0.57	0.70	25.00	460.76	0.00	0.03	94.57	18.43		
Mortality										0.01	0.07
ALL	0.24	0.19	0.29	13.00	116.26	0.00	0.01	88.82	8.94		
Study year											
2015 and before	0.26	0.19	0.33	7	48.9	0.00	0.009	85.1	6.72		
After 2015	0.21	0.13	0.29	5	48.3	0.00	0.009	91.3	11.57		
Region											
South	0.20	0.08	0.32	2	25.07	0.00	0.01	91.32	11.52		
Center	0.36	0.24	0.49	2	9.58	0.00	0.009	76.00	4.17		
North	0.24	0.16	0.32	3	20.10	0.00	0.005	84.16	6.31		
West	0.19	0.11	0.26	3	12.96	0.00	0.004	77.45	4.43		
AML	0.30	0.17	0.44	7.00	84.63	0.00	0.03	91.73	12.09		
Study year											
2015 and before	0.27	0.12	0.41	4	65.79	0.00	0.02	91.83	12.25		
After 2015	0.36	0.23	0.50	2	3.11	0.21	0.00	39.54	1.65		
Region											
South	0.23	0.16	0.30	1	0.00	1.00	0.00	0.00	1.00		
North	0.30	0.10	0.49	3	70.52	0.00	0.03	93.28	14.88		
West	0.40	0.26	0.55	1	0.57	0.45	0.00	0.00	1.00		

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Overall	0.26	0.21	0.31	21.00	205.00	0.00	0.01	89.76	9.76		
Relapse										0.11	0.001
ALL	0.19	0.12	0.26	6.00	79.72	0.00	0.01	92.47	13.29		
Study year											
2015 and before	0.31	0.24	0.38	2	4.54	0.10	0.002	58.24	2.39		
After 2015	0.11	0.09	0.13	3	3.63	0.30	0.00	0.01	1.00		
Region											
South	0.34	0.27	0.41	0	0.00	-	0.00	-	-		
North	0.10	0.08	0.12	2	0.09	0.95	0.00	0.06	1.00		
West	0.24	0.12	0.35	2	17.56	0.00	0.008	86.03	7.16		
AML	0.31	0.24	0.38	5.00	11.06	0.05	0.00	54.81	2.21		
Study year											
2015 and before	0.29	0.20	0.38	3	8.30	0.04	0.005	60.86	2.56		
After 2015	0.36	0.25	0.47	1	0.63	0.42	0.00	0.00	1		
Region											
South	0.31	0.20	0.42	0	0.00	0.00	0.00	-	-		
North	0.30	0.20	0.40	3	10.32	0.16	0.007	66.85	3.02		
West	0.34	0.17	0.52	0	0.00	0.00	0.00	-	-		
Overall	0.24	0.18	0.30	12.00	121.09	0.00	0.01	90.09	10.09		

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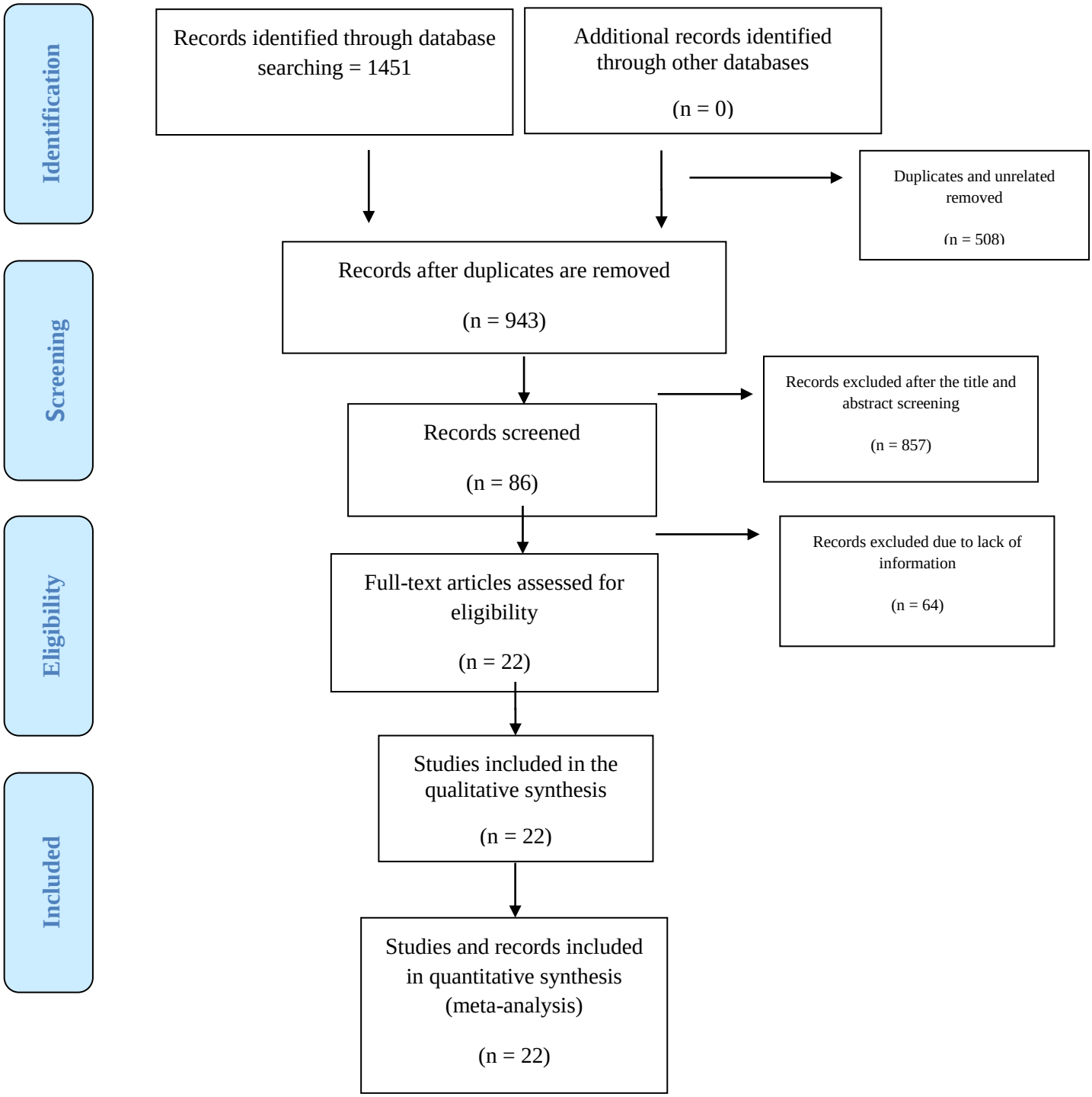

Figure 1. PRISMA Flow Diagram for the studies included in the current meta-analysis

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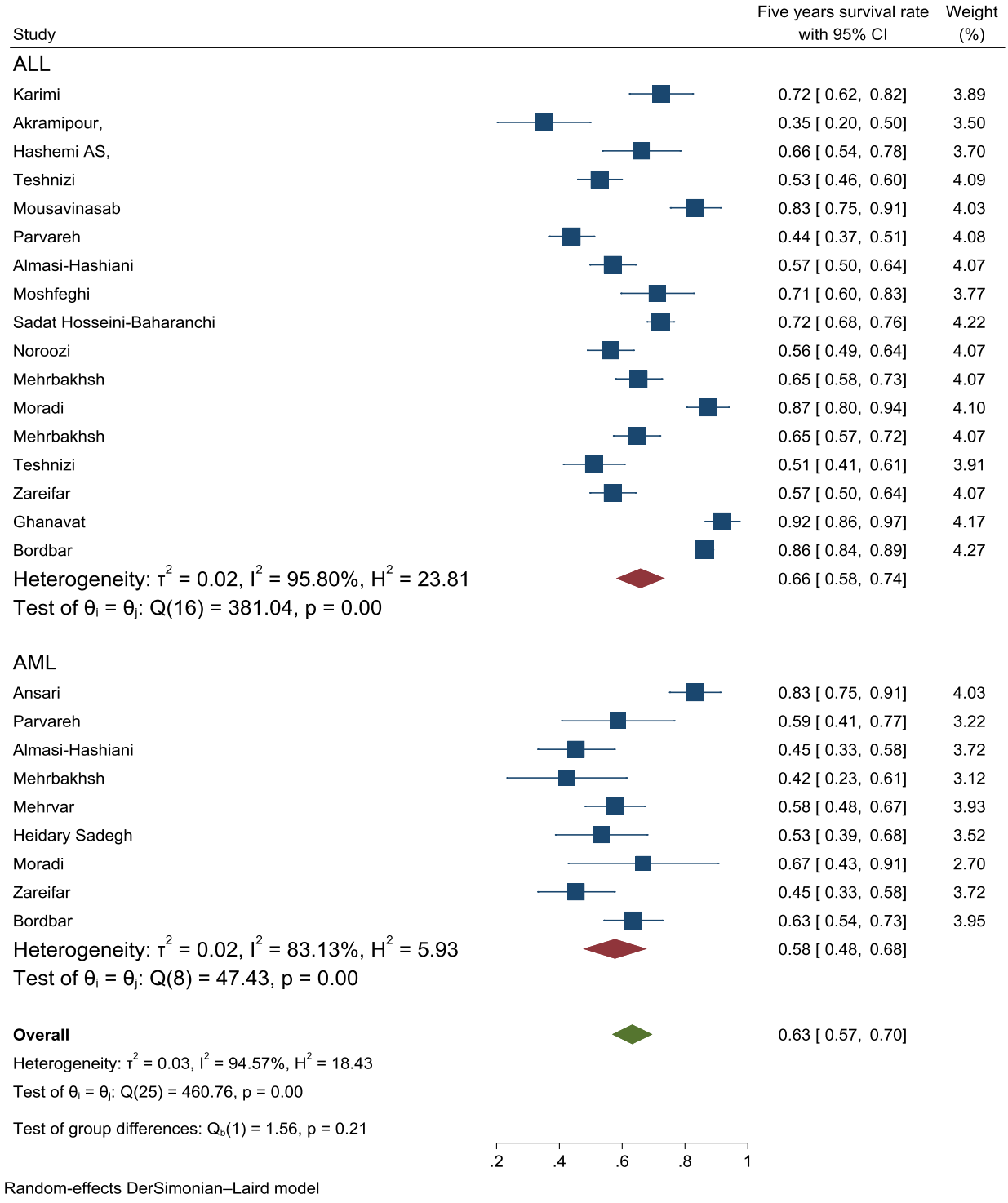

Figure 2. The pooled estimation of the 5-year survival rate according to leukemia type

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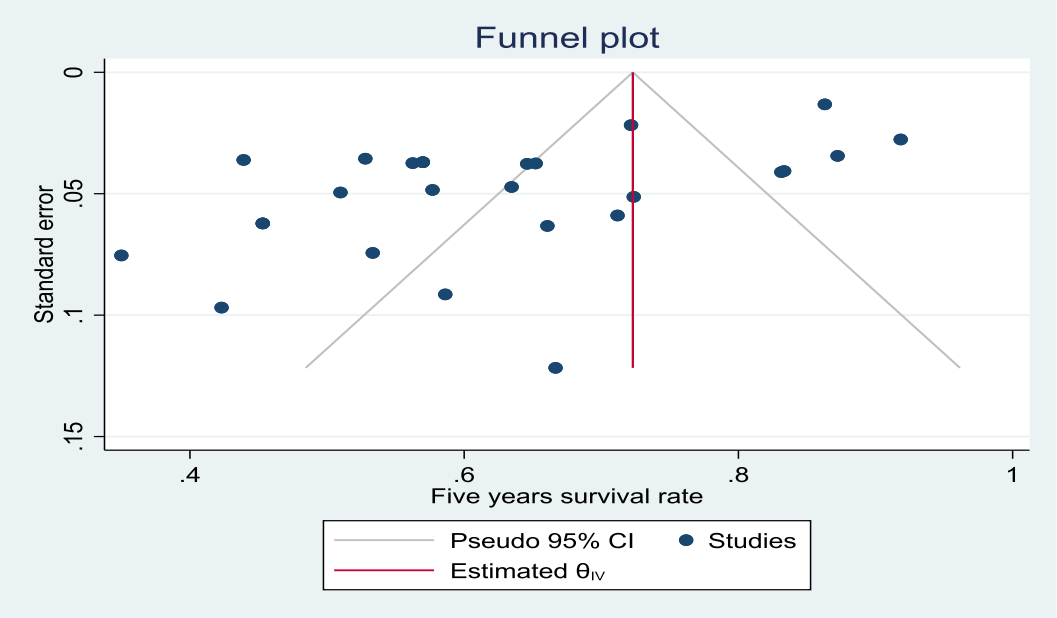

Figure 3. Funnel plot for the assessment of publication bias in the estimation of survival rate

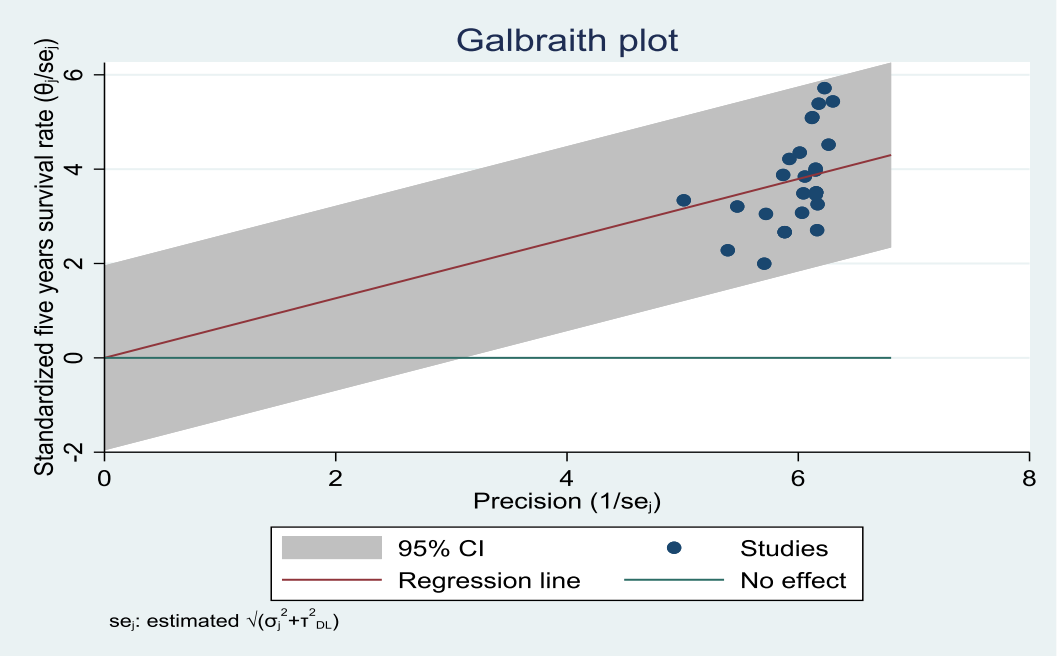

Figure 4. Galbraith plot in the assessment of heterogeneity in studies that estimate survival rate

[DOI: 10.18502/ijpho.v15i4.19635]

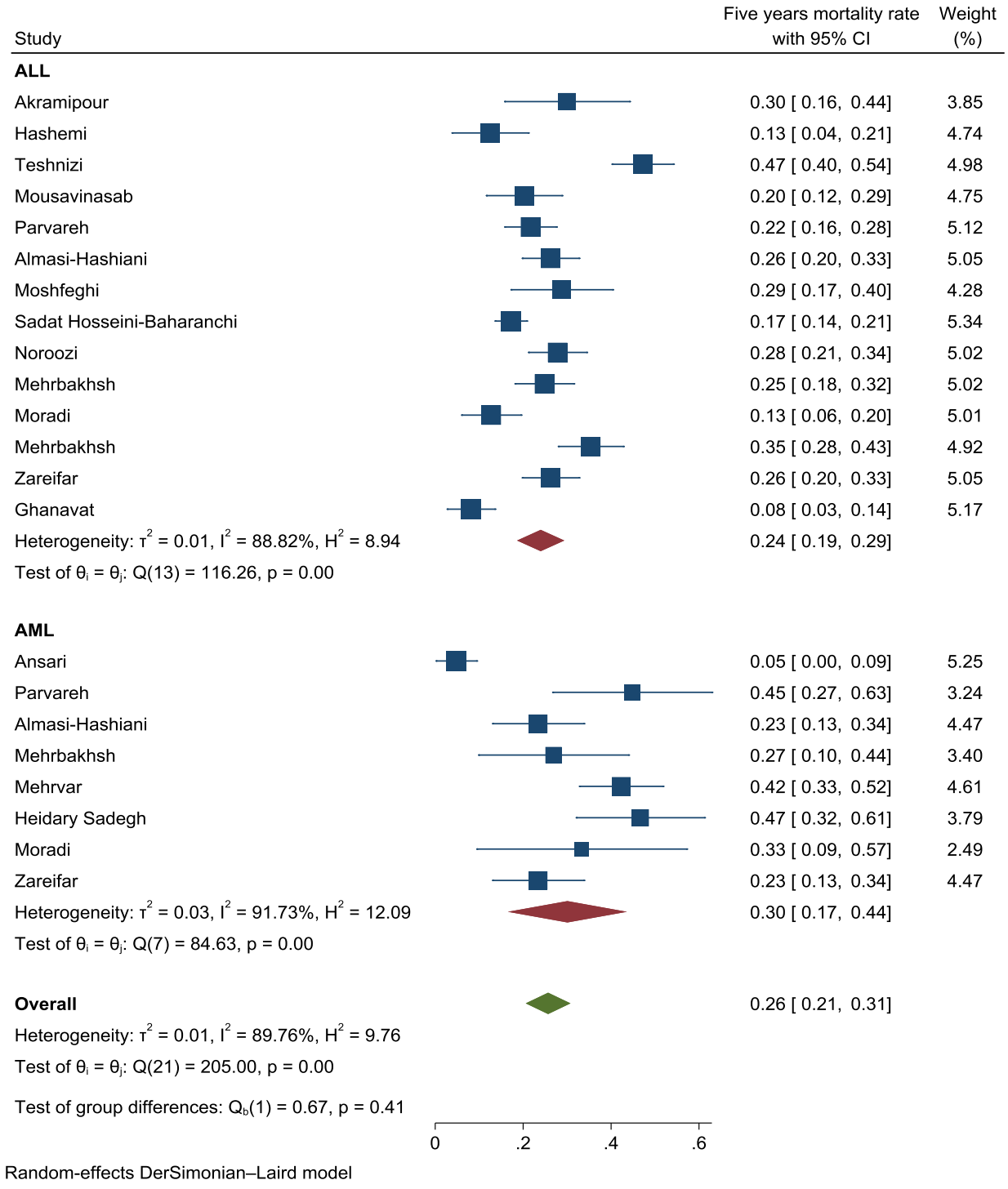

Figure 5. The pooled estimation of the 5-year mortality rate according to leukemia type

[DOI: 10.18502/ijpho.v15i4.19635]

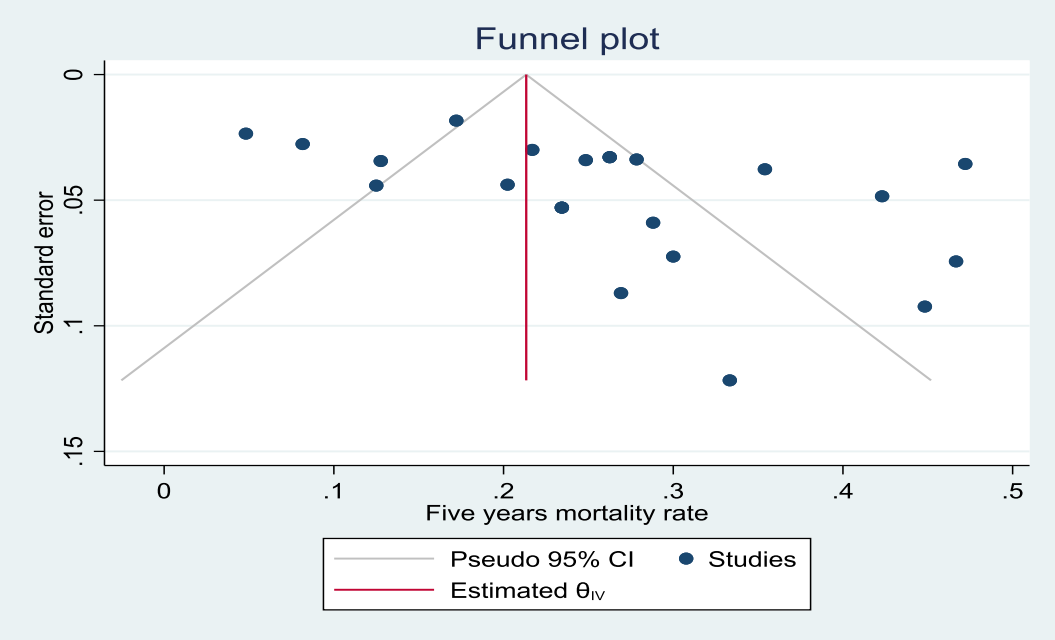

Figure 6. Funnel plot for assessment of publication bias in estimation of mortality rate

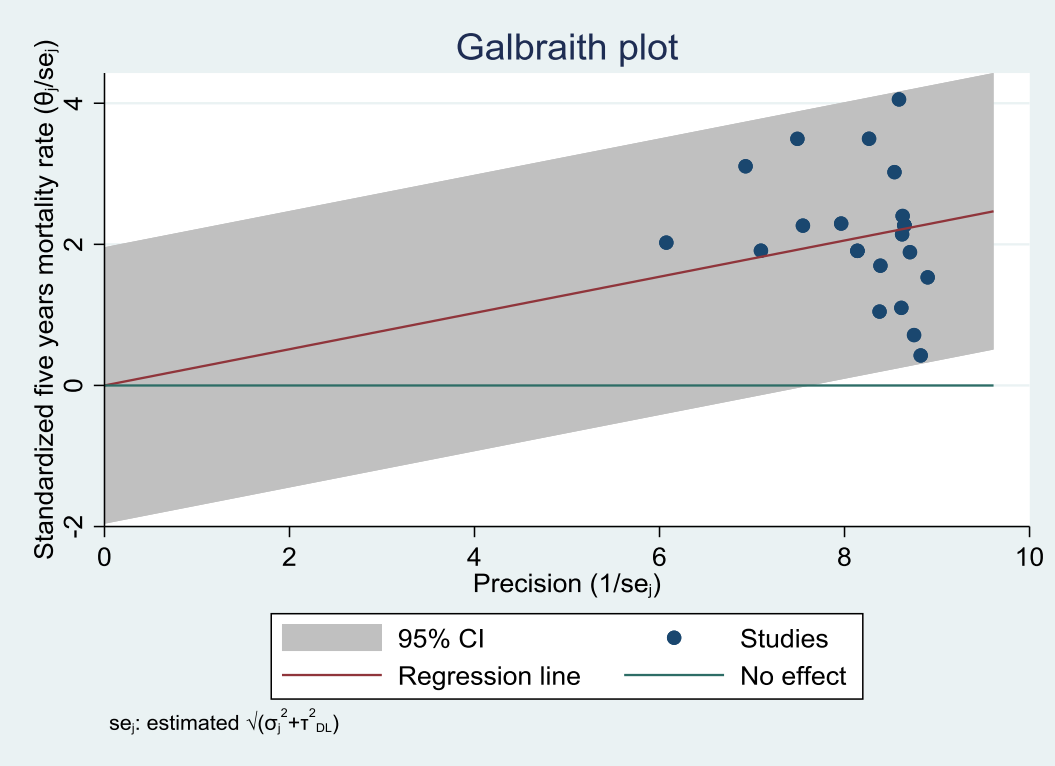

Figure 7. Galbraith plot in the assessment of heterogeneity in studies that estimate the mortality rate

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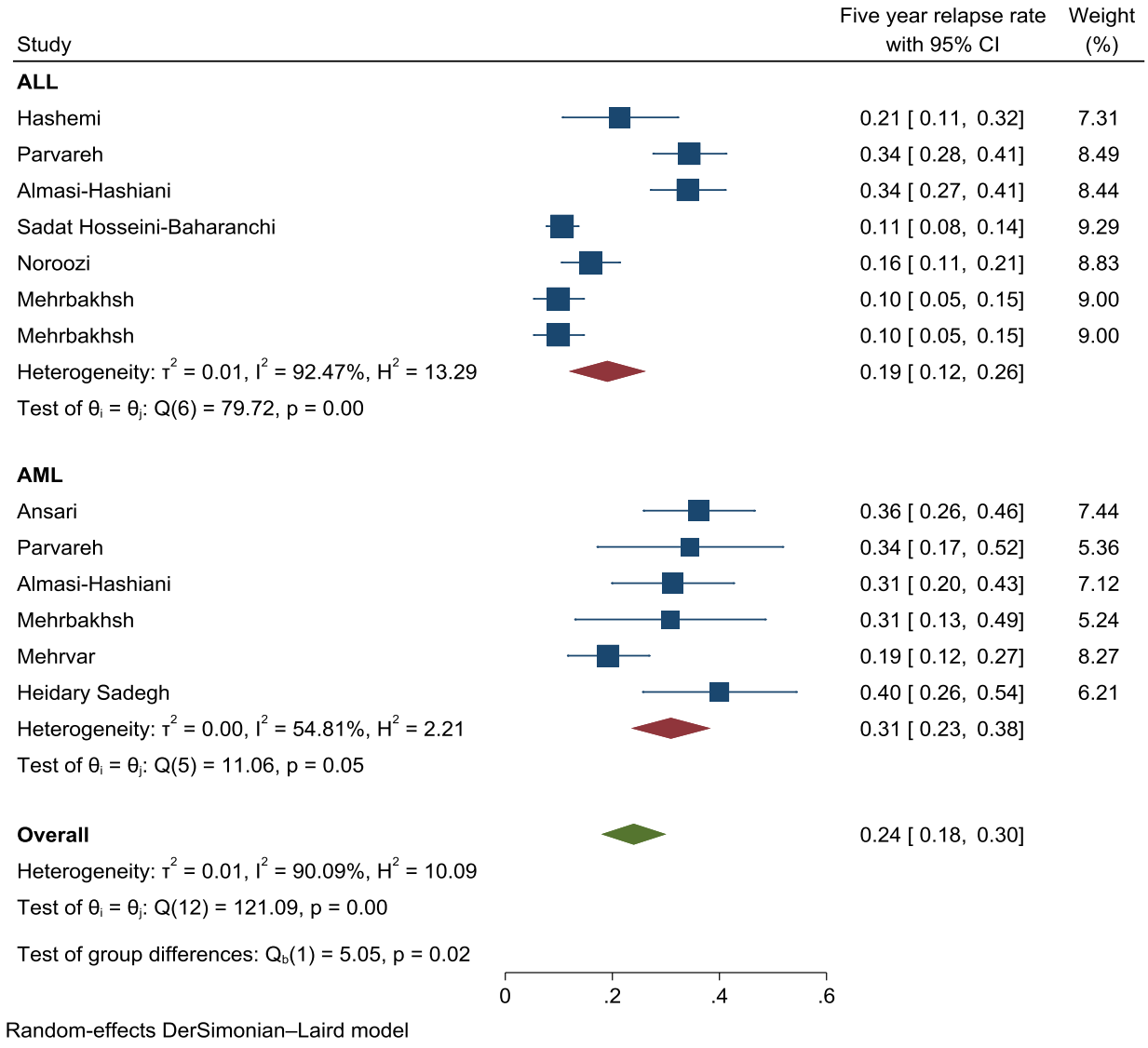

Figure 8. The pooled estimation of the 5-year relapse rate according to leukemia type

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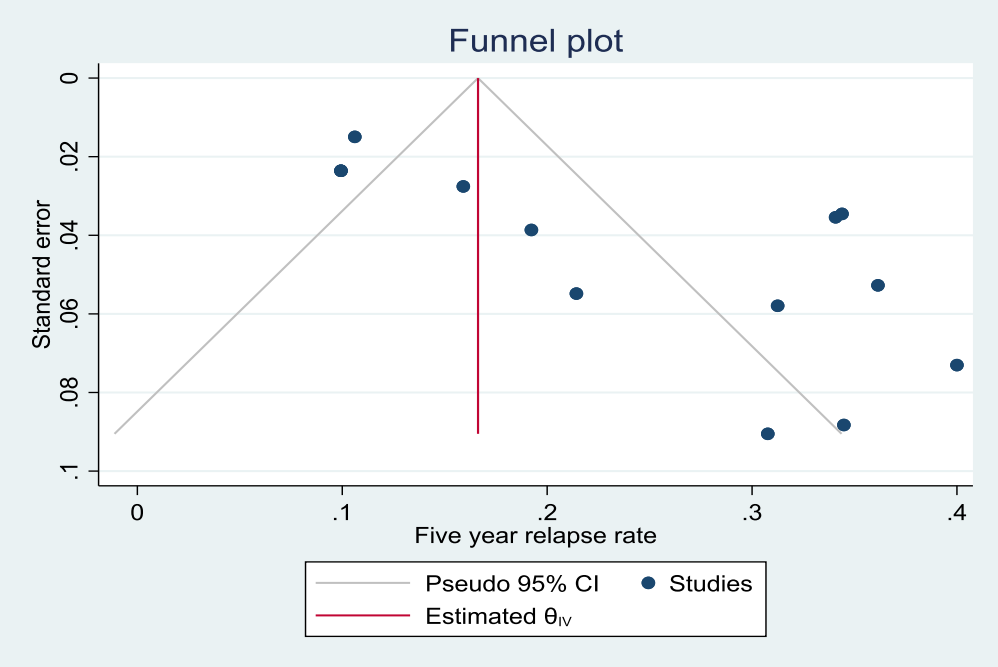

Figure 9. Funnel plot for the assessment of publication bias in the estimation of the relapse rate

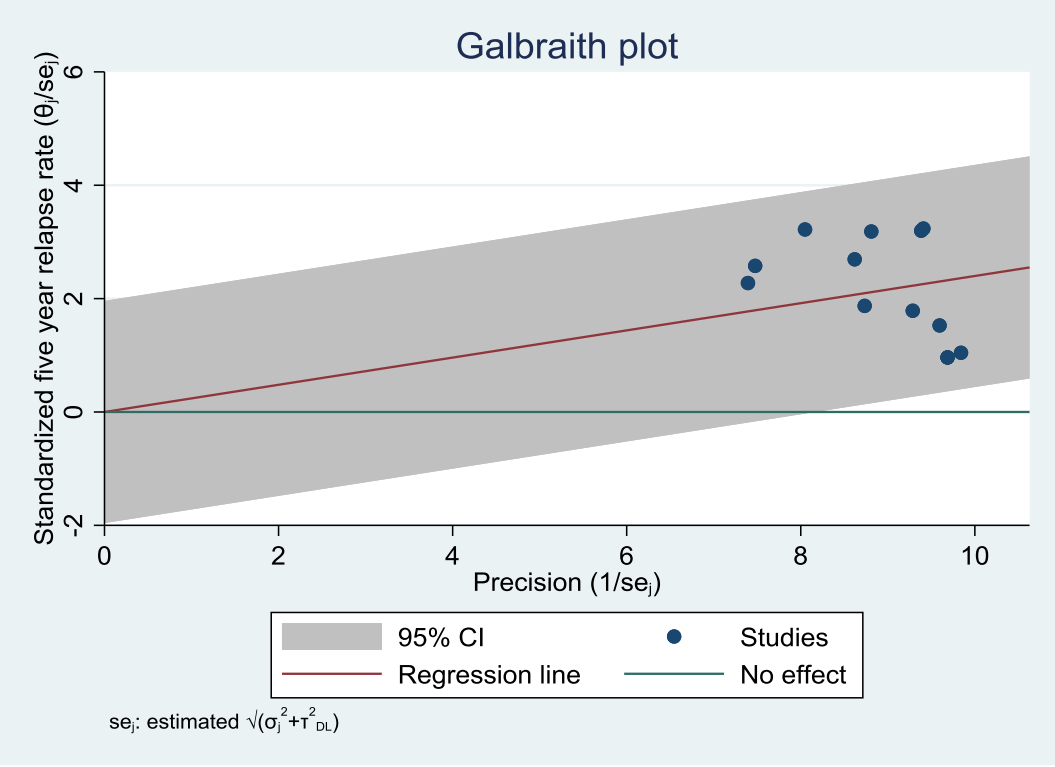

Figure 10. Galbraith plot in the assessment of heterogeneity in studies that estimate the relapse rate

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Discussion

Childhood leukemia represents a critical public health challenge in Iran, where outcomes reflect both advancements and persistent gaps within the nation's healthcare infrastructure. This is while high-income countries report survival rates exceeding 80% (19). Iran, as an upper-middle-income country, demonstrates progress tempered by regional inequities. Our study reveals a 63% overall 5-year survival rate for childhood leukemia, with notable disparities between ALL (66%) and AML (58%). These figures align with Iran's evolving cancer care landscape but fall significantly below the rates in developed economies (> 90%) (20-22), underscoring the need for targeted interventions. The survival rates observed here reflect significant improvement from historical benchmarks in Iran, attributable to expanded specialized care in centers like Tehran, Shiraz, and Mashhad, gradual adoption of risk-adapted treatment protocols, and government-subsidized chemotherapy under universal health coverage.

According to our results, the 5-year survival rate in the ALL and AML cases was 66% and 58%, respectively. Also, the overall survival rate in childhood leukemia was 63%. The 5-year mortality rate in the ALL and AML cases was 24% and 30%, respectively, and the overall mortality rate in childhood leukemia was 26%. The 5-year recurrent rate in the ALL and AML cases was 19% and 31%, respectively. The overall recurrent rate of childhood leukemia was 24%. The estimated survival rate in different studies in Iran was from 35 to 91%. These findings mean that the death rate due to leukemia is not the same in different parts of Iran; in some parts, it is higher than in other regions. Therefore, it is very important to develop the treatment infrastructure and create the necessary facilities for the treatment of these patients.

As shown in the current study, the 5-year survival rate in Iranian childhood leukemia was 63%. A review study in Iran reported that the 5-year survival rate in children with ALL and AML was 71% and 46%, respectively (23). Yet, the wide survival range (35-91%) across Iranian studies signals profound interprovincial disparities. Rural populations face delayed diagnosis due to limited pathology services, treatment abandonment driven by distance to centers and financial problems, and fragmented follow-up systems, which increases the relapse risk. In a comparative global context, Iran's outcomes surpass the rates in regional peers like 36.5% in Turkey (24), 81.8% in China (25), 51% in India (26), and 69.9% in Korea (27), where systemic investments have yielded dividends. Notably, Iran's AML survival (58%) remains as a concern compared to high-income nations (> 70%) (28, 29), highlighting gaps in hematopoietic stem cell transplantation (HSCT) access, intensive care support, and molecular diagnostics.

The higher AML mortality (30% vs. ALL: 24%) and relapse rates (AML: 31% vs. ALL: 19%) mirror global trends but are exacerbated by Iran-specific challenges. The 24% overall recurrence rate, tripling mortality risk (30), stems from suboptimal minimal residual disease (MRD) monitoring and limited salvage therapy outside major cities. Effective access to treatment facilities and the degree of development of countries can play an important role in reducing mortality and improving the survival rate of cancers. The improvement in the 5-year survival rate in children with leukemia can be due to the improvement of treatment regimens and the emergence of new drugs (31). The effect of treatment methods can be seen by comparing the current survival rate with the reported survival rate in distant years; the 50-year survival rate has increased from about 57% in the 80s to 96% in recent years (32-35). However, this

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survival rate is not the same in all countries. The mortality rate caused by ALL in children who live in low-income regions is higher than that in high-income countries, so the 5-year survival rate in these countries is not more than 75% (31, 36-38). Better treatment outcomes for children with AML in developed countries could be due to risk-adjusted intensive chemotherapy, HSCT, and better supportive care (39, 40). Various factors, such as late diagnosis of the disease, late provision of medical services, and malnutrition, are the main factors of low survival in low-income countries (41). According to the current study, the mortality rate of the AML patients was higher than that of the ALL cases, and the ALL patients showed better prognosis. This result is concordant with the findings of other studies (42). So, it can be concluded that the severity of the disease in the ALL cases was less than in AML. Similar to our results, other studies have shown that the relapse rate in patients with AML is higher compared to ALL, and the survival rate is correspondingly lower (30). Our study showed that the recurrence rate among the ALL and AML cases was 31% and 19%, respectively. The recurrence rate of ALL patients was reported to be 22.5% (30) and 20% with a 5-year survival rate of about 20-30% (31). The mortality of leukemia in people with a relapse was three times higher than in patients without relapses (30). Disease recurrence is one of the main factors determining the outcome of treatment in patients with leukemia (36). A higher recurrence of the disease means a lack of proper response to the treatment methods used. The main factors that determine the prognosis of patients with leukemia include the site of recurrence, the time of recurrence, and cytogenetic abnormalities (31). The current study has some limitations. There is a significant heterogeneity between studies, which can have affected the results. Different studies have used different sample sizes with different study designs. Therefore, the combination of these studies cannot be without problems. Significant heterogeneity across the reviewed studies reflects Iran's fragmented cancer data infrastructure, limiting direct comparability. Variations in diagnostic criteria (uneven immunophenotyping/MRD testing), treatment protocols in urban/provincial centers, and high loss-to-follow-up in remote areas underscore the need for national registries with standardized reporting. To bridge gaps, Iran should prioritize hub-and-spoke care networks to strengthen referrals, expand MRD/HSCT access for relapse prevention, eliminate out-of-pocket costs for vulnerable families, and implement nutritional support in high-poverty provinces. While Iran has elevated childhood leukemia survival above many LMICs through centralized expertise, our analysis reveals unfinished reforms. Reducing mortality requires confronting regional fragmentation, strengthening supportive care, embedding equity into cancer control policies, and offering a template for resource-constrained settings to balance scale with precision.

Conclusion

Despite the improvements in the survival, remission, and relapse rates of leukemia in Iranian children in recent years, the results of the present study showed that the 5-year survival rate of Iranian children with leukemia is not very high. Indeed, the death and recurrence rates among Iranian children suffering from the disease are remarkable. Therefore, developing health and treatment infrastructure to reduce morbidity and improve patient survival is essential.

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Data Availability
All the data generated or analyzed in the study are included in the manuscript. The corresponding author can be contacted for more information in this regard.

Ethical Considerations
The current study is a systematic review, and the ethical considerations are not applicable.

Acknowledgments
During the preparation of this work the author(s) did not use AI.

Author's Contribution
Mahsa Adibifar Conceptualization, Search strategy, Original draft preparation, Review and editing. Niloofar Amirniroomand Search strategy, Screening, Original draft preparation. Shervin Fatehi Search strategy, Screening. Saba Karami Search strategy, Screening, original draft preparation. Mahsasadat Sokout Formal analysis, Writing, Original draft preparation, Review and editing.

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Conflict of Interest
There are no potential competing interest regarding this publication.

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