

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

Mahsa Adibifar MD¹, Niloofar Amirniroomand MD¹, Shervin Fatehi MD¹, Saba Karami MD¹, Mahsasadat Sokout MD^{*1}

1. Department of Pediatrics, Aliasghar Children's Hospital, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

*Corresponding author: Dr. Mahsasadat Sokout, Department of Pediatrics, Aliasghar Children's Hospital, School of Medicine, Iran University of Medical Sciences, Tehran, Iran. Email: Mahsasokout@yahoo.com, ORCID ID: 0009-0000-1781-4332.

Received: 06 January 2025

Accepted: 28 July 2025

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, τ^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,

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 fill 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.

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).

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

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 | % I² | 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 | | |

| | | | | | | | | | | | |
|------------------------|------|------|------|-------|--------|------|-------|-------|-------|------|-------|
| Overall | 0.26 | 0.21 | 0.31 | 21.00 | 205.00 | 0.00 | 0.01 | 89.76 | 9.76 | 0.11 | 0.001 |
| Relapse | | | | | | | | | | | |
| 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 | | |

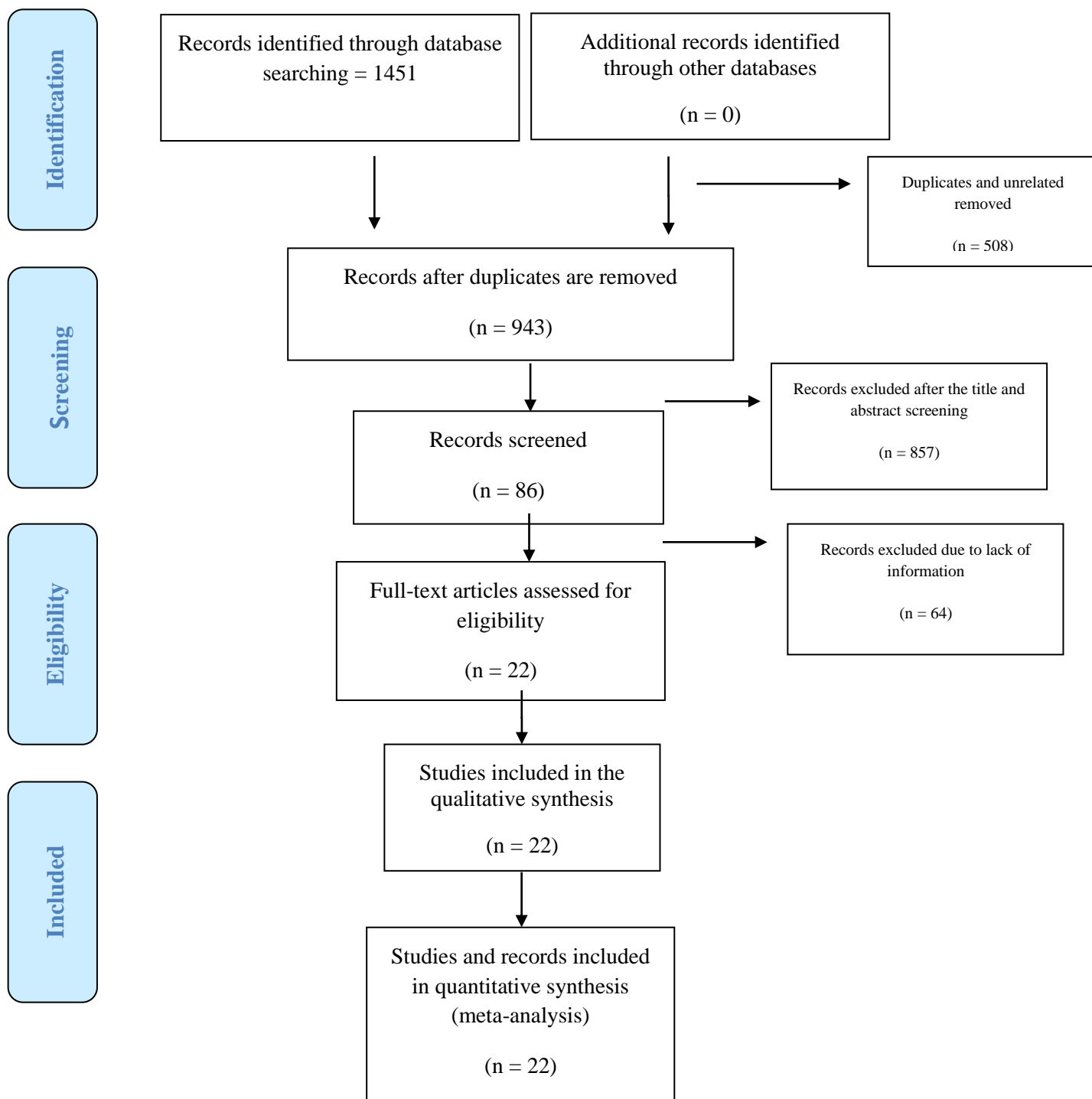


Figure 1. PRISMA Flow Diagram for the studies included in the current meta-analysis

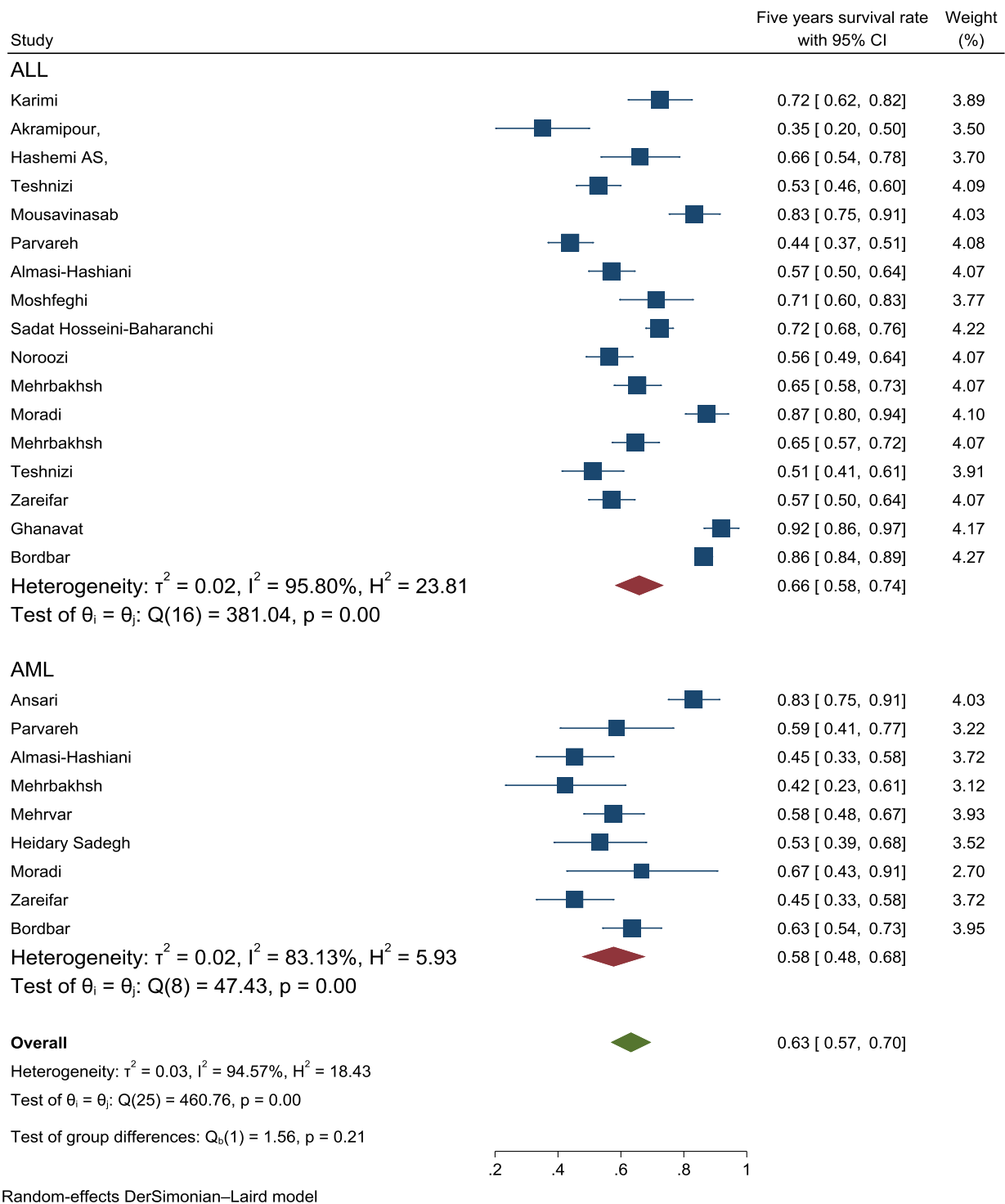


Figure 2. The pooled estimation of the 5-year survival rate according to leukemia type

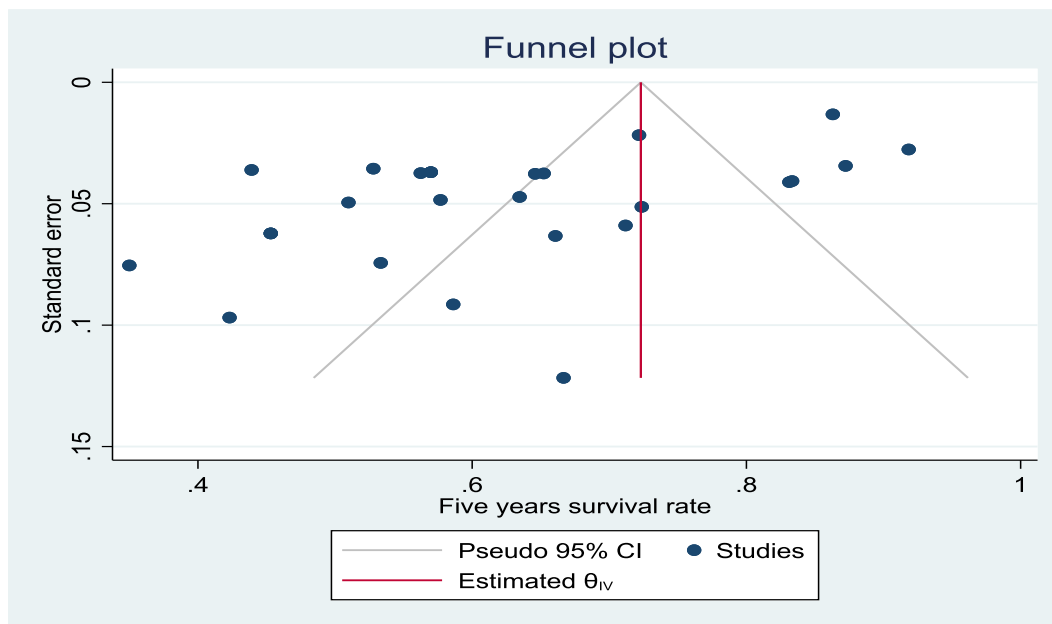


Figure 3. Funnel plot for the assessment of publication bias in the estimation of survival rate

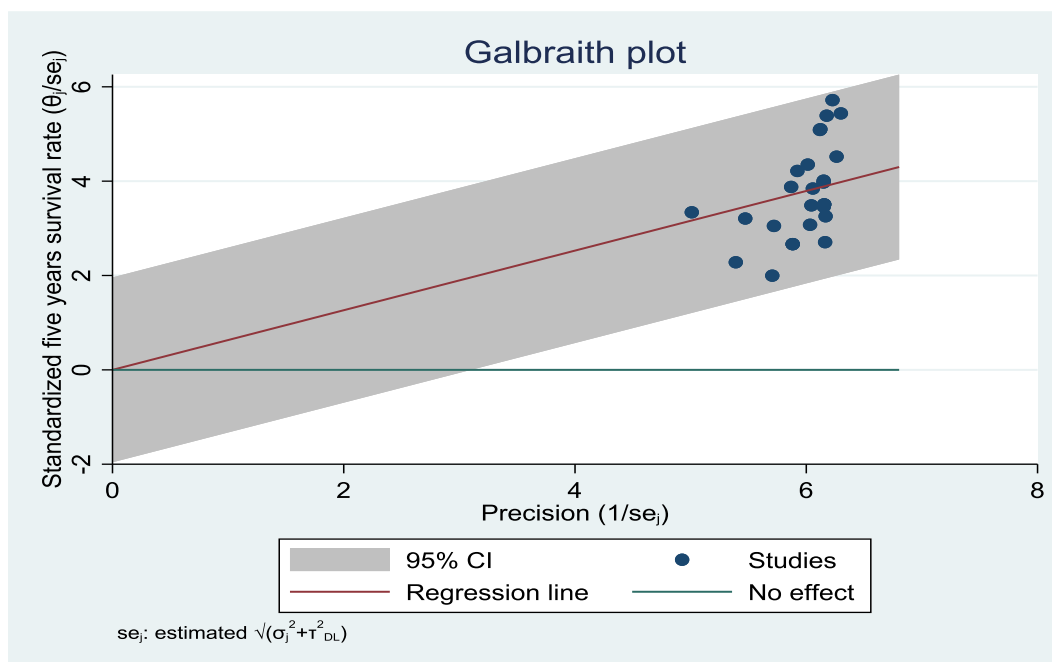


Figure 4. Galbraith plot in the assessment of heterogeneity in studies that estimate survival rate

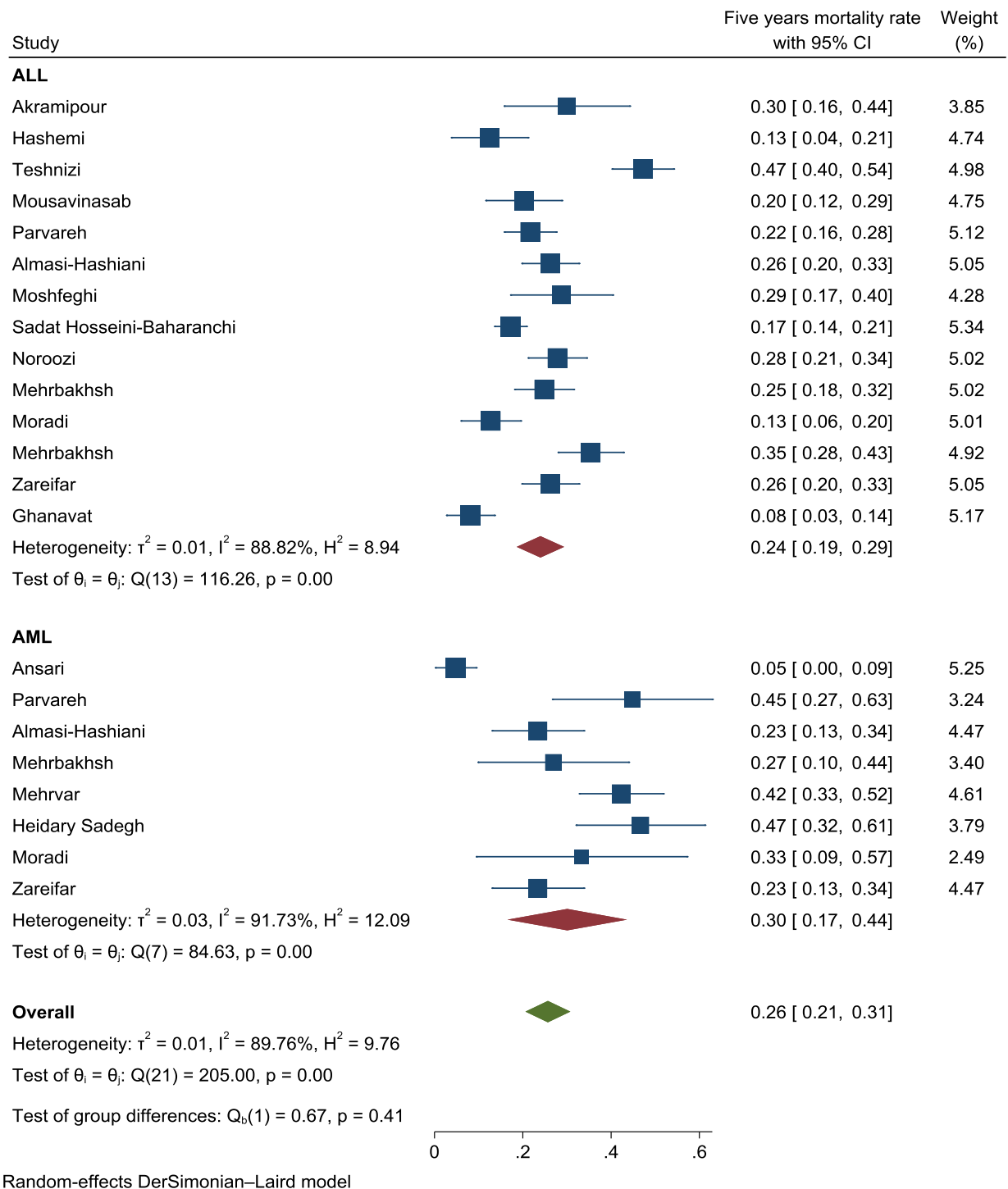


Figure 5. The pooled estimation of the 5-year mortality rate according to leukemia type

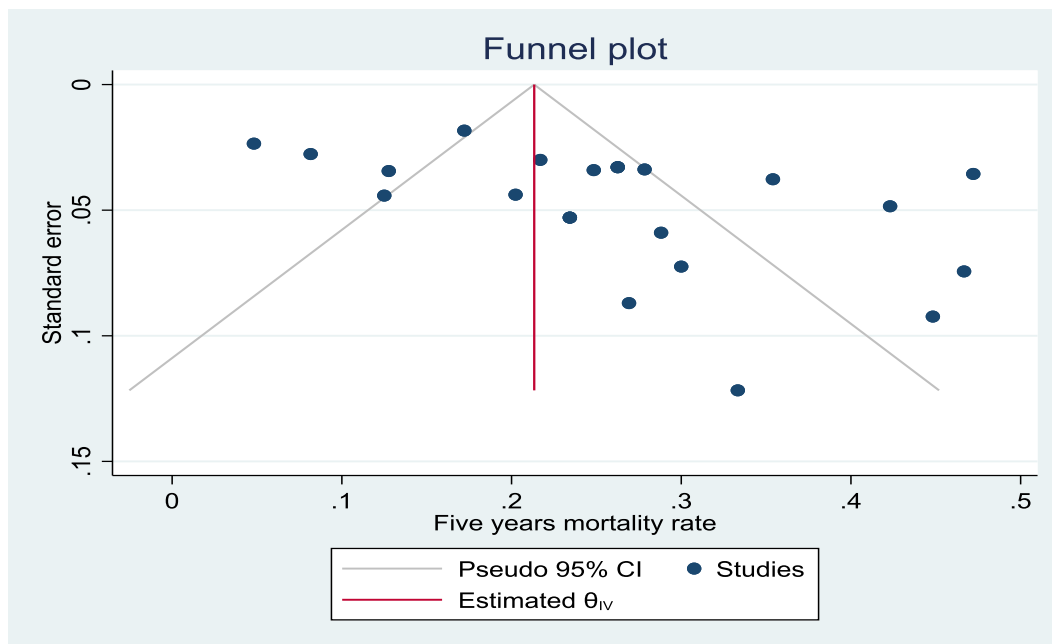


Figure 6. Funnel plot for assessment of publication bias in estimation of mortality rate

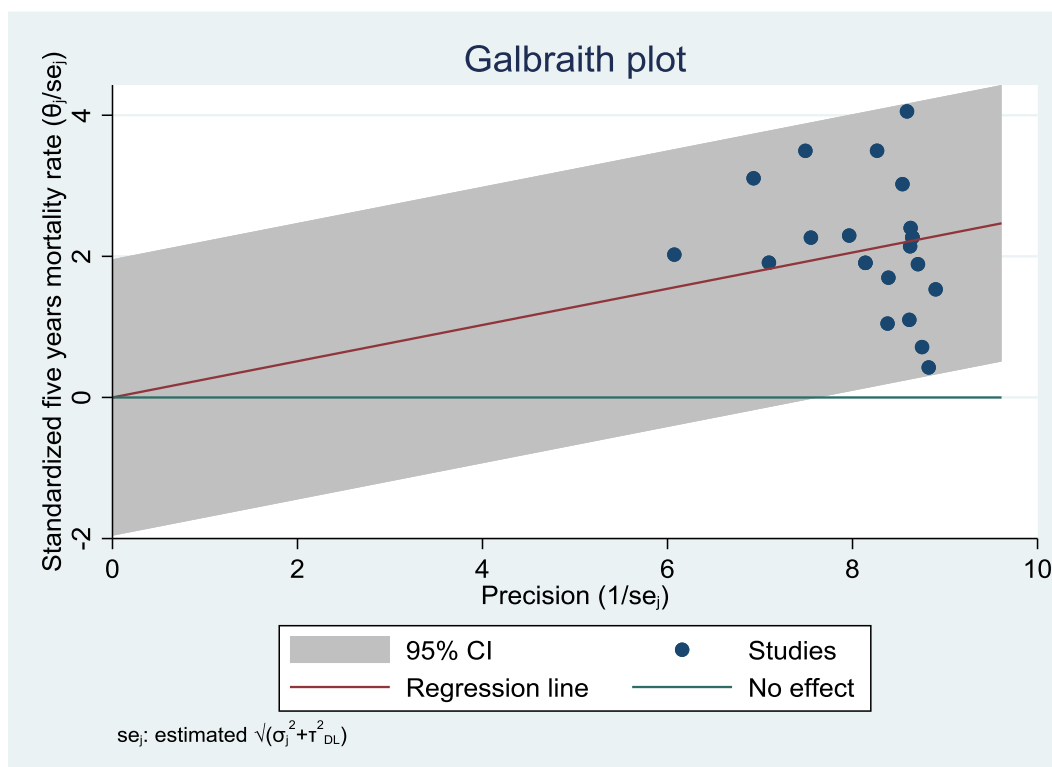


Figure 7. Galbraith plot in the assessment of heterogeneity in studies that estimate the mortality rate

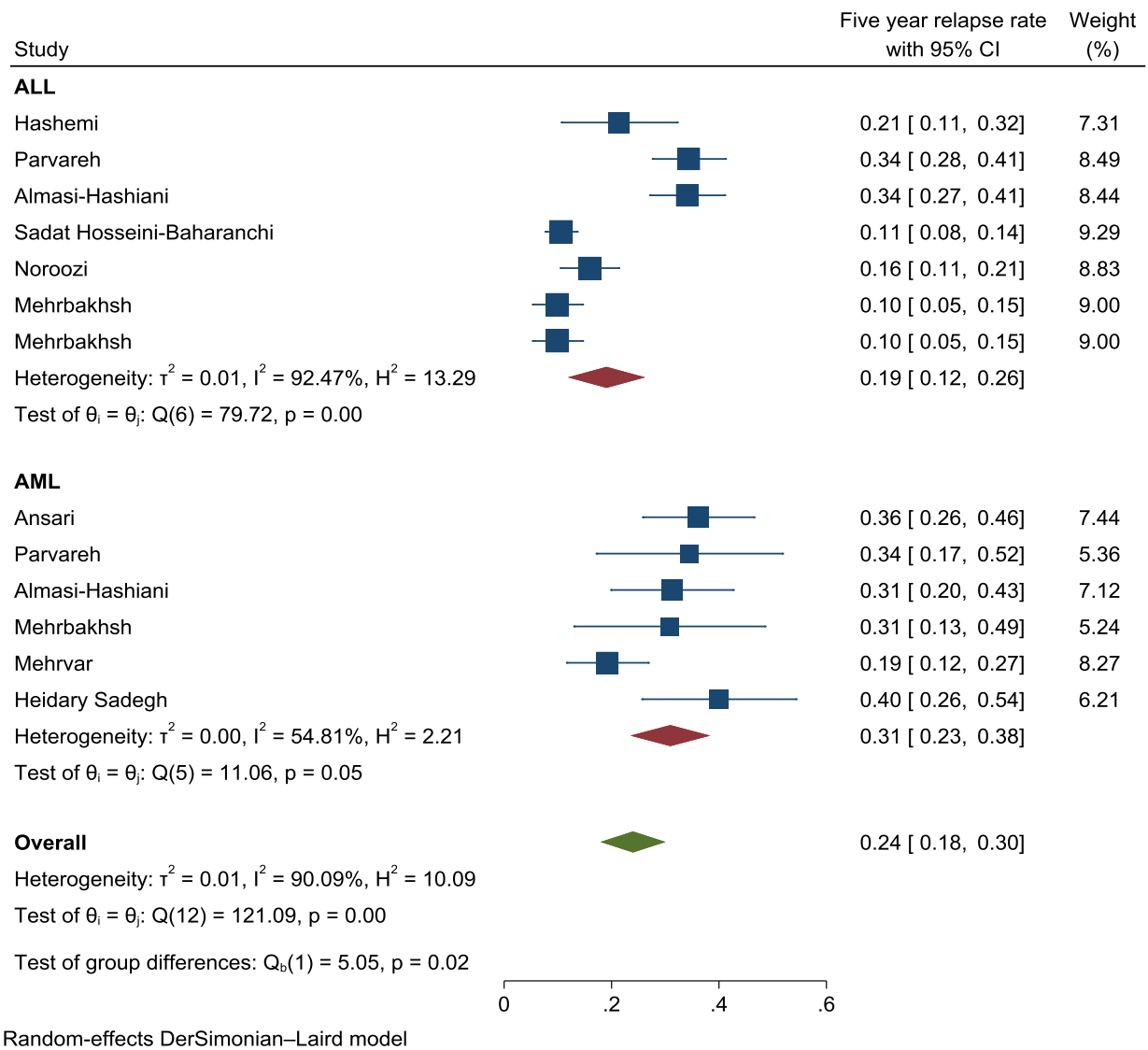


Figure 8. The pooled estimation of the 5-year relapse rate according to leukemia type

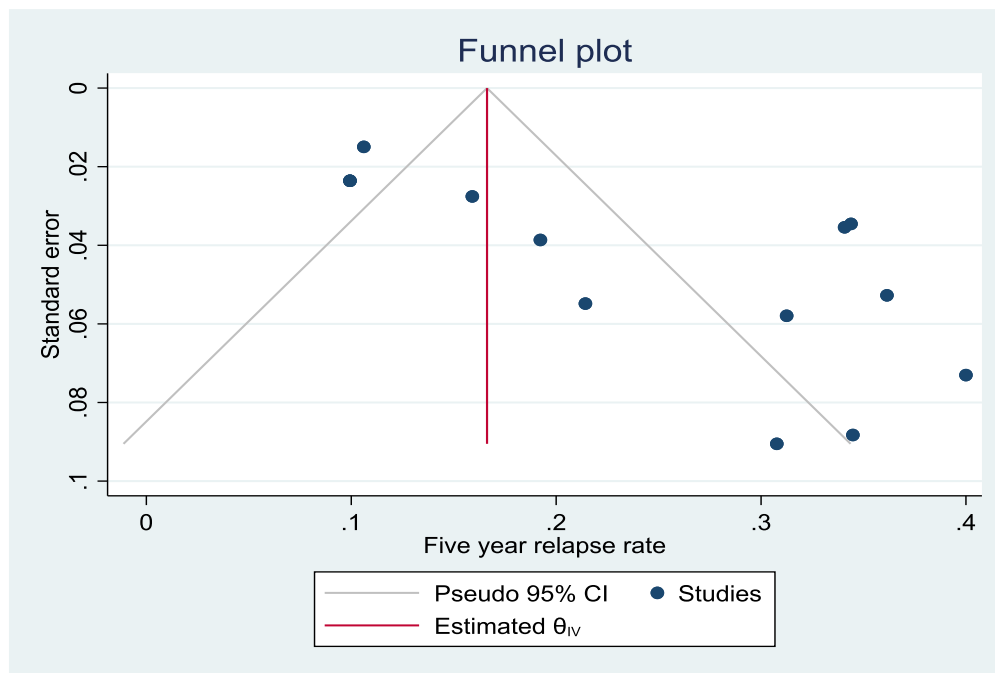


Figure 9. Funnel plot for the assessment of publication bias in the estimation of the relapse rate

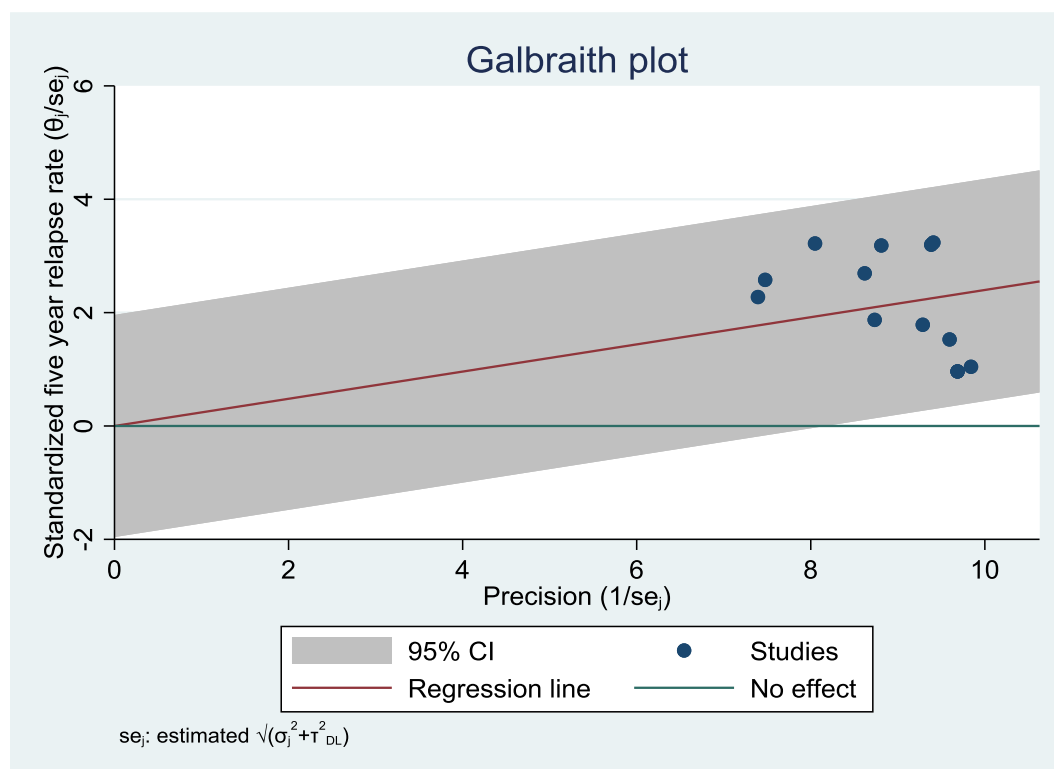


Figure 10. Galbraith plot in the assessment of heterogeneity in studies that estimate the relapse rate

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

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.

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.

Funding

This study did not obtain any specific financial support from public, commercial, or not-for-profit entities.

Conflict of Interest

There are no potential competing interest regarding this publication.

References

1. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin* 2014; 64(2):83-103.
2. Hunger SP, Teachey DT, Grupp S, Aplenc R. Childhood leukemia. *Abeloff's Clinical Oncology*; 2020: 1748-1764.
3. Wiemels J. Perspectives on the causes of childhood leukemia. *Chem.-Biol. Interact* 2012; 196(3):59-67.
4. Williams L, McCarthy M. Parent perceptions of managing child behavioural side-effects of cancer treatment: a qualitative study. *Child: Care Health Dev* 2015; 41(4):611-619.
5. Erdmann F, Kaatsch P, Schüz J. Family circumstances and survival from childhood acute lymphoblastic leukaemia in West Germany. *J. Cancer Epidemiol* 2015; 39(2):209-215.
6. Smith MA, Altekruse SF, Adamson PC, Reaman GH, Seibel NL. Declining childhood and adolescent cancer mortality. *Cancer* 2014; 120(16):2497-2506.
7. Namayandeh SM, Khazaei Z, Najafi ML, Goodarzi E, Moslem A. GLOBAL leukemia in children 0-14 statistics 2018, incidence and mortality and human development index (HDI): GLOBOCAN sources and methods. *APJCP* 2020; 21(5): 1487-1494.
8. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; 69(1):7-34.
9. Mohammadian-Hafshejani A, Farber IM, Kheiri S. Global incidence and mortality of childhood leukemia and its relationship with the Human Development Index. *PLoS One* 2024;19(7):1-14.
10. Torres-Roman JS, Valcarcel B, Guerra-Canchari P, Santos CAD, Barbosa IR, La Vecchia C, et al. Leukemia mortality in children from Latin America: trends and predictions to 2030. *BMC Pediatr* 2020; 20:1-9.
11. Li R, Ma J, Chan Y, Yang Q, Zhang C. Symptom clusters and influencing factors in children with acute leukemia during chemotherapy. *Cancer Nurs* 2020; 43(5):411-418.
12. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; 71(3):209-49.
13. Cho M, Schenker N, Taylor JM, Zhuang D. Survival analysis with

long-term survivors and partially observed covariates. *Can J Stat* 2001; 29(3):421-436.

14. Conneely SE, Stevens AM. Acute myeloid leukemia in children: emerging paradigms in genetics and new approaches to therapy. *Curr. Oncol. Rep* 2021; 23:1-13.

15. Zawitkowska J, Lejman M, Romiszewski M, Matysiak M, Ćwiklińska M, Balwierz W, et al. Results of two consecutive treatment protocols in Polish children with acute lymphoblastic leukemia. *Sci. Rep* 2020; 10(1):1-9.

16. Kraguljac AP, Croucher D, Christian M, Ibrahimova N, Kumar V, Jacob G, et al. Outcomes and predictors of mortality for patients with acute leukemia admitted to the intensive care unit. *Can Respir J* 2016; 2016(1):1-7.

17. Pulte D, Redaniel MT, Jansen L, Brenner H, Jeffreys M. Recent trends in survival of adult patients with acute leukemia: overall improvements, but persistent and partly increasing disparity in survival of patients from minority groups. *Haematologica* 2013; 98(2): 222-229.

18. Wells G. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute. 2000.

19. Organization WH. WHO global initiative for childhood cancer: an overview. Geneva: WHO. 2020:2-21.

20. Bonaventure A, Harewood R, Stiller CA, Gatta G, Clavel J, Stefan DC, et al. Worldwide comparison of survival from childhood leukaemia for 1995–2009, by subtype, age, and sex (CONCORD-2): a population-based study of individual data for 89 828 children from 198 registries in 53 countries. *The Lancet Haematology* 2017; 4(5):e202-e217.

21. Garniasih D, Susanah S, Sribudiani Y, Hilmanto D. The incidence and mortality of childhood acute lymphoblastic leukemia in Indonesia: A systematic review and meta-analysis. *PLoS One* 2022; 17(6):1-13.

22. Mostert S, Sitaresmi MN, Gundy CM, Sutaryo n, Veerman AJ. Influence of socioeconomic status on childhood acute lymphoblastic leukemia treatment in Indonesia. *Pediatrics* 2006; 118(6):e1600-e1606.

23. Veisani Y, Delpisheh A. Survival Rate and Associated Factors of Childhood Leukemia in Iran: A Systematic Review and Meta Analysis. *J. Pediatr. Rev* 2017; 5(2):9-18.

24. Pamuk ON, Pamuk GE, Soysal T, Ongoren S, Baslar Z, Ferhanoglu B, et al. Chronic lymphocytic leukemia in Turkey: experience of a single center in Istanbul. *SMJ* 2004; 97(3):240-246.

25. Wu T, Li Z-J, Wang Y-F, Zhao Y-Z, Qi J-Y, Qian L-S, et al. Prognostic factor analysis in 203 patients with chronic lymphocytic leukaemia. *Zhonghua Jie He He Hu Xi Za Zhi* 2009; 30(7):435-439.

26. Gogia A, Raina V, Gupta R, Gajendra S, Kumar L, Sharma A, et al. Prognostic and predictive significance of smudge cell percentage on routine blood smear in chronic lymphocytic leukemia. *Clin Lymphoma Myeloma Leuk* 2014; 14(6):514-517.

27. Oh C-M, Won Y-J, Jung K-W, Kong H-J, Cho H, Lee J-K, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2013. *CRT* 2016; 48(2):436-450.

28. Karimi M, Yarmohammadi H, Sabri MR. An analysis of prognostic factors and the five-year survival rate in childhood acute lymphoblastic leukemia. *Medical Science Monitor: Med Sci Monit* 2002; 8(12): CR792- CR796.

29. Almasi-Hashiani A, Zareifar S, Karimi M, Khedmati E, Mohammadbeigi A. Survival rate of childhood leukemia in Shiraz, Southern Iran. *Iran. J. Pediatr* 2013; 23(1):53-58.

30. Bordbar M, Jam N, Karimi M, Shahriari M, Zareifar S, Zekavat OR, et al. The survival of childhood leukemia: An 8-year single-center experience. *Cancer Rep (Hoboken)*. 2023; 6(4):1-7.

31. Irving JA, Enshaei A, Parker CA, Sutton R, Kuiper RP, Erhorn A, et al. Integration of genetic and clinical risk factors improves prognostication in relapsed childhood B-cell precursor acute lymphoblastic leukemia. *Blood. Am. J. Hematol* 2016; 128(7):911-922.
32. Malczewska M, Kośmider K, Bednarz K, Ostapińska K, Lejman M, Zawitkowska J. Recent advances in treatment options for childhood acute lymphoblastic leukemia. *Cancers*. 2022; 14(8):1-20.
33. Pui C-H. Precision medicine in acute lymphoblastic leukemia. *Front. Med* 2020; 14(6):689-700.
34. Yi M, Zhou L, Li A, Luo S, Wu K. Global burden and trend of acute lymphoblastic leukemia from 1990 to 2017. *Aging (Albany NY)* 2020; 12(22):22869-22891.
35. Pedrosa F, Coustan-Smith E, Zhou Y, Cheng C, Pedrosa A, Lins MM, et al. Reduced-dose intensity therapy for pediatric lymphoblastic leukemia: long-term results of the Recife RELLA05 pilot study. *Blood* 2020; 135(17):1458-1466.
36. Berry DA, Zhou S, Higley H, Mukundan L, Fu S, Reaman GH, et al. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: a meta-analysis. *JAMA Oncol* 2017;3(7):1-9.
37. Bonilha TA, Obadia DD, Valveson AC, Land MG. Outcome of childhood acute lymphoblastic leukemia treatment in a single center in Brazil: a survival analysis study. *Cancer Rep* 2022; 5(1):1-6.
38. Arora RS, Arora B. Acute leukemia in children: A review of the current Indian data. *South Asian journal of cancer* 2016; 5(03):155-160.
39. Taga T, Tomizawa D, Takahashi H, Adachi S. Acute myeloid leukemia in children: Current status and future directions. *Pediatr. Int* 2016; 58(2):71-80.
40. Klein K, de Haas V, Kaspers GJ. Clinical challenges in de novo pediatric acute myeloid leukemia. *Expert Rev. Anticancer Ther* 2018; 18(3):277-293.
41. Ghafoor T, Khalil S, Farah T, Ahmed S, Sharif I. Prognostic factors in childhood acute myeloid leukemia; experience from a developing country. *Cancer Rep* 2020; 3(5):1-9.
42. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *J Clin Oncol* 2012; 30(14):1663-1669.
43. Akramipour R, Pedram M, Zandian K, Hashemi A. A 5-year-study on children with acute myelocytic leukemia/AML, Ahvaz Shafa Hospital (1996-2001). *JKUMS* 2007; 11(2): 180-186.
44. Hashemi A, Eslami Z, Bahrami Ahmadi A, Kheirandish M, Rafieyan M. Evaluation of prognostic and predictive factors in pediatric acute lymphoblastic leukemia patients admitted to Shahid Sadoughi Hospital. *SSU Journals* 2009; 16(5):14-19.
45. Hosseini Teshnizi S, Tazhibi M, Tavasoli Farahi M. Comparison of Cox regression and Artificial Neural Network models in prediction of survival in acute leukemia patients. *KHOON* 2013; 10(2): 154-162.
46. Mousavinasab SN, Yazdani Cherati J, Karami H, Khaksar S. Risk Factors influencing the survival of pediatric acute leukemia using competing risk model. *JMUMS* 2015; 24(121):31-38.
47. Ansari S, Vosough P, Dehanzad M. Outcome of Treatment and survival analysis in pediatric aml non APL in Ali Asghar children's hospital (1988-2003). *RJMS* 2009; 16(63):12-17.
48. Parvareh M, Khanjani N, Frahmandinia Z, Nouri B. The Survival rate of childhood leukemia and its related factors in Kerman, Iran. *Iran. J. Health Sci* 2015; 3(4):24-32.
49. Moshfeghi K, Almasi-Hashiani A, Khosravi A, Mobarak-Abadi A. Survival rate of childhood leukemia and its

determinants: Cox proportional hazards model. *Sci. J. Kurdistan Univ. Med. Sci* 2015;62-69.

50. Teshnizi SH, Ayatollahi SMT. Comparison of cox regression and parametric models: application for assessment of survival of pediatric cases of acute leukemia in southern Iran. *Asian Pacific Journal of Cancer Prevention: APJCP*. 2017; 18(4): 981–985.

51. Hosseini-Baharanchi FS, Baghestani AR, Bashash D, Bonakchi H, Farhangi H. Relapse, mortality, and the associated factors in children with acute lymphoblastic leukemia; a competing risks analysis. *Int J Cancer Manag* 2021; 14(5):1-8.

52. Noroozi M, Khalkhali HR, Bahadori R, Omid T, Ghazizadeh F, Hejazi S, et al. The survival of childhood acute lymphoblastic leukemia and its related factors using competing risks model: A retrospective study from 2011 to 2019 in northwestern Iran. *MEJC* 2022; 13(3):531-42.

53. Mehrbakhsh Z, Tapak L, Behnampour N, Roshanaei G. Identification of Risk Factors for Relapse in Childhood Leukemia Using Penalized Semi-parametric Mixture Cure Competing Risks Model. *J Res Health Sci* 2024; 24(2):1-9.

54. Ayatollahi H, Bazi A, Sadeghian MH, Fani A, Siyadat P, Sheikhi M, et al. The survival of patients with t (15; 17) (q22; q12) positive acute promyelocytic leukemia: A study in north-east of Iran. *Iran. J. Pathol* 2020; 15(3): 175-181.

55. Mehrvar A, Rahiminejad MS, Asl AAH, Tashvighi M, Faranoush M, Alebouyeh M, et al. Features of childhood acute myeloid leukemia in Iran: a report from double center study. *Acta Med Iran* 2015; 53(12):749-752.

56. Bordbar M, Jam N, Karimi M, Shahriari M, Zareifar S, Zekavat OR, et al. The survival of childhood leukemia: An 8-year single-center experience. *Cancer Rep (Hoboken)* 2023; 6(4):1-7.

57. Heidary Sadegh M, Mozafari M, Vasei M, Movahedinia S, Hosseini M, Safavi M. Cytogenetics and Molecular Abnormalities in Pediatric Patients with Acute Myeloid Leukemia in a Referral Center in Tehran, Iran. *Middle East Journal of Cancer*. 2025; 16(1): 68-78.

58. Moradi G, Rasouli MA, Fathi F, Ghaderi B, Nikkhoo B, Roshani D, et al. Evaluation of the survival rate and its related factors in patients with leukemia in Kurdistan Province. *Sci. J. Kurdistan Univ. Med. Sci* 2018; 23(2):12-20.

59. Mehrbakhsh Z, Hassanzadeh R, Behnampour N, Tapak L, Zarrin Z, Khazaei S, et al. Machine learning-based evaluation of prognostic factors for mortality and relapse in patients with acute lymphoblastic leukemia: a comparative simulation study. *BMC Med Inform Decis Mak* 2024; 24(1):1-16.

60. Teshnizi SH, Zare S, Tazhibi M. The evaluation of Cox and Weibull proportional hazards models and their applications to identify factors influencing survival time in acute leukemia. *Hormozgan Univ Med Sci*. 2010; 15:269-278.

61. Zareifar S, Almasi-Hashiani A, Karimi M, Ghiasvand R. Five-year survival rate of pediatric leukemia and its determinants. *Koomesh*. 2012; 14(1): 13-19.

62. Ghanavat M, Mahmoudian-Sani M-R, Kabgani M, Alghasi A, Jaseb K. Mortality assessment of pediatric patients with acute lymphocytic leukemia in Southern Iran. *Immunopathol. Persa* 2024:1-5.