

Survival Rate and Associated Factors of Childhood Leukemia in Iran: A Systematic Review and Meta Analysis

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Abstract

Context: Recent reviews have shown that about 18% of all child cancers are leukemia. Track of the survival rate can help researchers improve quality of life of patients through improving screening or discovery of better treatments.

Objectives: This review aimed at estimating the 5-year survival rates and associated factors of childhood leukemia in Iran.

Data Sources: We carried out a systematic review through search of relevant studies published in English (PubMed, Scopus, Google scholar, and ISI) and Persian databases (Magiran, Medlib, SID, and Iran Medex).

Study Selection: The study included all epidemiologic studies that estimated survival rate in children with leukemia in Iran during years 2002 to 2015, and a standardized manner was used for extraction of information.

Data Extraction: The entire text or summary of all searched articles was extracted and then, related articles were selected, and irrelevant ones were excluded. Fixed and random effects models were calculated by the STATA using standard meta-analysis methods. Heterogeneity was assessed by I^2 statistics.

Results: The overall 5-year survival rate in patients with childhood leukemia in Iran was 0.65 (95% CI, 0.62 to 0.67, 10 studies), in the acute lymphoblastic leukemia (ALL) subtype was 71.0% (95% CI: 68.0 to 74.0), and in the acute myeloid leukemia (AML) subtype was 46.0%. Results of the meta analysis showed significant poor survival with relapse (heart rate (HR) 1.59, 95% confidence interval (CI) 1.27 to 1.98) and white blood count (WBC) counts $\geq 50,000$ (HR 2.92, 95% CI 1.23 to 4.60).

Conclusions: The results showed that 5-year survival rates in patients with AML were lower than patients with ALL. The results of this meta analysis strongly support the need for future research, action, and guidance for clinicians to improve health-related quality of life and outcomes for children with leukemia.

Keywords: Leukemia, Acute Myeloid Leukemia, Acute Lymphocytic Leukemia, Survival Rate, Meta-Analysis

1. Context

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children, followed by acute myeloid leukemia (AML), which involves only 20% to 25% of all newly diagnosed children with leukemia less than 15 years old (1). Leukemia remains the most frequent malignancy affecting children; about 18% of all child cancers. Chronic forms of leukemia are very rare in children (2). In childhood leukemia, factors such as parental exposure to ionizing radiation, maternal use of cigarettes, or contraceptives, parental age and education, genetic disorders, and early infections have been suggested as risk factors for leukemia, yet, these factors have not been definitively linked to leukemia and appear to explain only a small proportion of childhood leukemia (3, 4).

As a result of improvements in treatment and medical programs over the recent decades, the current 5-year survival rate is 89% for children with ALL under 15 years of age (5). In the USA, advances in therapeutic actions and sup-

portive care have improved the 5-year survival rate, with this rate being over 70% in the three recent decades (6). In the studies conducted in Iran, 5-survival rate in children with ALL and AML were estimated as 72.5% and 58.0%, respectively (7, 8). Many studies reported that more intensive treatment with or without stem cell transplantation increased the survival and cure rate in patients with ALL (9).

Several factors are known to predict survival of patients with leukemia, including age, smoking, bone marrow transplants, disease history, region, lodging, and resistance to treatment, as well as several laboratory factors (such as the number of white blood cells and red blood cells, mean corpuscular hemoglobin, sodium, potassium, and calcium) (10, 11). The role of some of these prognostic factors such as age and gender are controversial (12-14), may be due to a methodological issue. Keeping track of the survival rate can help researchers understand whether progress is being made, and could lead to better moni-

toring and improvement in the quality of life of patients through discovery of better treatments.

2. Objectives

This study aimed at conducting a systematic review and meta-analysis to objectively and quantitatively evaluate the existing literature using specified criteria to determine the 5-year survival rate and associated factors among childhood with ALL and AML in Iran.

3. Data Sources

We carried out a systematic review to identify epidemiological studies assessing the 5-year survival rates and associated factors in patients with leukemia in Iran. Relevant studies published in English (PubMed, Scopus, Google scholar, and ISI) and Persian databases (Magiran, Medlib, SID, and Iran Medex) were systematically searched.

4. Study Selection

The search strategy for English databases was performed by the MeSH heading leukemia and/or keyword combinations (acute lymphocytic leukemia, acute lymphoblastic leukemia, childhood leukemia, pediatric leukemia, ALL, AML, leukemia, survival, and Iran) in the title and affiliation; acute lymphoblastic leukemia [Title] OR childhood leukemia [Title] OR acute myeloid leukemia [Title] OR ALL [Title] OR AML [Title] OR pediatric leukemia [Title] AND Survival [Title] AND Iran [Affiliation]. For other international electronic databases (ISI, and Scopus) strategies were run separately regarding detailed practical instructions, including filters and refining processes, including: 1) The pediatric age group, that is, under 15 years, 2) Iran, and 3) 5-year survival rate through the medical subject headings.

This literature search was supplemented by reviewing relevant citations in the initial studies identified, and previous review articles examining similar outcomes; each title and abstract was checked for relevance. The full text was reviewed if the abstract indicated that the article reported survival rate of childhood leukemia. Furthermore, the identified articles were reviewed for relevant articles and cross-referring publications. We included all epidemiologic studies that estimated survival rate in children with leukemia in Iran from year 2002 to 2015. The inclusion criteria of the current study were, (1) age 15 years at diagnosis, (2) 5 years time of follow up, and (3) estimation of survival rate. In addition, articles were then restricted to children (aged 15 years) and duplicate articles (multiple publications of the same population) were excluded.

5. Data Extraction

The entire text or summary of all searched articles were extracted. After reviewing and studying the titles of documents, the repeated items were excluded, and then, the full texts of articles were carefully studied by researchers. The related articles were selected, and the irrelevant ones were excluded. The following key information were extracted: first author, year of publication, study design, characteristics of the subjects, number of subjects, follow up period, type of myeloid and assessed survival rate, statistical methods for estimation of survival, and associated factors for childhood leukemia. Initial disagreements on classifications of study characteristics were resolved by discussion within the team of authors. Meta-analyses were performed for survival rates for which results were available from at least 2 studies.

5.1. Quality Assessment

Quality of included studies was assessed with the STROBE statement tool for cross sectional studies. In this modified version, the quality tool contained 29 questions. The obtained scores were between 0 and 58 per article. Scores between 42 and 58 were recognized as strong-quality articles, 26 and 41 scores were moderate quality, and articles with less than 16 score were weak-quality articles.

5.2. Statistical Analysis

Heterogeneity was assessed by I^2 statistics. The fixed and random effects models were calculated by STATA using standard meta-analysis methods. The fixed effects model was used to estimate the variance of the summary odds ratio when heterogeneity was low ($I^2 \leq 25$), and the random effects model was used when study heterogeneity was moderate to high ($I^2 > 25$) (15). Indication of publication bias was assessed by Begg and Egger's test (16).

6. Results

Overall, 90 titles and abstracts were recognized in the initial search. After title screening, 55 abstracts were recognized as potentially relevant for inclusion in the meta analysis. A review of abstracts was performed to screen whether they met the inclusion criteria; 25 articles were reviewed in full text to identify the final enrolled articles. Of these 25 studies, 15 articles were excluded because of irrelevance, duplicated results, and follow up period less than 5 years since diagnosis. Finally, 10 studies included in final meta analysis (Figure 1). Details on the 10 studies, which were published from 2008 to June 2016, are shown in Table 1.

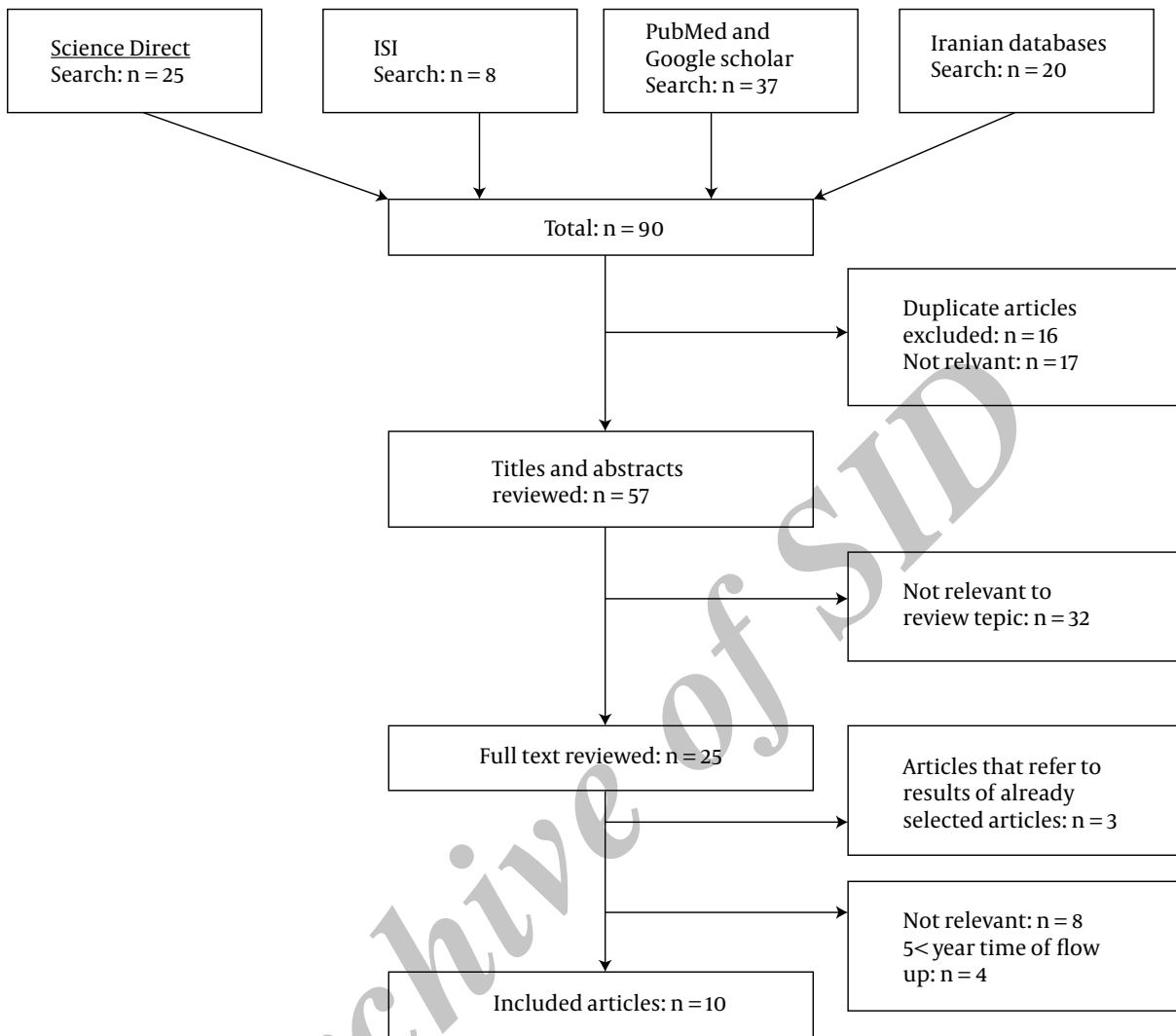


Figure 1. Flow Diagram of the Literature Search Process

A total of 1325 survivors (932 ALL and 393 AML) were included in this meta-analysis. Two of the 8 studies used a retrospective design and 8 articles had a cross sectional method. All 10 studies identified participants before completion of treatment at time of hospitalization. All of the included data sources were based on medical records data in hospitals. Age in all articles was below 15 years old.

Reviews of predictors of survival rate in childhood leukemia in Iran showed younger age, gender, white blood count (WBC) counts $\geq 50,000$, relapse and number of relapses, type of leukemia, induction chemotherapy, and bone marrow transplant were associated with survival. Among related factors, 2 parameters were associated with poor survival and HR was calculated in primary articles.

Results of the meta analysis showed: (1) Relapse (HR 1.59, 95% confidence interval [CI] 1.27 - 1.98) and results did not confirm heterogeneity among studies ($X^2 = 0.28$, $P = 0.599$, $I^2 = 00.0\%$); (2) WBC counts $\geq 50,000$ (HR 2.92, 95 % CI 1.23 - 4.60). Heterogeneity among these studies was not observed ($X^2 = 0.24$, $P = 0.889$, $I^2 = 00.0\%$).

The overall 5-year survival rate in patients with childhood leukemia in Iran was 0.65 (95% CI, 0.62 to 0.67). A significant heterogeneity among these studies was observed ($X^2 = 51.70$, $P \leq 0.001$, $I^2 = 91.0\%$, 95% CI 89.2 to 93.1). According to the statistical methods for estimation of 5-year survival rate, cumulative probability of 5-year survival rate and probability of 5-year survival rate was 0.62 (95% CI, 0.59 to 0.64) and 0.80 (95% CI, 0.74 to 0.85), respectively (Figure

Table 1. Characteristics of Studies Included in the Meta Analysis

No of Ref.	First Author, Years of Pub	Type of Myeloid		Age	Years of Flow Sitting	Survival Rate, %	Significant Factors (P < 0.01)
		ALL (N) ^{a,b}	AML (N) ^c				
	Hashiani, A. 2013	179	64	15 >	2004 - 2008; Shiraz	53.3	Age, Relapse, Number of relapses
(7)	Karimi, M. 2002	76		15 >	1995 - 2000; Shiraz	72.5	WBC counts, relapse in the CNS, and relapse in the bone marrow
(17)	Akramipour, R. 2007		40	15 >	1996 - 2000; Ahvaz	35	Induction chemotherapy
(11)	Hashemi AS, 2009		56	15 >	2001 - 2007; Yazd	87.5	WBC counts 50,000
(18)	Teshnizi, S. 2013	102	95	15 >	2006 - 2009; Isfahan	50.3	Gender (Female), WBC counts, Residence
(12)	Mousavinasab, N. 2015	84	13	15 >	2006 - 2014	79.7	Type of leukemia, Hemoglobin count and WBC count
(8)	Ansari, Sh, 2009		83	15 >	1988 - 2003; Tehran	58	Bone marrow transplant, chemotherapy
(19)	Parvareh, M. 2015	189	29	15 >	1998 - 2009 Kerman	51	WBC counts 50000, Relapse
(13)	Almasi-Hashiani, A. 2012	243		15 >	2004 - 2009; Shiraz	76.9	Relapses
(20)	Moshfeghi, K. 2015	59	13	15	2006 - 2011; Arak	70	Age, WBC counts

^a Acute lymphoblastic leukemia.

^b sample sizes.

^c Acute myeloid leukemia.

2).

When the meta-analysis was limited to studies enrolling only the ALL subtype, 5-year survival rate was 71.0% (95% CI: 68.0 - 74.0, 7 studies) and for the AML subtype this was 46.0% (95% CI: 39.0 - 52.0, 5 studies).

Subgroup analysis was performed to explore possible sources of heterogeneity among studies. Results of subgroup analysis showed a positive heterogeneity between quality of papers ($P \leq 0.001$). Figure 4 presents these results; 5-year survival rate in publications with high quality was lower than articles with medium quality, and higher than those with a low quality.

Results of meta-regression are shown in Figure 5; according to the results, follow up duration and year of publication had no association with heterogeneity of results. Thus, year of publication and number of subjects was not related to variability in the results of 5-year survival rate (regression coefficient = 0.287, $P = 0.63$) and (regression coefficient = 0.291, $P = 0.115$), respectively.

We finally created different funnel plots, using different exposure assessment methods, to explore the possibility of publication bias, yet, results were not evident of publication bias (bias: 4.25, 95% CI = -10.13 - 19.07; $P = 0.710$), so we tried to consider the most published articles on this subject (Figure 6).

7. Discussion

The current study was a systematic review and meta analysis to evaluate the existing literature to determine the prognostic factors and 5-year survival rates of children with ALL and AML leukemia in Iran. The results showed that survival rate for children with ALL was somewhat more and was 68.0% (95% CI: 65.0 to 71.0), in return, in the patients with AML this was 44.0% (95% CI: 38.0 to 49.0). The comparison of this finding with other countries showed the 5-year survival rates in USA for ALL and AML was 85% and 65%, respectively (6). The studies were found to be heterogeneous ($X^2 = 55.12$, $P \leq 0.001$, $I^2 = 93.2\%$, 95% CI 91.4 - 95.3). A Meta regression was used to explore important sources of heterogeneity in survival rate in primary articles; according to the results, year of study, quality of articles, and number of patients had no association with heterogeneity of results. Therefore, we did not find important sources of heterogeneity, yet, length of follow-up, source of primary data, and diagnosis stage of malignancy could be important predictors of heterogeneity.

We systematically assessed important prognostic factors of childhood leukemia in Iran. Two factors, relapse and initial white blood cell count, are thought to be the most important predictors in Iranian children. Previous studies have reported that younger patients respond better to treatment, some abnormalities in genetic characteristics are bad predictors (21), diagnosis at final stages have a bad outlook (22), high white blood cell counts are re-

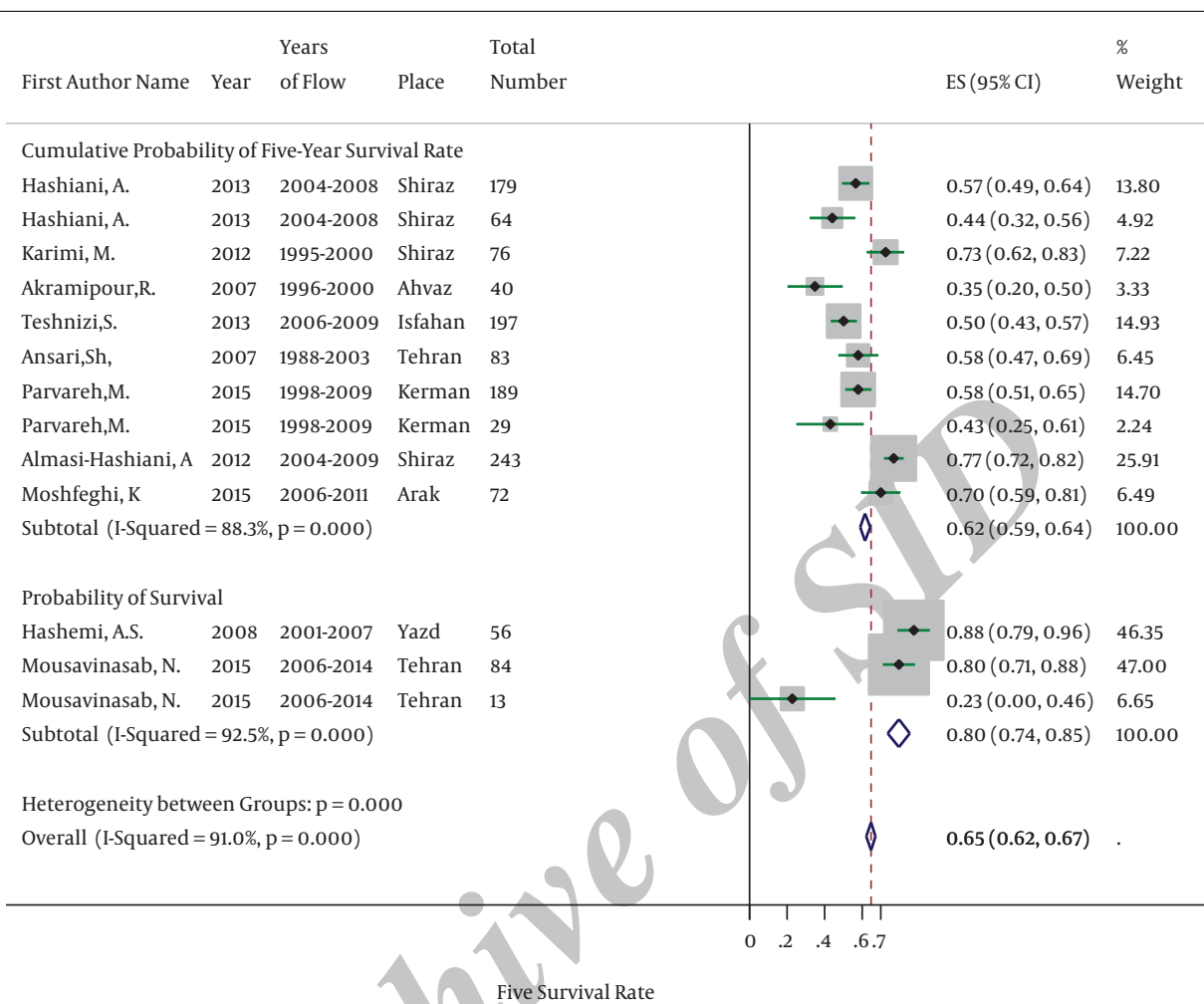


Figure 2. Forest Plot of the Five-Year Survival Rate of Childhood Leukemia by Statistical Methods in Iran

lated to better survival (23), process of chronic form into an acute form can effect the outcome, secondary leukemia occurs when damaged bone marrow cells form as a result of chemotherapy, and longer time of remission corresponds with greater difficulty in treatment (24).

Our systematic review had a number of limitations. First, stage of follow up in primary studies was unclear, however, it represents a relative lack of studies to compare survival rate in subtypes and subgroups, indicating the need for further research. Second, despite the lack of indication of major publication bias, it is impossible to be ruled out completely, especially in the light of low number of studies. Third, we could not specify the source of heterogeneity due to limitation in studies, because the majority of the characteristics could not be acquired from the studies. Another limitation of this study was the sources of primary data that were all recruited from hospital records

due to lack of a cancer registry center nationwide. Hospital records in our country is very limited because data is not gathered for investigation purposes, and records usually involve missing data and typing mistakes. In addition to this, patients from one distinct hospital cannot represent all patients in the population.

8. Conclusions

In summary, in this meta analysis, reliable results were obtained about 5-year survival rates in childhood leukemia patients. According to our results, 5-year survival rate in AML patients was lower than ALL patients. Important prognostic factors in this systematic review, relapse, and WBC counts lower than 50000, have shown a relationship with poor prognosis. To sum up, the results of this meta analysis strongly support the need for future research and guid-

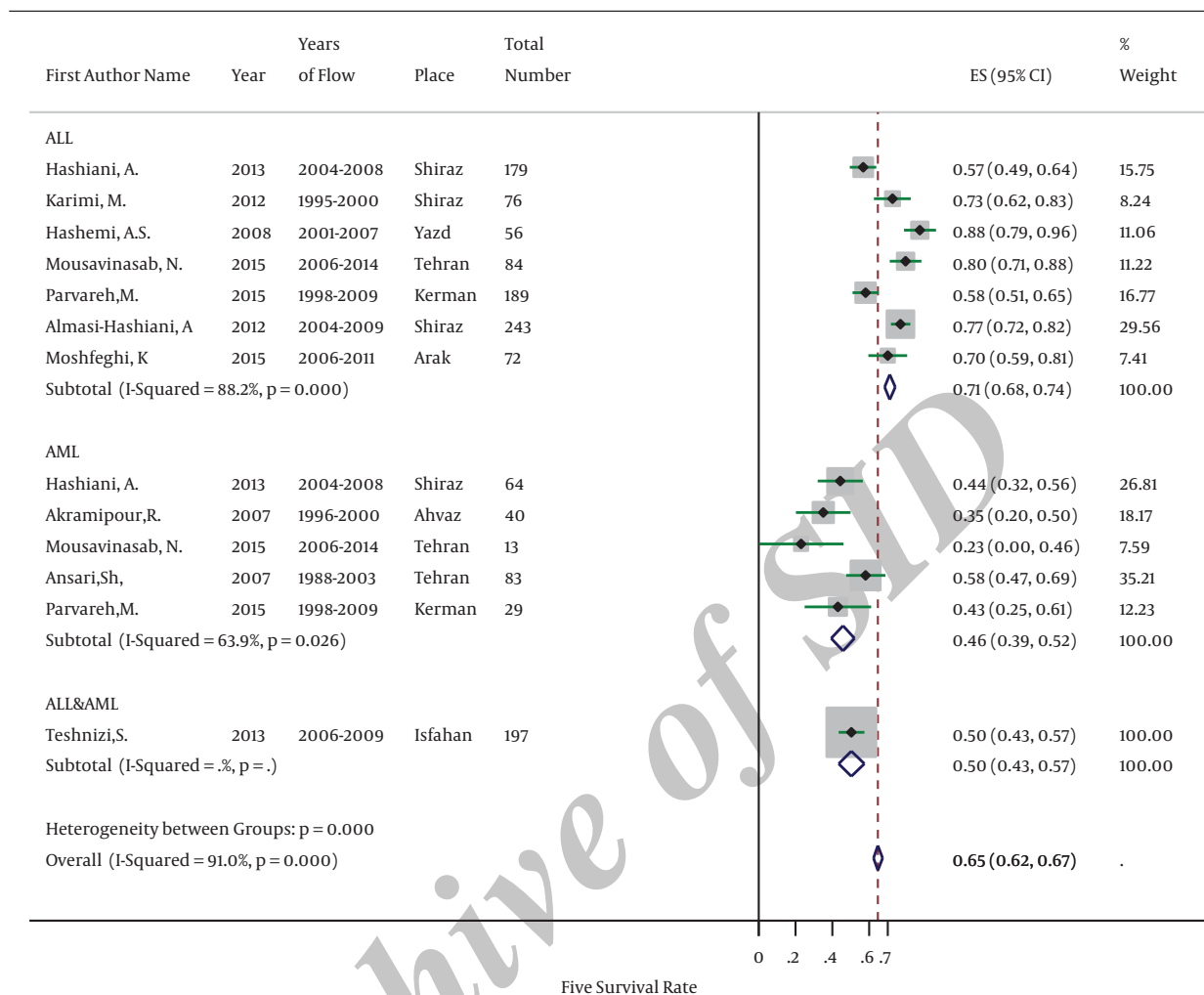


Figure 3. Forest Plot for Five-Year Survival Rate by Type of Childhood Leukemia

ance for clinicians to improve long-term outcomes in children with leukemia.

Footnotes

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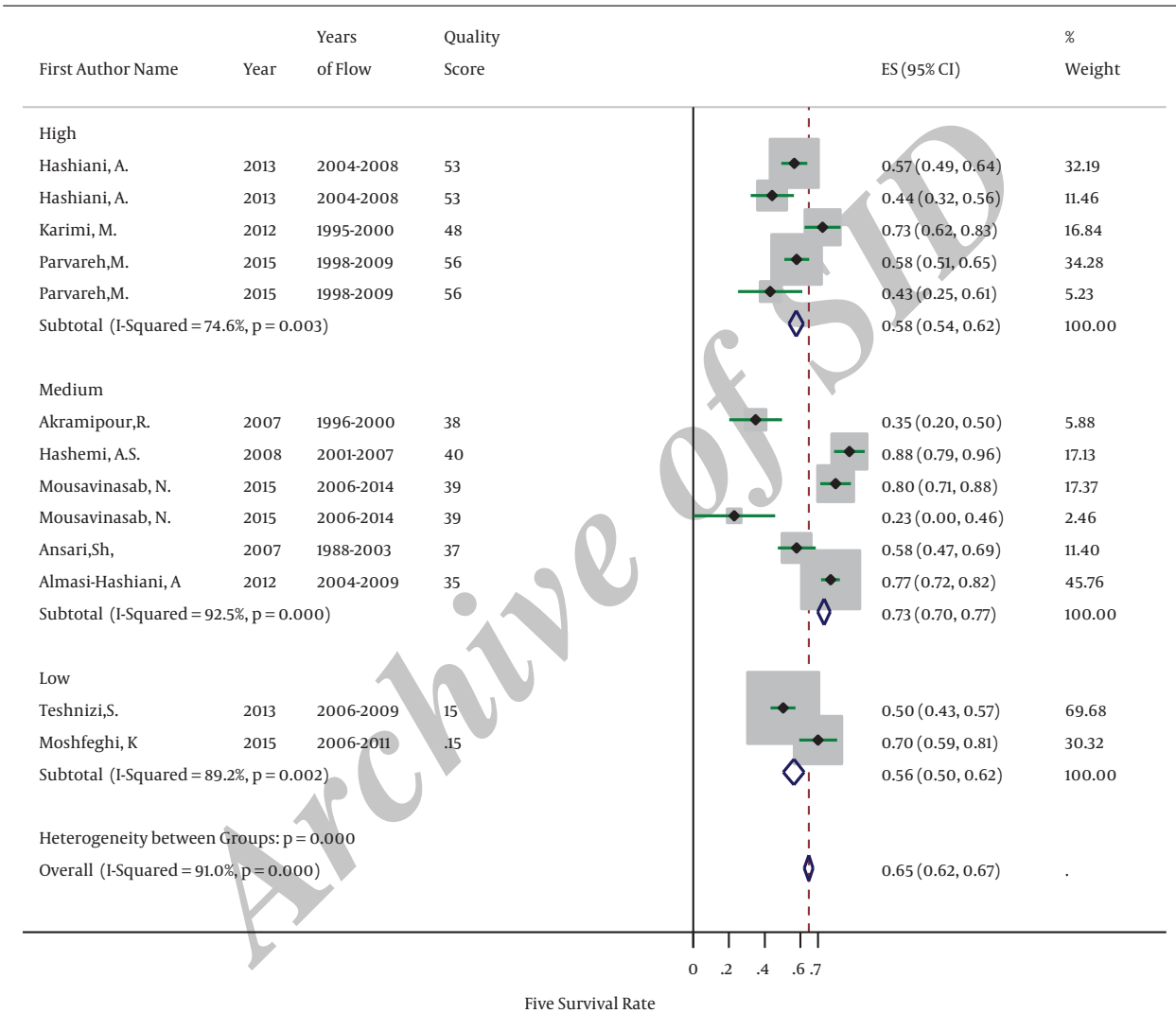


Figure 4. Subcategories Analysis of Five-Year Survival Rates by Quality of Imported Articles

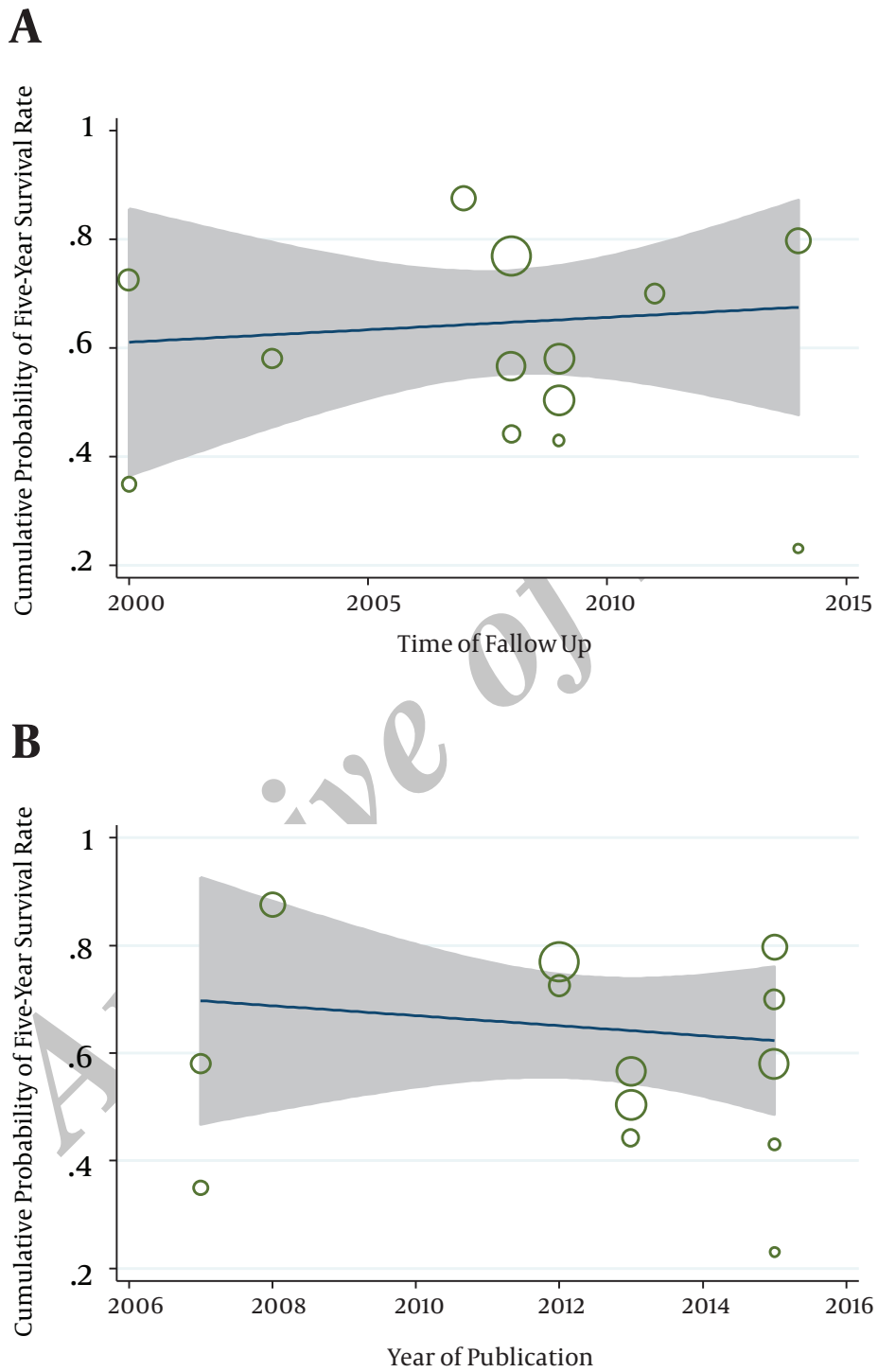


Figure 5. Meta-Regression Plots of Change in Five-Year Survival Rate of Leukemia According to Changes in Continuous Study Moderator's Time Of Follow Up And Year Of Publication.

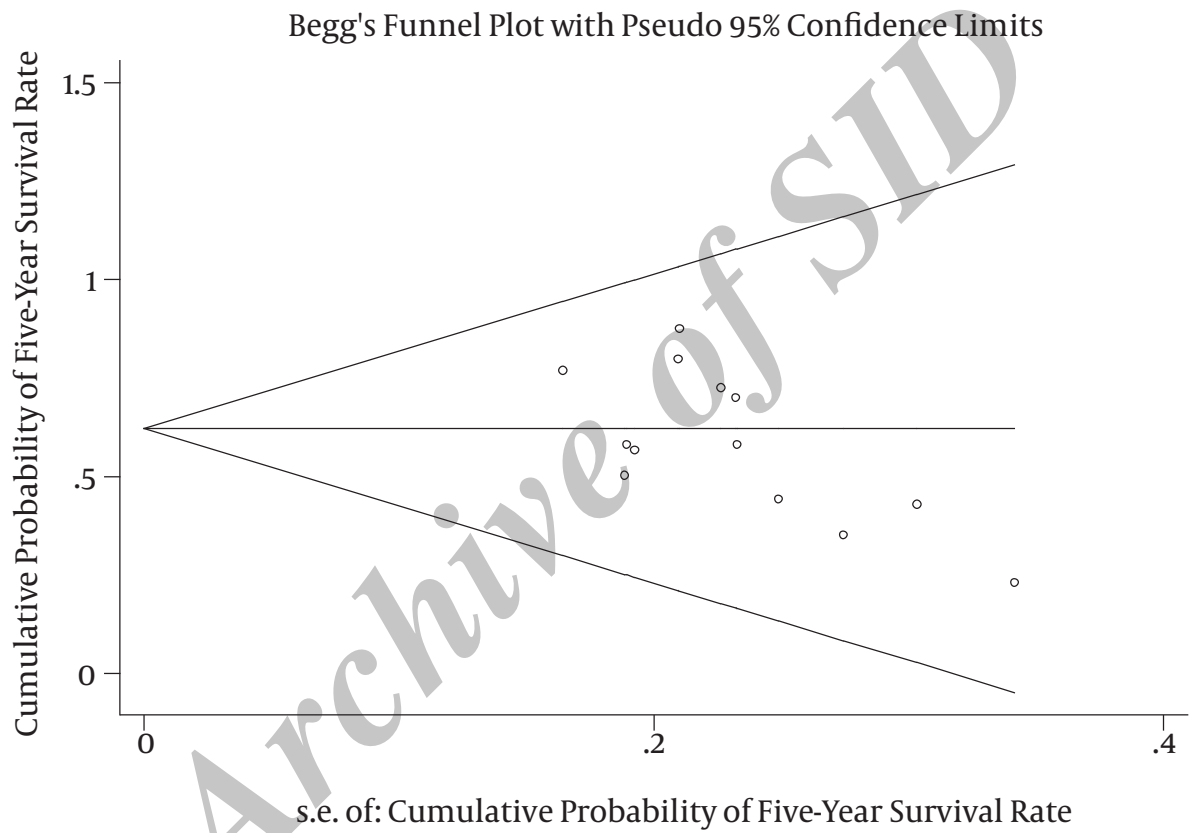


Figure 6. Begg's Funnel Plot (Pseudo 95% Confidence Limits) Showing Mean Difference in Cumulative Probability of Five-Year Survival Rate by Standard Error of Mean Difference According to Enrolled Articles

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