Comparative study between fixed effect model and random effect model in meta-analysis with application to acute lymphoblastic leukemia(ALL)

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Abstract:

The phenomenon of acute lymphoblastic leukemia(ALL) is an important field of study, and in this study, the meta-analysis methodology of 20 randomized controlled trials was used to investigate the prognostic impact of mutations in (ALL),The study used fixed effects and random effects models to study odds ratios, the number of controls and cases event-free with hazard ratios. The study conducted subgroup analyzes based on population status and mutation, after retrieving relevant studies.

Fixed effects models and random effects models are two common statistical models for meta-analysis, and it may be misunderstood that these two models can be used interchangeably due to their use of similar sets of formulas to generate statistics and sometimes produce identical estimates for certain parameters. The study concluded that the best estimate of the risk ratio under publication bias was the Hunter-Schmidt method because it reduced the variance between studies.

Keywords : meta-analysis; fixed-effects; random-effects; Acute Lymphoblastic Leukemia, Randomized Controlled trials (RCTs)

1. Introduction

Acute lymphoblastic leukemia (ALL) is a disease that affects lymphoid cell tissues in a variety of ways. Precursor B-cell ALL (B-ALL) is the most frequent immunological subtype, and the Philadelphia chromosome (Ph-positive ALL) is the most common genetic defect in B-ALL, seen in about one-quarter of adult patients. Allogeneic hematopoietic stem cell transplantation (HSCT) is suggested after consolidation. For information of leukemia seeFaderl et al. (1998), Fielding (2011), Reaman and Smith (2014) and Iacobucci and Mullighan (2017).

Leukemia's rising prevalence poses a menace to human development and cancer control worldwide. Population aging, population growth, and huge industrial pollution, particularly from the establishment of large-scale petrochemical industrial complexes (PICs), are the main causes of an increase in leukemia incidence, see Fitzmaurice et al.(2018), Reynolds et al. (2003). Sharma et al. (2017) have shown Benzene and other pollutants used in the petrochemical manufacturing process to berecognized as important causes of leukemia see Buffler et al. (2005).

Meta-analysis is only partially a set of statistical procedures, as the other articles in this issue reveal. However, the statistical component makes up a significant portion of what a meta-analysis entail. We focus on the decisions made by a meta-analyst when doing such a review, with a specific focus on how these decisions affect the validity of meta-analysis conclusions. We hope that by scrutinizing the decisions made during a meta-analysis, others will be aware of the ways in which biases and subjectivity might influence the results

reached from meta-analytic data. We provide prescriptions and suggestions for dealing with bias and subjectivity in meta-analysis whenever possible. In the literature study, we also explore the costs and benefits of quantification in general.

A variety of meta-analysis models can be used to incorporate summary statistics from each study, which are categorized as fixed-effect models, in which studies are weighted according to the amount of information they contain; or random effects models, in which studies are weighted using an estimate of inter-study variance (heterogeneity). A forest plot, where results from each research are presented as a square and a horizontal line, reflecting the intervention effect estimate and its confidence interval, is usually included in the meta-analysis.

We've shown how meta-analysis is used to combine effect sizes from individual studies to try to determine true effect sizes (i.e., effect sizes in a population). Fixed-effects and random-effects models are two ways to think about this process. Hedges (1992) and Hedges and Vevea (1998) do an excellent job of explaining the differences between these models.

The study assumes that all the studies included in the meta-analysis have the same effect size in the population because, in essence, the effect sizes in the community are fixed, but they are not known constants in the fixed effect model. (Hunter & Schmidt, in press). The homogeneous case is the name given to this scenario.

Another explanation is that the population impact sizes differ at random from one study to others. Each research in a meta-analysis in this situation comes from a population with a different effect size than the other studies in the meta-analysis. As a result, population effect sizes can be conceived of as being drawn from a vast array of possible outcomes the kind of "superovulation" (Hedges, 1992, Becker, 1996). The heterogeneous case describes this issue.

We begin in section 2 with presentation of data description model specification.The comparison of two competing models for fixed and random experimental effects has been shown in section 3. We proceed to examine and illustrate the estimation methods analysis such as maximum likelihood, Dersimonian-Laird, Sidik-Jonkman, Hedges-estimator, and Hunter-Schmidt methods in section 4. The applied study is shown in section 5.

2. Data Description

Some authors such as (Al-Achkar etal.,2014), (Razmkhah etal., 2011), (Aydin etal.,2006)and (Jiang etal.,2008) used meta-analysis to study the relation among CYP1A1 polymorphisms and risk of leukemia(ALL,AML,CML).They found that A24 55G GG genotype might have an increased risk of ALL and there is no association between CYP1A1*2C polymorphism AG and AML patients.

Also,(Taspinar etal.,2008) studied the influence of cytochromes P450(CYP450)1A1*2C insusceptibility to chronic myeloid leukemia

(CML).They concluded that polymorphic CYP1A1 andGSTT1 genes appear to affect susceptibility to CML.

Studying the risk of childhood acute leukemia (ALL) has been introduced by (Bonaventure etal.,2012) by exploring the interactions between prenatal exposure to maternal smoking and polymorphisms in metabolic genes. This study concluded that there is no relation between maternal smoking and any of the polymorphisms under study. Also,(Saenz, etal.,2018) to diagnose childhood leukemia and relapse or death, it assessed the relationship between overweight/obesity (body mass index ≥ 85 percent). This study did not find any significant associations between overweight/obesity and relapse or mortality due to the small sample size, while the results of meta-analyses revealed an increased risk of death for overweight/obese patients. In addition, the findings may suggest a possible association between obesity and relapse that may be restricted to children less than 10 years old.

(Bolufer etal., 2007) delibratedcommon polymorphisms in the genes for glutathione S-transferase (GST), cytochrome P450 (CYP), quinone oxoreductase (NQO1), methylene tetrahydrofolate reductase (MTHFR), and thymidylate synthetase (TYMS) and the role of gender associated with the susceptibility to de novo acute leukemia (AL). They concluded that gender might influence the risk of (AL) associated with these genetic polymorphisms. (Krajinovic, etal.,1999) Examined the glutathione S-transferase and cytochrome P450 genes in determining susceptibility to pediatric cancers. The results have been suggested that the risk of ALL may actually be associated with xenobiotics-metabolism, and thus with environmental exposures.

Explaining the associations of three CYP1A1 polymorphisms (T3801C, A2455G, and C4887A) with risks of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML) using a meta-analysis, has been introduced by (Jiang etal.,2008).The results indicated that Asians carrying the T3801C allele C may be at increased risk of acute myelogenous leukemia (AML) and Caucasians with the A2455G GG genotype may have an increased risk of ALL.

A study of (Yamaguti etal., 2009) Studied the environmental exposure to benzene and tobacco's polycyclic aromatic hydrocarbons (PAH) has been associated with an increased risk for acute myeloid leukemia (AML). The study showed that the increased risks of AML related to the variant genotypes of the *CYP1A1* T6235C, *CYP1A1* A4889G and *NQO1* C609T polymorphisms, isolated and particularly combined, suggest that the inherited abnormalities of these carcinogens' detoxification pathways are important determinant of the disease in their country.

A study (Agha etal., 2014) analyzed the frequency of CYP1A1 allelic variants in Egyptian patients with ALL, to assess their role in the development of ALL and then correlate these allelic variants with clinical and biological characteristics of the patients. Their results suggested that polymorphic variants in the CYP1A1*4 gene may raise the risk of childhood ALL, particularly in male patients aged 2-10 years. Also, (Alexandar etal.,2018) determined the efficacy and risks of levofloxacin prophylaxis in children receiving intensive chemotherapy for acute leukemia or undergoing HSCT. Among children with acute leukemia receiving intensive chemotherapy,

receipt of levofloxacin prophylaxis compared with no prophylaxis resulted in a significant reduction in bacteremia and (Valenzuela etal.,2020) performed a phenotypic and functional characterization of NK cells in ALL Mexican children now of diagnosis and before treatment initiation. A case-control study was conducted by the Mexican Interinstitutional Group for the Identification of the Causes of Childhood Leukemia (MIGICCL).They concluded that there was positive correlation between low SAP expression and decreased NK cell-mediated cytotoxicity was observed in ALL patients.

Carrying out a cohort analysis has been studied by (Tyneretal.,2018) to determine the correlation between drug sensitivity patterns and mutational events or gene expression levels. They showed that the response to drugs is related to mutational status, containing instances of drug sensitivity that are specific to combinatorial mutational events.

Discussing the nuances of common AML trial endpoints and their data presentation introduced by (Medeiros, B.,2018) to better inform evaluation and understanding of clinical trial data. (Paz, etal.,2018) reported Galectin-1 at various levels in and on different subclasses of BP-ALLs. The effects of Galectin-1 inhibition on both BP-ALL cell proliferation and migration suggest both the leukemia cells as well as the microenvironment that protects these cells may be targeted.

A research of (Jabbour & Kantarjian, 2018) Discuss the cytogenetic and molecular criteria for patients undergoing treatment. Also introduced (Jakšić, etal., 2018) new therapies based on the results of first-line, multicenter, randomized trials of salvage therapy. They show that new therapeutic

research, including genetic diagnosis, offers new options that may eventually lead to time-limited therapies without chemotherapy and more effective clinical care for B-CLL based on individualized precision medicine.

In this research, we look at the results of a meta-analysis of numerous acute leukemia treatments. This research includes data from twenty studies of leukemia from *pubmed*. site. The data contains the number of patients, risk ratio, publication year and number of events for experimental and control group of each study. O based on this systematic review of these studies we will depend on the data of 20 study of ALL.

3. Model Specification

There are three types of statistical models for meta-analysis: the fixed effects models, random effects models and mixed effects models (Heges,1992).In this paper we will show the first two types. In this section we describe the difference between fixed and random effects meta-analysis(Kelley and Kelley,2012).

3.1. Fixed effects model

This model assumes that all observed variations are caused by within-study sampling errors. Thus, since all studies are assumed to measure the same overall effect, the effect size represents quantative measure of the phenomena of the research. It indicates a difference between two groups from using tests of statistical significance. The effect size concentrates on the weight of the difference between groups rather than the sample size. There are various types

of effect size in this research, we use effect size based onodds ratio and risk ratio.

The odds ratio take the form: -

$$\beta = \frac{\prod_{11}\prod_{22}}{\prod_{12}\prod_{21}} \qquad (1)$$

Where: -

$\prod_{11}$: −The ratio of exposed risk units of both variables;X, Y.

$\prod_{12}$: -The ratioof exposed risk of variable X to the non-exposed risk unit of variable$Y$.

$\prod_{21}$: -The ratio of non-exposed risk of variable X to the expose risk unit of variable$Y$

$\prod_{22}$: - The ratio of non-exposed risk of the two variables;X, Y.

Also, the risk ratio represents the ratio of the probability of an outcome in an experimental group to the probability of an outcome in control group: -

$$Risk\ Ratio = \frac{CI_e}{CI_c} \qquad (2)$$

Where: -

CI_e: −The cumulative incidence in the experimental group.

CI_c: − The cumulative incidence in the control group.

The fixed effects model can be denoted as:

$$\widehat{\boldsymbol{\beta}}_{\boldsymbol{k}} = \boldsymbol{\beta} + \boldsymbol{\varepsilon}_{\boldsymbol{k}} \quad , \ \boldsymbol{\varepsilon}_{\boldsymbol{k}} \sim \boldsymbol{N}(\mathbf{0}, \mathbf{1}) \qquad (3)$$

Where:

$\boldsymbol{\varepsilon_k}$: represents the sampling error for $\boldsymbol{\widehat{\beta}_k}$.

In view of the fixed effects model, the observed effects are sampled from the real effect distribution β and the variance σ^2. More weight is given to studies with more information because all studies aresampled from a population with an effect size β and we are dealing with a single source Only for sampling error - within studies. Each study is weighted by sample size. Each study has its description as follows: -

$$\boldsymbol{W_i = \frac{1}{v_i}}$$

Where: -

$\boldsymbol{v_i}$: represents the within–study variance for study(i).

We note that the combined effect exceeds the estimation of the combined effect size, since we assume that the true effect is shared by all included studies.

Under fixed-effects models, the accuracy of the joint effect is the only source of error when estimating the combined effect as the random error in the studies. Therefore, the error will tend towards zero as the sample size increases sufficiently. This is achieved whether the large sample is confined to one study or distributed across many studies.

3.2. Random effects model: -

Under this model the combined effect size cannot represent the only common effect as there is no single true effect but there is a distribution of true effect sizes and thus represents instead the mean of the population of true effects.

When assigning weights to estimate the true effect, we need to deal with both the source of sampling error within studies and between studies, since the random effects model has two sampling levels and two sources of error (Borenstein et al., 2007).

This model can be referred to as: -

$$\widehat{\boldsymbol{\beta}}_{\boldsymbol{k}} = \boldsymbol{\beta} + \boldsymbol{\sigma}_{\boldsymbol{k}} + \boldsymbol{\varepsilon}_{\boldsymbol{k}} \quad , \ \boldsymbol{\varepsilon}_{\boldsymbol{k}} \sim \boldsymbol{N}(\mathbf{0}, \mathbf{1}) \tag{4}$$

Where: -

$\boldsymbol{\sigma}_{\boldsymbol{k}}$: represents sample estimation of $var(\hat{\beta}_k)$.

The main aim of a meta- analysis will often be to estimate the overall, or combined effect. We could simply compute the mean of the effect sizes if all studies in the analysis were equally precise. In contrast, if some studies were more precise than others, we could assign more weight to the studies that carried more information.So, we compute aweighted mean of the effect sizes with more weight given to some studies and less weight given to others rather than compute a simple mean.

The assigned weight for each study is: -

$$\boldsymbol{W}_{\boldsymbol{i}} = \frac{\mathbf{1}}{\boldsymbol{v}_{\boldsymbol{i}} + \boldsymbol{\tau}_{\boldsymbol{i}}} \tag{5}$$

Where: -

$\boldsymbol{v}_{\boldsymbol{i}}$ is the within –study variance for study (i).

$\boldsymbol{\tau}_{\boldsymbol{i}}$is the between study variance for study (i).

To compute the precision of the combined effect sizesaccording to this model which has two levels of sampling and two levels of errors, each study is used to estimate the true effect in a specific population first. Second, all the true effects are used to estimate the meaning of the true effects.

4. Estimation Methods: -

In the following, we consider the commonly used Dersimonian and Laird(DL), Maximum Likelihood (ML), Sidik Jonkman, Hedges estimator, and Hunter Schmidt.

4.1 Maximum Likelihood (ML) Method

For a meta – analysis with m studies a model for trend estimation can be written: -

$$y_i = \beta_i x_i + \varepsilon_i \quad , i = 1,2, \dots \dots, m \qquad (6)$$

where $var(\varepsilon_i) = \Omega_i$

If we consider a random- effects model, we can further assume that β_i has a normal distribution, as:

$$\beta_i \sim N(\beta, \tau^2)$$

f bothΩ_i and τ^2 are given, the estimate of βcan be calculatedby using maximum likelihood method. As:

$$\hat{\beta}_R = \frac{\sum_{i=1}^{m} x_i^T \Omega_i^{-1} y_i}{\sum_{i=1}^{m} x_i^T \Omega_i^{-1} y_i} \qquad (7)$$

which depends on τ^2.

Thus, the CI of β based on the random- effects model can be constructed as e follows:

$$\hat{\beta} \pm Z_{\frac{\alpha}{2}}\left(\sum_{i=1}^{m} x_i^T \Omega_i^{-1} x_i\right)^{-\frac{1}{2}}, \qquad (8)$$

where $Z_{\frac{\alpha}{2}}$ is the$\frac{\alpha}{2}$ upper quantile of the standard normal distribution.

4.2 Dersimonian and Laird method

From the estimation of the effect size under random effects models, we get the variance of $\hat{\beta}_R$ as follows:

$$var\left(\hat{\beta}_R\right) = \frac{1}{\sum_{i=1}^{m} x_i^T \sum_i^{-1} x_i} \qquad (9)$$

Thus, the Dersimonian and Laird estimation of effect size is(Shi, etal.,2015):

$$\hat{\beta} \pm Z_{\frac{\alpha}{2}}\left(\sum_{i=1}^{m} x_i^T \Sigma_i^{-1} x_i\right)^{-\frac{1}{2}}, \qquad (10)$$

Where:-

$$\sum_i = \Omega_i + \tau^2 x_i x_i^T$$

4.3 Sidik and Jonkman CI Method: -

To construct CI in meta-regression models, weuse the fact that:

$$\sum_{i=1}^{m} \left(y_{i-}\hat{\beta}_R x_i\right)^T \Sigma_i^{-1} (y_i - \hat{\beta}_R x_i) \sim \chi^2_{N-1} \qquad (11)$$

We know that:

$$\frac{(\hat{\beta}_R - \beta)/\left(\sum_{i=1}^{m} x_i^T \Sigma_i^{-1} x_i\right)^{-\frac{1}{2}}}{\sqrt{\sum_{i=1}^{m}\left(y_{i-}\hat{\beta}_R x_i\right)^T \Sigma_i^{-1}(y_i - \hat{\beta}_R x_i)/N - 1}}$$

has t–distribution with$N - 1$ degrees of freedom,which leads tothe following approximate CI: -

$$\hat{\beta}_R \pm t_{N-1,\frac{\alpha}{2}}\sqrt{\sum_{i=1}^{m}\frac{\left(y_{i-}\widehat{\beta}_R x_i\right)^T \Sigma_i^{-1}\left(y_i-\widehat{\beta}_R x_i\right)}{N} - 1\sum_{i=1}^{m} x_i^T \Sigma_i^{-1} x_i} \quad (12)$$

where$t_{N-1,\frac{\alpha}{2}}$ is the upper $\frac{\alpha}{2}$ quantile of the related t- distribution.

4.4 Hunter-Schmidt method

This method assumes that between –studies variance is small, so it will underestimate the standard error and overestimate Z if between- studies variance is not small (Anker, etal., 2010). The Hunter and Schmidt (2004) estimator is given by: -

$$\hat{\tau}_{HC} = max\left\{0, \frac{Q-N}{\sum W_{i,RE}}\right\} \quad (13)$$

5. AppliedStudy

Meta- analysis is used to collect results from various studies to achieve high level of statistical precision unlike the estimations based on a single study.

The effects size contains many measures such as odds ratio, risk ratio and effect size based on correlation. This section will depend on risk ratio to compute the effect size of chemotherapy on decreasing the leukemia risk.

This section contains the application of leukemia patient's data on the random effects model of twenty studies. Also, it covers the parameters estimation of this model by various methods of estimation and a comparison between these methods.

The data set includes the following:

1-Risk ratio of each study (Effect Size).

2- Number of experimental cases.

3-Number of controls.

4-Number of events for experimental group.

5- Number of events for control group.

6- publication year of each study.

Table1: The Risk ratio, Confidence interval and weight of fixed effects model and Random effects model of each study.

Study	Risk Ratio	95% CI	Weight (Fixed)	Weight (Random)
1	34.09	[2.04; 570.44]	0.2%	1.2%
2	3.78	[0.16; 91.90]	0.2%	1.0%
3	0.37	[0.02; 8.92]	0.2%	1.0%
4	0.28	[0.05; 1.52]	0.6%	2.9%
5	0.32	[0.07; 1.52]	0.7%	3.2%
6	0.40	[0.02; 8.39]	0.2%	1.1%
7	0.89	[0.53; 1.52]	6.5%	8.7%
8	0.09	[0.00; 1.49]	0.2%	1.2%
9	3.82	[1.90; 7.69]	3.7%	7.4%

10	1.50	[0.55; 4.10]	1.8%	5.5%
11	0.88	[0.08; 9.63]	0.3%	1.6%
12	1.61	[0.27; 9.55]	0.6%	2.6%
13	1.06	[0.53; 2.09]	3.9%	7.5%
14	1.17	[0.88; 1.56]	22.1%	10.3%
15	2.54	[0.30;21.60]	0.4%	2.0%
16	2.23	[1.54; 3.22]	13.3%	9.8%
17	5.13	[1.76; 14.91]	1.6%	5.1%
18	0.72	[0.56; 0.92]	30.4%	10.5%
19	1.00	[0.57;1.74]	5.9%	8.5%
20	1.00	[0.60;1.66]	7.1%	8.9%

Table1 contains risk ratio and weight of each study from published studies under fixed effects model and random effects model, where the weight equals the inverse of the variance $W_i = \frac{1}{v_i}$;$v_i = \varepsilon_i$ represents the variance within studies under fixed effects model and represents the variance within studies in addition to the variance between studies under random effects model$v_i = \varepsilon_i + \tau_i$.

For effect size (Risk ratio), the first study represents the highly effect size from all twenty studies and this means that the number of experimental cases is greater than the number of control cases. For weight: the highest weight was 30.4% for fixed effects model and 10.3% for random effects model.

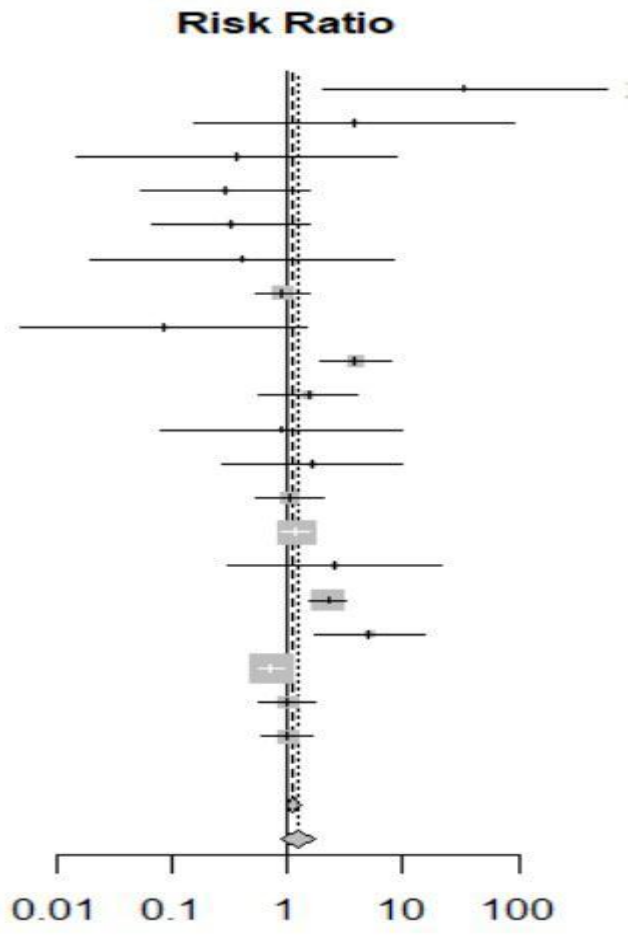

Figure (1): the forest plot of single studies of acute lymphoblastic leukemia

The forest plot in figure(1), shows all results of all studies in one graph. The points represent risk ratio of each study, the lines represent confidence intervals estimations of contribution of each study in meta- analysis. The vertical line shows that there is no any significant difference between experimental and control group, so, from this graph it can be determined which study is significant. So, from this plot we can see that the significant studies are the first, eighth, sixteenth and seventeenth study.

Table(2): Overall effect size estimation of fixed effects model and random effects model of single studies.

Model	Risk Ratio	95%CI	Z	P-Value
Fixed effects model	1.1149	[0.9743; 1.2757]	1.58	0.1139
Random effects model	1.2506	[0.8991; 1.7345]	1.33	0.1892

From table (2) we can find that the effect size of fixed effects model is smaller than the one of random effects modelwhere the studies has been taken from the same population.

Table(3): The estimation of variance between studies of random effects model.

$\hat{\tau}^2$	$\hat{I}^2$	H
0.2536	69.9%	1.82

Table (3), represents the estimation of the variation of effect size between studies, where:-

$\hat{\tau}^2$represents the variation between effect size and it represents small value,

$\hat{I}^2$ represents the ratio of variability between effect size estimations.

So from previous table we found that there is a heterogeneity between studies.

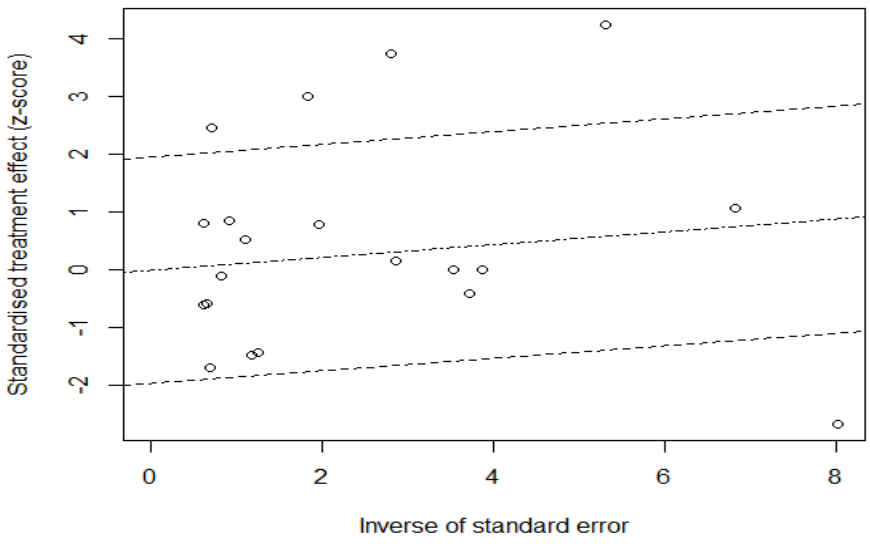

Figure (2): The radial plot of risk ratio of each study

The radial plot is used to compare the estimations which are different in their accuracy, so it represents scatter plot of standard estimations versus the inverse of standard error$\frac{1}{SE_i}$, in addition, it is used to show the heterogeneity of data. Studies with higher weight are close to the Y axis where the symmetry line begins from the point (0, 0). The studies that lies between confidence intervals lines represent homogeneous studies, and the studies that lies outside the symmetry line represent extreme values. From the previous figure there are five studies lies outside the lines and represents extreme values.

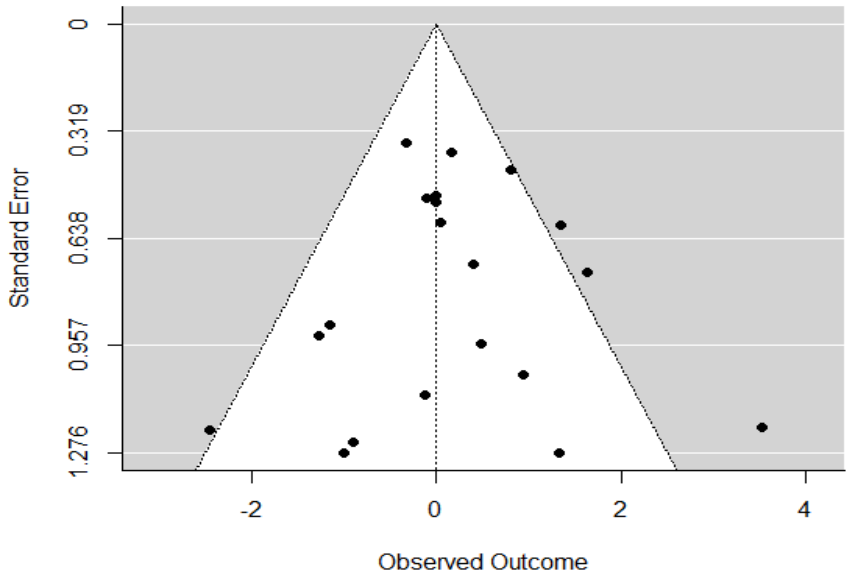

Figure (3). The funnel plot of risk ratio of each study.

The funnel plot represents in figure (3) scatter plot of effect size estimations from single studies versus the accuracy of each published study. This plot is used to test the presence of publication bias. So, the studies with high precision are close to the mean in contrast to the studies with low precision that are spread on the plot sides and the deviation from this plot performs publication bias. From the previous plot, there is a publication bias because of the presence of some studies on the right side of the plot.

Table 4: The estimation methods of the effect size.

Method	Estimate	SE	Z-Value	P-Value	Confidence Intervals
Maximum Likelihood	0.2013	0.2347	0.8575	0.3912	[-0.2588, -0.6613]
Sidik-Jonkman	0.2238	0.3127	0.7156	0.4742	[-0.389,0.8366]
Hedges Estimator	0.2199	0.2964	0.7420	0.4581	[-0.3610, 0.8009]
Hunter-Schmidt	0.1983	0.2270	0.8736	0.3823	[-0.2466, 0.6432]
Dersimonian and Laird	0.20	0.24	0.85	0.39	[-0.2618, 0.67]

From table(4) we can find that the largest effect size is the estimate of Sidik- Jonkman method and this means that the number of experimental cases is greater than the number of controls, while the other methods represent less effect size.

Table 5: The test of heterogeneity of single studies.

Q	**df**	**P-Value**
63.21	**19**	**<0.0001**

From table(5) the test of heterogeneity is significant and this represents that there is variation between studies.

Table 6: Ratio of variation between studies (variance between studies).

$\hat{I}^2$	$\hat{\tau}^2$	**P-Value**
70%	**0.2536**	**<0.01**

From table (6), the variance between studies is large and significant. This means that there is variation between studies, and they have been taken from different populations.

Table7: The test of heterogeneity of each estimation method.

Method	**Q**	**df**	**P-Value**
Maximum Likelihood	51.1405	19	<0.0001
Sidik-Jonkman	51.1405	19	<0.0001
Hedges estimator	51.1405	19	<0.0001
Hunter-Schmidt	51.1405	19	<0.0001
Dersimonian and Larid	51.14	19	<0.01

The test of heterogeneity of each method according to table (7) is significant. This indicates that there is heterogeneity between studies.

Table8: Comparison between estimation methods under publication bias problem.

Method	$\hat{\tau}^2$	SE	$\hat{I}^2$	$\hat{H}^2$
Maximum Likelihood	0.5264	0.2347	62.23%	2.65
Sidik-Jonkman	1.2351	0.3127	79.45%	4.8
Hedges estimator	1.0631	0.2964	76.45%	4.33
Hunter-Schmidt	**0.4723**	**0.2270**	**59.65%**	**2.48**
Dersimonian and Laird	0.54	0.24	62.85%	2.69

From table (8), the best estimation of risk ratio under publication bias problem is Hunter-Schmidt method because it has decreased the variation between studies (Variance between studies), standard error and ratio of variation.

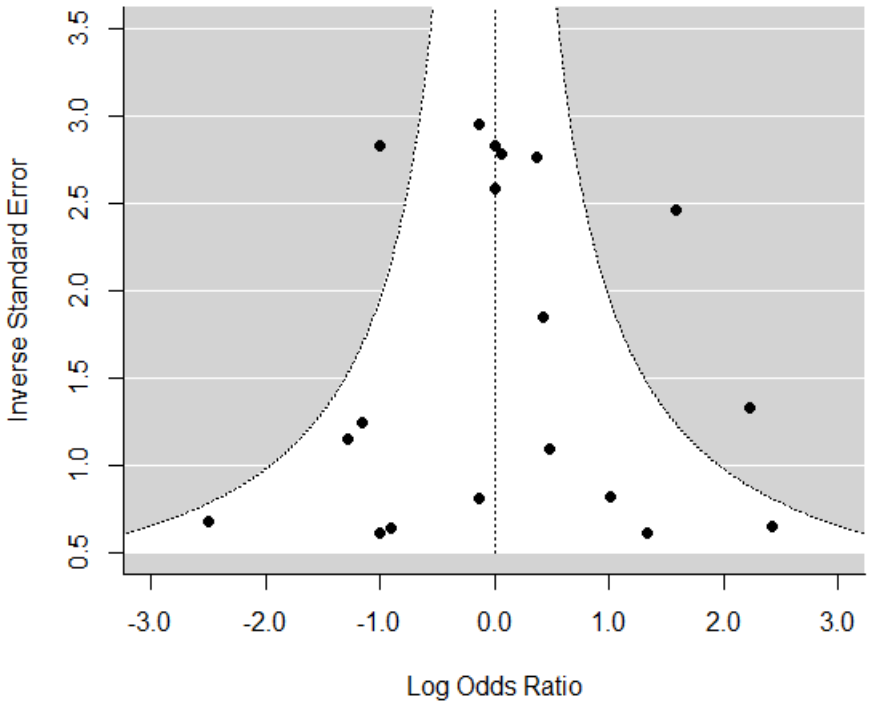

Figure (4): Shows the funnel plot of log effect size.

From figure (4) the effect size closes to the mean, and this means that the overall estimation decreases the publication bias problem.

Conclusion

In this paper we proposed two models of meta-analysis to estimate the parameters of these models under methods of estimation. The data includes the patients of leukemia, and we estimate the odds ratio as an estimator of the effect size. We concluded that the best estimation of the risk ratio under publication bias is Hunter-Schmidt method because it decreased the variation between studies.

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دراسة مقارنة لنماذج التأثيرات الثابتة ونماذج التأثيرات العشوائية في التحليل البعدي بالتطبيق علي بيانات سرطان الدم الليمفاوي

المستخلص:

تمثل ظاهرة الإصابة بسرطان الدم الليمفاوي الحاد مجالًا هاما للدراسة، وفي هذه الدراسة تم استخدام منهجية التحليل البعدي لـ 20 محاولة تحكم عشوائية وذلك لفحص دلالات الاصابة بسرطان الدم الليمفاوي الحاد. استخدمت الدراسة نماذج التأثيرات الثابتة والتأثيرات العشوائية لدراسة نسب الأرجحية، عدد وحدات التحكم وعدد وحدات الإصابة المرتبطة بنسب الخطر. وقامت الدراسة بإجراء تحليلات المجموعات الفرعية بناءً على حالة مجتمع الدراسة والتغير الناتج بعد مراجعة الدراسات ذات الصلة.

وتمثل نماذج التأثيرات الثابتة ونماذج التأثيرات العشوائية نموذجين إحصائيين شائعين للتحليل البعدي، وقد يفهم بشكل خاطئ أن هذين النموذجين يمكن استخدامهم بالتبادل نظرا لاستخدامهم مجموعات متشابهة من المعادلات لاستنتاج الإحصاءات وفي بعض الاحيان الحصول على تقديرات متطابقة للمعالم. وباستخدام تقدير نسبة الخطر لقياس حجم الاثر توصلت الدراسة أن أفضل تقدير لنسبة المخاطر في ظل تحيز النشر هو طريقة Hunter-Schmidt لأنها خفضت من التباين بين الدراسات.

الكلمات المفتاحية:

التحليل البعدي، التأثيرات الثابتة، التأثيرات العشوائية، سرطان الدم الليمفاوي الحاد، محاولة التحكم العشوائية