International Journal of Quantitative and Qualitative Research Methods
Vol.12, No.3, pp.15-24, 2024
Print ISSN 2056-3620 (Print)
Online ISSN 2056-3639(Online)
Website: https://www.eajournals.org/
Publication of the European Centre for Research Training and Development -UK

Randomized Controlled Trial Based Meta-Analysis of the Risk of Mortality in Sickle Cell Patients

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doi: https://doi.org/10.37745/ijqqrm.13/vol12n31524 Published November 10, 2023

Citation: Adehi M.U., Omole O.O., Adenomon M.O. and Bilkisu M. (2024) Randomized Controlled Trial Based Meta-Analysis of the Risk of Mortality in Sickle Cell Patients, *International Journal of Quantitative and Qualitative Research Methods*, Vol.12, No.3, pp.15-24

Abstract: *Meta-analysis is a systematic approach in selecting and integrating multiple finding across studies in order to give chances in control of potential bias. This paper aims to estimate the summary effect on the risk of mortality in sickle cell patient. The effect size index was risk ratio and date was sourced via Pubmed, Science Direct, Web of Science, Medline, Rechargegate and Google scholar. The random-effects model was employed for the analysis. The studies in the analysis were assumed to be random sample from a universe of sickle cell disease studies. The summary effect size was 0.877, with a 95% confidence interval of 0.672 to 1.146. The Z-value tested the null hypothesis that the summary effect size is 1. We found Z = -0.962 with p = 0.336 for α = 0.05; hence, we cannot rejected the null hypothesis and concluded that the summary effect size was precisely 1. The Q-statistic provided a test of the null hypothesis that 16 studies in the analysis share a common effect size; the Q-value is 77.927 with 15 degrees of freedom (k-1) and p < 0.001. For α = 0.100, we rejected the null hypothesis that the true effect size was the same in all the 16 studies since Q=k-1, k being the number of studies. The I-squared statistic was 81%, which tells us that some 81% of the variance in observed effects reflected variance in true effects rather than sampling error. Tau-squared, the variance of true effect sizes, was 0.196 in log units. Tau, the standard deviation of true effect sizes, was 0.443 in log units. Since we assumed that the true effects were normally distributed (in log units), we estimated the prediction interval to lie between 0.325 and 2.368.*

Keywords: Meta-Analysis, Risk Ratio, Forest Plot, Mortality, Sickle Cell.

INTRODUCTION

Sickle-cell disease (SCD) is a group of disorders that causes the red blood cells to become misshapen and breakdown. SCD is an inherited hemoglobinopathy, with an estimated 300,000

babies born worldwide with the disease (Piel et al., 2017). In the United States, an estimated 100,000 – 120,000 people live with SCD, primarily of African American or Hispanic descent (Hassell, 2010). Africa has been associated with the highest prevalence of the sickle cell trait, with figures suggesting that between 10% and 40% of the entire population may be affected Adigwe et al., (2023).

Adehi et al., (2017) concluded that Meta-Analysis of a Non Common Outcome is associated with publication bias and substantial heterogeneity, sensitivity analysis and subgroup analysis could help identify sources of bias and Heterogeneity to filter studies and derive reasonable and scientific quantitative estimates. Series of sensitivity analyses, multi-level subgroup analyses and I-squared (I^2) statistics tests were done to identify sources of bias, methodological and statistical heterogeneity respectively. It provides a systematic approach to selecting and integrating findings across studies and to control for chance and potential bias. It is a methodology used for contrasting and combining results of different studies, where the individual unit of the statistical analysis is the study result. Study characteristics are first carefully coded, then mean effect sizes are examined according to different study characteristics, in order to look for patterns among studies that might explain discrepant findings. This approach allows hypothesis testing regarding sources of heterogeneity and quantification of biases. Meta-analysis can also help to identify gaps in knowledge found in the published literature and thus can help provide guidance for future research.

LITERATURE REVIEW

Clinical studies are conducted among human participants to generate new knowledge by evaluating the impact of interventions. The main aim of all clinical studies is to evaluate interventions with respect to an associated outcome (Zabor et al., 2020). There are many different clinical study designs and the quality of evidence generated by any study is determined by its experimental design (Bhide et al., 2014). Of all the clinical study designs, evidence generated from randomized controlled trials (RCTs) is considered to be at top of the evidence pyramid.

Randomized trials are epidemiological studies in which a direct comparison is made between two or more treatment groups, one of which serves as a control for the other. Study subjects are randomly allocated into the differing treatment groups, and all groups are followed over time to observe the effect of the different treatments. The control group may either be untreated (placebo-controlled) or undergo a “gold standard” established regimen against which the new regimen will be assessed (active-controlled). Randomized trials provide the most direct evidence for causality. However, they are also fraught with a number of additional considerations not present for observational research.

With the explosive growth of medical information, it has become almost impossible for healthcare providers to review and evaluate all related evidence to inform their decision making (Stroup et al., 2000). Furthermore, the inconsistent and often even conflicting conclusions of different studies can confuse these individuals. Systematic reviews were developed to resolve

such situations, which comprehensively and systematically summarize all relevant empirical evidence.

The use of statistical models is pervasive. In almost every general area of research, models are used to explain relationships among variables or provide tools for prediction. There are numerous classes of models with countless options within each class. In general, however, a model has one (or more) dependent variables, or outcomes, and one (or more) independent variables, or predictors. No matter the type of model, the choice must be made (implicitly or explicitly) whether to treat the predictors as fixed or random effects. Defining fixed and random effects, and comparing and contrasting the two, has been a focus of much discussion over the decades. There is no consensus mechanism for distinguishing between the two, and often interpretation depends on the context in which they are being used. In general, often the classification of a variable as a fixed or a random effect is driven by the motivation for that variable in the analysis. Variables where the analyst is interested in making statistical comparisons between its levels are typically viewed as fixed effects. As an example, consider a study comparing a new exercise regimen aimed at reducing falls among the elderly, and nursing home residents are randomized to either the new regimen (‘intervention’) or a standard exercise program (‘control’).

Adehi et al., (2019) concluded that Meta-Analysis of a Non Common Outcome is associated with publication bias and substantial heterogeneity, sensitivity analysis and subgroup analysis could help identify sources of bias and Heterogeneity to filter studies and derive reasonable and scientific quantitative estimates. Series of sensitivity analyses, multi-level subgroup analyses and I-squared (I^2) statistics tests were done to identify sources of bias, methodological and statistical heterogeneity respectively. From 17 Studies that met the inclusion criteria, the mortality Hazard Ratio (HR) and 95% confidence interval (CI) among depressed HIV patients was 1.80 and (1.23 – 2.61) respectively, with significant statistical heterogeneity (I^2 = 92.8%).

METHODS

Literature Search and Articles Selection was explored through Inclusion and Exclusion Criteria. We excluded case reports, editorials, letters, abstracts and studies without sufficient data of interest. If two or more studies had the same patient population, the recent study with more complete data was included to avoid duplication.

Inclusion and Exclusion Criteria, the methodology developed from the preferred reporting items for systematic reviews and meta-analysis statement (Liberati et al., 2009). We included case series and case reports that captured any reported rare or uncommon side effects of any of these therapies. All were original studies of L-glutamine, Hydroxyurea, Crizanlizumab, or Voxelotor on children or adults with SCD, with reports of clinical efficacy, side effects, or prescribing data.

Data Extraction, the following data elements were extracted from the articles retrieved and meeting inclusion criteria: author name, year of study report, country of population studied, outcome measured, study design, age of study population, sample size, and a descriptive summary of findings related to clinical efficacy, side effects, and prescribing data.

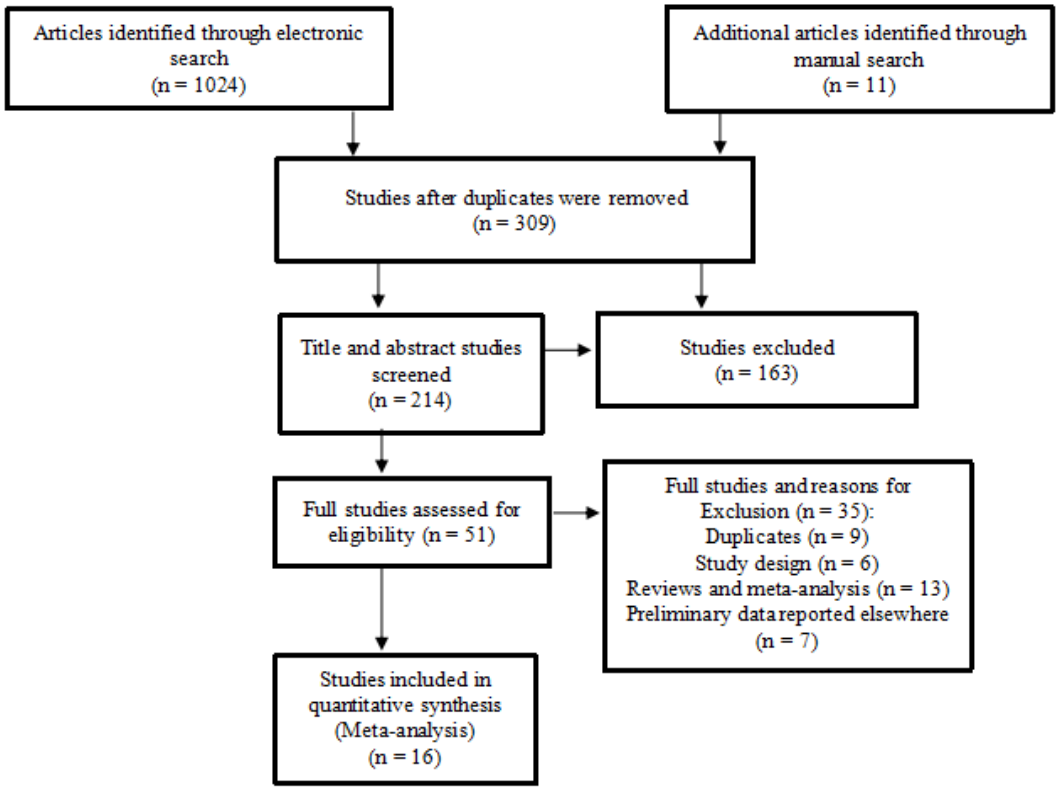

Figure 3.1: Flow diagram of included and excluded studies.

The dersimonian and Laired, (1986) methods are used on random or fixed effects models, the methods have been expanded to provide exploration to the randomized controlled trial based meta-analysis on the efficacy of casgevy therapy in the treatment of sickle cell disease. Considerable collection of k controlled trial related studies on sickle cell disease intervention and efficacy of casgevy, ith of which has estimated size Yi and the true effect size ϑ_i, the general models are:-

$$Y_1 = \begin{cases} \vartheta + E_i & fixed\ effect \\ \mu + \vartheta_i + e_i & random\ effect \end{cases} \quad (3.1)$$

Where

$$E_i and\ e_i \sim N(0, \sigma_i^2), i = 1,2, \dots, k$$

Let $y_i = y_1, y_2, \dots, y_k$ be effect sizes (risk ratio) for k studies (16), and $f(y_i, \vartheta, \sigma_i^2)$ a parametric density for some random quantity y, where ϑ is a parameter of interest and σ_i^2 is a nuisance parameter which may not be present in the model. The following assumptions follow:-

$f(y_i, \vartheta, \sigma_i^2)$ is assumed to be the normal density (for available measures, $y_i, I = 1, 2, 3, \dots, k$).

Heterogeneity distribution, say P, is assumed to be normal with parameters, μ and τ^2.

The individual study variances are known.

The marginal distribution is normal with parameters μ and $\hat{\sigma}_i^2 + \tau^2$.

ϑ is not a constant.

The fixed effects model assumes $\vartheta_i = \mu$ for $i = 1, 2, \dots, k$, implying that each study in the meta-analysis has the same underlying effect. The estimator of μ is generally a simple weighed average of the Y_i, with the optimal weights equal to the inverse of the variance and

$$W_i = \frac{1}{V_{Y_i}} \quad (3.2)$$

Where V_{Y_i} is within the study variance for study i.

The weighed mean (M) is then computed as

$$M = \frac{\sum_{i=1}^{k} W_i Y_i}{\sum_{i=1}^{k} W_i} \quad (3.3)$$

This is, the sum of the products $W_i Y_i$ (effect size multiplied by weight) divided by the sum of the weights. The variance of the summary effect is estimated as the reciprocal of the sum of the weights,

$$V_M = \frac{1}{\sum_{i=1}^{k} W_i} \quad (3.4)$$

And the estimated standard error of the summary effect is the square root of the variance,

$$SE_M = \sqrt{V_M} \quad (3.5)$$

Then, $(1 - \alpha)\%$ lower and upper limits for the summary effect are estimated

$$\left.\begin{aligned} LL_M &= M - t_{(1-a/2)} \times SE_M \\ UL_M &= M + t_{(1-a/2)} \times SE_M \end{aligned}\right\} \quad (3.6)$$

Finally, a t-test to test the null hypothesis that ϑ is zero can be computed using

$$t = \frac{M}{SE_M} \quad (3.7)$$

For a one-tailed test the p-value is given by

$$P = 1 - \phi(t) \quad (3.8)$$

Where we chose positive if the difference is in the expected direction and negative, otherwise, and for a two-tailed test by

$$P = 2[1 - \phi(t)] \quad (3.9)$$

To compute a study's variance under the random-effect model, we need to know both the within-study variance and τ^2, since the study's total variance is the sum of the two values.

Tau squared (τ^2) is estimated using the method of moments or the D & L, DerSimonian and Laird (1986). The parameter τ^2 is between the studies variance (the variance of the effect size parameters across the population of studies.

T is an estimate for τ^2, it is possible that T is negative due to sampling error, but it is unacceptable as a value for τ^2, so we define;

$$\tau^2 = \begin{cases} T \; if \; T > 0 \\ 0 \; if \; T \leq 0 \end{cases} \quad (3.10)$$

LetT^2 be an estimator for τ^2

$$T^2 = \frac{Q - df}{C} \quad (3.11)$$

Where

$$Q = \sum_{i=1}^{k} W_i Y_i^2 - \frac{\left(\sum_{i-1}^{k} W_i Y_i\right)^2}{\sum_{i=1}^{k} W_i} \quad (3.12)$$

$$df = k - 1$$

Where k is the number of studies, and

$$C = \sum_{i=1}^{k} W_i - \frac{\sum_{i-1}^{k} W_i^2}{\sum_{i=1}^{k} W_i} \quad (3.13)$$

From (3.2) under the random-effects model the weight assigned to each study is

$$W_i^{\cdot} = \frac{1}{V_{Y_i}^*} \quad (3.14)$$

Where $V_{Y_i}^*$ is the within-study variance from study I plus the between-study variance,τ^2.

$$V_{Y_i}^* = V_{Y_i} + T^2 \quad (3.15)$$

The weighted mean, M^*, is

$$M^* = \frac{\sum_{i=1}^{k} W_i^* Y_i}{\sum_{i=1}^{k} W_i^*} \quad (3.16)$$

That is, the sum of the products (effect size multiplied by weight) divided by the sum of the weights.

The I^2 – statistics is an alternative and stronger measure of heterogeneity compared to the Q-measure (Borenstein et al., (2009).

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\% \quad (3.17)$$

Use value of Q from (3.12)

Heterogeneity in the $I^2 -$ statistics may be termed low, moderate, or high based on the intervals $0 \leq I^2 < 25\%, 25\% \leq I^2 < 50\%, or \; I^2 \geq 50\%$ respectively (Borenstein et al., 2009).

RESULTS AND DISCUSSION

The research analysis is based on sixteen (16) studies. The effect size index is risk ratio (RR). The random-effects model was employed for the analysis. The studies in the analysis are

assumed to be a random sample from a universe of potential studies, and this analysis will be used to make an inference to that universe. The mean effect size is 0.877 with a 95% confidence interval of 0.672 to 1.146. The mean effect size in the universe of comparable studies could fall anywhere in this interval. The Z-value tests the null hypothesis that the mean effect size is 1.000. The Z-value is -0.962 with p = 0.336. Using a criterion alpha of 0.050, we can reject this null hypothesis.

The Q-statistic provides a test of the null hypothesis that all studies in the analysis share a common effect size. If all studies shared the same true effect size, the expected value of Q would be equal to the degrees of freedom (the number of studies minus 1). The Q-value is 77.927 with 15 degrees of freedom and p < 0.001. Using a criterion alpha of 0.100, we can reject the null hypothesis that the true effect size is the same in all these studies. The I-squared statistic is 81%, which tells us that some 81% of the variance in observed effects reflects variance in true effects rather than sampling error. Tau-squared, the variance of true effect sizes, is 0.196 in log units. Tau, the standard deviation of true effect sizes, is 0.443 in log units. If we assume that the true effects are normally distributed (in log units), we can estimate that the prediction interval is 0.325 to 2.368. The true effect size in 95% of all comparable populations falls in this interval.

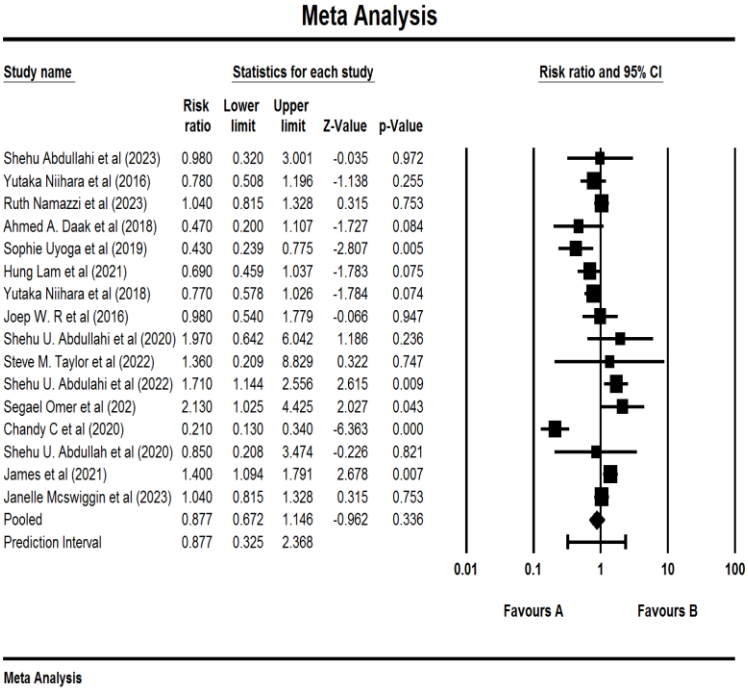

Figure 4.1: Summary Effect on the Risk of Mortality in Sickle Cell Patients.

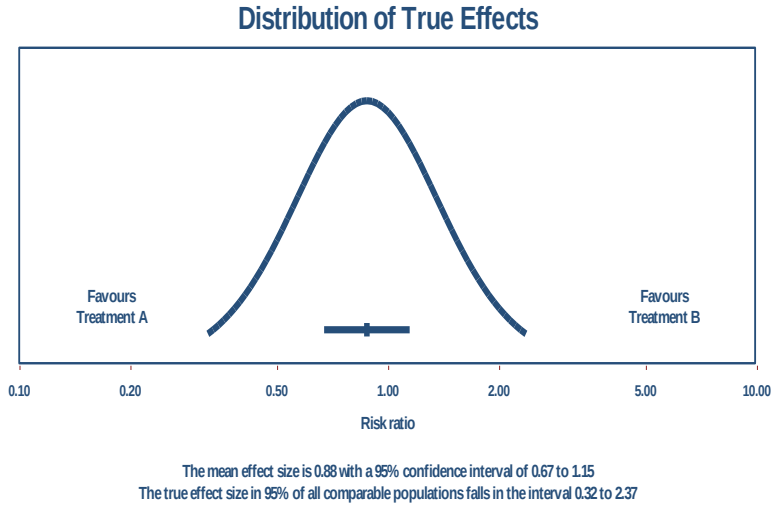

Figure 4.2: Distribution of True Effects on the Risk of Mortality in Sickle Cell Patients.

CONCLUSION

In conclusion, meta-analysis pose to have a potential impact to establish statistical significant in conflicting results in decision making and public practices. In this research work, the results estimate are located to the left, it means that the outcome of interest (mortality) occurred less frequently in the intervention group than in the control group (ratio < 1). The overall combined result is not statistically significant. Hence, the pooled estimate suggest that the overall outcome rate in the intervention group is much the same as in the control group.

Future Research

One of the future research in this regard could be checking the level of heterogeneity and the risk factors of this heterogeneity using meta-regression.

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