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Systematic Review and Meta-Analysis: An overview with the help of R Software

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1. Introduction

When a clinician wants to take a decision on a treatment, procedure or diagnosis with respect to a disease or condition, outcome from a single research may not be right or helpful. Systematic review [1] provides the clinician with the strongest evidence about the available treatment or procedure related to a particular disease by including the evidences from the research studies which are similar in nature with respect to the scope, objective and the inclusion criteria of the study. Systematic reviews are different from the normal review or literature review as the later will not include all the relevant studies with respect to the particular problem and hence the conclusion drawn from it are not valid and generalizable. Meta-Analysis [2] is a statistical tool helps us to combine the results from the studies under consideration and arrive at an aggregate value for the parameters under study such as odds ratio, survival rate etc. This paper provides an overview of systematic review and meta-analysis with the use of an illustrative example. Meta-analysis is carried out using the r statistical software package.

2. Systematic Review process [3]

i. **Define research problem or question**
Systematic review starts with the defining the research question based on Participants, Interventions, Comparison, Outcomes, Study design (PICOS)

ii. **Define objectives for the study**
Develop objectives for the study which helps to focus on the research question or problem under study.

iii. **Define inclusion and exclusion criteria** [4]
It allows us to select the studies for research question under study. Criteria includes the following parameters
   a. Study population
   b. Type of the studies (Randomized Control Studies, observational studies etc)
   c. Randomization methods
   d. Outcome measures
   e. Time period
   f. Sample size
   g. Patient characteristics

iv. **Define Search process**
The research papers can be searched through various
   a. Free databases such as PubMed, Cochrane Library, Google Scholar and also through
   b. Paid databases such as EMBASE, Psychinfo, NIAHL based on the type of the study question.
   c. Search for unpublished papers from the university and clinical repositories, conference proceedings

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d. During this phase of the systematic review there are possible bias can occur

i. **Publication bias**[5]

This is the most important bias in the process of systematic review which will affect the quality of the review as a whole. Generally the studies with the positive results or outcome tend to be published more and studies with the negative results will be published rarely.

ii. **Language Bias**[6]
Majority of the journals or databases contains studies which are written in the English language and the papers written in the other languages tend to left out during the search process

v. Select studies and evaluate the quality of selected studies [7]
Studies to be selected from the pool of studies obtained through the search process matching the including criteria and not fulfilling exclusion criteria. Further the studies to be evaluated for possible bias in study design, analytical tools, reporting structure, relevancy of the outcome measures etc.

vi. Extract data
Once the studies are selected and evaluated for possible bias, the next to step is to extract data from the selected studies for further processing

vii. Synthesize the evidence
Evidence from various can be synthesized or combined with or without the help of meta-analysis.

viii. Meta-Analysis[2]
Meta-analysis helps us to arrive at pooled estimates of outcomes measures such as odd ratio, survival rate or effect size.

The effect size is the standardized mean difference between the two groups [8]. Effect size is calculated from the difference between the mean of the treatment group and control group divided by the pooled standard deviation of the two groups. The effect size can be interpreted using the method suggested Cohen [9] wherein if effect size is less than 0.2 it is interpreted as low, if it is between 0.2 and 0.5 it is interpreted as average and if it is above 0.8 it is interpreted as high.

Forest Plot [10]
Forest plot is used to plot the effect size of outcomes measure with respect to each study. It also contains the overall effect size combined from for all the studies under review represented by black diamond shaped component in the bottom of the plot. Forest plot is vertically split into two portions one is for the control group and another is for the treatment group. If the effect size lines are there in the treatment group then it can be inferred that the treatment group is better than the control. If the black diamond is placed after 0.8 in the horizontal scale then the effect size is also high.

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Funnel plot [11]

Funnel plot is helps us to detect any publication bias or heterogeneity in terms of the selected study by comparing the treatment effect against the precision of the selected studies. If a symmetric inverted funnel is obtained based on the data, then the systematic review does not have publication bias otherwise there is a possibility of publication bias or difference between the studies

ix. **Draw inferences , conclusion and report**

The last but the important step in the systematic review process is draw inferences from the information summarized from the various studies and preparing the report.

3. Systematic Review Standards

The widely used and popular standards for systematic review are the Cochrane review standards [12]. Cochrane collaboration consists of independent contributors from different countries, gathers and summarizes the evidences for health care decision making.

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [13] helps us to provide guidelines on minimum set of items for reporting in systematic reviews and meta-analysis.

4. Illustrative Example

The following section provides an example for carrying out Systematic review and Meta-analysis. The main important point to be considered by the readers that the following example is it is just for illustrative purpose as it involves only few studies and the actual systematic review is more rigorous, voluminous and takes 8 months to 1 year to complete.

1. **Research problem**
   Is stent placement is effective than angioplasty in the treatment of coronary artery disease
2. **Objective of the study**
   To assess effect of the stent placement in comparison with the angioplasty in treating the coronary artery disease
3. **Inclusion criteria for studies**
   Studies which are comparing the effects of stent with the angioplasty in treating the coronary artery disease

Table-1 : Sample Inclusion criteria

Parameters	Inclusion Criteria
Study population	Ischemic heart disease and new lesions of the native coronary circulation
Treatment group	Stent
Control group	Angioplasty
Study design	RCT
Outcome measures	1. Procedural success 2. Reduction in stenosis 3. Survival rate 4. Myocardial infraction rate 5. CABG rate

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Table-2: Sample Exclusion criteria

Parameters	Exclusion Criteria
Study population	1. Myocardial infraction within previous 7 days 2. Serious disease in left main coronary artery

4. Search Process

The following studies are retrieved from the google scholar and PubMed database based on the search term

"Comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease"

1. Fischman, D. L., Leon, M. B., Baim, D. S., Schatz, R. A., Savage, M. P., Penn, I., ... & Cleman, M. (1994). A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *New England Journal of Medicine*, *331*(8), 496-501.
2. Serruys, P. W., De Jaegere, P., Kiemeneij, F., Macaya, C., Rutsch, W., Heyndrickx, G., ... & Belardi, J. (1994). A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. New England Journal of Medicine, 331(8), 489-495.
3. Serruys, P. W., van Hout, B., Bonnier, H., Legrand, V., Garcia, E., Macaya, C., ... & Kiemeneij, F. (1998). Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *The Lancet*, *352*(9129), 673-681.
4. Betriu, A., Masotti, M., Serra, A., Alonso, J., Fernández-Avilés, F., Gimeno, F., ... & Calabuig, J. (1999). Randomized comparison of coronary stent implantation and balloon angioplasty in the treatment of de novo coronary artery lesions (START): a four-year follow-up. *Journal of the American College of Cardiology*, *34*(5), 1498-1506.
5. Savage, M. P., Douglas Jr, J. S., Fischman, D. L., Pepine, C. J., King, S. B., Werner, J. A., ... & Leon, M. B. (1997). Stent placement compared with balloon angioplasty for obstructed coronary bypass grafts. *New England Journal of Medicine*, *337*(11), 740-747.
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8. Rubartelli, Paolo, Luigi Niccoli, Edoardo Verna, Corinna Giachero, Marco Zimarino, Alessandro Fontanelli, Corrado Vassanelli et al. "Stent implantation versus balloon angioplasty in chronic coronary occlusions: results from the GISSOC trial." *Journal of the American College of Cardiology* 32, no. 1 (1998): 90-96.
9. Savage, M. P., Fischman, D. L., Rake, R., Leon, M. B., Schatz, R. A., Penn, I., ... & Baim, D. (1998). Efficacy of coronary stenting versus balloon angioplasty in small coronary arteries. *Journal of the American College of Cardiology*, *31*(2), 307-311.
10. Versaci, F., Gaspardone, A., Tomai, F., Crea, F., Chiariello, L., & Gioffrè, P. A. (1997). A comparison of coronary-artery stenting with angioplasty for isolated stenosis of the proximal left anterior descending coronary artery. *New England Journal of Medicine*, *336*(12), 817-822.

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It is important to note that the above 10 studies are retrieved only from two databases (Google scholar and PubMed) with a basic search operation. In real time search more studies can be retrieved from the above mentioned databases as well as other databases such as EMBASE and NIAHL etc.

5. Selection of Studies

The above studies to be evaluated for matching the inclusion criteria and also those studies which are matching inclusion criteria should not match the exclusion criteria. The studies 1 and 4 can be included from the above set of studies for further analysis (only for illustrative purpose. The two selected studies evaluated for possible bias such study design and sample size. Both the studies used the RCT and it was explicitly mentioned. Though the sample size is different for the studies, it is acceptable (205 vs 229). The outcomes measures such as Procedural success, diameter of the lumen, restenosis rate, survival rate, myocardial infraction rate, CABG rate etc are also defined in both the studies

Here also it is important to note that the two studies are selected and evaluated for possible bias with few parameters only for the illustrative purpose. In real time analysis more studies can be included and evaluated before proceeding to the next step.

6. Extraction of data

The following data needs to be extracted from the today studies for the synthesizing the information from the two studies (but not limited to) and data extracted is only for illustrative purpose

i. Study citation

a. @article{fischman1994randomized,
title={A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease},
author={Fischman, David L and Leon, Martin B and Baim, Donald S and Schatz, Richard A and Savage, Michael P and Penn, Ian and Detre, Katherine and Veltri, Lisa and Ricci, Donald and Nobuyoshi, Masakiyo and others},
journal={New England Journal of Medicine},
volume={331},
number={8},
pages={496--501},
year={1994},
publisher={Mass Medical Soc}
}

b. @article{betriu1999randomized,
title={Randomized comparison of coronary stent implantation and balloon angioplasty in the treatment of de novo coronary artery lesions (START): a four-year follow-up},
author={Betriu, Amadeo and Masotti, Monica and Serra, Antoni and Alonso, Joaquin and Fern{\'a}ndez-Avil{\'e}s, Francisco and Gimeno, Federico and Colman, Thierry and Zueco, Javier and Delcan, Juan L and Garc{\i}a, Eulogio and others},
journal={Journal of the American College of Cardiology},
volume={34},
number={5},
pages={1498--1506},
year={1999},
publisher={Elsevier}
}

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ii. **Sample size**

Study 1 – Stent group – 205, Balloon Angioplasty group - 202

Study 2 – Stent group -229, Balloon Angioplasty group -223

iii. **Duration of the study**

Study1 - Six months

Study2- Four years (Duration of the study varies significantly)

iv. **Follow up period**

Study1 – Six months (restenosis)

Study2 – Six months (restenosis),Four years for death, myocardial infarction (MI) and target vessel revascularization (Follow up period varies significantly)

v. **Analytical tool used**

Study-1

Continuous data – two tailed t test was used to test the difference between the sample means

Categorical data - Chi-Square test was used

Composite clinical end point – Kaplan Meir survival curve with Wilcoxon test to test the difference between the two means

Study-2

Continuous data – two tailed t test was used to test the difference between the sample means

Categorical data - Chi-Square test was used. For discrete variables Fisher's Exact test is used

Comparison of treatment means – Relative Risk with confidence interval used

Composite clinical end point – Kaplan Meir survival curve with log rank statistics to test the difference between the two means

vi. **Outcome measures**

Table-3: Sample Outcome Measures

	Study 1 Stent group	Angioplasty group	Study 2 Stent group	Angioplasty group
Procedural success	96.1%	89.6%	95%	84%
Increase in the Diameter of the luman	1.72±0.46mm	1.23±0.48mm	2.02±0.6mm	1.43±0.6mm
Restenosis rate	31.6%	42.1%	22%	37%
Coronary related disease rate	19.5%	23.8%	2.2%	2.8%
Revascularization rate	10.2%	15.4%	12%	25%

vii. **Results and conclusion**

Stent was effective in both the studies than the Balloon Angioplasty

viii. **Meta-Analysis**

Effect size of the outcome measures is calculated and forest and funnel plot are plotted as below

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This paper uses R software [14] to carry out the Meta-analysis. R is open source statistical software and it includes number of packages developed by the R community for specific purposes. R – Studio [15] is a widely used environment for executing R codes. This paper uses the following R packages for carrying out the Meta-Analysis which needs to be installed through R-Studio.

R package – Metafor [16]

It includes functions and plots to carry out Meta-analysis

The R code for calculating the effect size, forest plot and funnel plot is given below:

```
##install metafor package
Install.packages(metafor)
install xlsx package to import excel  extracted data set to r environment, The excel data set contains the following variable Study , Sample size, Mean and standard deviation of increase in size of luman for 8 sample studies
```

1. sno
2. study
3. s_samplesize_s
4. s_luman_mean
5. s_luman_std
6. a_samplesize_s
7. a_luman_mean
8. a_luman_stda

```
install.packages(xlsx)
# Load package metafor and xlsx
library(metafor)
library(xlsx)
Read data from metadata.xlsx from c directory with first row contains the variable name
mydata <- read.xlsx("C:/metadata.xlsx", 1)
##Calculate effect size using mean difference
effect <- rma(m1 = s_luman_mean, m2 = a_luman_mean,
              sd1 = s_luman_std, sd2 = a_luman_stda,
              n1 = s_samplesize_s, n2 = a_samplesize_s,
              method = "FE", measure = "MD",
              data = mydata)
##Plot forest plot
forest(effect)
##Plot funnel  plot
funnel(result.md)
```

Output

The forest plot is shown in the below chart-1

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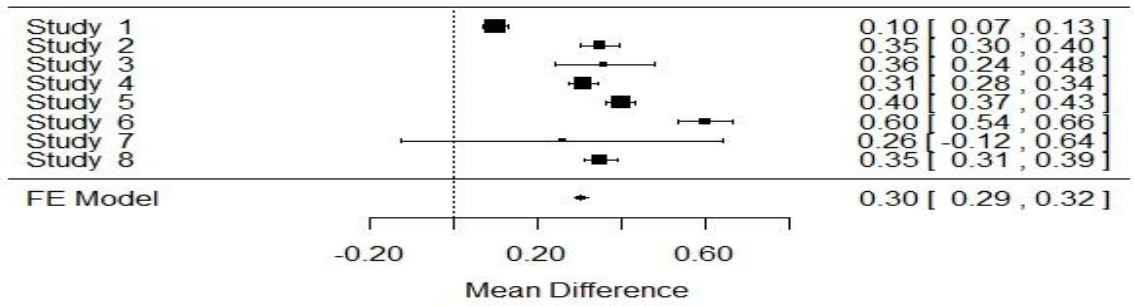
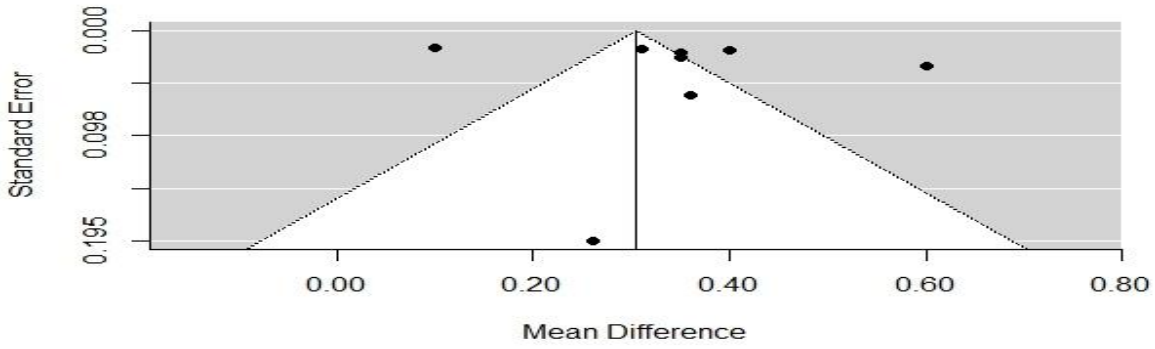
Chart-1: Forest Plot



The forest plot provided the effect size on the increase in luman size with respect to the stent group in comparison with angioplasty group based on the standardized mean difference. The right side of forest plot belongs to the stent group and left hand side belongs to the angioplasty group. It can be inferred that all lines are in the right hand side indicating the stent group is effective than the angioplasty group. The black diamond falls between 0.2 and 0.6, indicating the effect size is average.

The following chart-2 provides Funnel plot

Chart-2: Funnel Plot



The above chart shows there is a bias in the data which may be due to publication bias as the mean difference values does not fall into the inverted funnel area

Conclusion

The paper provided an overview of systematic review and meta-analysis. An illustrative example is used to explain the systematic review and meta-analysis process and m eta-analysis was carried out using the R statistical software.

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