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Evidence based Decision and Meta-Analysis with Applications in Cancer Research Studies

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Abstract: In the age of evidence based decision making through a systematic review of the literature, statistical meta-analysis has been extensively used to synthesise published summary data on a particular topic of interest from a number of independent studies in order to make credible and scientifically valid conclusions. The main objective is to estimate the common effect size as a pooled statistic for any selected outcome variables from the relevant data. There are several issues concerning the quality and type of the published summary statistics and inherent heterogeneity among the estimates of the effect size across the studies. This paper covers several estimators of the common effect size and some of their major impacts in meta-analysis through redistribution of weights to the individual studies. Some examples from recent literature on cancer research studies are used to illustrate the alternative estimators and discuss their usefulness in analysing data from randomised controlled trials in medicine.

Keywords: Evidence based decision, systematic review, meta-analysis, heterogeneity, randomised control trial

1 Introduction

Evidence based decision making is no more limited to medical and health studies, although it is yet the most frequently used technique in those fields. It has found its place in social sciences, education, agriculture, and many other disciplines. Government departments and international agencies are increasingly relying on the evidence based approach to undertake, analyse and evaluate programs and projects. Systematic reviews are the key to evidence based decision making. Recently the daily Guardian of the UK published an example of how the government is using and emphasising evidence based decision making (see [1]).

There are obvious advantages of using an evidence based approach to policy making and many researchers have come up with valid arguments supporting its application throughout the policy making cycle. Some of the key benefits (cf [2]) of using an evidence based approach to policy making include ensuring that policies are responding to the real needs of the community, highlighting the urgency of an issue or problem which requires immediate attention, sharing of information amongst other members of the public sector, potentially reduce government expenditure (which may otherwise be directed into ineffective policies or programs), and finally producing an acceptable return on the financial investment through decisions that are characterised by transparency and accountability.

The systematic review process ensures that all relevant studies are considered and properly evaluated to extract all the information to be used in the evidence based decision making. A significant part of the systematic review is the literature review that focuses on the research problem/topic based on all relevant publications identified from a search of electronic and printed sources. The aim is to locate and access all related materials, critically scrutinise and appraise them to synthesize all the research evidences relevant to that topic. Systematic reviews of related published randomized controlled trials are crucial to evidence based decision making in medicine and health sciences.

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Evidence based medicine (EBM) is an approach in medicine that aims to optimize decision-making by emphasising the use of evidence from well designed and conducted randomised controlled trials. It uses evidence from the outcomes of systematic reviews and randomised controlled trials as opposed to weaker types of results from research based on case-control and observational studies. Results obtained by meta-analysis form a crucial part of many evidence based decisions as it provides objective and strong evidence based on the published data. The summary statistics on various outcome variables are gathered from the published studies as part of a systematic review of the literature on a topic of interest. Meta-analysis enables pooling of results of independent studies on a particular topic. The final pooled effect size of any relevant outcome variable is taken to be the results produced by meta-analysis.

2 Systematic Review

In the evidence based decision process the systematic review of the literature plays a pivotal role. To ensure coverage of all relevant publications on the topic of interest for a given period of time extensive search is conducted on the all available electronic databases, published journals and conference proceedings in all or selected languages. The search keywords and phrases must include all possible combinations and synonyms in order to capture all studies published. In a medical study search is also needed on the name of the disease and the type of treatments in place.

As an example, in a recent study on ”Suture cruroplasty versus prosthetic hiatal herniorrhaphy for large hiatal hernia” (cf [7]) extensive searches on databases such as PubMed, Medline, Embase, Science Citation Index, Current Contents, and the Cochrane Central Register of Controlled Trials were conducted. The search used medical subject headings (MESH); ”hernia,” ”hiatal,” ”hiatus,” ”paraoesophageal/paraesophageal hernia,” ”laparoscopic repair,” ”comparative study,” ”prospective studies,” ”randomized/randomised controlled trial,” ”random allocation,” ’clinical trial,” and ”Human”. Furthermore searches were extended to the bibliographies of all the included primary studies and existing reviews by hand for additional citations. Moreover emails to the original authors of some of the trials were sent for clarification of data and to obtain unpublished, missing or additional information on various outcome measures.

2.1 Steps and actions in systematic reviews and meta-analyses

To ensure the quality of the studies included in the meta-analysis various steps and procedures were proposed and are in practice. The Cochrane Handbook (see [3]) outlines eight general steps for preparing a systematic review: (1) Defining the review question(s) and developing criteria for including studies, (2) Searching for studies, (3) Selecting studies and collecting data, (4) Assessing risk of bias in included studies, (5) Analysing data and undertaking meta-analyses, (6) Addressing reporting biases, (7) Presenting results and ”summary of findings” tables, and (8) Interpreting results and drawing conclusions.

2.2 Study quality standard

Until recently the common practice was to use the criteria set by the Quality of Reporting of Meta-analyses (QUOROM) (cf. [4]) statement to select studies for meta-analyses. This is now replaced by a more updated and rigorous set of criteria known as the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) statement (see [5]). There are many quality scales for studies included in a meta-analysis, and one of them is the Jadad score (cf. [6]) used to assess the quality of rendomised controlled trials. The scale ranges from zero to five, zero being the lowest quality and five being the highest achievable quality based on reporting of randomization, blinding, and withdrawals reported during the study period.

3 Statistical meta-analysis - quantitative analysis

Meta-analysis is a statistical method used to estimate combined or common effect size of the outcome variables in any randomised control trial or independent studies aiming to estimate the same parameters. The method provides a scientific mechanism to pool summary statistics from independent studies and to compute an estimate of the common effect of interest. The results from the pooled data of independent studies are used to make conclusions on the outcome variables. From a statistical view point, meta-analysis enables incorporation of summary data from independent studies/trials on the same topic. The increase in sample size in the meta-analysis, due to adding a number of studies, provides much more precise estimate of the common effect size and increases the power of statistical tests. In meta-analysis application of appropriate statistical model for the outcome variables is absolutely essential to reach the correct conclusion. The choice of a fixed effects model (FEM) or random effects model (REM) depends on the assumption that the common effect is fixed or differs from trial to trial.

In the FE model the inverse of the sample variance is used as weight in the calculation of the estimate of the common effect size, and the subsequent confidence

interval (CI). This leads to higher weights to studies with more precise outcomes or less spread. Under this model, larger studies gain higher weight than the smaller studies. This estimator is inappropriate for heterogeneous studies as it under estimates the statistical error.

In an attempt to address heterogeneity the RE model weights are calculated as the inverse of the sum of the sample variance and the between studies variance.

The recently proposed inverse variance heterogeneity (IVhet) estimator (see [9]) redistributes weight as with the FE model. But unlike the FE and RE model based estimators, the IVhet estimator solves the problem of over dispersion and is a better estimator than the RE estimator in terms of mean squared error (MSE) criterion. . Also the coverage probability of the CI of the common effect size based on IVhet estimator remains much closer to the nominal level than that of the RE model estimator.

4 Estimation of common effect size

Statistical meta-analysis uses summary statistics such as mean and standard deviation of the outcome variables from the published articles to estimate the common effect size. The estimation of the common effect size in the meta-analysis depends on the type of the outcome variable of interest. For binary (categorical) outcome variables the point estimate of the effect size is based on the odds ratio or relative risk or risk ratio, and the related confidence interval (CI) is based on the sampling distribution of their logarithm which approximately normally distributed. A slight adjustment is used for trails with zero cell counts to avoid division by zero. The estimation of effect size for the quantitative/continuous outcome variables is normally based on weighted mean difference (WMD) when all trials use the same unit of measurement, and the standardised mean difference (SMD) when different unit of measurements are used by different trials. In both cases the CI is constructed based on the normal distribution of the WMD or SMD.

The forest plot summarises all the numerical results and represents the confidence intervals of individual studies as well as the common effect estimate of meta-analysis with a diamond showing the actual position of the CI of the relevant mean effect measure. From the forest plot one could observe any trend towards a particular intervention as well as finds out if the effect size is statistically significant. If appropriate subset analysis is also included in the forest plot to investigate if there are significant differences of the effect size within any subset of studies. Often sensitivity analysis is also undertaken to find out how sensitive the estimate of the common effect is with respect to one or more studies included in the meta-analysis.

Another issue in meta-analysis is the publication bias. This occurs because of selective publication of the outcomes of the research that favour the sponsor's proposition, and ignores the ones with negative or unfavourable outcomes. To detect publication bias in meta-analysis funnel plots are used. This plot indicates presence of publication bias if it demonstrates asymmetry.

4.1 The estimators of common effect

Consider a meta-analysis of k independent studies. Let δ_j be the true effect size of an outcome variable for the jth study and $\hat{\delta}_j$ be its estimate. Let the common or average effect be θ, and the individual study effects $\delta_1, \delta_2, \ldots \delta_k$ depart from θ with random and/or systematic errors. Furthermore, θ is estimated from the estimated effect size of the k studies using an empirically weighted mean estimator $\hat{\theta}_w$. This estimator can be quantified in terms of its difference from the non-empirically weighted arithmetic mean estimator,

$$\hat{\theta}_{AM} = \frac{1}{k}\sum_{j=1}^{k}\hat{\delta}_j \tag{1}$$

by the following expression

$$\begin{aligned}\hat{\theta}_w &= \hat{\theta}_{AM} + \frac{1}{k}\sum_{j=1}^{k}\left(w_j - \frac{1}{k}\right)\left(\hat{\delta}_j - \hat{\theta}_{AM}\right)\\ &= \hat{\theta}_{AM} + k\rho_{w\hat{\delta}}\sigma_w\sigma_{\hat{\delta}}\end{aligned} \tag{2}$$

where $\sigma_{\hat{\delta}}$ and σ_w are the standard deviation of $\hat{\delta}_j$ and the weights, and $\rho_{w\hat{\delta}}$ is the coefficient of correlation between the weights and the effect estimates. For the FE model, the weighted inverse variance estimator,

$$\hat{\theta}_{IVhet} = \frac{1}{k}\sum_{j=1}^{k} w_j\hat{\delta}_j \tag{3}$$

has weights

$$w_j = \frac{\frac{1}{v_j}}{\sum_{j=1}^{k}\frac{1}{v_j}} \tag{4}$$

where w_j sums to 1, and the sampling error variance of the estimator of the jth study is v_j . The arithmetic mean estimator, as in (1) is unbiased. But, is a biased estimator. However, the FE estimator does improve over the arithmetic mean estimator because the weights don't just increase the bias, but (by doing so) they also make the variance of the estimator much smaller and trade off this bias.

Under the RE model the weighted estimator is defined as

$$\hat{\theta}_{RE} = \frac{1}{k}\sum_{j=1}^{k} w_j^*\hat{\delta}_j \tag{5}$$

where the weights are

$$w_j^* = \frac{\frac{1}{\sigma_j^2}}{\sum_{j=1}^{k}\frac{1}{\sigma_j^2}} \tag{6}$$

Table 1: Summary of the three alternative estimators of the common effect size

	IVhet	RE	AMhet
Weight	$w_j = \frac{\frac{1}{v_j}}{\sum_{j=1}^{k}\frac{1}{v_j}}$	$w_j^* = \frac{\frac{1}{\sigma_j^2}}{\sum_{j=1}^{k}\frac{1}{\sigma_j^2}}$	$\frac{1}{k}$
Estimator	$\hat{\theta}_{IVhet} = \frac{\sum_{j=1}^{k} w_j\hat{\delta}_j}{k}$	$\hat{\theta}_{RE} = \frac{\sum_{j=1}^{k} w_j^*\hat{\delta}_j}{k}$	$\hat{\theta}_{AM} = \frac{1}{k}\sum_{j=1}^{k}\hat{\delta}_j$
Variance	$\sum_{j=1}^{k} w_j^2(v_j+\tau^2)$	$\frac{1}{\sum_{j=1}^{k}\frac{1}{\sigma_j^2}}$	$\sum_{j=1}^{k}\frac{v_j+\tau^2}{k^2}$

Table 2: Summary of all the RCTs included in the study

Authors	Year/Country	Type of Study	Number of Patients	
			D1	D2
Dent et al	1988/ South Africa	RCT	22	21
Robertson et al	1994/ Hong Kong	RCT	25	29
Bonenkamp et al	1995/ Netherlands	RCT	513	483
Cuschieri et al	1999/ UK	RCT	200	200
Degiuli et al	2004/ Italy	RCT	76	86
Chew-Wun Wu et al	2006/ Taiwan	RCT	110	111
Total			**946**	**930**

Table 3: Summary statistics of the outcome variables under RE model

Outcome Variables	Pooled OR or WMD (95% CI)	Test for overall effect		Test for heterogeneity		
		Z	p-value	Q	p-value	I^2 Index
Length of hospital stay	-5.67 (-9.83, -1.51)	-2.56	0.01	36.34	0.0001	86.2% [72.2%; 93.2%]
Complication rate	0.42 (0.27, 0.66)	4.33	0	11.85	0.0369	57.8% [0%; 82.9%]
Anastomotic leak rate	0.40 (0.25, 0.63)	4.13	0	1.72	0.8868	0% [0%; 26.1%]
Re-operation rate	0.33 (0.15, 0.72)	2.23	0.023	3.52	0.3179	14.8% [0%; 87%]
30-day mortality rate	0.59 (0.40, 0.85)	5.14	0	1.86	0.8684	0% [0%; 31.7%]
5-year survival rate	0.97 (0.78; 1.20)	9.03	0	1.67	0.797	0% [0%; 50.1%]

with $\sigma_j^2 = v_j + \tau^2$ in which v_j is the sampling error variance and τ^2 is a moment-based estimate of the between-studies variance, which is assumed to be a constant for each study. The variance of any weighted estimator is given by

$$var(\hat{\theta}_w) = \sum_{j=1}^{k} w_j^2 var(\hat{\delta}_j) \qquad (7)$$

where w_j's are the weights that sum to 1. Table 1 provides the three different estimators along with their weights and variances. Tables 2 and 3 contain information about the RCTs included in the meta-analysis and summary statistics of the relevant data respectively.

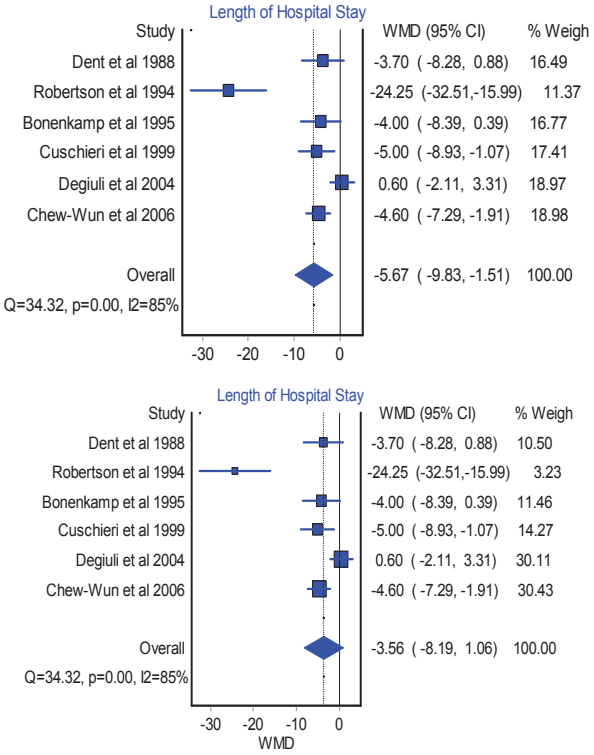

Fig. 1: Forest plot of length of hospital stay under RE (top) and IVhet models (LHS favours D1)

4.2 Heterogeneity issue

The heterogeneity of the estimated effect size for different studies is often a major issue in meta-analysis. The obvious reason for heterogeneity is the sampling error/variation due to random causes. But in case of the independent RCTs there is additional variation due to the differences in the quality of the trials such as the hospital environment, surgeon, equipment etc and the associated bias. These non-random variation makes significant impact on the overall spread of the estimator of common effect size causing significant heterogeneity as shown in Doi et al. [8].

As a routine procedure the heterogeneity among the estimated effect size of outcome variables of different studies is assessed using the Cochran's Q and I^2 statistics. The p-value of the test indicates the plausibility of the null hypothesis (of homogeneity of mean effects), given the observed data. Thus for a very small p-value (usually less than 5%) the hypothesis of equality of the variances of mean effects is rejected. As a consequence researchers are required to use appropriate method of estimation to overcome the problem of heterogeneity. The current choice is to use the RE model, but alternative methods such as the IVhet method should be encouraged given the flaws with the RE method. The RE model allows for an extra between-study variation in estimating the common

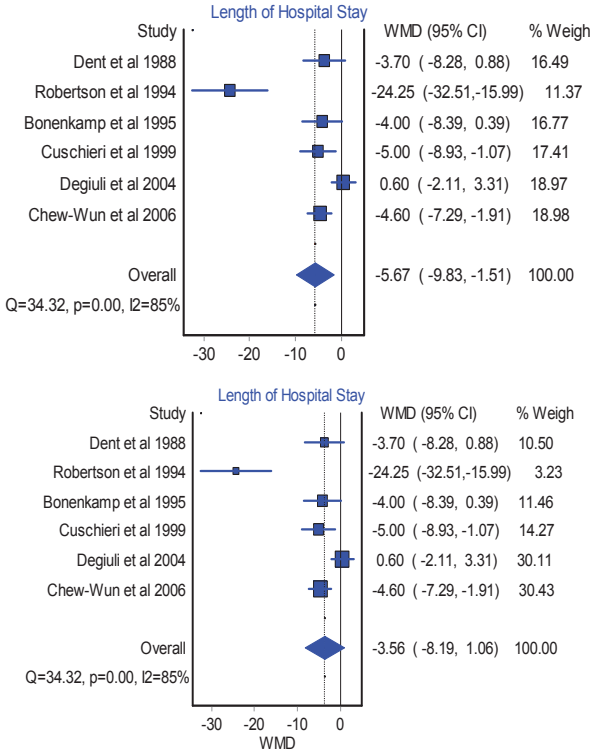

Fig. 2: Forest plot of operation complications under RE (top) and IVhet models (LHS favours D1)

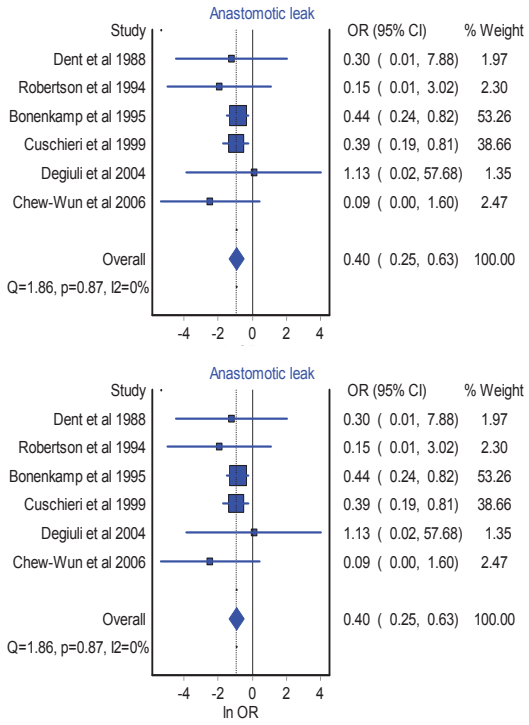

Fig. 3: Forest plot of anastomotic leak under RE (top) and IVhet models (LHS favours D1)

effect. But there have been many criticisms of the RE method due to its inappropriate distribution of weights with effectively smaller weights for larger studies and higher weights for smaller studies. Another better alternative the quality effect (QE) model has also been proposed by Doi and Thalib [10], and an implementation platform MetaXL has been created by Barendregt and Doi [12] as an add-on to MS Excel that is free of charges. Further details on quality effect model see Doi and Thalib [11]. This method has been refreshed by Doi et al. [8].

4.3 Mean and median issue

Normally published studies use mean and standard deviation as summary measures for centre and spread of common outcome variables. However, in some studies median and interquartile range (IQR) are reported for the same measures. In other studies the minimum, maximum, IQR, and range are used. Unfortunately, meta-analysis method could only use the mean and standard deviation. If the distribution of the outcome variable is approximately symmetrical, the median is no different from the mean, but in case of skewed distribution the issue becomes serious. Hozo et al. [13] provides some useful conversion formula to mean and standard deviation from median and other summary statistics. Sometimes the authors of the published paper are helpful to access the appropriate summary statistics via email or any other mode of communication.

5 Meta-analysis in a cancer research study

The statistical meta-analysis has been applied in many different fields in recent years. But no other discipline has used it more than medical and health sciences. There are many meta-analyses in the literature in the area of cancer research and randomised controlled trials (RCTs) on various surgical procedures in cancer treatment.

Recently Memon et al. [14] conducted a meta-analysis of randomized controlled trials to evaluate the efficacy and drawbacks of limited (D1) versus extended lymphadenectomy (D2) for proven gastric adenocarcinoma based on the studies published from 1988 to 2006 using RE model. We consider the data from the same six RCTs to produce meta-analysis using the IVhet estimator and compare it with the RE model estimator using the MetaXL package. Each of the six independent studies reported on six outcome variables, namely (1) length of hospital stay, (2) complication rate, (3) anastomotic leak rate, (4) re-operation rate, (5) 30-day mortality rate, and (6) 5-year survival rate.

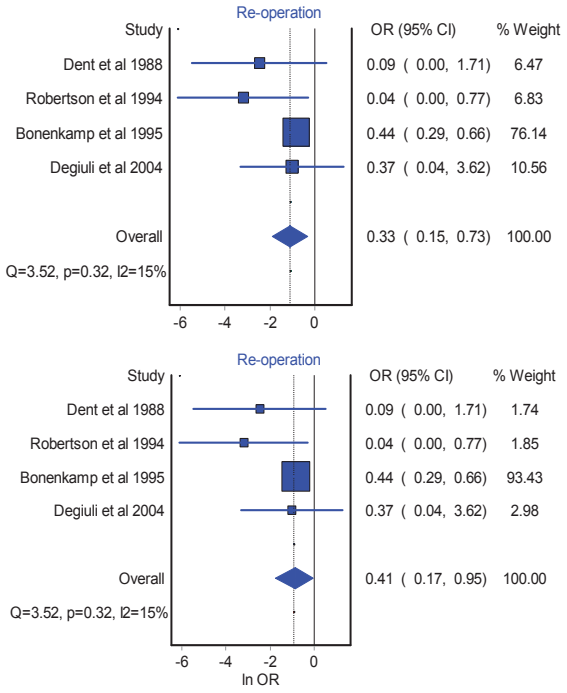

Fig. 4: Forest plot of re-operation under RE (top) and IVhet models (LHS favours D1)

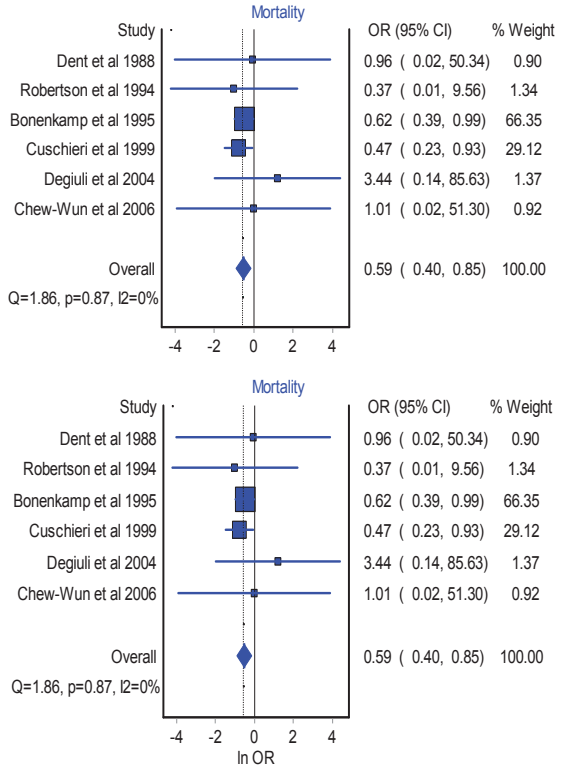

Fig. 5: Forest plot of mortality under RE (top) and IVhet models (LHS favours D1)

5.1 Forest plots

Forest plots draw the 95% confidence intervals for the common effect size such as (log) odds ratios, or weighted mean differences (WMD) as horizontal lines. Confidence intervals show arrows when they exceed specified limits. In the forest plot, a square indicates the estimated treatment effect with the size of the square representing the weight attributed to the relevant study. The pooled estimated (log) OR/WMD is obtained by combining (log) ORs/WMDs of all the studies using the two methods. The pooled common effect is represented by the diamond and the width of the diamond depicts the 95% confidence interval. For the binary outcomes the null (log) OR line is drawn at zero or for OR at one, and for the continuous outcomes, the null WMD line is drawn at zero. The forest plots for the six outcome variables of the randomised controlled trials to evaluate the efficacy and drawbacks of limited (D1) versus extended (D2) lymphadenectomy for proven gastric adenocarcinoma are given in Figures 1-6.

5.2 Funnel plots for publication bias

Funnel plots represent the scatterplot of the log odds ratios or WMDs against their standard errors. A funnel plot of standard error versus treatment effect from individual studies in a meta-analysis should look like a symmetrical inverted funnel if there is no publication bias. Points falling to one side of the funnel indicate presence of publication bias. Funnel plots for the outcome variables of the study to evaluate the efficacy and drawbacks of limited (D1) versus extended (D2) lymphadenectomy for proven gastric adenocarcinoma are given in Figures 7-11.

6 Results and conclusions

In the six trials there were a total of 1876 patients ($D1 = 946,\ D2 = 930$). The meta-analysis of the six outcome variables shows all of them favoured D1 over D2 group. Under the RE model there is a statistically significant reduction of (i) 5.67 days in hospital stay (WMD -5.67, CI -9.83, -1.15, $p = 0.01$), and only 3.56 days under IVhet model, which is insignificant, with (WMD -3.56, CI -8.19, 1.06, $p = 0.13$); (ii) 58% reduction in relative odds of developing postoperative complications (OR 0.42, CI 0.27, 0.66, $p = 0.0002$) under RE model, and 52% reduction (OR 0.48, CI 0.28, 0.82, $p < 0.001$) under IVhet model; (iii) 60% reduction in anastomotic breakdown (OR 0.40, CI 0.25, 0.63, $p = 0.0001$) under RE model, and the same under IVhet model (since the $I^2 = 0$); (iv) 67% reduction in re-operation odds (OR 0.33, CI 0.15, 0.72, $p = 0.006$) under RE model, and 59% reduction under IVhet model

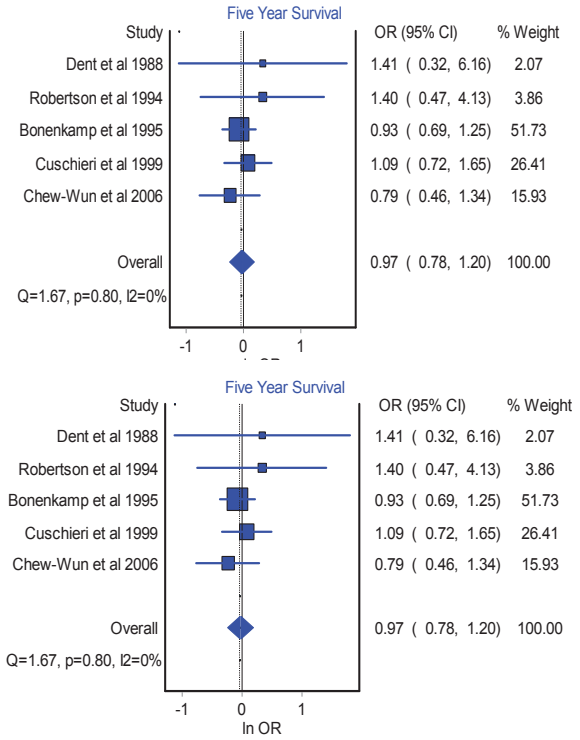

Fig. 6: Forest plot of five-year survival time under RE (top) and IVhet models (LHS favours D1)

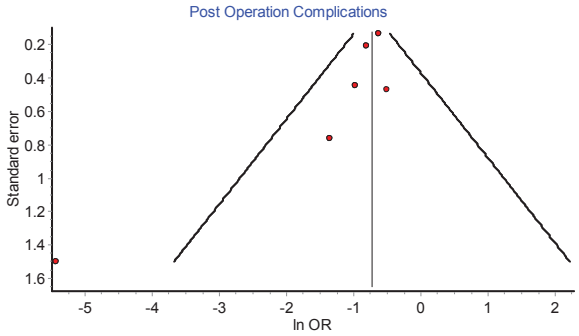

Fig. 7: Funnel plot of post operation complications

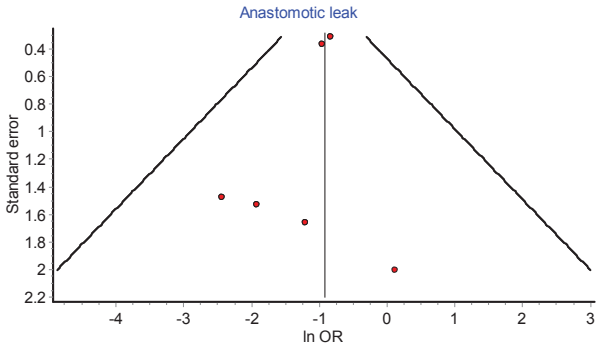

Fig. 8: Funnel plot of anastomotic leak

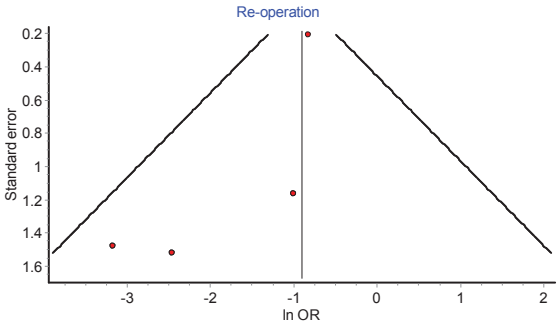

Fig. 9: Funnel plot of re-operation

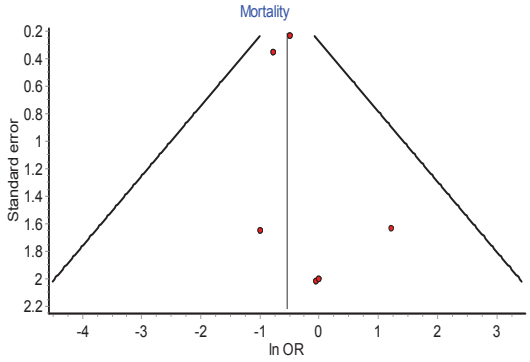

Fig. 10: Funnel plot of mortality

with (OR 0.41, CI 0.17, 0.95, $p = 0.04$) ; (v) 41% reduction in 30-day mortality odds (OR 0.59, CI 0.40, 0.85, $p = 0.0054$) under RE model, and the same for the IVhet model (as $I^2 = 0$); and only 3% reduction in the odds of 5-year survival (OR 0.97, CI 0.78, 1.20) in D1 over D2 gastrectomy patients under both models.

Based on this meta-analysis under the RE model we conclude that D1 gastrectomy is associated with significant fewer anastomotic leaks, postoperative complication rate, re-operation rate, decreased length of hospital stay, less 30-day mortality rate, and the 5-year survival in D1 gastrectomy patients compared to the D2 cohort. The conclusions on the estimate of the common effect for the outcome variables anastomotic leak, mortality and five year survival are the same under both the models. This is because there is no significant variation (heterogeneity) among the studies. For the other three outcome variables there are some differences in the estimate of the common effect size. For the analysis under the IVhet model, there is slightly less reduction of number of days (3.56 under IVhet vs 5.67 under RE) of hospital stay, slightly less reduction in postoperative complications (52% under IVhet vs 58% under RE) and re-operation rate (59% under IVhet vs 67% under RE).

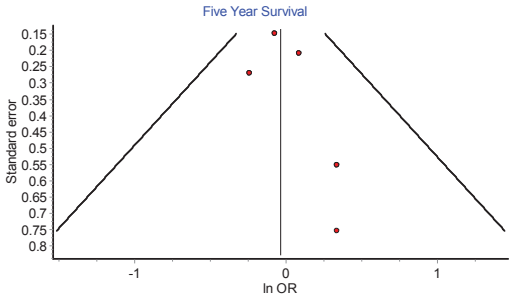

Fig. 11: Funnel plot of five-year survival

Overall the D1 limited surgery is supported by the data over its competitor D2 extended surgery for all the outcome variables under both the models. Given the problems with the RE method, we conclude it under estimated the statistical error with hospital stay leading to a spuriously significant result.

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