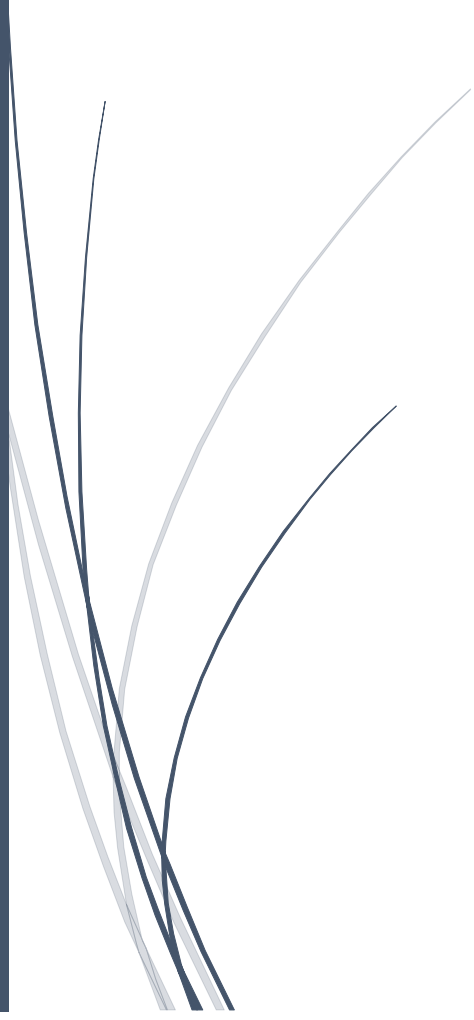
5/12/2020

Clinical Biostatistics

(BCA_CLB – Assignment 2)



Student ID: 6707

(Unikey-skau6707)

Report 1 (Diagnostic Tests Performance)

Introduction

Pancreatic cancer is the disease caused by development of malignant cells in the parts of pancreas which is leading cause of cancer death worldwide but serum biomarker-based screening for pancreatic cancer could greatly improve survival in appropriately targeted high-risk populations. In this study, two serum biomarker values recorded on 137 patients were compared to choose best marker for early detection of the tumor and a threshold for the best marker is obtained that results in high sensitivity and high specificity.

Methodology

To investigate the best serum biomarker, area under the ROC curve is used as accuracy measure to compare the performance of two diagnostic tests where ROC curve is a plot of the true positive rate against the false positive rate for the different possible cut-points of a diagnostic test. (http://gim.unmc.edu/dxtests/roc1.htm). Usually, the closer the area is to 1 better is the performance of the test. Next, the cut-point for the best marker is selected as a value for which sensitivity and specificity measures are maximised. The analysis was performed in statistical software R (version 3.6.1) using "cutpointr" package.

Descriptive analysis

Out of total 137 patients, 87 patients were found to have a positive test for pancreatic cancer and 50 had negative results. The first and second cancer serum values varies between 2.4 to 24000 units and 3.70 to 1024 units respectively. Further, 50% of the patients were recorded with serum levels less than 44.2 units, when diagnosed using first serum biomarker and 50% of the patients had below 16.70 units of serum value when diagnosed using second serum bio marker. And, the average value for the serum levels recorded for first and second biomarker are 1132.5 units and 43.18 units respectively. The detailed summary of the two biomarkers are given in table 1.1.

Biomarker	Minimum	Q1	Mean	Median	Q3	Maximum	Std. Dev
Y1(first)	2.4	10	1132.5	44.2	521.5	24000	3086.3
Y2(second)	3.70	10.5	43.18	16.70	35	1024	114.8

Table 1.1: Descriptive statistics of two cancer serum biomarkers.

Statistical analysis

On investigation, first cancer serum biomarker was found to perform better than the second biomarker as the area under the ROC curve was greater for the curve obtained using values of the first serum biomarker (i.e. 86.64%) and the area under the curve obtained using values of second biomarker is 70%. The plots of ROC curves are given in Figure 1.1(a) and 1.1(b).

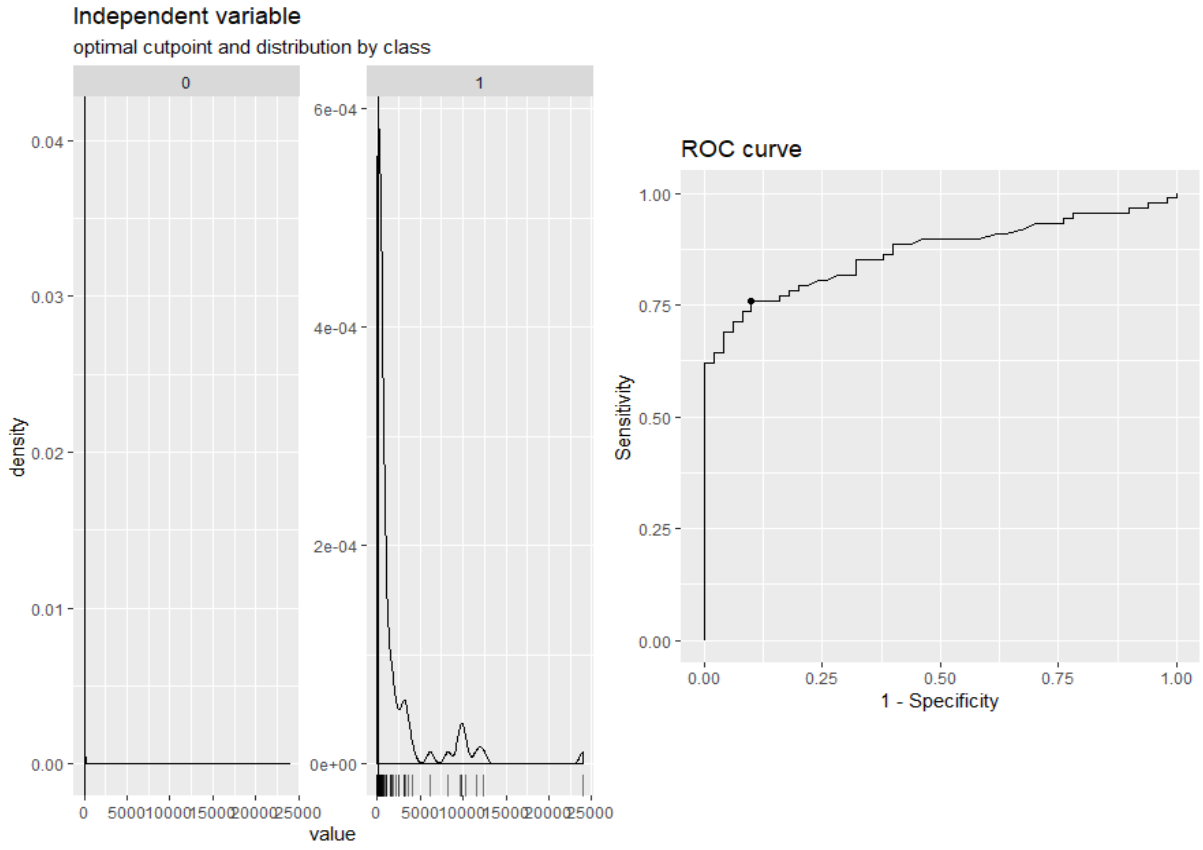


Figure1.1(a): ROC curve of values obtained for first serum biomarker (far right)

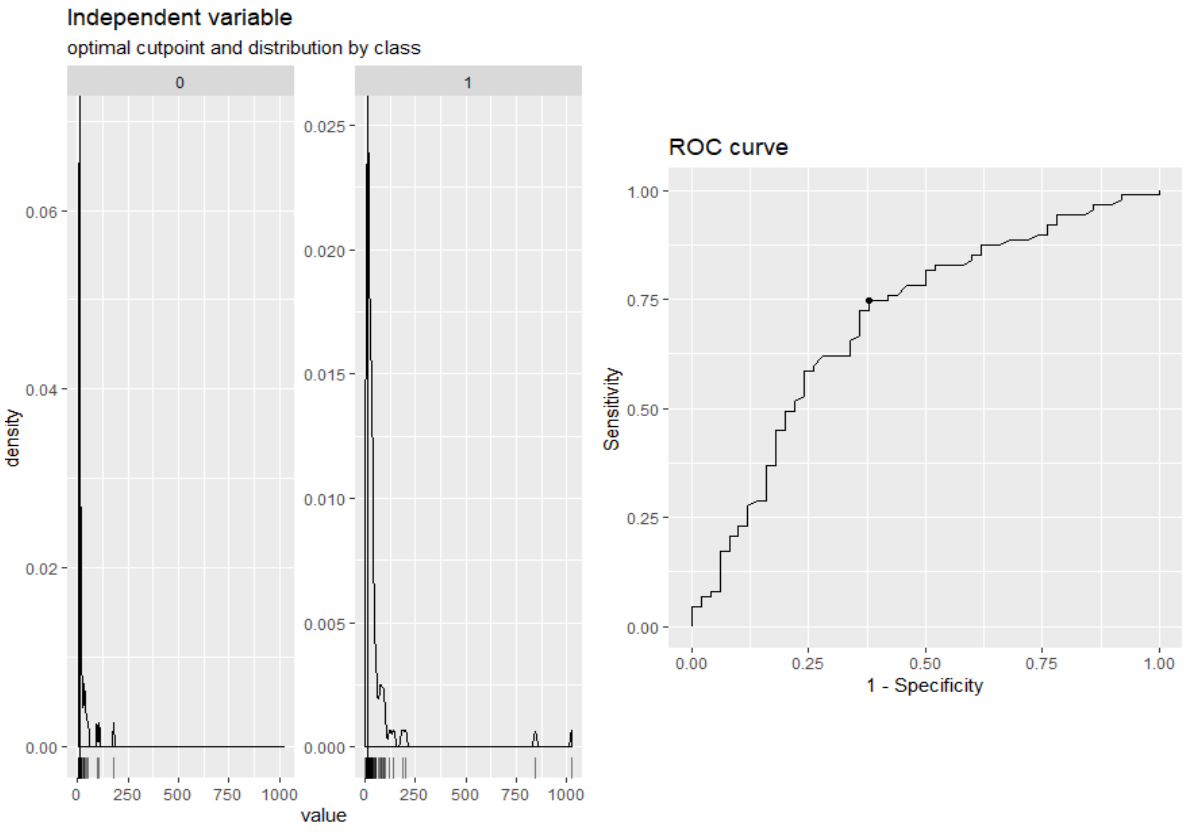


Figure1.1(b): ROC curve of values obtained for second serum biomarker (far right).

Further, the optimal cut-point of 39.3 units was obtained for the best biomarker (i.e. first biomarker) to distinguish between healthy and diseased patients. Thus, the patients with serum levels below 39.3 units would be treated as healthy patients and the ones who have serum levels > 39.3 units would be treated as positive for pancreatic cancer. In addition, the measures such as sensitivity and specificity are 76% and 90% respectively, for the first biomarker whereas the probability of correctly classifying the diseased and healthy patients is 0.75 and 0.62 respectively for the second biomarker. Moreover, the accuracy measure for the first biomarker is about 10% more of that obtained for second biomarker. It is evident from the accuracy measures given in table 2.1 that first serum biomarker is more efficient than second.

Biomarker	AUC	Cut-point	Sensitivity %	Specificity %	Accuracy %	TP	FN	FP	TN
Y1	0.87	39.3	76	90	81	66	21	5	45
Y2	0.70	13	75	62	70	65	22	19	31

Table 2.1: Statistical summary of measures for two diagnostic tests.

Discussion

In summary, ROC analysis is overall an efficient method in diagnostic test evaluation. This study was carried by assuming that the values of serum levels are recorded for same group of patients and there is no confounding factor. However, while we compare the diagnostic tests, other factors such as age or sex could impact the analysis as then the cut-off would not be treated equivalently. Thus, a proper study design is necessary for vital and reliable conclusion. Moreover, we could use test results of first serum biomarker in conjunction with second biomarker as the accuracy for second biomarker is also fairly good with about 70%.

Report 2 (Meta-analysis)

Introduction

Aminoglycosides are a class of antibiotics used mainly in the treatment of aerobic gram-negative bacilli infections. But, the occurrence of aminoglycoside-induced acute renal failure remains commonplace. Therefore, an antibiotic is required that limits the side effects and is better than the commonly used antibiotic such as aminoglycosides. Thus, 11 studies were conducted in order to evaluate the effect of two antibiotics but due to small sample size of few studies, no significant findings were obtained to reach best conclusion. Hence, meta-analysis was carried on these 11 studies to investigate whether overall new antibiotic 2 has lower rate of abnormal kidney function positive tests. In addition, heterogeneity was assessed to find if there are genuine differences underlying the results of studies.

Methodology

Meta-analysis is a statistical procedure for combining data from multiple studies and can be performed when there are multiple scientific studies addressing the same question. Thus, meta-analysis was performed on 11 studies to estimate overall effect of antibiotic 2 as we want to know whether it has lower rate of nephrotoxicity compared to antibiotic 1. To begin with the analysis, group of patients with antibiotic 2 was treated as experimental group and another group with antibiotic 1 as control group. There are several measures to estimate the treatment effect for binary outcome data but in this study, the estimates are obtained in the form of odds ratio (OR) where OR is the ratio of the odds of an event, with 1 indicating no effect and value greater or smaller than 1 indicating higher or lower effect respectively . The pooled estimate is obtained using Mantel-Haenszel method and it is obtained by calculating a weighted average of the treatment effects from the individual trials. The choice of pooling method is for a reason that it has been shown to be more robust when data are sparse.

Both fixed effect and random effects meta-analysis was conducted during the analysis. In fixed effect model the true effect of treatment is assumed to be fixed for each study whereas in random effects model this assumption is relaxed and incorporates the estimate of between study variation. The heterogeneity estimate τ^2 is computed using DerSimonian and Laird method and heterogeneity is assessed using Cochran's Q statistic by comparing with χ^2 distribution at 10 degrees of freedom and p-value compared at 10% significance level. I^2 is another measure to assess heterogeneity that describes the percentage of total variation across studies.

Moreover, the forest plot is used to summarise the results and funnel plot is constructed for detecting bias, which plot each study's summary outcome measure against sample size.

All these measures and plots were obtained by performing the meta-analysis in statistical software R (version 3.6.1) using "meta" package.

Descriptive Statistics

In total 11 studies were combined to assess the overall treatment effect. The outcome of the study was binary means either a patient is tested positive or negative for nephrotoxicity given the antibiotic. Out of 11 studies, the smallest study from control group involves just 11 patients in total out of which 2 were tested positive for the abnormal kidney function and from largest study of 223 patients, 37 were tested positive. On the other hand, from treatment group smallest

study was performed on 15 patients out of which 2 were tested positive for nephrotoxicity and from largest study of 241 patients, 26 were tested positive. On average, the number of patients who are tested positive for the disease in treatment group are about 10 and those in control group are 14 patients among 11 studies.

Group	Min	Q1	Median	Mean	Q3	Max	Std Dev
Control							
(Sample)	11	41.5	83	83.3	102.5	223	58.1
(Tested Positive)	2	8	13	14.2	18.5	37	9.6
Treatment							
(Sample)	15	43.5	92	90.7	100	241	65.2
(Tested Positive)	2	4	9	9.5	12.5	26	7.1

Table 2.1: Descriptive statistics for the sample size of treatment and control group and the number of individuals tested positive for the test in each group.

Statistical Analysis

The pooled estimate of odds ratio obtained from both fixed and random effect model suggested that the newer Antibiotic 2 has a lower rate of abnormal kidney function positive tests. The results obtained are discussed as follows:

- **Fixed effects model**

  On performing the meta-analysis using Mantel-Haenszel method an overall estimate of odds ratio is obtained as 0.56 which means that the odds of abnormal kidney function among patients who are given antibiotic-2 is 44% lower than the odds among patients given antibiotic-1. The confidence-interval obtained for the combined odds ratio is (0.43, 0.73) which suggests that the odds of abnormal kidney function for patients given antibiotic-2 can be as low as 27% and as high as 57% compared to patients given antibiotic-1.

- **Random effects model**

  The odds ratio obtained using random effects model is similar to that of fixed effect model which is 0.57 means the odds of abnormal kidney function among patients who are given antibiotic-2 is 43% lower than the odds among patients given antibiotic-1. And, the corresponding confidence interval is (0.43, 0.75) which is slightly wider than the fixed effect model. From confidence interval, it can be stated that the odds of abnormal kidney function among individuals given antibiotic-2 varies between 25% to 57%.

The Cochran's Q statistic (i.e.10.13) when compared to χ^2 distribution with 10 degrees of freedom gives p-value of 0.43 which is greater than 0.1 (at 10% significance level). This clearly indicates that all studies are evaluating the same effect. Also, I^2 = 1.3% represents low heterogeneity, which is consistent with the result obtained from statistical test for heterogeneity. The forest plot given in Figure 2.1 includes the treatment effect estimates for individual study as well as combined studies estimate with their confidence intervals. We can see that the distribution of weights is similar in both fixed and random effects model where more weights are given to large studies and less weight given to small studies which also favours the homogeneity assumption.

Lastly, the funnel plot (in Figure 2.2) seems to be little asymmetric which might be an indication of publication bias as there are no studies with odds ratio greater than 1 in the lower right end which means the studies with odds ratio unfavourable to intervention (i.e. antiobiotic-2) are not published.

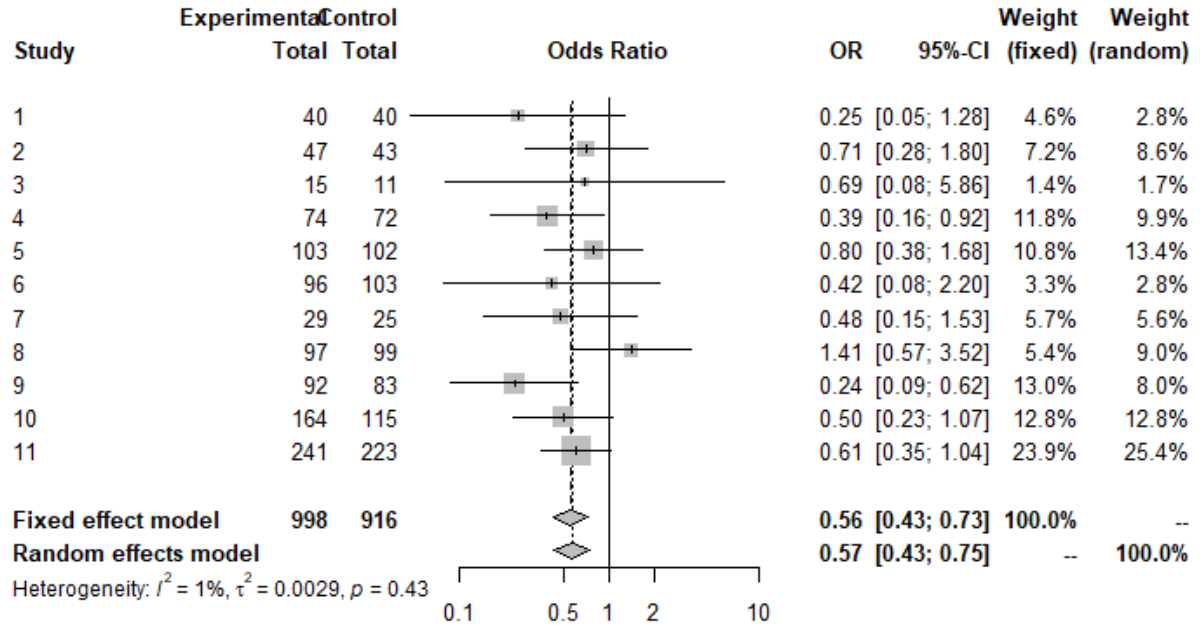


Figure 2.1: Forest plot of the meta-analysis (displaying summary of the statistics)

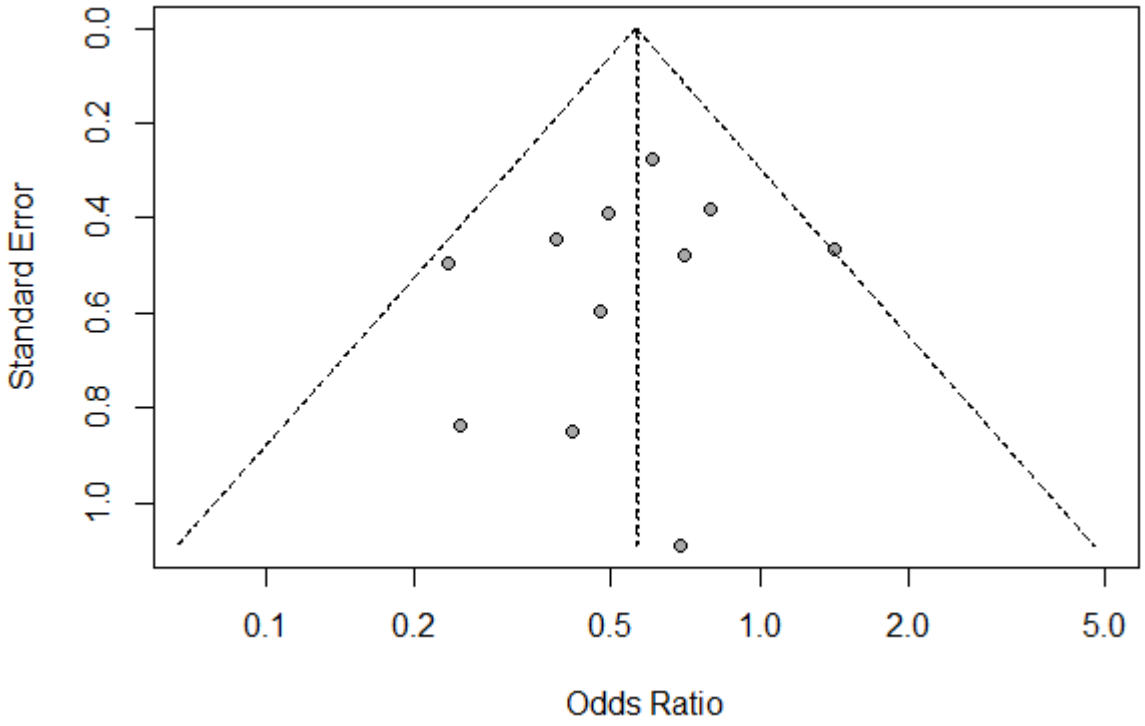


Figure 2.2: Funnel plot to assess bias

Discussion

The collective findings of the analysis strongly suggest that overall, antibiotic-2 has lower rate of abnormal kidney function compared to antibiotic-1. This means the commonly used antibiotic-1 can substantially increase the risk of nephrotoxicity. However, several issues should be considered while interpreting the results. Since, the trial specific odds ratio for 10

studies out of 11 are less than 1 indicating decreased risk in nephrotoxicity when using antibiotic-2 which indicates some sort of publication bias. Moreover, the studies involved in meta-analysis are quite less in number, so overall estimate should be employed with care. Another issue is that Cochran's Q has a limitation that it is less effective at detecting true heterogeneity with small number of trials but I^2 can be calculated and compared across meta-analyses of different sizes, of different study types, and using different types of outcome data. Thus, I^2 would be much more reliable measure at detecting true heterogeneity.

References:

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3075824/ (Introduction-1)
2. Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3755824/
3. http://gim.unmc.edu/dxtests/roc1.htm
4. Meta-analysis-Chapter 6: Choosing effect measures and computing estimates of effect https://training.cochrane.org/handbook/current/chapter-06#section-6-1

APPENDIX

```
######### QUESTION 1 ############

suppressMessages(library(tidyverse)) # suppress startup messages
## use 'col_types = cols()' to supress the column guessing messages

marker<-read_csv("markers.csv",col_types = cols())
library(cutpointr)
table(marker$d)
summary(marker$y1);summary(marker$y2)
(s1=sqrt(var(marker$y1)));(s2=sqrt(var(marker$y2)))

m1<-cutpointr(data= marker,x=y1,class = d)
summary(m1)
plot(m1)
m2<-cutpointr(data= marker,x=y2,class = d)
summary(m2)
plot(m2)


######## QUESTION 2 ############

akf<-read_csv("akf.csv",col_types = cols())
summary(akf$ag1.n);summary(akf$ag1.pos)
(s3<-sqrt(var(akf$ag1.n)));(s4<-sqrt(var(akf$ag1.pos)))
summary(akf$ag2.n);summary(akf$ag2.pos)
(s5<-sqrt(var(akf$ag2.n)));(s6<-sqrt(var(akf$ag2.pos)))
library(meta)

meta <- metabin(event.e = ag2.pos,n.e = ag2.n,event.c = ag1.pos, n.c = ag1.n,
            studlab = Study, data = akf,sm="OR")
summary(meta)
forest(meta, leftcols = c("studlab", "n.e", "n.c"), fontsize=10,showweights=T)
funnel(meta)
```