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Procedia Computer Science 86 (2016) 212 – 215

Procedia Computer Science

2016 International Electrical Engineering Congress, iEECON2016, 2-4 March 2016, Chiang Mai, Thailand

Interval estimation of diagnostic odds ratio in meta-analysis by means of profile likelihoods

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Abstract

The objectives of this paper are to (1) derive the profile maximum likelihood estimator $(PMLE)$ for a true diagnostic odds ratio over across k studies in meta-analysis, (2) build the confidence intervals by replacing $PMLE$ into the variance of logarithm of each diagnostic odds ratio, leading to two profile likelihood intervals ($WPLF$, $WPLR$), (3) create bootstrapping confidence interval ($BOOT$) from $PMLE$ distribution by using the percentile, (4) compare the interval performance between all profile intervals with the conventional intervals, such as Mantel-Haenszel method (MH) and Weighted least squares method (WLS) in terms of the coverage probability and the width of interval. The results under a simulation plan indicated that for moderated study size (k = 8, 16) and small sample size ($n_i^D, n_i^H \leq 50$), there were only three proposed interval estimates ($WPLF$, $WPLR$, and $BOOT$) that could be calibrated the coverage probability at 95% and the interval widths of $WPLF$ and $WPLR$ are narrower than the $BOOT$. Hence, we recommend to use $WPLF$ and $WPLR$ rather than the conventional intervals in such situations.

Peer-review under responsibility of the Organizing Committee of iEECON2016

Keywords: Diagnostic Odds Ratio; Interval Estimation; Profile Likelihood Estimate; Meta-analysis

1. Introduction

Meta-analysis is the statistical procedure to integrate all various results of several studies into one true result. Conventionally, the weighted average estimators such as Mantel-Haenszel method and Weighted Least Square

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Peer-review under responsibility of the Organizing Committee of iEECON2016
doi:10.1016/j.procs.2016.05.071

method are used to estimate the effect size. According to the book of Böhning et al. [1], the profile maximum likelihood estimator $(PMLE)$ under effect homogeneity of relative risks (RR) performs better than the Mantel-Haenszel estimator with the smaller bias and smaller variance when RR ranged between 0.0001 to 0.3333. Conversely, information of the $PMLE$ for the diagnostic odds ratio (DOR) as the effect of interest is limited. A gap of study is based on the insufficient knowledge of the $PMLE$ on the DOR.

2. Deriving the profile likelihood under effect homogeneity

Suppose that the diagnostic odds ratio is defined by the ratio of the odds of positivity in disease relative to the odds of positivity in the non-diseased group. The diagnostic odds ratio estimator is $\widehat{DOR} = (TP/FN)/(FP/TN) = \left[(1-\hat{p}^D)/\hat{p}^D\right]/\left[\hat{p}^H/(1-\hat{p}^H)\right]$, where the false negative rate $\left(\hat{p}^D = x^D/n^D\right)$ is the probability that the test is negative among diseased persons and the false positive rate $\left(p^H = x^H/n^H\right)$ is the probability that the test is positive among healthy persons. After maximizing the binomial log-likelihood with respect to the nuisance parameter p_i^D for the $i-th$ study $(i=1,2,...,k)$, the solution is as

$$p_i^D = f_i\left(DOR_i\right) = -\left(\frac{n_i + X_i - X_i \cdot DOR_i - p_i\left(DOR_i\right)}{2\left(DOR_i - 1\right)\left(n_i^D\right)}\right)$$

where $X_i = x_i^D - x_i^H$, $n_i = n_i^D + n_i^H$, $p_i\left(DOR_i\right) = \sqrt{\left(n_i + X_i - X_i \cdot DOR_i\right)^2 + 4\left(DOR_i - 1\right)\left(n_i^D\right)\left(X_i + n_i^H\right)}$. Under homogeneity of $DOR_1 = ... = DOR_k = DOR$, the solution of the pooled diagnostic odds ratio of profile likelihood is

$$DOR_{PMLE} = \frac{\sum_{i=1}^{k}\left(n_i^H - x_i^H\right)}{\sum_{i=1}^{k}\left(\frac{\left(n_i^D - X_i\right) f_i'\left(DOR\right)}{1 - f_i\left(DOR\right)} + \frac{n_i^H\left(\left(DOR \cdot f_i'\left(DOR\right) + f_i\left(DOR\right)\right) - f_i'\left(DOR\right)\right)}{1 - f_i\left(DOR\right) + DOR \cdot f_i\left(DOR\right)} - \frac{\left(n_i^H + X_i\right) f_i'\left(DOR\right)}{f_i\left(DOR\right)}\right)}.$$

3. Recalling the conventional inverse-variance weighted estimator

Under effect homogeneity for estimating $T = log(DOR)$ over all k studies, the conventional weighted least squares estimator [1, 2] is of the form $\hat{T}_{WLS} = \sum_{i=1}^{k} w_i \hat{T}_i \Big/ \sum_{i=1}^{k} w_i$ where $\hat{T}_i = log\left(\widehat{DOR_i}\right)$, $w_i = 1/V(\hat{T}_i)$, and the variance of $\hat{T}_i$ is estimated by $\hat{V}(\hat{T}_i) = \frac{1}{\hat{w}_i} \approx \frac{1}{n_i^D\left(\hat{p}_i^D\right)\left(1-\hat{p}_i^D\right)} + \frac{1}{n_i^H\left(\hat{p}_i^H\right)\left(1-\hat{p}_i^H\right)}$. In addition, the variance estimate of $\hat{T}_{WLS}$ is given as $\hat{V}(\hat{T}_{WLS}) = 1\Big/\sum_{i=1}^{k}\hat{w}_i$. The 95% confidence interval (CI) for population effect of $T = log(DOR)$ under normal approximation is given as $\hat{T}_{WLS} - 1.96\sqrt{\hat{V}(\hat{T}_{WLS})} \le log\left(DOR\right) \le \hat{T}_{WLS} + 1.96\sqrt{\hat{V}(\hat{T}_{WLS})}$, leading to the 95% CI of DOR as $\widehat{DOR}_{WLS} \cdot exp\left(\pm 1.96\sqrt{\hat{V}(\hat{T}_{WLS})}\right)$ where $\widehat{DOR}_{WLS} = exp\left(\hat{T}_{WLS}\right)$.

4. Constructing two confidence intervals of profile likelihood estimator

The idea to create the confidence intervals ($WPLR$, $WPLF$) of the $PMLE$ for estimating a true constant DOR over across k studies is based on the substitution of the $PMLE$ into the variance formula of logarithm of each diagnostic odds ratio. Referring above, the conventional variance of $\hat{T}_i = log\left(\widehat{DOR_i}\right)$ is

$$\hat{V}(\hat{T}_i) = \frac{1}{\hat{w}_i} \approx \frac{1}{n_i^D\left(\hat{p}_i^D\right)\left(1-\hat{p}_i^D\right)} + \frac{1}{n_i^H\left(\hat{p}_i^H\right)\left(1-\hat{p}_i^H\right)} \quad (1)$$

Replacing $\hat{p}_i^D = f_i\left(\widehat{DOR}_i\right)$ and $\hat{p}_i^H = \left(1-\hat{p}_i^D\right)/\left(1-\hat{p}_i^D + \widehat{DOR}_i \cdot \hat{p}_i^D\right)$ into (1), the first variance estimate of $\hat{T}_i = log\left(\widehat{DOR}_i\right)$ can be rewritten as

$$\hat{V}_1(\hat{T}_i) = \frac{1}{\hat{w}_{1i}} \approx \frac{1}{n_i^D f_i\left(\widehat{DOR}_i\right)\left(1-f_i\left(\widehat{DOR}_i\right)\right)} + \frac{\left(1-f_i\left(\widehat{DOR}_i\right)+\widehat{DOR}_i f_i\left(\widehat{DOR}_i\right)\right)^2}{n_i^H \widehat{DOR}_i f_i\left(\widehat{DOR}_i\right)\left(1-f_i\left(\widehat{DOR}_i\right)\right)} \tag{2}$$

Thus the first variance estimate of $\hat{T}_{PMLE} = log(\widehat{DOR}_{PMLE})$ over across k studies is $\hat{V}_{WPLR}(\hat{T}_{PMLE}) = 1\Big/\sum_{i=1}^{k}\hat{w}_{1i}$ where $\hat{w}_{1i} = 1/\hat{V}_1(\hat{T}_i)$ and the associated 95% confidence interval $WPLR$ for DOR is

$$\widehat{DOR}_{PMLE} \cdot exp\left(\pm 1.96\sqrt{\hat{V}_{WPLR}(\hat{T}_{PMLE})}\right). \tag{3}$$

Under homogeneity of $DOR_1 = ... = DOR_k = DOR$ and substitution of $\widehat{DOR}_i$ with $\widehat{DOR}_{PMLE}$, the second variance estimate of $\hat{T}_i = log\left(\widehat{DOR}_i\right)$ is obtained as

$$\hat{V}_2(\hat{T}_i) = \frac{1}{\hat{w}_{2i}} \approx \frac{1}{n_i^D f_i\left(\widehat{DOR}_{PMLE}\right)\left(1-f_i\left(\widehat{DOR}_{PMLE}\right)\right)} + \frac{\left(1-f_i\left(\widehat{DOR}_{PMLE}\right)+\widehat{DOR}_{PMLE} f_i\left(\widehat{DOR}_{PMLE}\right)\right)^2}{n_i^H \widehat{DOR}_{PMLE}\, f_i\left(\widehat{DOR}_{PMLE}\right)\left(1-f_i\left(\widehat{DOR}_{PMLE}\right)\right)}. \tag{4}$$

So the second variance estimate of $\hat{T}_{PMLE} = log(\widehat{DOR}_{PMLE})$ over across k studies is $\hat{V}_{WPLF}(\hat{T}_{PMLE}) = 1\Big/\sum_{i=1}^{k}\hat{w}_{2i}$ where $\hat{w}_{2i} = 1/\hat{V}_2(\hat{T}_i)$ and the associated 95% confidence interval $WPLF$ for DOR is

$$\widehat{DOR}_{PMLE} \cdot exp\left(\pm 1.96\sqrt{\hat{V}_{WPLF}(\hat{T}_{PMLE})}\right). \tag{5}$$

Under bootstrapping, the confidence interval ($BOOT$) is obtained from $\widehat{DOR}_{PMLE}$ distribution by using the percentile at 2.5% and 97.5%. Finally, three confidence intervals of profile likelihood estimators are obtained.

5. Results on application data

According to report of Jun Zhang et al. [3] concerning a meta-analysis of 14 studies on the diagnosis of serum p53 antibody in patients assessed esophageal cancer, Table 1 shows that the widths of 95% confidence interval of all estimates are not significantly different since all intervals are overlapped. However, the percentile confidence interval of $BOOT$ seems likely most wide.

Table 1. 95% confidence intervals of the diagnostic odds ratios in serum p53 antibody of patients with esophageal cancer

Method	Diagnostic odds ratio	95% CI of diagnostic odds ratio
WLS	7.74309	5.80467 - 10.32884
MH	8.26025	6.26509 - 10.89078
WPLF	8.88593	7.10488 - 11.11345
WPLR	8.88593	7.07971 - 11.15295
BOOT	8.88593	6.30322 - 15.66805

6. Results of simulation plan

A comparison of the interval performance is used under simulations with R-language over 2000 replicates for each parameter combination. We let a true DOR be fixed with 10, 20, 40 and 80, the number of studies k is 4, 8, 16 and 32, the number of sample sizes n_i^D, n_i^H in each arm is balanced and unbalanced cases with 25, 50, 150 and 450. The criteria of good interval must be able to keep the nominal coverage probability values previously and then

determine the narrower width average values. There are a lot of results that we cannot explain at all. So this section will show only the interval results at the value of *DOR* equal to 10.

Figure 1 showed the empirical coverage probabilities for *DOR*. When the number of studies is small (k = 4) and the number of sample sizes is moderate (n = 50, 150), the *WPLF* and *WPLR* intervals could control the desired 95% nominal coverage probability containing the true value of interest. For the number of studies is moderate (k = 8, 16), the *BOOT* interval could control the 95% coverage probability when sample size is small to moderate (n = 25, 50 and 150); the *WPLF* and *WPLR* intervals were closer to 95% interval for small to moderate sample sizes (n = 25, 50). Lastly, when the number of studies is large (k = 32) and the number of sample size is small (n = 25), the *WPLF* and *WPLR* intervals were closer to 95% coverage probability.

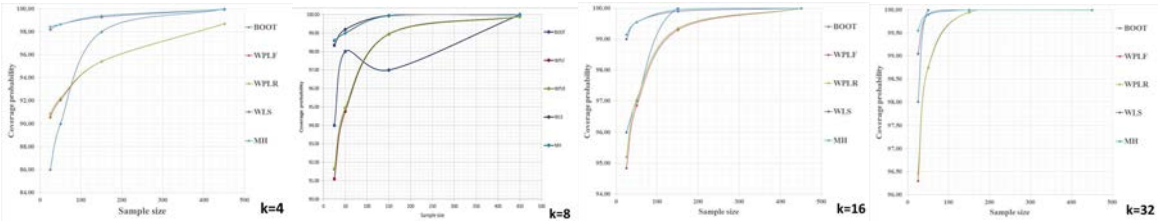

Fig. 1. The 95% coverage probability when *DOR* =10 and equal sample sizes ($n_i^D = n_i^H = n$)

In Figure 2, before comparing the width average, we found that there were only 3 interval estimates (*BOOT*, *WPLF* and *WPLR*) that could be calibrated with the 95% coverage probability. At the small to moderate study sizes (k = 4, 8 and 16), the proposed intervals *WPLF* and *WPLR* had the width average smaller than the *BOOT* for all sample sizes.

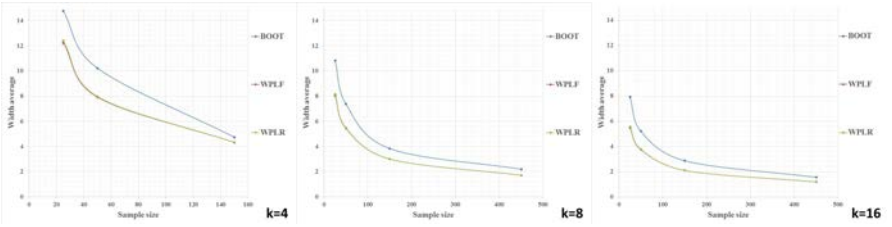

Fig. 2. The 95% width average when *DOR* =10 and equal sample sizes ($n_i^D = n_i^H = n$)

In summary, the results found that three proposed interval estimators (*WPLF*, *WPLR*, and *BOOT*) can control the desired 95% nominal coverage probability when sample sizes are small to moderate (n_i^D, n_i^H =25, 50, 100), regardless the study size. The *WPLF* and *WPLR* perform best when n_i^D, n_i^H = 25, 50 and $k \le 16$. Thus, the idea of replacement of profile likelihood estimates into the variance formulas of logarithm of each *DOR* works well.

Acknowledgements

This study was partially supported for publication by the China Medical Board (CMB), Faculty of Public Health, Mahidol University, Bangkok, Thailand.

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