Interval estimation of the cost-effectiveness ratio

Chen, Yuh-Ing
Institute of Statistics, National Central University
No. 300 Junda Road, Jhongli 32001, TAIWAN
E-mail: ychen@stat.ncu.edu.tw

Introduction

Due to the limited resource for possible health cares, the evaluation of their economic benefits is needed. Let μ_{C_j} and μ_{E_j} be the mean cost and mean effectiveness associated with the *i*th health care for j =1 (treatment), 2 (control). A comparison of the two health cares is usually made based on the incremental cost-effectiveness ratio (ICER):

$$\text{ICER}=(\mu_{C1}-\mu_{C2})/(\mu_{E1}-\mu_{E2}), \quad (1)$$

which is, relative to the control health care, the additional cost of the treatment health care for each additional unit of health benefit. The interval estimation for the ICER has been extensively discussed by, for example, Chaudhary and Stearns (1996), Laska et al. (1997), Polsky et al (1997), and among others.

Let $\bar{C}_1-\bar{C}_2$ and $\bar{E}_1-\bar{E}_2$ be the estimators of $\mu_{C1}-\mu_{C2}$ and $\mu_{E1}-\mu_{E2}$, respectively. In general, the relevant confidence intervals are all constructed based on the ratio estimator, that is, $(\bar{C}_1-\bar{C}_2)/(\bar{E}_1-\bar{E}_2)$, and hence suffer a statistical difficulty. Note that the Fieller confidence interval is conventionally constructed for the ICER. However, Fieller's interval was originally developed for the ratio of two binormally distributed variables. Also, note that, in an ICER plane with mean cost-difference in y-axis and mean effectiveness-difference in x-axis, a line through the origin with slope ρ, representing a willing to pay, is often employed as a reference. Therefore, a point below (above) the reference line in the plane indicates that the first health care is superior (inferior) to the second one. However, the negative increments are misleading and the interpretation of ICER is ambiguous, especially, when two points in quadrants I and III, respectively, give the same ratio but one locates above and the other lies below the reference line.

To avoid the ambiguity of the ICER with negative increments, we propose herein to measure the ratio of cost and effectiveness (RCE) for the *j*th health care as follows:

$$\theta_j = \mu_{C_j} / \mu_{E_j} \text{ for } j = 1, 2. \quad (2)$$

The RCE has a better understandable meaning as the mean cost per unit of effectiveness. If the effectiveness of the health care is measured by its mean lifetime, then RCE can be interpreted as the mean cost for prolong, on the average, one unit of lifetime. In fact, a comparison of the two health cares can further be made by contrasting the related RCEs.

In fact, both the cost and lifetime of subjects who are undertaking the health care are usually right-skewed. To make the evaluation of RCE widely applicable in practical situations, we consider employing different generalized gamma (GG) distributions (Cox et al., 2007) to describe the marginal distributions of cost and lifetime variables, respectively. Moreover, to account for possible correlation between the two variables, we suggest using an appropriate copula function (Nelson, 2006) to link the two GG marginal distributions for describing their joint distribution. Therefore, in this paper, we are primarily concerned with a parametric interval estimation for the individual RCE.

Interval estimation for the ratio of cost and effectiveness

Let C_i and T_i be the cost and lifetime variables, respectively, for subject *i*, $i=1,...,n$. Suppose that the marginal distribution of C_i is a generalized gamma distribution, denoted by $GG(\beta_C,\sigma_C,\gamma_C)$ and that of T_i is $GG(\beta_T,\sigma_T,\gamma_T)$. Then, the related probability density function (*pdf*) is given by

$$f(t;\beta,\sigma,\gamma)=\frac{|\gamma|}{\sigma t\Gamma(\gamma^{-2})}[\gamma^{-2}(e^{-\beta}t)^{\gamma/\sigma}]^{\gamma^{-2}}\exp[-\gamma^{-2}(e^{-\beta}t)^{\gamma/\sigma}]$$

and the associated mean is $\gamma^{2\sigma/\gamma}e^{\beta}\Gamma(\gamma^{-2}+\sigma/\gamma)/\Gamma(\gamma^{-2})$. Hence, the RCE is given by

$$RCE=\frac{E(C)}{E(T)}=\frac{\gamma_C^{2\sigma_C/\gamma_C}e^{\beta_C}\Gamma(\gamma_C^{-2}+\sigma_C/\gamma_C)/\Gamma(\gamma_C^{-2})}{\gamma_T^{2\sigma_T/\gamma_T}e^{\beta_T}\Gamma(\gamma_T^{-2}+\sigma_T/\gamma_T)/\Gamma(\gamma_T^{-2})}$$

Moreover, we assume that (C_i, T_i) is distributed according to the joint distribution *Copula*(GG_C, GG_T; κ), where GG_C and GG_T are the distribution functions of cost and lifetime variables, respectively, and *Copula* ($u,v;\kappa$) is a copula function that links distribution functions *u* and *v*. For example, if we employ the Frank copula, then we have the joint distribution function

$$C^F(u,v;\kappa)=\begin{cases}-\frac{1}{\kappa}\ln(1+\frac{(e^{-\kappa u}-1)(e^{-\kappa v}-1)}{e^{-\kappa}-1}), & if\ \kappa\neq 0\\ uv &, if\ \kappa=0\end{cases}$$

Note that, in this paper, we also consider the clayton copula function as given by

$$C^C(u,v;\kappa)=\begin{cases}(u^{-\kappa}+v^{-\kappa}-1)^{-1/\kappa}, & if\ \kappa>0\\ uv &, if\ \kappa=0\end{cases}$$

To find the maximum likelihood estimates (MLEs) of the mean cost and mean lifetime based on the observed data {(c_i, t_i), *i*=1,…, n}, we need to construct the likelihood function of the related parameters. Note that the joint *pdf* for Frank copula is

$$c^F(u,v;\kappa)=\begin{cases}\dfrac{\kappa e^{-\kappa(u+v)}\left(1-e^{-\kappa}\right)}{\left(e^{-\kappa}+e^{-\kappa(u+v)}-e^{-\kappa u}-e^{-\kappa v}\right)^2}, & if\ \kappa\neq 0\\ 1 & , if\ \kappa=0\end{cases}$$

and that for Clayton copula is

$$c^C(u,v;\kappa)=\begin{cases}(1+\kappa)(uv)^{-(1+\theta)\kappa}(u^{-\kappa}+v^{-\kappa}-1)^{-1/\kappa-2}, & if\ \kappa>0\\ 1 & , if\ \kappa=0\end{cases}$$

Therefore, the likelihood function of $\theta=(\beta_C,\sigma_C,\gamma_C,\beta_T,\sigma_T,\gamma_T,\kappa)$ is

$$\prod_{i=1}^{n} f(c_i,t_i)=\prod_{i=1}^{n} c\left(GG_C(c_i),GG_T(t_i);\kappa\right)f_C(c_i;\beta_C,\sigma_C,\gamma_C)f_T(t_i;\beta_T,\sigma_T,\gamma_T)$$

As usual, we obtain the MLEs of θ, denoted by $\hat{\theta}$, and find the estimators of the mean cost and mean lifetime, denoted by $\hat{\mu}_C$ and $\hat{\mu}_T$, respectively. Since both the estimators are functions of $\hat{\theta}$, we apply Delta's method to find the variances of the estimators and then obtain their estimators as $s^2(\hat{\mu}_C)$ and $s^2(\hat{\mu}_T)$, respectively. We also find the estimated covariance between $\hat{\mu}_C$ and $\hat{\mu}_T$ and denoted it by s($\hat{\mu}_C$, $\hat{\mu}_T$).

Let z_a be the 100*a*-th percentile of a standard normal distribution. The original 100 $(1-\alpha)$% Fieller confidence interval is

$$\text{F}=\left\{\theta:\frac{|\,\overline{C}-\theta\overline{T}\,|}{\sqrt{s^2(\overline{C})+\theta^2 s^2(\overline{T})-2\theta s(\overline{C},\overline{T})}}\leq z_{1-\alpha/2}\right\},\tag{3}$$

In this paper, we consider the corresponding modified Fieller confidence interval, that is,

$$\text{MF}=\left\{\theta:T(\theta)=\frac{|\,\hat{\mu}_C-\theta\hat{\mu}_T\,|}{\sqrt{s^2(\hat{\mu}_C)+\theta^2 s^2(\hat{\mu}_T)-2\theta s(\hat{\mu}_C,\hat{\mu}_T)}}\leq z_{1-\alpha/2}\right\}\tag{4}$$

In the MF interval, we use the estimated means instead of the simple sample averages.

To adapt to the non-binormally distributed cost and lifetime variables, Wang and Zhao (2008) suggest a bootstrap Fieller (BF) confidence interval where $z_{1-\alpha/2}$ is replaced by a more suitable critical value obtained from a bootstrap method. In this paper, we also consider the bootstrap modified Fieller (BMF) confidence interval. The algorithm is stated in the following:

Step 1. Generate a random samples of size n from the paired cost and lifetime data.

Step 2. Find $\hat{\mu}_C^b$, $\hat{\mu}_T^b$ and the associated variances and covariance based on the bootstrap sample generated on Step 1, and compute

$$T^*(\hat{\theta}) = \frac{|\hat{\mu}_C^* - \hat{\theta}\hat{\mu}_T^*|}{\sqrt{s^2(\hat{\mu}_C^*) + \hat{\theta}^2 s^2(\hat{\mu}_T^*) - 2\hat{\theta}s(\hat{\mu}_C^*, \hat{\mu}_T^*)}} .$$

Step 3. Repeat the first two steps B times and obtain the bootstrap replications $T_b^*(\hat{\theta}),\ b = 1,...,B$.

Step 4. Let q_a be the $100a$-th empirical percentile of $T^*(\hat{\theta})$ based on $T_b^*(\hat{\theta})$, $b = 1,...,B$, then the $100(1-\alpha)\%$ confidence interval for θ is given by

$$\text{BMF} = \left\{ \theta : q_{\alpha/2} \le \frac{|\hat{\mu}_C - \theta\hat{\mu}_T|}{\sqrt{s^2(\hat{\mu}_C) + \theta^2 s^2(\hat{\mu}_T) - 2\theta s(\hat{\mu}_C, \hat{\mu}_T)}} \le q_{1-\alpha/2} \right\} .$$

Again, the original bootstrap Fieller (BF) interval uses the sample average cost and average lifetime.

Simulation study

We conducted a simulation study to investigate the coverage probability and length of the proposed 95% confidence intervals, MF and BMF, and the previous ones, F and BF. Note that the critical values used for Bootstrap procedures are obtained based on 1,000 replicates. We assume a Weibull marginal distribution with scale parameter 2819.8 and shape parameter 0.5, denoted by W(2819.8, 0.5), for the cost variable and W(11.6, 1.9) for lifetime variable. Moreover, we consider the correlation with Kendal's τ ranging over 0.2, 0.5 and 0.8 under the Frank and Clayton copula functions, respectively. The coverage probability and length of each confidence interval are respectively estimated as the proportion of 1,000 intervals correctly including the true ratio of cost-effectiveness and the average length of the 1,000 intervals. To see if the procedure can give a reasonable one-sided confidence bound, we also estimate the upper (lower) error rate as the proportion of 1,000 intervals with upper (lower) bound smaller (larger) than the true ratio. Therefore, the standard deviation of the estimated coverage probability is about 0.007(= $\sqrt{0.95\text{x}0.05/1000}$) and that of the one-sided error rate is roughly 0.005(= $\sqrt{0.025\text{x}0.975/1000}$). The related results are presented in Tables I and II, where we use + or – to note the estimate if it is more than two standard deviations from its expected value.

The results in Table I show that either the MF or the BMF interval maintains well its confidence level at 95%. Moreover, since the coverage probability of the F interval is smaller than 95%, it is not surprising that the length of the F interval is shorter than that of the MF interval. The BF is also, in general, not able to keep its confidence level, but, for some situations, it has a wider length than does the corresponding BMF interval. In addition, the results in Table II reveal that all the F, BF and MF intervals are not symmetric on the error rate performance. In these situations, the proposed BMF interval is the only one that can be used to construct the upper or lower confidence bound for the ratio of cost-effectiveness.

Table I. Estimated coverage probability and length of 95% confidence intervals for the ratio of cost-effectiveness

Copula	τ	n	CP				Length			
			F	BF	MF	BMF	F	BF	MF	BMF
Frank	0.2	200	92.2 -	95.4	94.6	94.5	364.85	422.23	400.39	404.97
		500	93.4 -	92.8 -	94.4	95.3	237.09	228.46	246.15	254.45
	0.5	200	93.1 -	92.6 -	94.2	95.8	344.56	365.15	372.95	394.52
		500	91.8 -	92.6 -	94.4	95.5	220.49	212.72	232.87	223.14
	0.8	200	91.5 -	95.0	94.7	96.1	323.07	351.45	328.68	366.26
		500	92.6 -	94.5	94.5	95.8	204.90	218.29	205.89	222.96
Clayton	0.2	200	92.6 -	93.2 -	94.2	94.1	371.61	386.24	404.15	401.73
		500	93.5 -	97.3 +	94.8	95.2	237.99	262.61	249.25	242.38
	0.5	200	90.5 -	94.8	94.3	94.2	350.57	383.18	393.63	364.31
		500	93.7	92.8 -	95.4	94.3	226.59	223.30	240.74	228.04
	0.8	200	91.6 -	94.2	94.0	94.4	328.11	371.78	335.80	311.69
		500	93.4 -	96.3	95.0	95.7	210.55	238.64	209.48	212.88

Table II. Estimated 100xlower and upper error rates of 95% confidence intervals for the ratio of cost-effectiveness

Copula	τ	n	F		BF		MF		BMF	
			L	U	L	U	L	U	L	U
Frank	0.2	200	0.5 -	7.3 +	2.3	2.3	0.2 -	5.2 +	2.5	3.0
		500	1.1 -	5.5 +	2.4	4.8 +	0.6 -	5.0 +	2.2	2.5
	0.5	200	0.1 -	6.8 +	2.0	5.4 +	0.0 -	5.8 +	2.0	2.2
		500	1.2 -	7.0 +	2.4	5.0 +	0.3 -	5.3 +	1.8	2.7
	0.8	200	0.3 -	8.2 +	0.9 -	4.1 +	0.2 -	5.1 +	1.5	2.4
		500	0.5 -	6.9 +	3.0	2.5	0.1 -	5.4 +	1.9	2.3
Clayton	0.2	200	0.8 -	6.6 +	2.1	4.7 +	0.2 -	5.6 +	2.5	3.4
		500	0.7 -	5.8 +	0.9 -	1.8	0.3 -	4.9 +	2.5	2.3
	0.5	200	0.6 -	8.9 +	2.8	2.4	0.1 -	5.6 +	3.0	2.8
		500	1.1-	5.2 +	2.2	5.0 +	0.3 -	4.3 +	2.8	2.9
	0.8	200	0.2 -	8.2 +	2.0	3.8 +	0.1 -	5.9 +	2.6	3.0
		500	0.7 -	5.9 +	1.0 -	2.7	0.6 -	4.4 +	2.0	2.3

REFERENCES

Chaudhary, M. A. and Stearns, S. C. (1996). Estimating confidence intervals for cost-effectiveness ratios: an example from a randomized trial. Statistics in Medicine **15**, 1447-1458.

Cox, C., Chu, H., Schneider, M. F. and Munoz, A. (2007). Parametric survival analysis and taxonomy of hazard functions for the generalized gamma distribution. Statistics in Medicine **26**, 4352-4374.

Laska, E. M., Meisner, M. and Siegel, C. (1997). Statistical inference for cost-effectiveness ratios. Health Economics **6**, 229-242.

Nelson, R. B. (2006). *An Introduction to Copula*. New York. NY: Springer Science.

Polsky, D., Glick, H. A., Willke, R. and Schulman, K. (1997). Confidence intervals for cost-effectiveness ratios: A comparison of four methods. Health Economics **6**, 243-252.

Wang, H. and Zhao, H. (2008). A study on confidence intervals for incremental cost-effectieness ratios. Biometrical Journal **50**, 505-514.