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Estimation of the proportion ratio under a simple crossover trial

Kung-Jong Lui [a,*], Kuang-Chao Chang [b]

[a] Department of Mathematics and Statistics, College of Sciences, San Diego State University, San Diego, CA 92182-7720, USA

[b] Department of Statistics and Information Science, Fu-Jen Catholic University, Taipei, Taiwan, ROC

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ABSTRACT

The proportion ratio (PR) of patient response is one of the most commonly used indices for measuring the relative treatment effect in a randomized clinical trial (RCT). Assuming a random effect multiplicative risk model, we develop two point estimators and three interval estimators in closed forms for the PR under a simple crossover RCT. On the basis of Monte Carlo simulation, we evaluate the performance of these estimators in a variety of situations. We note that the point estimator using a ratio of two arithmetic means of patient response probabilities over the two groups (distinguished by the order of treatment-received sequences) is generally preferable to the corresponding one using a ratio of two geometric means of patient response probabilities. We note that the three interval estimators developed in this paper can actually perform well with respect to the coverage probability when the number of patients per group is moderate or large. We further note that the interval estimator based on the ratio of two arithmetic means of patient response probabilities with the logarithmic transformation is probably the best among the three interval estimators discussed here. We use a simple crossover trial studying the suitability of two new inhalation devices for patients who were using a standard inhaler device delivering Salbutamol published elsewhere to illustrate the use of these estimators.

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1. Introduction

The proportion ratio (PR) of patient responses is certainly one of the most commonly used indices for measuring the relative treatment effect in a randomized clinical trial (RCT) (Fleiss, 1981; Fleiss et al., 2003; Lui, 2004, 2006). The PR, defined as the ratio of two adverse events rates between an experimental treatment and a standard treatment (or placebo), is also called the risk ratio or the relative risk (RR). When the experimental treatment is known to be beneficial and so the RR is less than 1, we may frequently use 1 − RR, which is called the relative difference (Sheps, 1958, 1959) or the relative risk reduction (Laupacis et al., 1988), to measure the relative treatment efficacy as well (Fleiss, 1981).

When the response to a treatment varies substantially among patients, we may consider use of a simple crossover design, in which patients are randomly assigned to one of two groups distinguished by the order of treatment-received sequences. Because each patient serves as his/her own control, the crossover design is a useful alternative to parallel groups design for increasing power or saving on the number of patients needed (Fleiss, 1986). However, if the treatment studied had a long-lasting effect, the crossover design would be inappropriate for use due to the possibility that the effect of the treatment administered in the latter period could be confounded with the residual effect of the treatment administered in the earlier period. Thus, the crossover design should be reserved for just those treatments with relatively short acting effects. In practice, we almost always apply an adequate wash-out period to assure that there is no carry-over effect due to the treatment

* Corresponding author. Tel.: +1 619 594 6191; fax: +1 619 594 6746.
E-mail address: kjl@rohan.sdsu.edu (K.-J. Lui).

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administered first. In fact, the research on a crossover design has been quite intensive (Senn, 2002, 2006). Using a logistic regression model (Cox, 1958; Cox and Snell, 1989), Gart (1969) discussed testing the equality of two treatment effects and developed exact test procedures. On the basis of the linear additive risk model (LARM) proposed by Grizzle (1965), Zimmermann and Rahlfs (1978) focused their discussion on testing equality in patient response rates under a two-period crossover design. Note that if we assumed the LARM, we would naturally use the proportion difference (PD) rather than the PR focused on here to measure the relative treatment effect. Ezzet and Whitehead (1992) proposed a random effects logistic regression model and discussed estimation of treatment and period effects under a simple crossover trial. Because the response rate in a RCT is generally not small, the odds ratio (OR) is no longer a good approximation of the PR. Thus, the estimators for the OR derived under the logistic regression model are not applicable when our interest is in estimating the PR. Recently, Schouten and Kester (2010) also have assumed the LARM for discussing testing equality and sample size calculation in dichotomous data for a simple crossover design. The discussion on estimation of the PR, as focused on here, has so far been limited under a simple crossover design (Senn, 2002, 2006).

In this paper, we concentrate our attention on estimation of the PR under a simple crossover RCT. Assuming a random effect multiplicative risk model, we derive two point estimators and develop three interval estimators for the PR in closed forms. On the basis of Monte Carlo simulations, we evaluate and compare the performance of these estimators in a variety of situations. We note that the point estimator of the PR using a ratio of two arithmetic means of patient response probabilities over the two groups is probably preferable to the one using a ratio of two geometric means of patient response probabilities with respect to the bias and mean squared error (MSE). We further note that the interval estimator using the ratio of two arithmetic means of patient response probabilities with the logarithmic transformation is likely the best among the three interval estimators developed here with respect to the coverage probability and the average length. We also study and discuss the bias of these interval estimators by calculating and comparing the non-coverage probabilities in their two tails. Finally, we use a simple crossover trial comparing the suitability of two new inhalation devices in patients who were using a standard inhaler device delivering Salbutamol (Ezzet and Whitehead, 1992) to illustrate the use of these estimators.

2. Notation, model assumptions and methods

Consider comparing an experimental treatment B with a standard treatment A. Suppose that we randomly assign n_1 patients to group (g =) 1 with A-then-B sequence, in which patients receive treatment A in period 1 and then cross over to receive treatment B in period 2, and n_2 patients to group (g =) 2 with B-then-A sequence, in which patients receive treatment B at the period 1 and then cross over to receive treatment A in period 2. As commonly assumed for a crossover design, we assume that there is no carry-over effect due to the treatment administered in period 1 on the patient response with an adequate wash-out time period. If the assumption of no carry-over effect cannot be ensured on the basis of our subject knowledge, as noted by Fleiss (1986, p. 270), then the crossover design should not be employed. For group g ($g = 1, 2$), we let Y_{giz} denote the outcome of patient i ($i = 1, 2, \ldots, n_g$) in period z (=1, 2), and $Y_{giz} = 1$ if the patient has the positive response of interest, and = 0 otherwise. Furthermore, we let X_{giz} denote the treatment-received covariate for the corresponding patient in period z, and $X_{giz} = 1$ for treatment B and = 0 for treatment A. We further let Z_{giz} represent the period covariate, and $Z_{giz} = (z - 1)$ for period z ($z = 1, 2$). We assume that the probability of a positive response for patient i ($i = 1, 2, \ldots, n_g$) assigned to group g($g = 1, 2$) in period z($z = 1, 2$) is given by the following random effect multiplicative risk model:

$$P(Y_{giz} = 1|X_{giz} = x, Z_{giz} = z - 1) = p_{gi} \exp(\eta x + \gamma(z - 1)), \tag{1}$$

where p_{gi} denotes the underlying probability of a positive response when the ith patient is assumed to receive treatment A in period 1 in group g and to follow an unspecified probability density function $f_g(p_{gi})$, η denotes the effect of treatment B relative to treatment A, and γ denotes the effect of period 2 versus period 1. Under model (1), we can easily show that the responses taken from the same patient between periods 1 and 2 are positively correlated. Because we do not assume any parametric distribution $f_g(p_{gi})$ in the derivation of the following estimators, our method can be regarded as a semi-parametric approach. For a fixed period, the PR of a positive response on a given patient between treatment B and treatment A is equal to $PR_T = \exp(\eta)$. Similarly, for a given treatment, the PR of a positive response on a given patient between period 2 and period 1 is $PR_P = \exp(\gamma)$. In this paper, the parameter $PR_T = \exp(\eta)$, representing the relative effect between treatments B and A, is our primary interest. Note that if we wished to use the PD rather than the PR to measure the relative treatment effect, as noted previously, we would assume the LARM (Grizzle, 1965). On the other hand, if we wished to use the OR to measure the relative treatment, we would assume the logistic regression model (Ezzet and Whitehead, 1992). This is because we cannot express the PD or OR in terms of an easily interpreted and meaningful parameter under the multiplicative risk model (1). Also, note that since it is generally more difficult for clinicians to appreciate the ratio of two odds, the OR is seldom used to measure the relative treatment effect in RCTs, except for testing non-inferiority (or equivalence) or meta-analysis (Fleiss, 1981; Lui and Chang, 2011).

Let n_{grc} denote the number of patients in group g (=1, 2) with the vector ($Y_{gi1} = r$, $Y_{gi2} = c$) (where $r = 1, 0$; $c = 1, 0$) among n_g patients. The random frequencies $\{n_{grc}|r = 1, 0; c = 1, 0\}$ then follow the quadrinomial distribution with parameters n_g and $\{\pi_{grc}|r = 1, 0; c = 1, 0\}$, where π_{grc} denotes the cell probability that a randomly selected patient from group g has the bivariate vector ($Y_{gi1} = r$, $Y_{gi2} = c$). For example, the parameter π_{g10} denotes the cell probability that a randomly selected patient from group g has a positive response in period 1 and a negative response in period 2. Similarly,

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