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Assessing non-inferiority for incomplete paired-data under non-ignorable missing mechanism

Huiqiong Li [a], Guoliang Tian [b], Niansheng Tang [a], Hongyuan Cao [c,d,*]

[a] Department of Statistics, Yunnan University, PR China
[b] Department of Mathematics, Southern University of Science and Technology, PR China
[c] Center for Applied Statistical Research, School of Mathematics, Jilin University, PR China
[d] Department of Statistics, University of Missouri-Columbia, USA

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ABSTRACT

Testing equivalence of incomplete paired data arises frequently in biomedical studies. Most existing work impose the missing at random assumption, which is not realistic in practice. Two Bayesian approaches for testing the non-inferiority of incomplete paired data under non-ignorable missing mechanism are presented. In addition, Bayesian credible intervals and highest posterior density intervals for the risk difference are constructed. Simulation studies are conducted to evaluate the performance of the two Bayesian testing procedures and the credible intervals. Two datasets are used to illustrate the proposed methods.

1. Introduction

Assessing the non-inferiority of a new method or treatment with the standard one is an important topic in comparative clinical studies. Non-inferiority trials are often employed to evaluate whether a less toxic, easier to administer or inexpensive new treatment is not inferior to the standard treatment in terms of efficacy. Non-inferiority assessment has received a lot of attention for matched-pair trials in the past decades. For example, Tango (1998) derived a score statistic to test non-inferiority via relative risk in a re-parameterized model with a matched-pair design. Tang et al. (2003) developed an alternative score test procedure to test equivalence or non-inferiority via relative risk in a matched-pair design. Chan et al. (2003) proposed an exact method to assess non-inferiority via rate ratio with small-sample matched-pair design.

In practice, in comparative studies of two treatments or reviewers, incomplete matched-pair data are often encountered. For example, in a study of medical malpractice cases (Greenberg et al., 2007; Lin et al., 2009; Altham and Hankin, 2010; Konietschke et al., 2012), two surgeon-reviewers used a structured instrument to evaluate 69 errors, and to identify important human and system factors contributing to the errors. Among many possible factors is communication breakdown, each surgeon-reviewer was asked to determine whether a handoff in care was associated with the communication breakdown. In this study, 8 reviews were missing for Surgeon 1 and 11 reviews were missing for Surgeon 2. Thus, the resultant data include two parts: the complete observations and the incomplete observations. This dataset is displayed in Table 1.

Under the assumption of missing at random (MAR), the probability of missing only depends on observed data. In the case of MAR, various authors have studied the problem of the equivalence test and confidence interval construction for

* Corresponding author at: Department of Statistics, University of Missouri-Columbia, USA.
E-mail address: caohong@missouri.edu (H. Cao).

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Table 1
Counts of two surgeon reviewers' answer in a study of medical malpractice.

Reviewer 1's answer	Reviewer 2's answer			Total
	Yes	No	Missing	
Yes	26	1	2	29
No	5	18	9	32
Missing	4	4	0	8
Total	35	23	11	69

Table 2
Data structure for a matched-pair design with missing observations.

Treatment 1	Treatment 2		
	Positive response ($Y = 1$)	Negative response ($Y = 0$)	Missing
Positive response ($X = 1$)	$n_1\,(\theta_1)$	$n_2\,(\theta_2)$	m_{12}
Negative response ($X = 0$)	$n_3\,(\theta_3)$	$n_4\,(\theta_4)$	m_{34}
Missing	m_{13}	m_{24}	m_{1234}

two correlated proportions with incomplete matched-pair data (Choi and Stablein, 1982; Ekbohm, 1982; Tang and Tang, 2004; Tang et al., 2009; Lin et al., 2009; Tang et al., 2011). Non-ignorable missing or missing not at random (MNAR) refers to the case that the probability of missing is related to the value of the missing data. In the case of MNAR, Choi and Stablein (1988) proposed several methods for testing the equality of two correlated proportions. Nandram and Choi (2002) proposed a Bayesian approach for a non-ignorable non-response model. To the best of our knowledge, there is no published work to date that deals with incomplete paired-data under non-ignorable missing mechanism. In this paper, we develop Bayesian methods to test non-inferiority and to construct Bayesian credible intervals and highest posterior density (HPD) intervals for incomplete paired-data.

The rest of this paper is organized as follows. In Section 2, we present two Bayesian p-values to assess non-inferiority for incomplete paired data under the non-ignorable missing mechanism. Section 3 develops a new Bayesian interval estimation of the risk difference for incomplete paired data under nonignorable missing mechanism. Simulation studies are conducted to investigate the performance of various methods in Section 4. We illustrate the proposed methodology with two dataset in Section 5. Concluding remarks are given in Section 6.

2. Bayesian methods for the non-inferiority test

2.1. Data structure and non-inferiority test

Consider a trial for comparing two treatments. Suppose that X and Y are two correlated binary variables. Let $X = 1$ (or $X = 0$) if a subject has a positive (or negative) response under treatment 1 and let $Y = 1$ (or $Y = 0$) if the same subject has a positive (or negative) response under treatment 2. Let $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_4)^\top$ denote model parameters, where $\theta_1 = \Pr(X = 1, Y = 1)$, $\theta_2 = \Pr(X = 1, Y = 0)$, $\theta_3 = \Pr(X = 0, Y = 1)$ and $\theta_4 = \Pr(X = 0, Y = 0)$. Naturally, we have $\boldsymbol{\theta} \in \mathbb{T}_4$, where $\mathbb{T}_n := \{(x_1, \ldots, x_n)^\top : x_i > 0, \sum_{i=1}^{n} x_i = 1\}$.

Suppose that in a comparative trial there are a total of N participants containing $n = \sum_{j=1}^{4} n_j$ complete cases and $m_{12}+m_{34}+m_{13}+m_{24}+m_{1234}$ incomplete cases, where n_1 subjects have both positive responses, n_2 subjects have a positive response for Treatment 1 and a negative response for Treatment 2, n_3 subjects have a negative response for Treatment 1 and a positive response for Treatment 2, n_4 subjects have both negative responses; m_{12} (or m_{34}) subjects only have a positive (or negative) response for Treatment 1, m_{13} (or m_{24}) subjects only have a positive (or negative) response for Treatment 2; and the responses for m_{1234} subjects are totally missing for both treatments. These observed outcomes are reported in Table 2. We denote the observed data by $Y_{\text{obs}} = \{n_1, \ldots, n_4; m_{12}, m_{34}, m_{13}, m_{24}, m_{1234}\}$ with $N = \sum_{j=1}^{4} n_j + m_{12} + m_{34} + m_{13} + m_{24} + m_{1234}$.

Treatment 1 is said to be not inferior to Treatment 2 if $\Pr(X = 1) > \Pr(Y = 1) - \delta_0$, i.e., $\theta_1 + \theta_2 > \theta_1 + \theta_3 - \delta_0$, where $\delta_0 > 0$ is the non-inferiority margin of clinical interest. Thus, testing the non-inferiority of Treatment 1 to Treatment 2 is equivalent to testing the following hypothesis:

$$H_0 : \theta_2 \leqslant \theta_3 - \delta_0 \quad \text{against} \quad H_1 : \theta_2 > \theta_3 - \delta_0. \tag{2.1}$$

The objective of this paper is to develop Bayesian methods for testing H_0 versus H_1 under the non-ignorable missing mechanism.

2.2. Formulation of the non-ignorable missing mechanism

To describe the non-ignorable missing mechanism in Table 2, we first define a 4-category response random variable R, where $R = 12$ if a subject has response to both treatments, $R = 1\bar{2}$ if a subject has response only to Treatment 1, $R = \bar{1}2$