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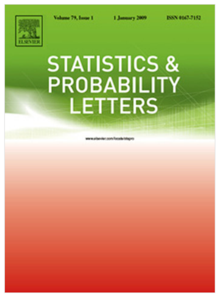

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On asymptotic normality of certain linear rank statistics

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Abstract

We consider asymptotic normality of linear rank statistics under various randomization rules met in clinical trials. Exposition relies on some general limit theorem given in [11]. Examples of applications include well known results as well as new ones. Though exposition is tightly attached to the context of clinical trials, the obtained results equally well apply to situations where randomization of similar kind takes place.

Keywords: randomization rule, asymptotic normality, linear rank statistics, clinical trial
2000 MSC: 62G10, 62G20, 62P10

1. Introduction

In order to adequately measure an effect of treatment, it is a common practice in clinical trial to randomize patients. To achieve the goals of the study, different randomization rules may be applied. We consider the ones randomizing into two groups sequentially and aiming to produce approximately equal treatment and placebo groups. Each such rule may be described as follows. Let n denote a total number of patients to be randomized (for convenience, we assume that n is even); let $T_{n,j} = 1$, provided j-th patient was assigned to receive investigated therapy, and let $T_{n,j} = -1$ otherwise. Then the rule is defined by conditional probabilities

$$\mathrm{p}_{n,j}(t_j) = \mathrm{P}(T_{n,j} = t_j \mid T_{n,j-1} = t_{j-1}, \ldots, T_{n,1} = t_1), \tag{1.1}$$

according to which actual randomization takes place in practice. Several popular rules considered in the sequel are listed in Table 1. Let Y_j denote an outcome of j-th patient measured on an arbitrary scale. One can apply different models to measure an effect of treatment. The linear rank statistics (see [12], Chap. 7 and Chap. 14, or [13], Chap. 6; further on, we use abbreviation LRS) is one of possible choices. To construct LRS, one should proceed as follows. Given realization $y_1, \ldots, y_n$, of $Y_1, \ldots, Y_n$, associate with each y_j the score $a_{n,j}$ (one of possible and frequent choices is to take $a_{n,j}$ equal to a simple rank obtained after ranking $y_1, \ldots, y_n$; other popular choices of scores are given in Table 2). Put

$$L_n = \sum_{j=1}^{n} (a_{n,j} - \bar{a}_n) T_{n,j}, \quad \bar{a}_n = \frac{1}{n} \sum_{j=1}^{n} a_{n,j}; \tag{1.2}$$

Consider $a_n = (a_{n,1}, \ldots, a_{n,n})^T$ being fixed, and $T_n = (T_{n,1}, \ldots, T_{n,n})^T$ being random. Then L_n is a LRS. To introduce one of its possible applications in the context of randomized clinical trial (RCT), we describe an underlying statistical model. Following [10], we name the corresponding model *the randomization model*. Within the model framework, one treats the set of observed patients' response values as fixed and assumes that these are unaffected by treatment. This is the *null randomization hypothesis*. Under this hypothesis, the observed difference between the groups depends only on the way the patients were randomized. L_n is then a frequent choice to assess whether the difference is indeed present. The strong sides of the approach are the following:

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