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Original Article

Confidence Interval for skewed distribution in outcome of change or difference between methods

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ABSTRACT

Background: When we have pre and post measurements on same subjects and the outcome of interest is change or to compare the reliability across two methods, then it is required to present mean change and the 95% Confidence Interval (CI) for the change. However, when the distribution of the 'change' is skewed, then it is not possible to calculate CI using normal approximation. This study was to demonstrate an appropriate method in such situations.

Methods: Hypothetical data was considered. Difference of two methods was obtained that included positive and negative values and 95% CI using normal approximation with log transformation, Hodges–Lehmann CI, shifting the origin with log transformation and the Bootstrap CI was obtained.

Results: Data consisted of 399 observations. The mean (sd) of the outcome was 96.9 (465.6). The 95% CI using the normal approximation with log transformation was obtained as (245.8, 307.5) with only 194 observations while Bootstrap CI was calculated as (54.1, 139.4) using all observations.

Conclusion: When the outcome of interest is to compare the 'change' which is skewed, then we discourage the log transformed normal approximation method or adding constant and taking log transformation method to calculate CI and encourage researchers to use Bootstrap CIs.

1. Introduction

Very often in clinical trials, the main objective of the study is to compare the change before (pre) and after (post) intervention. Also, in some reliability studies, it is of interest to see if two methods are significantly different when measuring the same quantity. In such situations, the main interest is to estimate the amount of change and the likely variability in the long run (95% CI). However, in order to test whether the change is significant or not, we examine the 95% CI, whether that CI includes zero or not. If 'change' is defined as post measurement minus the pre measurement, then there are positive values when the post measurements are greater than the pre and negative values when the pre measurements are greater than post. The only way to test for such a hypothesis is to perform a one sample *t*-test or a non-parametric Wilcoxon Signed Rank Test for the difference or change. However, one sample *t*-test is appropriate when the distribution of the difference is approximately normal. When the distribution of the difference or 'change' is positively skewed, then it is recommended to take a log

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transformation.[1,2] But many software packages like SAS, SPSS, STATA, etc. produce missing values for all the negative differences as the log transformation of negative values does not exist. The main objective of the study is to demonstrate the misuse of taking log transformations when the outcome of interest is 'change' with positive and negative values and obtain the CI using Bootstrap method in such situations.

2. Methods

2.1. *Data*

The data used is a hypothetical data of individuals comparing the Total Liver Volume (TLV) (in cubic cm) as was measured from CT scan of the abdomen or thorax and the TLV (in cubic cm) obtained using the Indian formula with the Body Surface Area (BSA), gender and age as the independent variables. The TLV difference between the two methods was obtained, named as "Difference in TLV", was the outcome of interest. The 'Difference in TLV' had both positive and negative values.

2.1.1. *Normal approximation for log transformed data*
The log transformation of the 'Difference in TLV' was obtained and the normal approximation method of calculating 95% CI was obtained.

2.1.2. *Change of origin and its log transformation*
The minimum value for the 'Difference in TLV' was obtained. One positive value that was greater than the minimum value in the data was added to all observations and thereby all observations were only positive in the modified data. The log transformation was taken for the modified data and 95% CI was obtained for log transformed data. Then that 95% CI was back transformed to its original scale (antilog of the CI was taken and the value added was then subtracted from the upper and lower limits of CI) and was interpreted.

2.1.3. *Hodges–Lehmann Confidence Interval*
A non-parametric method of obtaining CI for median was also calculated. This method was known as Hodges–Lehmann CI for ordered statistics.[3] As this method is a non-parametric method, this method is computed using ranks.[4]

2.2. *Bootstrap simulation*

A random sample of the 'Difference in TLV' of all ($n = 399$) observations was obtained using sampling with replacement. 'Sampling with replacement' represents that any observation from the dataset can be obtained in the Bootstrap sample more than once. For example, observation 5 in the dataset can occur more than once in the Bootstrap sample and each Bootstrap sample has 399 observations. This process of obtaining the sample was repeated for 10,000 times. After arranging the 10,000 sample means in ascending order, the 2.5th and the 97.5th percentiles provided the 95% CI,[5] which is generally use when the statistics of interest is median or intra class correlation, ratio measures etc. Usually these statistics have complicated distributions. This method is the Bootstrap Percentile method. R software was used to analyze the data. R software is an open source software that can be downloaded.[6] The codes to obtain the Bootstrap percentile CI and Bias Corrected and Accelerated (BCa) CI have been provided in the Appendix. When the distribution of the statistic is skewed, there is a better way of providing CI in bootstrap known as BCa. The BCa provides CI correcting for bias when the data is skewed.[7]

3. Results

The hypothetical data consists of 399 observations. The mean (sd) of the 'Difference in TLV' was 96.9 (465.6). Fig. 1 shows the distribution of 'Difference in TLV'. The figure shows that the data had both positive and negative values and it is quite evident that the distribution is skewed to the right, indicating that data consists of more positive change values. Table 1 shows the CI using normal approximation for log transformed data, CI obtained after changing origin and log transformation, Hodges–Lehmann CI and, the Bootstrap method for 'Difference in TLV'. The CI using log transformed data, Change in origin and log transformed, Hodges–Lehmann CI was obtained as (245.8, 307.5), (−100.9, −9.5), (−6.5, 80.6) respectively. The Bootstrap BCa CI was found to be (53.2, 147.7). This indicated that there was a clear evidence of significant difference between the two methods (Table 1). The 95% CI for the mean using the log transformed normal approximation showed an evidence of significance. However, when the log transformed values of the mean difference was considered, the number of observations got reduced to 194 instead of 399. The reason for this is that the log transformation of the negative values is not possible, thereby producing missing values and hence excluded from the analysis. The 95% CI using Hodges–Lehmann ordered statistics was found to be (−6.5, 80.6) suggesting that there was no significant difference between two hypothetical methods. The method that used adding an appropriate constant and taking log transformation provided with the 95% CI which

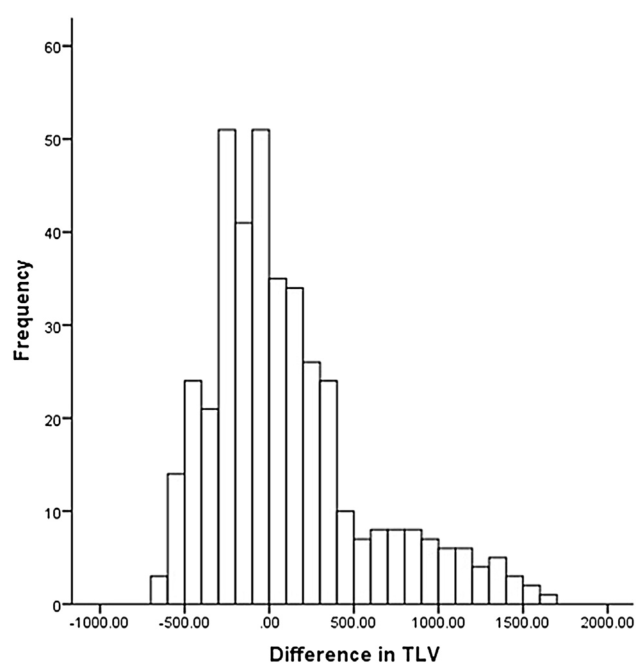

Fig. 1 – Distribution of difference in TLV.