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Attach importance of the bootstrap t test against Student's t test in clinical epidemiology: a demonstrative comparison using COVID-19 as an example

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Abstract

Student's t test is valid for statistical inference under the normality assumption or asymptotically. By contrast, although the bootstrap t test was proposed in 1993, it is seldom adopted in medical research. We aim to demonstrate that the bootstrap t test outperforms Student's t test under normality in data. Using random data samples from normal distributions, we evaluated the testing performance, in terms of true-positive rate (TPR) and false-positive rate and diagnostic abilities, in terms of the area under the curve (AUC), of the bootstrap t test and Student's t test. We explore the AUC of both tests with varying sample size and coefficient of variation. We compare the testing outcomes using the COVID-19 serial interval (SI) data in Shenzhen and Hong Kong, China, for demonstration. With fixed TPR, the bootstrap t test maintained the equivalent accuracy in TPR, but significantly improved the true-negative rate from the Student's t test. With varying TPR, the diagnostic ability of bootstrap t test outperformed or equivalently performed as Student's t test in terms of the AUC. The equivalent performances are possible but rarely occur in practice. We find that the bootstrap t test outperforms by successfully detecting the difference in COVID-19 SI, which is defined as the time interval between consecutive transmission generations, due to sex and non-pharmaceutical interventions against the Student's t test. We demonstrated that the bootstrap t test outperforms Student's t test, and it is recommended to replace Student's t test in medical data analysis regardless of sample size.

Introduction

Statistical hypotheses testing is an essential approach adopted for medical and healthcare data analysis [1]. Student's t test is one of the crucial tests that is widely used to conduct statistical inference for normally (or approximately normally) distributed dataset or those with sufficiently large sample size when the central limit theorem (CLT) is applicable [2, 3]. Student's t test may yield unsatisfactory testing outcome when samples are skewed [4], mostly likely with small sample size. Bootstrap methods have been proposed in 1970s, and have been used to analyse such as not normally distributed data [5, 6]. It is (asymptotically) more accurate than the standard estimates using sample variance and based on the assumptions of normality [7, 8]. Although a bootstrap t test was proposed by Efron and Tibshirani in 1993 [9], it was considered the percentile of bootstrapped test statistic samples at the significant level. To avoid repetition, we omit the algorithm of bootstrap t test in this study since the detailed algorithm was already introduced in [9]. This improved version of t test is seldom adopted in medical research.

Objectives

As mentioned, it is commonly accepted to use Student's t test when normality of the data suffices, whereas the bootstrap approach could be adopted to resolve the situation without normality. In this study, we demonstrated that for data from normal population, the bootstrap t test outperforms Student's t test in terms of different measures of the testing accuracy. We explored the general features of the data sample with which bootstrap t tests are likely to have more plausible testing outcome.

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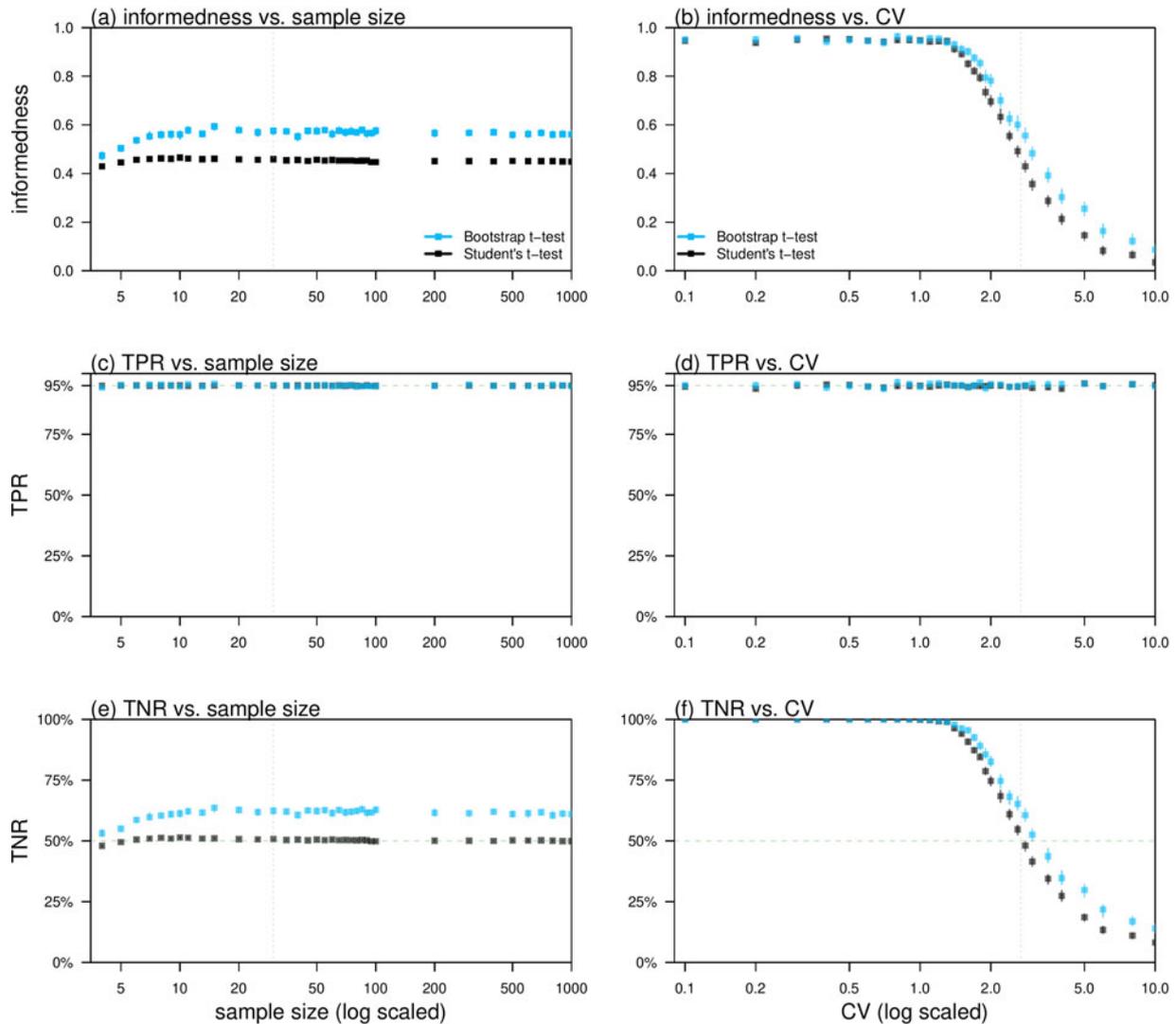


Fig. 1. Relations between the testing accuracies of the bootstrap t test (blue) and Student's t test (black), including informedness, TPR and TNR, and the features of the data samples including sample size and CV. Panels (a) and (b) show the relations between informedness ($= \text{TPR} + \text{TNR} - 1$) and sample size and CV respectively. Panels (c) and (d) show the relations between TPR and sample size and CV respectively. Panels (e) and (f) show the relations between TNR and sample size and CV respectively. The CVs (of the data samples) were determined by $\sqrt{n} \times t_{p=0.975, df=n}^*$, where n denotes the sample size, t^* is the quantile of the t distribution and 'df' is the degree of freedom, in panels (a), (c) and (e). The sample size was fixed to be 30 in panels (b), (d) and (f). The level of α was fixed to be 5% in all panels. The vertical bars in each panel represent the 95% CIs.

Methods

The details of the testing procedures of bootstrap t test could be found in [9]. The pairwise two-sample t tests are conducted based on the null hypothesis, \mathbf{H}_0 , that assumes the means of the two populations equal. Data samples are randomly generated from normally distributed populations, which will be used to compare the testing outcome based on data samples and the facts of populations. We evaluated the testing performance in two scenarios including

- scenario (i): the \mathbf{H}_0 is true; and
- scenario (ii): the \mathbf{H}_0 is false.

Then, the possibility that \mathbf{H}_0 was not rejected in scenario (i) is the true-positive rate (TPR), i.e. sensitivity. The possibility that \mathbf{H}_0 was rejected in scenario (ii) is the true-negative rate (TNR), i.e. specificity. Theoretically, the TPR is $(1 - \alpha)$, where α is known

as the rate of the type I error, i.e. false-alarm rate, and similarly, TNR is $(1 - \beta)$, where β is the rate of the type II error, i.e. miss rate. It is a common practice to set α at 5%, and the test is formulated with the aim to minimise β [1, 10].

Fixed TPR

With $\text{TPR} = (1 - \alpha) = 95\%$, i.e. $\alpha = 5\%$, we evaluated

- the consistency in TPR,
- the levels of TNR and
- informedness (i.e. Youden's J statistic)

of two types of t tests with varying sample size and coefficient of variation (CV) = S.D./difference in mean, in the samples [11]. Here, the informedness = $\text{TPR} + \text{TNR} - 1$, ranging from 0 to 1 (inclusive), is a single statistic that estimates the probability of an informed decision [12], which evaluates the performance of

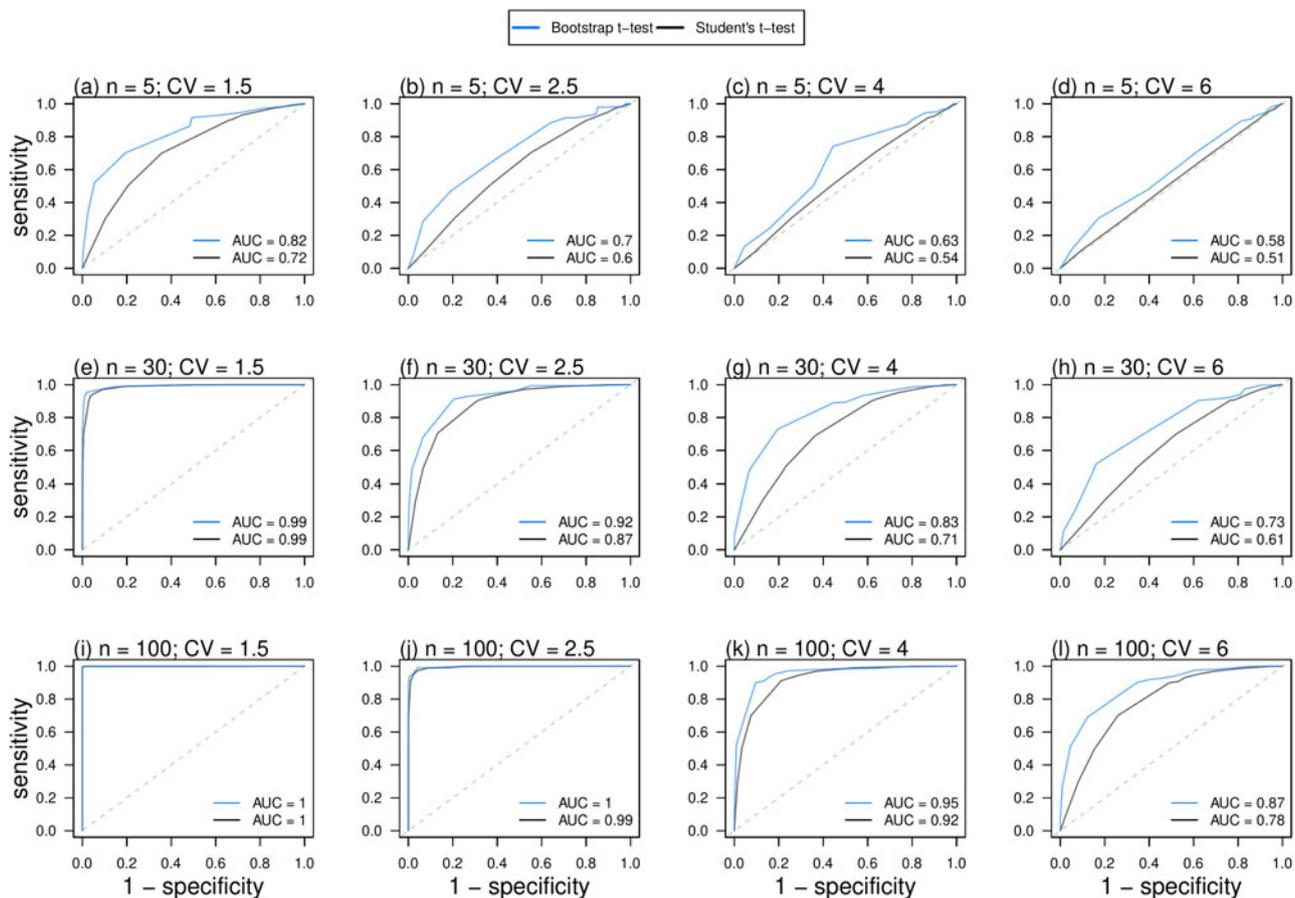


Fig. 2. ROC curves and AUCs of the bootstrap t test (blue) and Student's t test (black) with varying sample sizes, n , and CVs of the data samples. The diagonal dashed lines show the testing performance of a random classifier.

diagnostic tests. The informedness is 0 when a diagnostic test gives the same proportion of positive results for both true and false groups, which implies the testing outcome is totally uninformed. The informedness 1 indicates an ideal situation that $\text{TPR} = \text{TNR} = 1$, which implies that the testing outcome is perfectly informed. Since the test statistic of t test is mainly determined by CV and sample size, these two factors are thus included in the testing performance evaluation.

Varying TPR

With varying TPR, i.e. $(1 - \alpha)$, we could measure the diagnostic performance of both tests by using TPR and TNR in pairs. With all pairs of TPR and TNR, we could construct the receiver operating characteristic (ROC) curve to illustrate the diagnostic abilities of the two t tests in terms of the area under the curve (AUC).

Testing performance evaluation

For each set of sample size, CV and α , we tested 10 000 pairs of random-generated data samples to estimate the TPR and TNR, and then to calculate the informedness and AUC. We ran 1000 bootstrap samples to conduct the bootstrap t test. We also ran 1000 bootstrap samples in the testing outcomes of the two t tests to generate the 95% confidence intervals (CIs) of the estimated metrics.

For demonstration, we compare the testing outcomes by using the COVID-19 serial interval (SI), which is defined as the time interval between consecutive transmission generations, data in Shenzhen and Hong Kong, China. This demonstrative example is considered as a part of results (instead of methodology), and thus elaborated in the next section.

Results and discussion

We found that the informedness of bootstrap t test outperformed Student's t test for both a wide range of varying sample sizes and CVs, see Figure 1(a) and (b). Since the TPRs were consistently stabilised at 95%, see Figure 1(c) and (d), the difference in the informedness was due to the differences in the TNRs, see Figure 1(e) and (f). With fixed α , the bootstrap t test maintained the equivalent accuracy in TPR, but significantly improved the TNR compared to the Student's t test, see Figure 1(c)–(f). This can be interpreted as the bootstrap t test is more likely to exclude the unrealistic hypothesis, when H_0 is false, compared to the Student's t test and meanwhile maintained its judgement to the true statement, when H_0 is true. Since the null hypothesis is known *a priori* to be false [13], H_0 is commonly expected to be rejected based on sufficient (statistical) evidence [1, 4, 10]. Thus, the improvement in TNR was remarkably desirable.

In Figure 2, the diagnostic ability of bootstrap t test outperformed or equivalently performed as Student's t test in terms of the AUC. The diagnostic ability of bootstrap t test outperformed Student's t test not

Table 1. Summary of the situations to be tested and the recommendation of Student's or Bootstrap *t* tests

Normality	Sample size	Dispersion	Student's or Bootstrap <i>t</i> test	Remark	Reference
No	Small	Small	Bootstrap <i>t</i> test	Non-parametric tests are also preferred	7, 14, 15
		Large			
	Large	Small	None		
		Large	None		
Yes	Small	Small	Bootstrap <i>t</i> test	None	This study
		Large	Bootstrap <i>t</i> test	None	
	Large	Small	Both	Equivalent AUC	
		Large	Bootstrap <i>t</i> test	None	

Note: The 'dispersion' in this study is measured by the CV.

only when the sample size is small, e.g. see Figure 2(b) and (c), but also when the sample size becomes large, e.g. see Figure 2(i) and (k). Although Student's *t* test can be conducted with sufficiently large sample size when the CLT is applicable [2, 3], we found that bootstrap *t* test outperformed or equivalently performed as Student's *t* test regardless of the sample size.

On one hand, the AUC of Student's *t* test approached that of bootstrap *t* test, i.e. equivalent performance, when the sample size became larger and CV became smaller, e.g. see Figure 2(e) and (j). Under these circumstances, the distributions of samples to be tested are distinguishably separated, and thus straightforwardly, the two tests could yield 'to reject H_0 ' outcomes equivalently. This finding indicated that given sufficiently large sample size, Student's *t* test was capable of achieving equivalent diagnostic ability as bootstrap *t* test when the two datasets were discriminative in the central tendency and had low dispersion. It is also interesting to note that the equivalent performance only appears when the values of the AUC of two tests equal to 0.5, i.e. random classifier, or 1, i.e. perfect classifier. Either AUC = 0.5 or AUC = 1 would rarely occur due to the unusual features of the testing datasets, e.g. extremely large sample size and small CV or extremely small sample size and large CV.

On the other hand, when the sample size is small and CV is large, e.g. see Figure 2(b), (c), (d), (g) and (h), the distributions of samples to be tested are difficult to differentiate. In these situations, the diagnostic ability of bootstrap *t* test outperformed Student's *t* test in terms of the AUC.

In summary, for data samples from normally distributed populations, both testing performance and diagnostic abilities of the bootstrap *t* test outperformed Student's *t* test regardless of varying sample size and CV. We have summarised our findings and the situation when normality fails in Table 1. Specially, for small samples, when data fail to meet normality assumption, other non-parametric tests and their bootstrap versions are also recommended to fit the study purpose.

Demonstrative example of COVID-19

We demonstrate the performance of bootstrap *t* test against the Student's *t* test by using the COVID-19 SI dataset from the early outbreaks in Shenzhen and Hong Kong, two neighbour cities on the southeast coast of China. In infectious disease transmission, the SI is defined as the difference between the onset date of a secondary case and that of its associated primary case in a consecutive transmission chain [16]. With the pathogen's

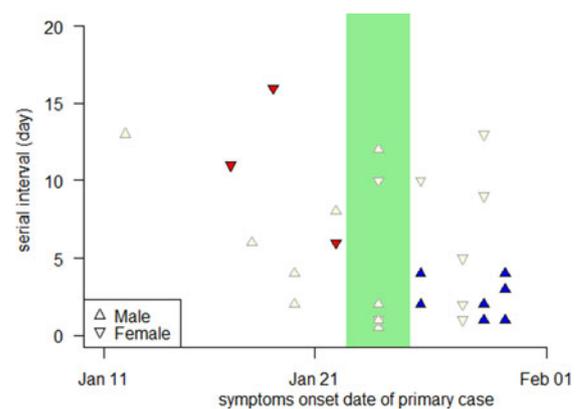


Fig. 3. SIs of the COVID-19 transmission pairs in Shenzhen and Hong Kong, China, during the early outbreaks. The SI with male or female primary case is represented by upward or downward triangle, respectively. The hollow or filled (red for female and blue for male) triangle represents the SI data excluded or included in the *t* tests, respectively. The green shading area highlights the CLNY.

transmissibility fixed, a shorter SI implies that the disease may transmit more rapidly in terms of the epidemiological outcomes at the population scale, e.g. number of cases. The SI is one of the key epidemiological parameters to characterise the disease transmission process, and it is of importance in determining the changing patterns of the epidemic curve [17–20]. The SI can be inferred from the contact tracing surveillance data and reconstruction of the transmission chains, which is well studied in previous studies [21–33], and widely adopted in modelling analysis [34–47].

The SI data were collected via the public domains until 22 February 2020 for Shenzhen, and until 15 February 2020 for Hong Kong. The study periods cover the major epidemic wave in Shenzhen and the first-epidemic wave in Hong Kong. This dataset was published previously in [48, 49] as well as studied in [50]. We extract transmission pairs, i.e. one secondary case is epidemiologically linked to one and only one primary case, with no missing information of the primary case's sex. We obtained a total of 34 transmission pairs including 22 (14 male and 8 female primary cases) from Shenzhen, and 12 (6 male and 6 female primary cases) from Hong Kong. There were 33 (out of a total of 34) transmission pairs with primary cases' symptoms onset date in January 2020, see Figure 3.

We evaluate the two *t* tests by examining whether they are able to identify the difference in COVID-19 SI due to sex and non-pharmaceutical interventions (NPIs). Thus, we conduct the *t*

test on two groups of SI samples separated from the original dataset based on two epidemiological evidences. They include

- evidence (i): according to the previous studies [28, 50], a female COVID-19 primary case is likely having longer SI than male; and
- evidence (ii): due to non-NPIs, e.g. social distancing, city lockdown, travel suspension, wearing face mask, regular sterilisation, the SI was shortened, i.e. became smaller, over time [31, 50].

Hence, we divide the COVID-19 SI samples based on the sex of primary case, and Chinese Lunar New Year (CLNY) from 23 to 26 January 2020 [51], after which most of the NPIs (including city lockdown) were implemented and enhanced. Two groups of SI samples are selected for the *t* tests. They are

- samples from population (i): SI samples with *female* primary case whose symptoms onset was *before* CLNY (sample size is 3, see red dots in Fig. 3), and
- samples from population (ii): SI samples with *male* primary cases whose symptoms onset was *after* CLNY (sample size is 10, see blue dots in Fig. 3).

Straightforwardly, the mean SI of population (i) is expected higher than the mean SI of population (ii), which is also supported by the evidence found in previous studies [28, 31, 50].

As for the outcomes from the *t* tests, we report the one-side bootstrap *t* test yields a *P* value = 0.04 of statistical significance, whereas the one-side Student's *t* test yields a *P* value = 0.05. Therefore, we demonstrate that the bootstrap *t* test outperforms the Student's *t* test by successfully detecting the difference in COVID-19 SI due to sex and NPIs.

Limitations

This comparison analysis study has limitations. As one of the classic drawbacks mentioned in [52], for the bootstrap on samples from a population without a finite variance, the bootstrap will be unlikely to converge. However, medical data samples are (commonly) from the real-world samples and thus the variance are expected to be finite. Although we have demonstrated the testing performances by using large sets of randomly generated data samples, the study would benefit from real-world examples that have different conclusions from the bootstrap *t* test and Student's *t* test, respectively.

Conclusions

We demonstrated that the bootstrap *t* test outperforms Student's *t* test, and it is recommended to replace Student's *t* test in medical data analysis regardless of sample size.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0950268821001047>

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Author contributions. SZ conceptualised the study, conducted the analysis, drafted the manuscript and critically revised the contents. SZ, ZY and DH discussed the results. All authors had full access to the data, contributed to the study, approved the final version for publication and take responsibility for its accuracy and integrity.

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Conflict of interest. DH received support from an Alibaba (China) Co., Ltd. Collaborative Research grant. MHW is a shareholder of Beth Bioinformatics Co., Ltd. Other authors have no conflict of interest.

Ethical standards. There was no experiment conducted. This research was based on the computer simulation, and publicly available dataset. Hence, the ethics approval was not applicable.

Data availability statement. The COVID-19 data used in this study are available via the Supplementary materials.

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