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Efficient estimation of log-normal means with application to pharmacokinetic data

Haipeng Shen[1,*,†], Lawrence D. Brown[2,‡] and Hui Zhi[3,§]

[1]*Department of Statistics and Operations Research, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, U.S.A.*
[2]*Department of Statistics, The Wharton School, University of Pennsylvania, Philadelphia, PA 19104, U.S.A.*
[3]*Clinical Pharmacology Statistics and Programming, GlaxoSmithKline, RTP, NC 27709, U.S.A.*

SUMMARY

In this paper, the problem of interest is efficient estimation of log-normal means. Several existing estimators are reviewed first, including the sample mean, the maximum likelihood estimator, the uniformly minimum variance unbiased estimator and a conditional minimal mean squared error estimator. A new estimator is then proposed, and we show that it improves over the existing estimators in terms of squared error risk. The improvement is more significant with small sample sizes and large coefficient of variations, which is common in clinical pharmacokinetic (PK) studies. In addition, the new estimator is very easy to implement, and provides us with a simple alternative to summarize PK data, which are usually modelled by log-normal distributions. We also propose a parametric bootstrap confidence interval for log-normal means around the new estimator and illustrate its nice coverage property with a simulation study. Our estimator is compared with the existing ones via theoretical calculations and applications to real PK studies. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS: arithmetic mean; clinical pharmacokinetics; maximum likelihood; parametric bootstrap; squared error risk; uniformly minimum variance unbiased

1. INTRODUCTION

It is well known that pharmacokinetic (PK) parameters, especially area under the concentration-time curve (AUC) and maximum concentration (Cmax), should be analysed on the log-scale under the assumption of log-normality [1]. Currently, PK data are usually summarized by arithmetic (or sample) means and/or geometric means [2]. A deeper look at the log-normal distribution reveals that these summaries are actually estimating different parameters of the

*Correspondence to: Haipeng Shen, Department of Statistics and Operations Research, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, U.S.A.
†E-mail: haipeng@email.unc.edu
‡E-mail: lbrown@wharton.upenn.edu
§E-mail: hui.2.zhi@gsk.com

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distribution. Arithmetic means or sample means are naive estimates of population means, while geometric means are plug-in estimates of population medians.

Suppose estimation of population means is of primary interest. Several estimators have been proposed in Reference [3], including the naive unbiased sample mean estimator, the maximum likelihood (ML) estimator and the uniformly minimum variance unbiased (UMVU) estimator. Recently, Zhou [4] proposed a conditional minimal mean squared error (MSE) estimator, and showed that it has smaller squared error risk than the three estimators mentioned above. In the current paper, we revisit this classical problem, and derive a simple efficient estimator under the squared error loss using a different approach. Our approach is motivated by the special connection between normal distributions and log-normal distributions. The proposed estimator is compared with the existing ones via theoretical risk calculations. We show that this new estimator has much smaller squared error risk (or MSE) than the sample mean, the MLE and the UMVUE. For small coefficient of variation (CV), the new approach has comparable performance with the conditional minimal MSE estimator. The new estimator improves considerably on the conditional minimal MSE estimator, when the underlying log-normal distribution has a large CV and the sample size is small. Such scenarios are common in PK studies. As illustrated below, our estimator is very easy to calculate in practice, and hence provides an alternative way to estimate the mean parameters for PK data. We also complement the new estimator with a parametric bootstrap confidence interval, and show that it has comparable coverage property with existing approaches, especially for situations encountered in PK studies.

In Section 2, first we review several existing estimators for log-normal means. Then we describe our proposed estimator in Section 3. The squared error risk of the estimators is compared in Section 4. The parametric bootstrap confidence interval is derived in Section 5. The estimators are applied to two real PK studies in Section 6, and we show that the estimates can be very different. All technical details are relegated to the Appendix.

2. EXISTING ESTIMATORS OF LOG-NORMAL MEANS

Suppose Z is a random variable which has a log-normal distribution with mean $v = E(Z)$. Then $\log(Z)$ will be normally distributed with some mean μ and variance σ^2. We will denote the above Z as '$Z \sim \mathrm{LN}(\mu, \sigma^2)$ with mean v'. Then, the three parameters, v, μ and σ^2, have the following relation:

$$v = \exp\left(\mu + \frac{\sigma^2}{2}\right) \tag{1}$$

In addition, as noted, for example, in Reference [3], the CV of Z can be written as

$$\mathrm{CV}(\%) = \frac{\mathrm{SD}(Z)}{E(Z)} = \sqrt{\mathrm{e}^{\sigma^2} - 1} \times 100$$

The CV is thus a function only of the variance of the normal random variable, $\log(Z)$.

Suppose $Z_1, \ldots, Z_n \overset{\text{i.i.d.}}{\sim} \text{LN}(\mu, \sigma^2)$ with mean v. Then $X_i = \log(Z_i) \overset{\text{i.i.d.}}{\sim} \text{N}(\mu, \sigma^2)$ for $i = 1, \ldots, n$. Define

$$\bar{Z} = \sum_{i=1}^{n} Z_i/n, \quad \bar{X} = \sum_{i=1}^{n} X_i/n \quad \text{and} \quad S^2 = \sum_{i=1}^{n} (X_i - \bar{X})^2 \tag{2}$$

Below we would like to review several existing estimators, and discuss their performance. See References [3, 4] for detailed references.

2.1. The naive unbiased estimator

Currently, PK data (especially AUC and Cmax), which are log-normally distributed, are usually summarized by arithmetic means $\bar{Z}$ as defined in (2). Indeed, it was pointed out by Zhou *et al.* [5] that

$$\hat{v}_1 = \bar{Z}$$

is the most commonly used estimator so far (at least) in biomedical research. It is obvious that $\hat{v}_1$ is a naive unbiased estimator for the log-normal mean. However, as shown by Zhou [4] and confirmed later in Section 4, it can be very inefficient as an estimator of v especially when the CV is large. This is true even for large samples.

2.2. The maximum likelihood (ML) estimator

As we know, $\bar{X}$ and S^2/n are the ML estimators for μ and σ^2, respectively. Based on (1), the plug-in principle leads to the ML estimator for v:

$$\hat{v}_2 = \exp\left(\bar{X} + \frac{S^2}{2n}\right)$$

As the MLE, $\hat{v}_2$ has some nice properties of being strongly consistent, asymptotically normal and asymptotically efficient for estimating v.

2.3. The uniformly minimum variance unbiased (UMVU) estimator

Finney [6] proposed the following estimator for v:

$$\hat{v}_3 = \mathrm{e}^{\bar{X}} g\left(\frac{S^2}{2}\right)$$

where the function g has the following form:

$$g(t) = \sum_{i=0}^{\infty} \frac{\Gamma((n-1)/2)}{i!\Gamma((n-1)/2 + i)} \left(\frac{n-1}{2n}\, t\right)^i \tag{3}$$

It can be shown that $\hat{v}_3$ is the UMVU estimator. (The UMVU property can be proved by showing that $E(\mathrm{e}^{\bar{X}} g(S^2/2)) = v$ and noticing that $\bar{X}$ and S^2 are complete sufficient statistics.) Being UMVUE, $\hat{v}_3$ has the smallest squared error risk (or variance in this case) among all unbiased estimators including the sample mean $\bar{Z}$.

2.4. A conditional minimal mean squared error (MSE) estimator

Rukhin [7] showed that both $\hat{v}_2$ and $\hat{v}_3$ are inadmissible under squared error loss. Some research has been done in the literature trying to derive estimators with everywhere smaller MSE.

For example, conditioning on σ^2, Zellner [8] claimed that the estimator,

$$\exp(\bar{X} + (n-3)\sigma^2/(2n))$$

is the conditional minimal MSE estimator among the class of estimators of the form $e^{\bar{X}} f(\sigma^2)$. When σ^2 is unknown, Evans and Shaban [9] proposed to estimate $\exp((n-3)\sigma^2/(2n))$ using an unbiased estimator, $g((n-3)S^2/(2(n-1)))$, with $g(\cdot)$ defined as in (3), and suggested the following estimator:

$$\hat{v}_4 = e^{\bar{X}} g\left(\frac{n-3}{2(n-1)} S^2\right)$$

Zhou [4] proposed a slightly different estimator,

$$\hat{v}_5 = e^{\bar{X}} g\left(\frac{n-4}{2(n-1)} S^2\right)$$

where $g((n-4)S^2/(2(n-1)))$ is an unbiased estimator of $\exp((n-4)\sigma^2/(2n))$, and named it the conditional minimal MSE estimator. Zhou [4] also compared the MSE of the four estimators, $\hat{v}_1$, $\hat{v}_2$, $\hat{v}_3$ and $\hat{v}_5$, and found out that $\hat{v}_5$ has the smallest MSE regardless of the sample size and the CV. Our analysis suggests that $\hat{v}_5$ has smaller MSE than $\hat{v}_4$ as well. However, the improvement is mainly apparent for small sample sizes. When n is large, the two estimators are almost identical as indicated by their expressions. Since $\hat{v}_5$ has the smallest MSE among the existing estimators, we will use it as a benchmark in Section 4, and first compare our proposed estimator $\hat{v}_6$ with it.

3. A NEW ESTIMATOR

The estimators $\hat{v}_3$, $\hat{v}_4$ and $\hat{v}_5$ are defined in terms of sums of infinite series. Their practical use may be limited due to the somewhat complicated form. We want to take a different approach, and propose a rather simple estimator, which still improves over the aforementioned estimators in terms of squared error risk.

The estimator we propose is the following:

$$\hat{v}_6 = \exp\left(\bar{X} + \frac{(n-1)S^2}{2(n+4)(n-1)+3S^2}\right)$$

The proposed estimator can be viewed as a 'degree-of-freedom-adjusted' ML estimator. In practice, it is very easy to obtain this estimator, because $\bar{X}$ and S^2 can be readily calculated. Below we will describe how this estimator is derived.

3.1. Derivation of the estimator

In light of the special relationship (1), we propose to look at the following class of estimators:

$$\delta_c : \delta_c = \exp(\bar{X} + cS^2/2), \quad c = \frac{1}{n+d}, \quad d > -n \tag{4}$$

where $\bar{X}$ and S^2 are defined in (2). Intuitively, this class of estimators are of simple form, and can be described as plug-in estimators relative to the basic formula (1) with $\bar{X}$ and $cS^2 = S^2/(n+d)$ serving as the estimators of μ and σ^2, respectively.

The estimators within class (4) are asymptotically equivalent, and they are asymptotically efficient since the ML estimator $\hat{v}_2$ belongs to this class with $c = 1/n$. Note that another plausible choice for c would be $c = 1/(n-1)$, corresponding to a plug-in estimator with using the usual unbiased estimator $S^2/(n-1)$ for σ^2. Our goal is to find an estimator from this class which can minimize the squared error risk, and hopefully has smaller risk than the estimators mentioned in Section 2.

The squared error risk of an estimator of the form δ_c is $R(\delta_c, v) = E(\delta_c - v)^2$. This can be shown to be

$$e^{2\mu+\sigma^2}[e^{[(2-n)/n]\sigma^2}(1-2c\sigma^2)^{-(n-1)/2} - 2e^{[(1-n)/2n]\sigma^2}(1-c\sigma^2)^{-(n-1)/2} + 1] \tag{5}$$

under the condition that $c < 1/(2\sigma^2)$.

According to the definition in (2), S^2/σ^2 is a χ^2_{n-1} random variable. Then (5) can be obtained using the moment-generating function (MGF) of a χ^2_{n-1} random variable, i.e. when $c\sigma^2 < 1/2$,

$$E(e^{cS^2}) = (1-2c\sigma^2)^{-(n-1)/2}$$

When $c\sigma^2 \geqslant 1/2$, the MGF does not exist; and the risk is infinite. The condition $c\sigma^2 < 1/2$ is equivalent to $d > 2\sigma^2 - n$. Our proposed estimator thus has finite risk whenever $\sigma^2 < (n+4)/2$. In real applications this is not a serious restriction. Furthermore, this condition is satisfied whenever the risk of the MLE $\hat{v}_2$ is finite, since $\hat{v}_2$ corresponds to the choice $d = 0$ which has finite risk when $\sigma^2 < n/2$.

The following proposition suggests that the risk approaches 0 asymptotically for estimators in class (4).

Proposition 1
$R(\delta_c, v) \to 0$ as $n \to \infty$.

Proof
Note that $cn \to 1$ as $n \to \infty$. Then we need to use (5) plus the following result:

$$\text{if } a_n \to \infty \quad \text{and} \quad a_n b_n \to \lambda \quad \text{then } (1+b_n)^{a_n} \to e^{\lambda} \qquad \square$$

A direct minimization of risk (5) seems implausible as a path to a convenient, satisfactory procedure. As an alternative, we look at the second-order asymptotics to find a constant c that can asymptotically minimize $R(\delta_c, v)$. Let $V(\delta_c, v) = R(\delta_c, v)/e^{2\mu+\sigma^2}$. Then finding c to minimize risk (5) is equivalent to finding c to minimize the relative MSE, $V(\delta_c, v)$.

Note the following standard expansion:

$$c = \frac{1}{n+d} = \frac{1}{n} - \frac{d}{n(n+d)} = \frac{1}{n} - \frac{d}{n^2} + o\left(\frac{1}{n^2}\right)$$

which justifies consideration of estimators of the form δ_c with $c = 1/n - d/n^2 + o(1/n^2)$.

Theorem 1
Suppose $c = 1/n - d/n^2 + o(1/n^2)$. Then

$$V(\delta_c, v) = \frac{\sigma^2}{n}\left\{1 + \frac{\sigma^2}{2} + \frac{\sigma^2}{4n}\left[d^2 - (8 + 3\sigma^2)d + 8\sigma^2 + \frac{7}{4}\sigma^4\right]\right\} + o\left(\frac{1}{n^2}\right)$$

Under squared error loss, the risk can be written as a sum of the squared bias and the variance. The bias and variance decomposition of the risk is summarized in Corollary 1.

Corollary 1

$$\mathrm{Bias}_v^2(\delta_c) = v^2\left(\frac{d^2}{4n^2}\sigma^4 - \frac{d}{4n^2}\sigma^6 + \frac{1}{16n^2}\sigma^8\right) + o\left(\frac{1}{n^2}\right)$$

$$\mathrm{var}_v(\delta_c) = v^2\frac{\sigma^2}{n}\left[1 + \frac{\sigma^2}{2} + \frac{2\sigma^2}{n}\left(-d + \frac{4-d}{4}\sigma^2 + \frac{3}{16}\sigma^4\right)\right] + o\left(\frac{1}{n^2}\right)$$

Suppose we want to find a constant c that can minimize the risk up to the order of $1/n^2$, Theorem 1 suggests that it suffices to find d to minimize $d^2 - (8 + 3\sigma^2)d$. According to the quadratic form, the minimizer depends on σ^2 and is

$$(8 + 3\sigma^2)/2 = 4 + 3\sigma^2/2$$

This means that the constant c which minimizes the approximate risk should be of the order of $1/(n+4+3\sigma^2/2)$. This is thus the value an oracle would choose. However, in real applications, the true variance σ^2 is usually unknown. We propose to use an 'adaptive' estimator by replacing σ^2 with its consistent estimate, $S^2/(n-1)$. As a result, our proposed estimator is

$$\hat{v}_6 = \exp\left(\bar{X} + \frac{(n-1)S^2}{2(n+4)(n-1) + 3S^2}\right)$$

In Section 4 we will compare the squared error risk of our estimator $\hat{v}_6$ with the existing estimators described in Section 2.

4. RISK COMPARISON

To compare these estimators, we take into account both the bias and the variance of the estimators and consider their risks under the squared error loss. Due to the log-normality, there exist convenient expressions for the risks of all the estimators. The risks for $\hat{v}_3$, $\hat{v}_4$ and $\hat{v}_5$ can be calculated from numerical summations of infinite series. The risk of $\hat{v}_6$ can be obtained via numerical integration. These are summarized in the following proposition.

Proposition 2

$$R(\hat{v}_1, v) = v^2\frac{e^{\sigma^2} - 1}{n}$$

$$R(\hat{v}_2, v) = v^2\left(e^{[(2-n)/n]\sigma^2}\left(1 - \frac{2\sigma^2}{n}\right)^{-(n-1)/2} - 2e^{[(1-n)/2n]\sigma^2}\left(1 - \frac{\sigma^2}{n}\right)^{-(n-1)/2} + 1\right)$$

$$R(\hat{v}_3, v) = v^2 \left(e^{(1/n)\sigma^2} g\left(\frac{n-1}{2n} \sigma^4 \right) - 1 \right)$$

$$R(\hat{v}_4, v) = v^2 \left(e^{-(1/n)\sigma^2} g\left(\frac{(n-3)^2}{2n(n-1)} \sigma^4 \right) - 2e^{-(1/n)\sigma^2} + 1 \right)$$

$$R(\hat{v}_5, v) = v^2 \left(e^{-(2/n)\sigma^2} g\left(\frac{(n-4)^2}{2n(n-1)} \sigma^4 \right) - 2e^{-(3/2n)\sigma^2} + 1 \right)$$

$$R(\hat{v}_6, v) = v^2 (e^{[(2-n)/n]\sigma^2} f_1 - 2e^{[(1-n)/2n]\sigma^2} f_2 + 1)$$

where

$$f_1 = E\left(\exp\left(\frac{2(n-1)S^2}{2(n+4)(n-1)+3S^2} \right) \right) \quad \text{and} \quad f_2 = E\left(\exp\left(\frac{(n-1)S^2}{2(n+4)(n-1)+3S^2} \right) \right)$$

The formulas for $\hat{v}_2$ can be derived directly from (5) while some results from Evans and Shaban [10] are needed to obtain the formulas for $\hat{v}_3$, $\hat{v}_4$ and $\hat{v}_5$. See the Appendix for details. A different formula for $\hat{v}_3$ was previously provided by Mehran [11], which can be shown to be equivalent to the one given here.

Based on the formulas in the above proposition, the risks for these estimators can be calculated numerically for any given CV and sample size n. As for $R(\hat{v}_6, v)$, f_1 and f_2 can be calculated using numerical integration because S^2/σ^2 is a χ^2_{n-1} random variable. Zhou [4] illustrated that $\hat{v}_5$ has smaller risk than $\hat{v}_1$, $\hat{v}_2$ and $\hat{v}_3$. In our analysis (*not shown here*), we confirmed the results of Zhou [4] and also found that $\hat{v}_5$ has smaller risk than $\hat{v}_4$. Thus, we will use $\hat{v}_5$ as a benchmark, and first compare our proposed estimator $\hat{v}_6$ to $\hat{v}_5$ in terms of squared error risk. The risks are calculated as functions of CV and sample size n. The values of CV are chosen to be between 0.3 and 2.5, which are commonly observed in various clinical PK studies. The sample size n is chosen to be one of 6, 8, 10, 12, 25, 50, 75, 100 and 150. Some of these are common in PK studies while the others are chosen to show the overall effect.

For illustration purpose, Figure 1 plots the risk ratio of $\hat{v}_5$ over $\hat{v}_6$ as a function of CV when n is 6, 8, 12 and 25, respectively. As one can see, when n is small, our proposed estimator $\hat{v}_6$ improves over $\hat{v}_5$ in terms of risk in most cases, especially for moderate to large CVs. The improvement increases as the CV increases. As n increases to 25, $\hat{v}_6$ dominates $\hat{v}_5$ over the whole range of the CVs considered here, and remains so for larger sample sizes as well (*figures not shown here*). When sample sizes are large ($n \geqslant 100$), the improvement becomes smaller as one would expect. For a fixed sample size, the improvement increases as the CV increases, except for really small sample sizes and small CVs as shown by the top panels of Figure 1. Although the risk of our estimator is generally smaller than the risk of $\hat{v}_5$, the two risks are quite close except when the CV is large. It seems that the case could be made for either estimator, but some practitioners might prefer our estimator due to its simpler calculation and more explicit functional form. Its simpler form also enables us to provide an accompanying parametric bootstrap confidence interval in Section 5, which has nice coverage property.

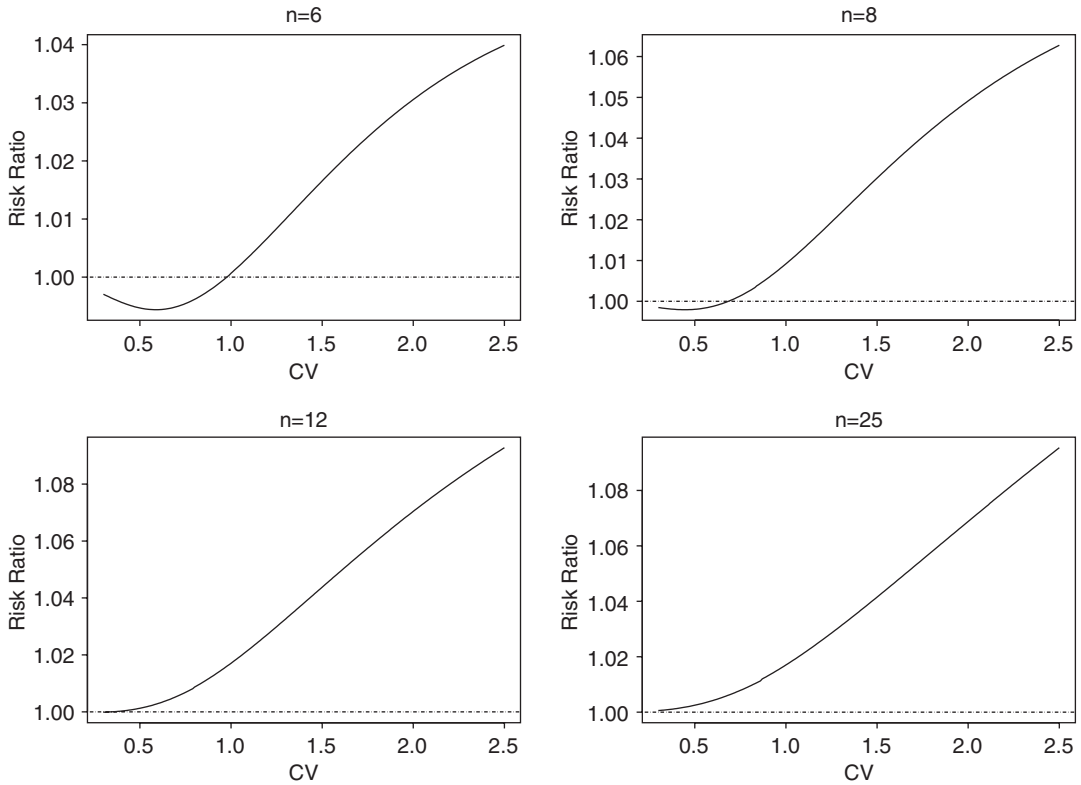

Figure 1. $R(\hat{v}_5, v)/R(\hat{v}_6, v)$ as a function of CV and sample size n.

In addition, our proposed estimator $\hat{v}_6$ has uniformly smaller squared error risk than the other four estimators. Figure 2 plots the risk ratios of $\hat{v}_1$, $\hat{v}_2$, $\hat{v}_3$ and $\hat{v}_4$ over $\hat{v}_6$. For the sake of space saving, only plots for $n = 6$, 25, 75 and 150 are shown. As one can see, the improvement of $\hat{v}_6$ over the other estimators is very substantial with small sample sizes and large CVs. Even with a large sample size ($n = 150$), there is still considerable amount of improvement especially over the sample mean $\hat{v}_1$. The plots suggest that, for moderate to large sample sizes, the risks of $\hat{v}_2$, $\hat{v}_3$ and $\hat{v}_4$ increase in the same order as $\hat{v}_6$ when the CV increases; however, the risk of $\hat{v}_1$ seems to increase in a much higher order (exponentially). This confirms the claim of Zhou [4] that the sample mean, $\hat{v}_1$, could be very inefficient even for large samples.

5. A PARAMETRIC BOOTSTRAP CONFIDENCE INTERVAL AROUND $\hat{v}_6$

For statistical inference purpose, it makes sense to investigate confidence intervals for the log-normal mean, v. Relation (1) suggests that confidence intervals for v can be derived by exponentiating confidence intervals for $\tau = \mu + \frac{1}{2}\sigma^2$. Zhou and Gao [12] compared four main methods for constructing confidence intervals for τ via a simulation study, and concluded

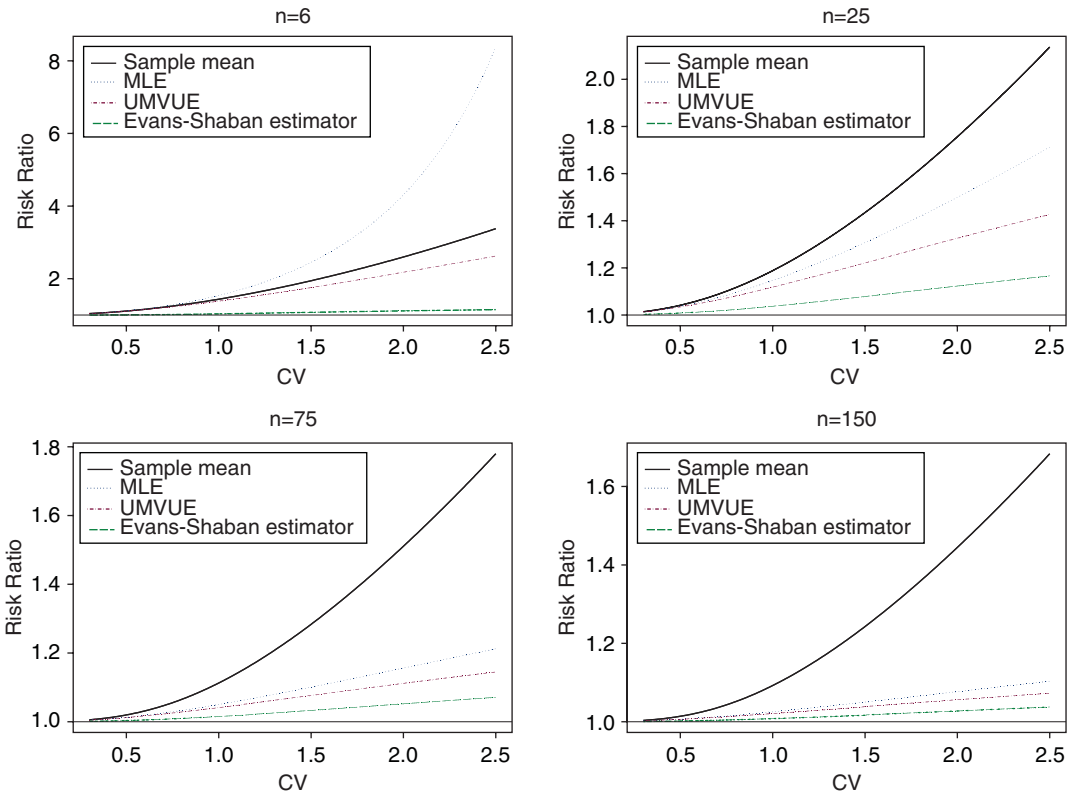

Figure 2. $R(\hat{v}_i, v)/R(\hat{v}_6, v)$ $(i = 1, 2, 3, 4)$ as a function of CV and sample size n.

that Cox's method [13] and Angus's parametric bootstrap method [14] have superior performances. In this section, we propose a parametric bootstrap confidence interval for τ around our estimator

$$\hat{\tau} = \log \hat{v}_6 = \bar{X} + \frac{(n-1)S^2}{2(n+4)(n-1) + 3S^2}$$

which then leads to a confidence interval for v around $\hat{v}_6$. When compared with the results in Reference [12], our simulation study suggests that the proposed confidence interval has nice and comparable coverage properties with Cox's and Angus's methods in scenarios common in PK studies. In general, our method also results in narrower confidence intervals.

We know that $\bar{X} \sim \mathrm{N}(\mu, \sigma^2/n)$ and $S^2 \sim \sigma^2 \chi^2_{n-1}$. Then, using the Delta method, we can obtain the following approximate expression for the variance of $\hat{\tau}$:

$$\mathrm{var}(\hat{\tau}) \approx \frac{\sigma^2}{n} + \frac{8(n-1)(n+4)^2\sigma^4}{(3\sigma^2 + 2(n+4))^4}$$

Note that σ^2 can be estimated using $S^2/(n-1)$. Define the following statistic:

$$K(\tau)=\frac{\hat{\tau}-\tau}{\sqrt{\widehat{\mathrm{var}}(\hat{\tau})}}=\frac{\bar{X}+\dfrac{(n-1)S^2}{2(n+4)(n-1)+3S^2}-\tau}{\sqrt{\dfrac{S^2}{n(n-1)}+\dfrac{8(n-1)(n+4)^2\dfrac{S^4}{(n-1)^2}}{\left(3\dfrac{S^2}{n-1}+2(n+4)\right)^4}}} \tag{6}$$

For a significance level α, let t_1 and t_2 be the $\alpha/2$ and $1-\alpha/2$ percentiles of $K(\tau)$, respectively. Then, one can obtain a $1-\alpha$ confidence interval for τ as

$$[\hat{\tau}-t_2\sqrt{\widehat{\mathrm{var}}(\hat{\tau})},\hat{\tau}-t_1\sqrt{\widehat{\mathrm{var}}(\hat{\tau})}]$$

To estimate the two percentiles, we observe from (6) that $K(\tau)$ has the same distribution as

$$T(\sigma)=\frac{N+\dfrac{\sqrt{n}\sigma}{2}\left[\dfrac{2(n-1)\dfrac{C}{n-1}}{2(n+4)+3\sigma^2\dfrac{C}{n-1}}-1\right]}{\sqrt{\dfrac{C}{n-1}+\dfrac{8\sigma^2n(n-1)(n+4)^2\left(\dfrac{C}{n-1}\right)^2}{\left(3\sigma^2\dfrac{C}{n-1}+2(n+4)\right)^4}}} \tag{7}$$

where $N\sim \mathrm{N}(0,1)$, $C\sim\chi^2_{n-1}$ and they are independent. Thus, we propose the following parametric bootstrap procedure to estimate t_1 and t_2:

1. Generate $N_i\sim \mathrm{N}(0,1)$ and $C_i\sim\chi^2_{n-1}$ independently for $i=1,\ldots,B$;
2. Calculate T_i according to (7) with N, C and σ replaced with N_i, C_i and $S/\sqrt{n-1}$;
3. Estimate t_1 by $\hat{t}_1$, the $\alpha/2$ percentile of $\{T_i: i=1,\ldots,B\}$, and t_2 by $\hat{t}_2$, the $1-\alpha/2$ percentile of the T_i's.

As a result, we obtain a $1-\alpha$ parametric bootstrap confidence interval for τ as

$$\left[\hat{\tau}-\hat{t}_2\sqrt{\widehat{\mathrm{var}}(\hat{\tau})},\hat{\tau}-\hat{t}_1\sqrt{\widehat{\mathrm{var}}(\hat{\tau})}\right] \tag{8}$$

Then, the corresponding $1-\alpha$ bootstrap confidence interval for v is

$$\exp\left(\left[\hat{\tau}-\hat{t}_2\sqrt{\widehat{\mathrm{var}}(\hat{\tau})},\hat{\tau}-\hat{t}_1\sqrt{\widehat{\mathrm{var}}(\hat{\tau})}\right]\right) \tag{9}$$

5.1. *Performance of the confidence interval (8)*

We use the following simulation set-up to investigate the performance of the proposed confidence interval (8): $n=11$, 101 and 400, $\sigma^2=0.1$, 0.5, 1.0, 2.0, 5.0, and 20.0, and $\mu=-\sigma^2/2$. The parameter configuration is the same as in Reference [12] so that we can compare the

Table I. Coverage probability (and length) of 90 per cent parametric bootstrap confidence intervals.

σ^2	0.1	0.5	1.0	2.0	5.0	20.0
CV	0.32	0.81	1.31	2.53	12.14	22026.47
$n=11$	0.897	0.886	0.856	0.830	0.774	0.628
	(0.347)	(0.838)	(1.232)	(1.897)	(3.379)	(8.919)
$n=101$	0.893	0.896	0.891	0.890	0.865	0.766
	(0.106)	(0.260)	(0.400)	(0.651)	(1.310)	(3.700)
$n=400$	0.899	0.910	0.884	0.908	0.892	0.874
	(0.053)	(0.130)	(0.202)	(0.327)	(0.680)	(2.275)

result with theirs. Note that μ is chosen such that $\tau=0$. This is without loss of generality, because different μ only shifts the confidence interval, given fixed n and σ^2. For each set-up, 1000 random samples are simulated from the corresponding distribution, and 5000 (B) bootstrap samples are used.

Table I reports the empirical coverage probabilities for the calculated 90 per cent confidence intervals, as well as the average interval lengths (*in parentheses*). The corresponding CV, are also reported. In most cases, our method leads to confidence intervals that have comparable coverage properties as those obtained by Cox's and Augus's methods [12], and are similar or shorter in length. The result shows that our method works well when n is moderate to large. When n is small, the performance is good for σ^2 in a range that is common for PK studies (up to 2.0). For $n=11$ and $\sigma^2=5.0$ or 20.0, our method undercovers the true parameter considerably. This is because, in these cases, our confidence intervals are much shorter than those generated by the other methods. For example, the average interval lengths are 4.277 and 15.328 for Cox's method, and 6.781 and 27.450 for Angus's method [12].

6. REAL PHARMACOKINETIC EXAMPLES

In this section, the different estimators are applied to two real clinical PK studies to illustrate their practical performance when estimating log-normal means. The intent of this discussion is to illustrate the extent of differences in practice that may result from the use of different estimators. Consequently, our description is intentionally brief of the context of these examples and various important details of the analysis not directly related.

6.1. The effect of aspirin on the pharmacokinetics of Compound X

This was a drug-interaction study conducted by GlaxoSmithKline (GSK) to estimate the effect of aspirin on the pharmacokinetics of Compound X. The outcome variable of interest is the area under the concentration-time curve (AUC) of Compound X. Treatment A means taking Compound X for five days, while treatment B stands for taking the combination of Compound X and aspirin for five days. Ten subjects complete the study; thus, $n=10$ in this study for each treatment. The observed between-subject CVs are around 35 per cent for both treatments.

A guidance of the U.S. Food & Drug Association (FDA) requires that outcome variables like AUC should be analysed on the log-scale, which implicitly assumes log-normality.

Table II. Aspirin-interaction study.

Treatment	A	B
CV (per cent)	38.16	33.11
$\hat{v}_1$	5047.80	5206.70
$\hat{v}_2$	5049.01	5197.87
$\hat{v}_3$	5047.31	5196.84
$\hat{v}_4$	4979.81	5143.45
$\hat{v}_5$	4946.31	5116.94
$\hat{v}_6$	4958.40	5126.93
CI	[4159.29, 6386.31]	[4364.18, 6408.11]

Nevertheless, we still performed the Shapiro–Wilk normality test on the log-transformed AUC data for both treatments, and the p-values are consistent with the log-normality assumption under a significance level of 0.05.

Table II lists the estimated means of AUC for each treatment separately using the six estimators. The bootstrap confidence intervals (9) for the means are also reported. As one can see from Table II, the first three estimators, $\hat{v}_1$, $\hat{v}_2$ and $\hat{v}_3$, give very similar estimates for each treatment, while the last three estimates are close and are smaller than the first three estimates. However, the values for treatments A and B are uniformly comparable with each other with respect to each estimator. This example illustrates the comparison of the estimators when CVs are small. In the current study, all the estimators have comparable risks due to the small CVs. According to the calculation in Section 4, the risk ratios of $\hat{v}_6$ relative to the other five estimators are, respectively, 0.96, 0.96, 0.96, 0.99 and 1.00 for treatment A; while they are 0.97, 0.97, 0.97, 0.99 and 1.00 for treatment B.

6.2. Evaluation for the bioavailability of Compound Y

This was a four-period cross-over study also conducted by GSK to estimate the bioavailability of two forms of Compound Y (liquid or tablet) before and after breakfast. The variable of interest is again the AUC of Compound Y. Treatments A and B stand for taking the two forms of Compound Y before breakfast, while C and D mean taking the two forms after breakfast. Sixteen subjects complete the study ($n = 16$), and the order for each subject to undergo the four treatments is randomized in order to avoid any period bias. The Shapiro–Wilk normality test is performed on the log-transformed data for the four treatments. The p-values are 0.41, 0.96, 0.61 and 0.50, respectively, which suggest that log-normality is not an implausible assumption. This study has larger between-subject CVs around 200 per cent. AUCs are estimated for each treatment separately; thus, we ignore the within-subject correlation across the four treatments. The results are summarized in Table III, along with the bootstrap confidence intervals (9) for the means.

The six estimators provide different summary results for AUC of every treatment. Although treatment B has a smaller average AUC relative to treatment A using all the estimators, $\hat{v}_6$ leads to the least difference among these estimators. The sample sizes are comparable to the drug-interaction study in Section 6.1 while the CVs are much larger. In this study, because of the rather large CVs, the estimators have very different risks. The risk ratios of $\hat{v}_6$ relative to the other estimators are, respectively, 0.44, 0.47, 0.62, 0.84 and 0.91 for treatment A; 0.55,

Table III. A bioavailability study.

Treatment	A	B	C	D
CV (per cent)	235.91	184.47	232.87	241.90
$\hat{v}_1$	158.57	122.62	158.39	142.25
$\hat{v}_2$	161.27	135.97	165.62	148.10
$\hat{v}_3$	154.81	132.49	158.83	141.63
$\hat{v}_4$	138.98	121.52	141.80	125.99
$\hat{v}_5$	131.63	116.34	133.92	118.77
$\hat{v}_6$	123.89	111.93	126.37	111.64
CI	[92.41, 436.32]	[82.96, 306.85]	[94.85, 452.28]	[83.19, 421.15]

0.58, 0.69, 0.88 and 0.94 for treatment B; 0.44, 0.46, 0.61, 0.84 and 0.92 for treatment C and 0.42, 0.44, 0.60, 0.83 and 0.91 for treatment D.

7. CONCLUSION

In this paper, we first reviewed several existing estimators for log-normal means. Then we proposed to look at a special class of estimators, which are asymptotically equivalent to the ML estimator, and derived their squared error risk function. Through the second-order asymptotics, we came up with an easy-to-calculate efficient estimator within the special class, which has approximately the smallest squared error risk. The estimator can be viewed as a 'degree-of-freedom-adjusted' ML estimator. The new estimator is compared with the existing ones in terms of squared error risk, and appears to improve greatly over the sample mean estimator, the ML estimator and the UMVU estimator. The improvement is more substantial with small sample sizes and large CVs. Our estimator also has comparable performance with the conditional minimal MSE estimator [4], and reasonably smaller squared error risk when the CV is large. However, our estimator has a more explicit expression, and is easier to implement. Thus, we recommend to use the proposed estimator to estimate log-normal means. A parametric bootstrap confidence interval is also developed to complement the new estimator, and it is shown to have nice coverage property except for cases of small n and very large CV.

APPENDIX A

A.1. Proof of Theorem 1

Here we give the proof of Theorem 1. The following two lemmas, which are needed during the proof, are established first.

Lemma A.1
Suppose $c = 1/n - d/n^2 + o(1/n^2)$. Then the following statements are true:

1. $A_n \equiv \dfrac{2}{n} - 1 + (n-1)c = \dfrac{1-d}{n} + o\left(\dfrac{1}{n}\right)$

2. $B_n \equiv \frac{1}{2n} - \frac{1}{2} + \frac{(n-1)c}{2} = -\frac{d}{2n} + o\left(\frac{1}{n}\right)$

3. $(n-1)c^2 = \frac{1}{n} - \frac{2d+1}{n^2} + o\left(\frac{1}{n^2}\right)$

4. $(n-1)c^3 = \frac{1}{n^2} + o\left(\frac{1}{n^2}\right)$

5. $(n-1)c^4 = o\left(\frac{1}{n^2}\right)$

6. $(n-1)^2c^4 = \frac{1}{n^2} + o\left(\frac{1}{n^2}\right)$

The proof of Lemma A.1 is straightforward. We only need to plug in the Taylor expansion of c. This lemma can be used to simplify the proof of the following Lemma A.2.

Lemma A.2
Let $f_1(x) = e^{((2/n)-1)x-[(n-1)/2]\ln(1-2cx)}$ and $f_2(x) = e^{((1/2n)-(1/2))x-[(n-1)/2]\ln(1-cx)}$. Then the following statements hold:

1. $f_1^{(1)}(0) = A_n$

2. $f_1^{(2)}(0) = A_n^2 + 2(n-1)c^2 = \frac{2}{n} + \frac{d^2-6d-1}{n^2} + o\left(\frac{1}{n^2}\right)$

3. $f_1^{(3)}(0) = A_n^3 + 6A_n(n-1)c^2 + 8(n-1)c^3 = -\frac{6d-14}{n^2} + o\left(\frac{1}{n^2}\right)$

4. $f_1^{(4)}(0) = A_n^4 + 12A_n^2(n-1)c^2 + 32A_n(n-1)c^3 + 12(n-1)^2c^4 + 48(n-1)c^4 = \frac{12}{n^2} + o\left(\frac{1}{n^2}\right)$

5. $f_1^{(k)}(0) = o\left(\frac{1}{n^2}\right)$ for $k \geqslant 5$

6. $f_2^{(1)}(0) = B_n$

7. $f_2^{(2)}(0) = B_n^2 + \frac{1}{2}(n-1)c^2 = \frac{1}{2n} + \frac{d^2-4d-2}{4n^2} + o\left(\frac{1}{n^2}\right)$

8. $f_2^{(3)}(0) = B_n^3 + \frac{3}{2}B_n(n-1)c^2 + (n-1)c^3 = -\frac{3d}{4n^2} + \frac{1}{n^2} + o\left(\frac{1}{n^2}\right)$

9. $f_2^{(4)}(0) = B_n^4 + 3B_n^2(n-1)c^2 + 4B_n(n-1)c^3 + \frac{3}{4}(n-1)^2c^4 + 3(n-1)c^4 = \frac{3}{4n^2} + o\left(\frac{1}{n^2}\right)$

10. $f_2^{(k)}(0) = o\left(\frac{1}{n^2}\right)$ for $k \geqslant 5$

To prove Lemma A.2, one must first calculate the derivatives of the functions $f_1(x)$ and $f_2(x)$. The calculations are standard but rather tedious, and we omit them here. Then one needs to use the Taylor expansions of the terms in Lemma A.1.

Proof of Theorem 1

Let $f(x) = f_1(x) - 2f_2(x)$ where f_1 and f_2 are defined in Lemma A.2. Then according to (5) and Lemma A.2, we have

$$V(\delta_c, v) = 1 + f(\sigma^2)$$

First we would like to look at some derivatives of the function $f(x)$. According to Lemmas A.1 and A.2, the following statements are true:

1. $f^{(1)}(0) = f_1^{(1)}(0) - 2f_2^{(1)}(0) = A_n - 2B_n = \dfrac{1}{n}$
2. $f^{(2)}(0) = f_1^{(2)}(0) - 2f_2^{(2)}(0) = \dfrac{1}{n} + \dfrac{d^2 - 8d}{2n^2} + o\left(\dfrac{1}{n^2}\right)$
3. $f^{(3)}(0) = f_1^{(3)}(0) - 2f_2^{(3)}(0) = \dfrac{3(8 - 3d)}{2n^2} + o\left(\dfrac{1}{n^2}\right)$
4. $f^{(4)}(0) = f_1^{(4)}(0) - 2f_2^{(4)}(0) = \dfrac{21}{2n^2} + o\left(\dfrac{1}{n^2}\right)$
5. $f^{(k)}(0) = f_1^{(k)}(0) - 2f_2^{(k)}(0) = o\left(\dfrac{1}{n^2}\right)$ for $k \geqslant 5$

Then, according to Taylor expansion, we have that

$$f(\sigma^2) = f(0) + f^{(1)}(0)\sigma^2 + \frac{f^{(2)}(0)}{2!}\sigma^4 + \frac{f^{(3)}(0)}{3!}\sigma^6 + \frac{f^{(4)}(0)}{4!}\sigma^8 + o\left(\frac{1}{n^2}\right)$$

$$= -1 + \frac{\sigma^2}{n} + \frac{\sigma^4}{2n} + \frac{(d^2 - 8d)\sigma^4}{4n^2} + \frac{(8 - 3d)\sigma^6}{4n^2} + \frac{7\sigma^8}{16n^2} + o\left(\frac{1}{n^2}\right)$$

Finally, it follows that

$$V(\delta_c, v) = \frac{\sigma^2}{n}\left\{1 + \frac{\sigma^2}{2} + \frac{\sigma^2}{4n}\left[d^2 - (8 + 3\sigma^2)d + 8\sigma^2 + \frac{7}{4}\sigma^4\right]\right\} + o\left(\frac{1}{n^2}\right) \qquad \square$$

A.2 Proof of Proposition 2

Here we give a brief proof for some of the risk formulas in Proposition 2. The following lemma is needed for the estimators $\hat{v}_3$, $\hat{v}_4$ and $\hat{v}_5$.

Lemma A.3

$$E(g(AS^2)) = \exp\left(\frac{n-1}{n}A\sigma^2\right), \quad E(g^2(AS^2)) = \exp\left(\frac{2(n-1)}{n}A\sigma^2\right) g\left(\frac{2(n-1)}{n}A^2\sigma^4\right)$$

where $g(t)$ is defined as in (3).

For a proof, see Reference [10].

Proof of Proposition 2

Let $A = (n-1+k)/(2(n-1))$. Then $\hat{v}_3$, $\hat{v}_4$ and $\hat{v}_5$ can be written as $\exp(\bar{X})g(AS^2)$ with k being 0, -2 and -3, respectively.

Using Lemma A.3, we can obtain that

$$E(\exp(\bar{X})g(AS^2) - v)^2 = v^2\left(e^{[(k+1)/n]\sigma^2} g\left(\frac{2(n-1)}{n}A^2\sigma^4\right) - 2e^{(k/2n)\sigma^2} + 1\right)$$

The risk formulas for $\hat{v}_3$, $\hat{v}_4$ and $\hat{v}_5$ can be derived by plugging in $A = (n-1+k)/(2(n-1))$ into the above expression, and letting k be 0, -2 and -3, respectively. □

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REFERENCES

1. Lacey LF, Keene ON, Pritchard JF, Bye A. Common noncompartmental pharmacokinetic variables: are they normally or log-normally distributed? *Journal of Biopharmaceutical Statistics* 1997; **7**:171–178.
2. Julious SA, Debarnot CAM. Why are pharmacokinetic data summarized by arithmetic means? *Journal of Biopharmaceutical Statistics* 2000; **10**:55–71.
3. Crow EL, Shimizu K. *Lognormal Distributions*: *Theory and Applications*. Marcel-Dekker: New York, U.S.A., 1998.
4. Zhou XH. Estimation of the log-normal mean. *Statistics in Medicine* 1998; **17**:2251–2264.
5. Zhou XH, Melfi CA, Hui SL. Methods for comparison of cost data. *Annals of Internal Medicine* 1997; **127**: 752–756.
6. Finney DJ. On the distribution of a variate whose logarithm is normally distributed. *Supplement to the Journal of the Royal Statistical Society* 1941; **7**:144–161.
7. Rukhin AL. Improved estimation in lognormal models. *Journal of the American Statistical Association* 1986; **81**:1046–1049.
8. Zellner A. Bayesian and non-bayesian analysis of the log-normal distribution and log-normal regression. *Journal of the American Statistical Association* 1971; **66**:327–330.
9. Evans IG, Shaban SA. New estimators (of smaller MSE) for parameters of a lognormal distribution. *Biometrische Zeitschrift* 1976; **18**:453–466.
10. Evans IG, Shaban SA. A note on estimation in lognormal models. *Journal of the American Statistical Association* 1974; **69**:779–781.
11. Mehran F. Variance of the MVUE for the lognormal mean. *Journal of the American Statistical Association* 1973; **68**:726–727.
12. Zhou XH, Gao S. Confidence intervals of the log-normal mean. *Statistics in Medicine* 1997; **16**:783–790.
13. Land CE. An evaluation of approximate confidence interval estimation methods for lognormal means. *Technometrics* 1972; **14**:145–158.
14. Angus JE. Bootstrap one-sided confidence intervals for the log-normal mean. *Statistician* 1994; **43**:395–401.

