Concepts for the construction of confidence intervals for measuring stability after hallux vulgus surgery: theoretical development and application.

By
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Submitted in fulfillment of the requirements for the degree of

Master of Science

in

Statistics

School of Mathemetics, Statistics and Computer Science
University of KwaZulu-Natal

July 2021

Declaration

I Ogutu Sarah Atieno, declare that;

1. The research reported in this thesis is my original work and was undertaken for the candidature of a masters' degree in Statistics at the University.

2. The research work was conducted as per the rules and regulations of the University, covering the period from January 2020 to March 2021.

3. I have duly acknowledged by particular reference in the text, the work of others used in this research.

4. This thesis has not been presented to any other university for any degree or examination.

5. The research was conducted under the supervision of Prof. Henry G Mwambi and Prof. Andreas Ziegler of the University of KwaZulu-Natal, School of Mathematics, Statistics and Computer Science.

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Acknowledgement

I convey my sincere appreciation to my supervisors Prof. Henry G. Mwambi and Prof. Andreas Ziegler, for their tireless counsel, teachings, support, and foundation of study they laid throughout the course. Heartfelt thanks to GSK-SSACAB (GlaxoSmithKline Research and Development Limited, Sub-Saharan African Consortium for Advanced Bio-statistics) for the financial support they provided during the research period. Many thanks go to the School of Mathematics, Statistics, and Computer Science for granting me the opportunity to explore this topic. Thanks to my postgraduate colleagues Dona Ongoma, Alexander Kasyoki, and Mohanad Mohammed for their tireless support.

Deepest gratitude to my husband, Zachariah Mbugua, for his unwavering support, assistance, and encouragement. You stood by me every step of the way and never gave up on me. You are indeed God's gracious gift, my friend, and my closest connfidant. To my son Peters, your tenderness, determination, sensitivity, creativity, joy, laughter, and courage were inspirational. Finally, I extend my sincere appreciation to my parents Meshack and Priscillah, and my siblings for their continuous support and encouragement. Thank you all for making this a success, and God bless you all.

Above all, I thank the Almighty God for the abundant love, care, and sufficient grace.

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Acronyms

Mg Magnesium

Ti Titanium

HV Hallux Valgus

HVA Hallux Valgus Angle

MTP Metatarsophalangeal

PACS Picture Archiving and Communication System

AOFAS-MTP-IP American Orthopedic Foot and Ankle Society Hallux Metatarsophalangeal Interphalangeal

VAS Visual Analogue Scale

PreOp Pre-Operation

PostOp Post-Operation

FU Follow Up

PDF Probability Density Function

MGF Moment Generating Function

CDF Cumulative Density Function

IMA Intermetatarsal Angle

Abstract

The absolute change in the corrected angle measured immediately after surgery and after bone healing is a clinically relevant endpoint to judge an osteotomy's stability. The primary objective of this research is to illustrate the non-inferiority of a novel screw used for fixation of the osteotomy compared with a standard screw. If the difference in the angles after surgery and after bone healing can be assumed to be normally distributed, the absolute change follows the folded normal distribution. The most natural approach to present the clinical study results is using a confidence interval to compare two folded normal distributions. We construct a confidence interval to compare two independent folded normal distributions using the ratio of two chi-square random variables, the difference of two chi-square distribution, and the bootstrap method. We illustrate the approaches from a study on hallux valgus osteotomy. The proposed confidence intervals permit an investigation of the non-inferiority for the two treatment groups in clinical trials with end points following a folded normal distribution. The application to real data results indicates that the confidence interval for the ratio of two chi-squares random variable and bootstrap is straightforward and easy to calculate. Bootstrapping was asymptotically more accurate than the standard interval obtained from samples that assume normality. Also, it was an appropriate way to ascertain the stability of the results. Judging by δ of the bootstrap method, we establish non-inferiority for the new surgical method. In conclusion, the approaches are promising, and we recommend them for use to compare other practical data that require the use of the folded normal distribution.

Chapter 1

Introduction

1.1 Background

Absolute measurements occur whenever a deviation or a difference is measured, and the algebraic sign is ignored. We find typical examples from clinical trials, industrial practices, sports, and the insurance sector. In clinical trials, an example is when blinded data is used for estimation of treatment differences and standard deviation (Chen and Kianifard, 2003). The absolute difference of an effect size is useful to estimate the sample size of subsequent trials and adjusting or re-estimating the sample size of an existing experiment. At the same time, the randomized treatment codes remain blinded. Other examples are absolute measured levels of Macrophage Migration Inhibitory Factor (MIF) and mRNA Interleukin-1-β, used for accurate prediction of antidepressant treatment responses across different laboratories (Cattaneo et al., 2016). Additionally, the absolute measurements of Hb levels and serum levels of EPO were important in predicting the response of Erythropoietin treatment for chronic anemia (Ludwig et al., 1994). The absolute measurements of post-treatment scores on the HRSD (Hamilton Rating Scale for Depression) have helped to illustrate and test new methods for integrating predictive information that aid individual treatment selection and recommendation (DeRubeis et al., 2014). Measurements of absolute CD4 count cells were used to determine the relationship of sexual orientation disclosure and immune functioning of psychiatric HIV positive patients (Strachan et al., 2007). Finally, Lin et al.

(1993) used absolute measurement of FEV1(Forced Expiratory Volume) to study the effects of albuterol dose given by either continuous or intermittent administration when treating acute asthma.

These examples share a common trait of missing algebraic signs. Tallying the negative values with the positive values is the result of removing the symbol, and mathematically, this corresponds to folding the negative part of the distribution to the positive part. If the algebraic values' underlying distribution is normal, then the absolute value distribution is known as the folded normal distribution. Leone et al. (1961) introduced the folded normal distribution then, Elandt (1961) derived the first four non-cetral moments, Johnson (1962) derived the mean and standard deviation using MLE and constructed cumulative sum control charts for the folded normal variates in 1963. Psarakis and Panaretoes (1990) studied folded t-distribution, and in their subsequent paper in 2001, they derived a bi-variate folded normal distribution. Bland (2005) studied the half-normal distribution as a unique example from folded normal when $\mu = 0$ and applied the findings to measurement error. Kim (2006) considered the ratio of independent folded normal random variables as important in the sampling distribution of different models, as Chakraborty and Chatterjee (2013) focused on multivariate folded normal.

Brazauskas and Kleefeld (2011) illustrated the importance of folded t-distribution model in modeling claims data by incorporating a scale parameter to the model. Before then, Cooray et al. (2006) had introduced the folded logistic distribution, which is very accurate in simulated and practical sets of data. Wang and Wang (2011) presented the statistical ordering of the folded normal random variables as Mutangi and Matarise (2012) tackled the procedure for finding the norming constants for the maxima of a folded normally distributed random variable. Gui et al. (2013) introduced a folded normal slash distribution which is defined by the quotient of two independent variables; the folded normal variable and the power of uniform distribution. The authors found this distribution to have higher kurtosis compared to the folded normal distribution. Nadarajah and Bakar (2015) introduced new folded distributions. They include the folded Gumbel, the folded Cauchy and the folded exponential power. The authors studied the statistical properties of each distribution and applied the results to real data. Kim (2016) introduced a new distribution class for the ratio of two dependent folded normal random variates, as Chatterjee and Chakraborty (2016) provided a simple value calculation algorithm for the folded normal distribution. A more recent model introduced by Nojoumizadeh and Saberi (2019) is the folded Laplace slash distribution to provide a choice in simulating and fitting heavy-tailed and skewed distribution whose probabilities are heavier than the folded normal slash distribution.

The applications of the folded normal distribution are vast. Johnson (1963) first applied it to the development of cumulative sum charts for folded normal random variates. Yadavalli and Singh (1995) used folded normally distributed failure rate random variable in the determination of reliability density. Cherny et al. (1999) did a quantitative analysis with the folded normal on DNA interactions visualized by electron microscopy. The known properties of the distribution were used by Chen and Kianifard (2003) to develop a framework for the estimation of both standard deviation and treatment difference of a blinded data in clinical trials. Naulin (2003) used this distribution to present the components of electromagnetic transmission and shear flows in drift-Alfven turbulence. The process capability measures utilized folded normal to assess the quality loss of manufactured products (Lin, 2005). Younis et al. (2011) used the distribution in modeling the learning-less vulnerability discovery rate of a software system, Liao (2010) modeled economic tolerance designs, and (Wang and Wang, 2011) used in primary arc analysis to direct product manifold. Further, the distribution was useful to model insurance claim data (Brazauskas and Kleefeld, 2011), body mass index (Tsagris et al., 2014), and modeling small-scale fading in the line-of-sight condition in wireless communication (Reig et al., 2019).

Application of the folded normal distribution is uncommon in clinical trials, maybe because of the nature of outcomes and results from them. A clinical trial is a prospective study that compares the effects and efficacy of interventions against a control group in human beings (Friedman et al., 2015). The trials are classified according to their goals and how they are structured. A clinical trial employs one or more intervention techniques that can be single or combinations of diagnostic, biologics, regimens, devices, procedures or educational approaches, preventive or therapeutic drugs (Friedman et al., 2015). Trials which utilizes therapeutic drug interventions provide knowledge about optimum treatment of various diseases and are conducted in phases depending on the purpose and stage of development. Phase I examines drug tolerance, interactions, and metabolism, while phase II focuses on therapeutic explanatory studies that explore the effects of different doses. Phase III comprises confirmatory therapeutic studies that illustrate clinical applicability and assess the safety profile. Final phase IV seeks to identify the uncommon adverse effects of the drug in a broad or unique population (Unnebrink and Pritsch, 2000).

In clinical trials, treatment efficacy assessment is one of the most critical activities in medical research. We evaluate the efficacy of the treatment in comparison to the control group. To ensure the internal validity of these comparisons, the groups must be similar at the beginning of the analysis, and this can be done by randomizing patients to the medication. It is sufficiently critical to prove the non-inferiority of the new treatment if we require to show its effectiveness (Snapinn, 2000). The goal is to demonstrate that the difference between the mean outcome of experimental and reference treatment does not exceed the non-inferiority margin and that the new treatment is non-inferior to the current active control group (Pigeot et al., 2003).

Clinical researchers are interested in the significant difference in mean values between two treatment groups when the outcome is a continuous random variable. Their goal is to evaluate the null hypothesis, which coincides with the overall assessment of the treatment differences (Simon, 1986). In the case of assessing the difference of two treatment groups that are independent and whose outcome variables are continuous, absolute, and normally distributed, then the difference between two independent folded normal distributions is considered. The most natural approach widely preferred by researchers to present results for the comparison of two independent distributions is the confidence intervals. Therefore, the confidence interval is useful to present the study results of the difference between two independent folded normal distributions.

Confidence intervals have broader use, and they encompass a significant test and provide an estimate of the magnitude of the effect (Ramasundarahettige et al., 2009). In clinical trials, estimation of the size of the impact is as critical as hypothesis testing because the researchers are concerned in estimating the size of the difference between mean outcomes and not just in examining whether there is such a difference (Simon, 1986). In a way, the observed difference in response levels is our best approximation of the difference in the actual response mean. However, if we take another group of patients, we are unlikely to find the very same difference in response level. We, therefore, accept that we do not know the actual difference with certainty. Nonetheless, we can measure an interval that will represent the actual difference with high probability. This threshold is called the confidence interval, and the likelihood that the real value lies in it is the confidence level (Simon, 1986).

This study seeks to construct confidence intervals to compare two folded normal distributions and explore its application to clinical studies where a comparison of two treatment groups is involved. The designed confidence interval is useful in the presentation of the clinical results. The motivation of this study arose from a practical medical problem where patients involved suffered hallux valgus, and they were enrolled in surgery to correct the deformity. They administered two types of treatments independently, one using biodegradable magnesium compression screw and the other used standard titanium screw for fixation in the surgical treatment. The outcome variables to measure the success of the surgery considered were continuous random variables (HVA and IMA) where their absolute difference between two time periods were assumed to follow a folded normal distribution. Hallux valgus is described in detail here.

1.2 Hallux valgus

Hallux valgus (HV) is a foot skeleton disorder, where the large toe is misaligned (Nguyen et al., 2010). It angles itself to the other toes and often displaces them. Sometimes even the toe shifts above or below each other. This crookedness tends to cause the ball region of the instep to protrude. A noticeable bulge can be seen or felt that alters the weight distribution around the entire foot and causes rolling of the foot when walking, which often entails a lot of foot pain (Hecht and Lin, 2014). HV is characterized by the medial deviation of the first metatarsal, lateral deviation with or without enlargement of the soft tissue of the first metatarsal head (Ray et al., 2019). It is a complicated deformity of the first ray and preceded by defects in the lesser toe (Chou, 2000). HV will hardly cause any discomfort at the early stages; however, at the advanced stage, there is difficulty in fitting shoes as a result of medial eminence, pain over prominence at the MTP joint, and other symptoms resulting from compression of the digital nerves (Piqué-Vidal and Vila, 2009).

1.2.1 Epidemiology

This disorder is one of the popular foot problems in the elderly population, with an incidence rate of about 35% in those older than 65 years worldwide and more often in women than men (Nguyen et al., 2010). Worldwide statistics indicate that 70% of people with the disorder have a family history that can be associated with intrinsic and extrinsic risk factors (Park and Chang, 2019). Intrinsic factors include a hereditary predisposition, cerebral palsy, ligamentous laxity, and second toe deformity. Other examples are pes planus, convex metatarsal head, and increased distal metaphyseal articular angle (DMAA). They weaken the connective tissues, thus increasing the risk of HV as the foot is susceptible to become deformed easily (Yamada et al., 2014). Extrinsic risk factors include wearing thin, pointed shoes, and high heels. (Park and Chang, 2019). Furthermore, studies have also shown that wearing socks for years presses the toes together and alters the natural shape of the foot (Hecht and Lin, 2014). HV is associated with certain types of diseases and infections particularly inflammatory types such as rheumatoid arthritis, gouty arthritis and psoriatic arthritis (Roddy et al., 2008).

1.2.2 Diagnosis

Diagnosis of HV uses imaging, where a standard series of X-rays are taken with the foot weight. Different views, such as Anteroposterior, LAT, and oblique, are taken (Ray et al., 2019). We generally measure angles to classify HV into three categories mild, moderate, or severe (Hecht and Lin, 2014) as portrayed in Figure 1.2. HVA, IMA, and DMAA are important angles for radiological assessment of HV as shown in figure 1.1.

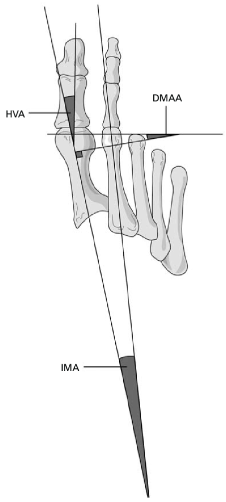
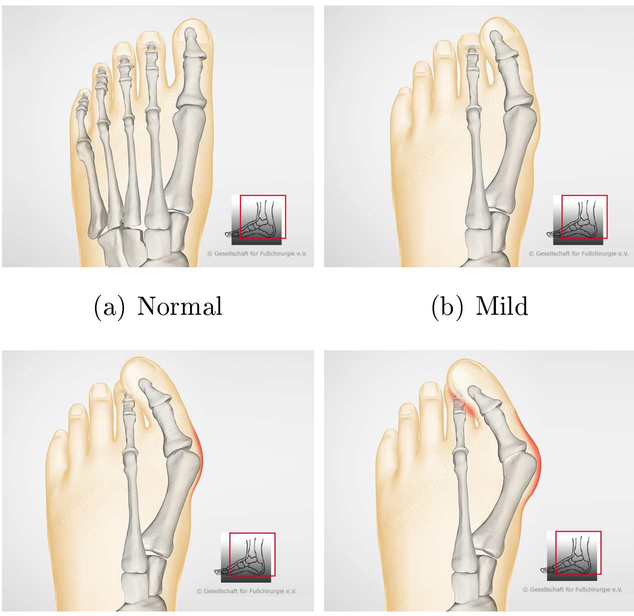


Figure 1.1: Angles for radiological assessment of HV (Robinson, 2005).



(a) Normal (b) Mild

(c) Moderate (d) Severe

Figure 1.2: Classification of HV (Society for Foot and Ankle Surgery, 2020)

HV is classified mild when HVA is 15°-20°, and IMA is 9°-11°. The moderate disorder is when HVA is 29°-31°, IMA is 12°-17°, and DMAA is 11°-14°. Severe HV is with HVA greater than 40°, IMA greater than 18°, and DMAA greater than 15°.

1.2.3 Treatment

1.2.3.1 Conservative treatment

Conservative treatment for HV focuses on non-operative treatments meant to relieve symptoms, but not to correct the real deformities. This care is considered mainly for patients with ligamentous laxity, general hypermobility, or neuromuscular disorders. The treatment varies from changing footwear, shoe adjustment, rest, and the use of ice (Ferrari, 2006). Physical therapy and exercises promote free movement of the big toe in all directions. The use of night splints straightens the misaligned toe at the same time, reducing pressure of the big toe to the adjacent toes(Park and Chang, 2019). Insoles, orthotics, and special shoes allow plenty of room for flexibility to minimize friction and inflammation (Fuhrmann et al., 2017). Pain medication such as acetaminophen, ibuprofen, and inflammatory drugs relieves pain resulting from the disorder. When the pain continues and becomes severe, surgical correction may always be necessary.

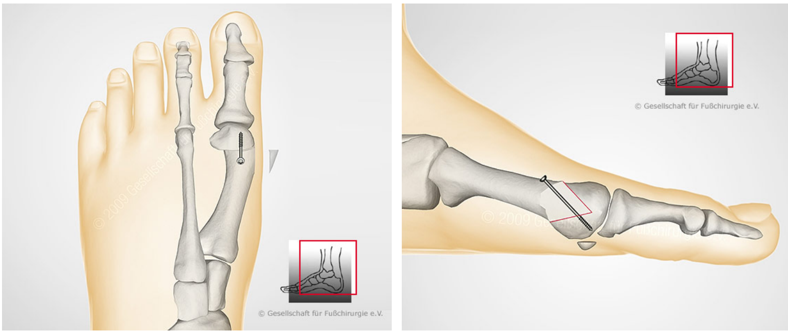
1.2.3.2 Surgical treatments

There are more than 100 different HV surgeries proposed in the literature. The surgeries have various effects at present where age, activity level, lifestyle, and health of the patient holds a vital role in the operation to be chosen (Ray et al., 2019). The surgical approaches are selected and designed to address a range of maladies that may be linked to HV. They work towards a common goal of treatment by removing the enlarged abnormal bone of the 1st metatarsal, realignment of the first metatarsal bones, and straightening of the large toe relative to adjacent toes (Pinney et al., 2006). Surgical corrections apply different techniques such as soft tissue procedure that aims to correct incongruent MTP joint (Schneider, 2013), osteotomies for mild deformities, and fusion procedures for advanced deformities

(Ray et al., 2019). Post-operative dressing of the big toe accompanies the surgical correction (Fraissler et al., 2016). Post-operative images are taken periodically until the patient achieves osseous healing. The discussions for the primary surgical treatments are next.

Chevron surgery

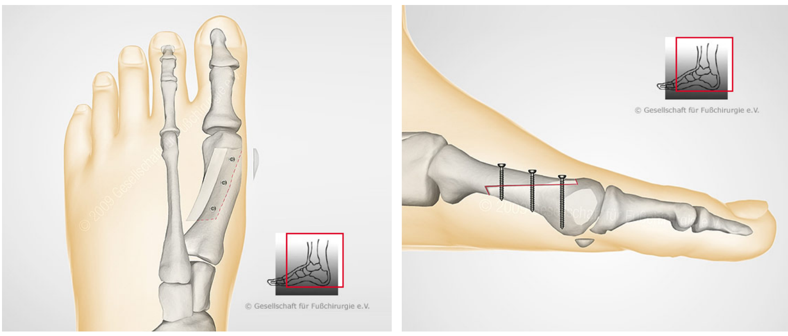
Here, saw cuts are made on the bone to change its axis. The bone is moved around the head and fixed with a small screw (Rossi and Ferreira, 1992). It is suitable for mild deformities, and healing takes several weeks, about 4-6 weeks.



(a) Anteroposterior view (b) Lateral view

Figure 1.3: Chevron surgery (Society for Foot and Ankle Surgery, 2020).

Scarf procedure



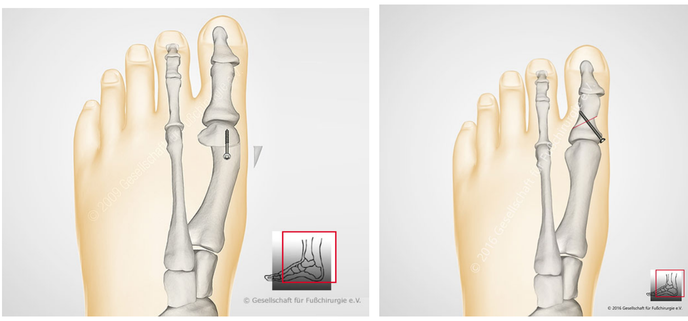
(a) Anteroposterior view (b) Lateral view

Figure 1.4: Scarf procedure (Society for Foot and Ankle Surgery, 2020).

Here, a z-shape cut is made on the shaft of 1^{st} metatarsal, and its position is corrected (Deenik et al., 2007). The procedure is appropriate for correction of moderate to severe HV, and healing takes several weeks, up to 6 weeks.

Chevron-Akin procedure

Chevron Akin is a double surgery, a combination of chevron and akin procedure. It involves making a chevron osteotomy, and the metatarsal head is shifted laterally, then osteotomy fixed with a smooth pin (Ray et al., 2019). In Akin surgery, a medial longitudinal opening is made along with the 1st proximal phalanx, and removal of a small wedge bone is done (Larholt and Kilmartin, 2010). The procedure allows the big toe to swivel in the right direction, and the severed bone fixed with a screw.



(a) Chevron procedure (b) Akin procedure

Figure 1.5: Chevron-Akin procedure (Society for Foot and Ankle Surgery, 2020).

1.3 Research Objectives

- To construct valid confidence intervals that compares two independent folded normal distributions.
- To apply the constructed confidence intervals to the real data and judge non-inferiority.

1.4 The Data

The data used was gratefully obtained from Doc. Dr. O. Kose from the University of Health Sciences Antalya Training and Research Hospital. A total of 31 patients underwent a surgery called Modified Distal Chevron Osteotomy to correct HV disorder between August 2014 and December 2017. Headless Mg compression screw fixation applied on 17 feet of 16 patients and headless Ti compression screw on 17 feet of 15 patients. Hospital database, medical reports, and patient charts, as well as follow-up notes and operation notes, were a useful source of extracting clinical findings and demographic information. The PACS was a crucial source of imaging and radiological findings for the patients. At the same time, both AOFAS-MTP-IP and VAS scale evaluated the clinical results. The HVA and IMA angles were measured before and after surgery. Osteotomy union time and any other complications after surgery were noted. We group patients according to the type of screw; thus, the Mg and the Ti group. There were a total of 25 variables collected and categorized into demographic, clinical, and radiological variables.

1.4.1 Data description

All the patients who underwent surgery were followed up for at least 12 months and were averagely aged 48 years with more females than males (13% male, 87% female). About 65% of the patients had moderate to severe HV disorder. We note that the oldest patient was 68 years from the Mg group and 72 years from the Ti group, with the youngest patient aged 17 years from both groups. Table 1.1 gives a comparative summary for the Mg and the Ti groups for absolute measurements of the difference between early post-operation and late follow up for HV Angles.
Figure 1.6 is a violin plot comparing the distribution of the Mg and Ti group for absolute measurements of the difference between early post-operation and late follow up for HV Angles. The shape of the distribution indicates that the values for the Ti group highly concentrate around the median compared to the Mg group. We note that the Mg group has a bimodal distribution. In contrast, the Ti group has multimodal distribution, with the median of the Mg group being more pronounced than for the Ti group.

Table 1.1: Comparative summary statistics for the Mg and the Ti group for absolute HV Angles.

Statistic	Mg	Ti
Mean	2.412	2.000
St.Deviation	2.599	2.699
Median	1.000	1.000
Maximum	9.000	10.000
Minimum	0	0

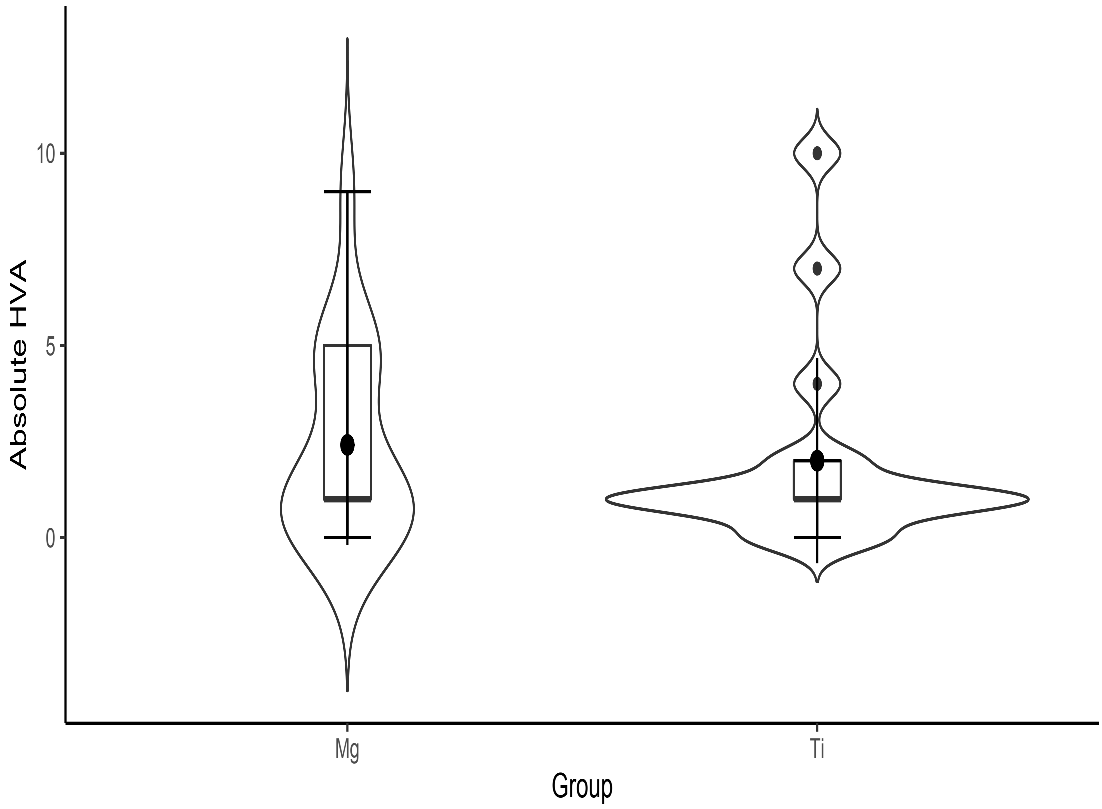


Figure 1.6: A comparative violin plot between the Mg and the Ti group for absolute HV Angles.

1.5 Thesis Outline

The remaining part of the thesis is detailed as follows; Chapter 2 is about the theory of the folded normal distribution, its fundamental properties, and features. Chapter 3 extensively discusses the methods to construct confidence intervals. In Chapter 4, we illustrate these methods' application to real data, present and discuss the results. We present a general conclusion and recommendation for the overall thesis in Chapter 5, after which the References and Appendices are given.

Chapter 2

Folded normal distribution

2.1 Introduction

The folded normal distribution is related to normal distribution arising when the symbol of the random variable is positive (Johnson, 1962). Given a random variable X that is normally distributed with mean μ and variance σ^2, then the random variable Y= |X| is folded normal distribution. According to Tweedie et al. (1957), the normal distribution has been emphasized before as perhaps the most crucial density in probability, and it has been very helpful in modeling an incredible variety of random phenomena. It holds an honored role in statistics due to the central limit theorem, a theorem that bridges two subjects (Peng, 2009).

2.2 Probability Density Function

To derive the pdf of folded normal, we first consider the pdf of a normal distribution. The Random variable $X \sim \mathcal{N}(\mu, \sigma^2)$ for $-\infty < X < \infty$ has a pdf,

$$f(x) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{1}{2\sigma^2}(x-\mu)^2} \tag{2.1}$$

Thus according to Leone et al. (1961) suggestion, the pdf of a univariate folded normal distribution for $Y \geq 0$ becomes,

$$f(y) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{1}{2\sigma^2}(y-\mu)^2} + \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{1}{2\sigma^2}(y+\mu)^2} \tag{2.2}$$

Equation (2.2) can be rewritten in a more attractive form by introducing cosine hyperbolic function (Tsagris et al., 2014).

$$\begin{aligned} f(y) &= \frac{1}{\sqrt{2\pi\sigma^2}} \left[e^{-(y-\mu)^2/2\sigma^2} + e^{-(y+\mu)^2/2\sigma^2} \right] \\ &= \frac{1}{\sqrt{2\pi\sigma^2}} \left[e^{-\left(y^2+\mu^2\right)/2\sigma^2} \left(e^{y\mu/2\sigma^2} + e^{-y\mu/2\sigma^2} \right) \right] \\ &= \frac{4}{\sqrt{2\pi\sigma^2}} \left[e^{-\left(y^2+\mu^2\right)/2\sigma^2} \left(e^{y\mu/2\sigma^2} + e^{-y\mu/2\sigma^2} \right) /2 \right] \\ &= \sqrt{\frac{2}{\pi\sigma^2}} \left[e^{-\left(y^2+\mu^2\right)/2\sigma^2} cosh \left(\frac{\mu y}{\sigma^2} \right) \right] \end{aligned} \tag{2.3}$$

Further, expanding cosh of equation (2.3) via Taylor series gives an infinite series which eases the study of certain functional properties, such as asymptotic behavior.

$$f(y) = \sqrt{\frac{2}{\pi\sigma^2}} \left[e^{-\left(y^2+\mu^2\right)/2\sigma^2} \right] \sum_{n=0}^{\infty} \frac{(-1)^n}{(2n)!} \left(\frac{\mu y}{\sigma^2} \right)^{2n} \tag{2.4}$$

2.2.1 Mean

It is impossible to evaluate the mean in a closed-form, hence it is given in terms of Φ, the cumulative distribution fuction for the standard normal distribution (Leone et al., 1961). Let $Y = \mid \mu + \sigma W \mid$ where $W \sim \mathcal{N}(0,1)$. Then the mean of Y is the same as, $E(Y) = E\left(\mid \mu + \sigma W \mid\right)$, which when expanded further we obtain,

$$E\left(Y\right) = E\left(\mu + \sigma W;\ \mu + \sigma W \geq 0\right) + E\left(-\mu - \sigma W;\ \mu + \sigma W < 0\right).$$

When we add $E\left(-\mu - \sigma W;\ \mu + \sigma W < 0\right)$ in the first part of the above equation then subtract the same in the second part, then factor out the minus we obtain,

$$E\left(Y\right) = E\left(\mu + \sigma W\right) - 2E\left(\mu + \sigma W;\ W < -\frac{\mu}{\sigma}\right)$$

$$= \mu - 2E\left(\mu;\ W < -\frac{\mu}{\sigma}\right) - 2E\left(\sigma W;\ W < -\frac{\mu}{\sigma}\right)$$

$$= \mu - 2\mu\Phi\left(-\frac{\mu}{\sigma}\right) - 2\sigma E\left(W;\ W < -\frac{\mu}{\sigma}\right)$$

First consider,

$$E\left(W; W < -\frac{\mu}{\sigma}\right) = \int_{-\infty}^{-\frac{\mu}{\sigma}} w\frac{1}{\sqrt{2\pi}}e^{-w^2/2}dw$$

$$= \int_{\infty}^{\frac{\mu^2}{2\sigma^2}} \frac{1}{\sqrt{2\pi}}e^{-v}dv = -\frac{1}{\sqrt{2\pi}}e^{-v}\Big|_{\infty}^{\frac{\mu^2}{2\sigma^2}}$$

$$= -\frac{1}{\sqrt{2\pi}}e^{-\mu^2/2\sigma^2}$$

Then,

$$E(Y) = \mu\left[1 - 2\Phi\left(-\frac{\mu}{\sigma}\right)\right] + \sigma\sqrt{\frac{2}{\pi}}\ e^{-\mu^2/2\sigma^2} = \mu_Y \tag{2.5}$$

Where, $\Phi\left(-\frac{\mu}{\sigma}\right) = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{-\frac{\mu}{\sigma}} e^{-t^2/2}dt$.

2.2.2 Variance

$$\begin{aligned} E\left(Y^2\right) &= E\left(X^2\right) = Var\left(X\right) + \left(E\left(X\right)\right)^2 = \sigma^2 + \mu^2 \\ Var\left(Y\right) &= E\left(Y^2\right) - \left(E\left(Y\right)\right)^2 \\ Var\left(Y\right) &= \sigma^2 + \mu^2 - \mu_Y^2 \end{aligned} \tag{2.6}$$

The mean μ and variance σ^2 of X of the initial normal distribution is the scale and location parameter of Y in the folded normal distribution (Leone et al., 1961).

2.2.3 Mode

Mode is the value of Y for which its density function is maximized. The value is calculated by taking the first derivative of the pdf with respect to Y and equated to zero, $\frac{df_Y}{dy} = 0$ (Tsagris et al., 2014).

$$\frac{d}{dy}\left[\frac{1}{\sqrt{2\pi\sigma^2}}e^{-(y-\mu)^2/2\sigma^2} + \frac{1}{\sqrt{2\pi\sigma^2}}e^{-(y+\mu)^2/2\sigma^2}\right] = 0$$

$$\frac{1}{\sigma^2\sqrt{2\pi\sigma^2}}\left[\left(y-\mu\right)e^{-(y-\mu)^2/2\sigma^2} + \left(y+\mu\right)e^{-(y+\mu)^2/2\sigma^2}\right] = 0$$

$$y\left[e^{-(y-\mu)^2/2\sigma^2}+e^{-(y+\mu)^2/2\sigma^2}\right]-\mu\left[e^{-(y-\mu)^2/2\sigma^2}-e^{-(y+\mu)^2/2\sigma^2}\right]=0$$

$$y\left[1+e^{-2y\mu/\sigma^2}\right]-\mu\left[1-e^{-2y\mu/\sigma^2}\right]=0$$

$$y\left[1+e^{-2y\mu/\sigma^2}\right]=\mu\left[1-e^{-2y\mu/\sigma^2}\right]$$

$$\mu-y=(y+\mu)\,e^{-2y\mu/\sigma^2}$$

$$\log\left(\frac{\mu-y}{y+\mu}\right)=-\frac{2\mu y}{\sigma^2}$$

$$y=-\frac{\sigma^2}{2\mu}\log\left[\frac{\mu-y}{y+\mu}\right] \tag{2.7}$$

The folded normal distribution converges to the normal distribution.
Tsagris et al. (2014) did a numerical investigation and saw that when $\mu < 0$, the maximum is met at $Y = 0$, when $\mu \geq \sigma$ the maximum is met at $Y > 0$ and when $\mu > 3\sigma$ the maximum approaches μ.

2.3 Distribution Functions

2.3.1 Characteristic Function

Characteristic Function gives an alternative way of describing the random variable by determining the behavior and properties of the pdf of Y (Sasvári, 2000).

$$\varphi_Y(t)=E\left[e^{ity}\right]=\int_0^\infty e^{ity}f(y)\,dy$$

$$=\int_0^\infty e^{ity}\frac{1}{\sqrt{2\pi\sigma^2}}\left[e^{-(y-\mu)^2/2\sigma^2}+e^{-(y+\mu)^2/2\sigma^2}\right]dy$$

$$=\int_0^\infty \frac{e^{ity-(y-\mu)^2/2\sigma^2}}{\sqrt{2\pi\sigma^2}}dy+\int_0^\infty \frac{e^{ity}e^{-(y+\mu)^2/2\sigma^2}}{\sqrt{2\pi\sigma^2}}dy$$

$$=\int_0^\infty \frac{e^{A}}{\sqrt{2\pi\sigma^2}}dy+\int_0^\infty \frac{e^{B}}{\sqrt{2\pi\sigma^2}}dy$$

$$A=ity-\frac{1}{2\sigma^2}(y-\mu)^2=-\frac{(y-a)^2}{2\sigma^2}-\frac{\sigma^2t^2}{2}+i\mu t;\quad where\ a=2i\sigma^2+\mu$$

$$B = ity - \frac{1}{2\sigma^2}(y+\mu)^2 = \frac{(y-b)^2}{2\sigma^2} - \frac{\sigma^2 t^2}{2} + i\mu t; \quad where\ b = 2i\sigma^2 - \mu$$

$$= \int_0^\infty \frac{e^A}{\sqrt{2\pi\sigma^2}} dy = e^{-\frac{\sigma^2 t^2}{2} + i\mu t} \int_0^\infty \frac{e^{-(y-a)^2}}{\sqrt{2\pi\sigma^2}} dy$$

$$= e^{-\frac{\sigma^2 t^2}{2} + i\mu t} \left[1 - P(Y \le 0)\right]$$

$$= e^{-\frac{\sigma^2 t^2}{2} + i\mu t} \left[1 - \Phi\left(-\frac{a}{\sigma}\right)\right]$$

$$= e^{-\frac{\sigma^2 t^2}{2} + i\mu t} \left[1 - \Phi\left(-\frac{\mu}{\sigma^2} - i\sigma t\right)\right]$$

$$\int_0^\infty \frac{e^B}{\sqrt{2\pi\sigma^2}} dy = e^{-\frac{\sigma^2 t^2}{2} - i\mu t} \left[1 - \Phi\left(\frac{\mu}{\sigma^2} - i\sigma t\right)\right]$$

$$\varphi_Y(t) = e^{-\frac{\sigma^2 t^2}{2} + i\mu t} \left[1 - \Phi\left(-\frac{\mu}{\sigma^2} - i\sigma t\right)\right] + e^{-\frac{\sigma^2 t^2}{2} - i\mu t} \left[1 - \Phi\left(\frac{\mu}{\sigma^2} - i\sigma t\right)\right] \quad (2.8)$$

2.3.2 Cumulant Distribution Function

The CDF of a non-negative random variable Y according to (Ziegel, 2001) is defined by;

$$F_Y(y) = \int_0^y f_Y(t)\, dt$$

$$F_Y(y) = \frac{1}{2}\left[erf\left\{\frac{(y-\mu)}{\sqrt{2\sigma^2}}\right\} + erf\left\{\frac{(y+\mu)}{\sqrt{2\sigma^2}}\right\}\right] \quad (2.9)$$

$$erf(y) = \frac{2}{\sqrt{\pi}} \int_0^y e^{-t^2} dy$$

2.3.3 Moment Generating Function

The MGF of a random variable Y is used to calculate the distribution's moments and is $M_Y(t) = E\left[e^{tY}\right]$ (Mukherjea et al., 2006). The n^{th} moment evaluated at 0 is the n^{th} derivative of the MGF calculated at 0. A vital property of MGF is that they are positive and log-convex at $M(0) = 1$. According to (Ziegel, 2001) to find the MGF of a distribution, the relationship of characteristic function and MGF is useful given as;

$$M_Y(t) = \varphi_Y(-it)$$

$$M_Y(t) = e^{\frac{\sigma^2 t^2}{2}+\mu t}\left[1-\Phi\left(-\frac{\mu}{\sigma^2}-\sigma t\right)\right]+e^{\frac{\sigma^2 t^2}{2}-\mu t}\left[1-\Phi\left(\frac{\mu}{\sigma^2}-\sigma t\right)\right] \tag{2.10}$$

2.3.4 Cumulative Generating Function

The CGF of a random variable Y is defined by the natural logarithm of MGF (Hald, 2000).

$$K_Y(t) = \log M_Y(t)$$

$$K_Y(t) = \log\left\{e^{\frac{\sigma^2 t^2}{2}+\mu t}\left[1-\Phi\left(-\frac{\mu}{\sigma^2}-\sigma t\right)\right]+e^{\frac{\sigma^2 t^2}{2}-\mu t}\left[1-\Phi\left(\frac{\mu}{\sigma^2}-\sigma t\right)\right]\right\}$$

$$K_Y(t) = \left(\frac{\sigma^2 t^2}{2}+\mu t\right)\log\left\{1-\Phi\left(-\frac{\mu}{\sigma}-\sigma t\right)+e^{-2\mu t}\left[1-\Phi\left(\frac{\mu}{\sigma}-\sigma t\right)\right]\right\} \tag{2.11}$$

2.3.5 Laplace transformation function

Laplace transformation is easily derived from MGF (Tsagris et al., 2014).

$$E\left(e^{-ty}\right) = e^{\frac{\sigma^2 t^2}{2}-\mu t}\left[1-\Phi\left(-\frac{\mu}{\sigma^2}+\sigma t\right)\right]+e^{\frac{\sigma^2 t^2}{2}+\mu t}\left[1-\Phi\left(\frac{\mu}{\sigma^2}+\sigma t\right)\right] \tag{2.12}$$

2.3.6 Fourier Transformation function

Fourier transformation of distribution functions has specific properties important in the probability theory(Lukacs, 1952). The function is closely related to characteristic function (Tsagris et al., 2014).

$$\hat{f} = E\left(e^{-2\pi i tY}\right) = \phi_Y(-2\pi t)$$

$$\hat{f} = e^{-\frac{4\pi^2\sigma^2 t^2}{2}-i2\pi\mu t}\left[1-\Phi\left(-\frac{\mu}{\sigma}-2i\pi\sigma t\right)\right]+e^{-\frac{4\pi^2\sigma^2 t^2}{2}+i2\pi\mu t}\left[1-\Phi\left(\frac{\mu}{\sigma}-2i\pi\sigma t\right)\right] \tag{2.13}$$

2.3.7 Mean Residual Function

The mean residual is a central concept that is well known for survival analysis and reliability (Tsagris et al., 2014) is given by;

$$
\begin{aligned}
&E\left(Y-t \mid Y>t\right)=E\left(Y \mid Y>t\right)-t \\
&E\left(Y \mid Y>t\right)-t=\int_{t}^{\infty} \frac{y f_{Y}}{P\left(Y>t\right)} dy-t=\int_{t}^{\infty} \frac{y f_{Y}}{1-F\left(t\right)} dy-t \\
&1-F\left(y\right)=1-\frac{1}{2}\left[erf\left(\frac{y-\mu}{\sqrt{2\sigma^{2}}}\right)+erf\left(\frac{y+\mu}{\sqrt{2\sigma^{2}}}\right)\right] \\
&\int_{t}^{\infty} y f\left(y\right) dy=\int_{t}^{\infty} y \frac{1}{\sqrt{2\pi\sigma^{2}}} e^{-\frac{1}{2\sigma^{2}}\left(y-\mu\right)^{2}} dy+\int_{t}^{\infty} y \frac{1}{\sqrt{2\pi\sigma^{2}}} e^{-\frac{1}{2\sigma^{2}}\left(y+\mu\right)^{2}} dy \\
&=\frac{\sigma}{\sqrt{2\pi}} e^{\frac{(t-\mu)^{2}}{\sigma^{2}}}+\mu\left[1-\Phi\left(\frac{t-\mu}{\sigma}\right)\right]+\frac{\sigma}{\sqrt{2\pi}} e^{\frac{(t-\mu)^{2}}{\sigma^{2}}}-\mu\Phi\left(\frac{t-\mu}{\sigma}\right) \\
&=\sqrt{\frac{2}{\pi}} \sigma e^{\frac{(t-\mu)^{2}}{\sigma^{2}}}+\mu\left[1-2\Phi\left(\frac{t-\mu}{\sigma}\right)\right]
\end{aligned}
$$

$$
E\left(Y-t \mid Y>t\right)=\frac{\sqrt{\frac{2}{\pi}} \sigma e^{\frac{(t-\mu)^{2}}{\sigma^{2}}}+\mu\left[1-2\Phi\left(\frac{t-\mu}{\sigma}\right)\right]}{1-\frac{1}{2}\left[erf\left(\frac{y-\mu}{\sqrt{2\sigma^{2}}}\right)+erf\left(\frac{y+\mu}{\sqrt{2\sigma^{2}}}\right)\right]}-t \tag{2.14}
$$

2.4 Parameter Estimation

The Maximum Likelihood Estimation procedure utilizes the concept of maximizing the likelihood function, and it possesses several properties such as consistency (series of MLEs converges with the expected value), efficiency(achieves Cramer-Rao lower bound), and functional invariance (Myung, 2003). If we have a random sample $Y_i = Y_1, Y_2, ...Y_n$ with assumed pdf that depends on an unknown parameter θ, then the primary goal is to find a good point estimator of θ that maximizes the likelihood of the distribution (Myung, 2003). Suppose $Y_i = Y_1, Y_2, ...Y_n$ has a joint density function $f\left(Y_i; \theta\right)$, the likelihood of θ based on Y_i is $L\left(\theta; Y_i\right) = f\left(Y_i; \theta\right)$ (Millar, 2011). The MLE $\hat{\theta}$ of θ is $L\left(\hat{\theta}; Y_i\right) \geq L\left(\theta; Y_i\right)$ for all θ. The MLE function is;

$$
L\left(\hat{\theta}; Y_i\right) = \max_{\theta}\left\{L\left(\theta; Y_i\right)\right\} \quad \frac{dL}{d\theta}\bigg|_{\theta=\hat{\theta}} = 0 \tag{2.15}
$$

Alternatively, we find MLE by maximizing the log-likelihood function given by;

$$\ell\left(\hat{\theta}; Y_i\right) = \max_{\theta} \left\{ l\left(\theta; Y_i\right) \right\} \quad \frac{dl}{d\theta}\bigg|_{\theta=\hat{\theta}} = 0 \tag{2.16}$$

The joint density function of the iid folded normal density of Equation (2.2) is;

$$f\left(Y_i; \mu, \sigma^2\right) = \prod_{i=1}^{n} \left[\frac{1}{\sqrt{2\pi\sigma^2}} \left(e^{-\frac{1}{2\sigma^2}(y_i-\mu)^2} + e^{-\frac{1}{2\sigma^2}(y_i+\mu)^2} \right) \right] \tag{2.17}$$

The likelihood function for Equation (2.2) becomes;

$$L\left(\mu, \sigma^2\right) = \left(2\pi\sigma^2\right)^{\frac{-n}{2}} \prod_{i=1}^{n} \left[e^{-\frac{1}{2\sigma^2}(y_i-\mu)^2} + e^{-\frac{1}{2\sigma^2}(y_i+\mu)^2} \right] \tag{2.18}$$

The log-likelihood function for Equation (2.18) is;

$$\ell\left(\mu, \sigma^2\right) = -\frac{n}{2} \log 2\pi\sigma^2 + \sum_{i=1}^{n} \log \left[e^{-\frac{1}{2\sigma^2}(y_i-\mu)^2} + e^{-\frac{1}{2\sigma^2}(y_i+\mu)^2} \right] \tag{2.19}$$

$$= -\frac{n}{2} \log 2\pi\sigma^2 + \sum_{i=1}^{n} \log \left[e^{-\frac{1}{2\sigma^2}(y_i-\mu)^2} \left(1 + e^{-\frac{1}{2\sigma^2}(y_i+\mu)^2} e^{-\frac{1}{2\sigma^2}(y_i-\mu)^2} \right) \right]$$

$$= -\frac{n}{2} \log 2\pi\sigma^2 - \sum_{i=1}^{n} \frac{\left(y-\mu\right)^2}{2\sigma^2} + \sum_{i=1}^{n} \log \left(1 + e^{-\frac{2\mu y}{\sigma^2}} \right) \tag{2.20}$$

The partial derivative for Equation (2.20) are:

$$\begin{aligned} \frac{\partial \ell}{\partial \mu} &= \sum_{i=1}^{n} \frac{\left(y_i-\mu\right)}{\sigma^2} - \frac{2}{\sigma^2} \sum_{i=1}^{n} \frac{y_i e^{-\frac{2\mu y_i}{\sigma^2}}}{1 + e^{-\frac{2\mu y_i}{\sigma^2}}} \\ &= \sum_{i=1}^{n} \frac{\left(y_i-\mu\right)}{\sigma^2} - \frac{2}{\sigma^2} \sum_{i=1}^{n} \frac{y_i}{1 + e^{\frac{2\mu y_i}{\sigma^2}}} \end{aligned} \tag{2.21}$$

$$\begin{aligned} \frac{\partial \ell}{\partial \sigma^2} &= -\frac{n}{2\sigma^2} + \sum_{i=1}^{n} \frac{\left(y_i-\mu\right)^2}{2\sigma^4} + \frac{2\mu}{\sigma^4} \sum_{i=1}^{n} \frac{y_i e^{-\frac{2\mu y_i}{\sigma^2}}}{1 + e^{-\frac{2\mu y_i}{\sigma^2}}} \\ &= -\frac{n}{2\sigma^2} + \sum_{i=1}^{n} \frac{\left(y_i-\mu\right)^2}{2\sigma^4} + \frac{2\mu}{\sigma^4} \sum_{i=1}^{n} \frac{y_i}{1 + e^{\frac{2\mu y_i}{\sigma^2}}} \end{aligned} \tag{2.22}$$

Equating the 1^{st} derivative w.r.t. μ of the log-likelihood equation (2.21) to zero we attain a good relationship;

$$
\begin{aligned}
\sum_{i=1}^{n} \frac{(y_i-\mu)}{\sigma^2} - \frac{2}{\sigma^2}\sum_{i=1}^{n} \frac{y_i}{1+e^{\frac{2\mu y_i}{\sigma^2}}} = 0 \\
\sum_{i=1}^{n} \frac{y_i}{1+e^{\frac{2\mu y_i}{\sigma^2}}} = \sum_{i=1}^{n} \frac{(y_i-\mu)}{2}
\end{aligned}
\tag{2.23}
$$

Equation (2.23) has three solutions; at zero, negative and positive signs. By substituting equation (2.23) to the 1^{st} derivative of the log-likelihood equation w.r.t. σ^2 equation (2.22) we get an expression for the variance.

$$
\begin{aligned}
-\frac{n}{2\sigma^2} + \sum_{i=1}^{n} \frac{(y_i-\mu)^2}{2\sigma^4} + \frac{2\mu}{\sigma^4}\sum_{i=1}^{n} \frac{(y_i-\mu)}{2} = 0 \\
\sigma^2 = \sum_{i=1}^{n} \frac{(y_i-\mu)^2}{n} + \frac{2\mu\sum_{i=1}^{y_i-\mu}}{n} \\
= \sum_{i=1}^{n} \frac{(yi^2-\mu^2)}{n} \\
= \sum_{i=1}^{n} \frac{y_i^2}{n} - \mu^2
\end{aligned}
\tag{2.24}
$$

We obtain the MLE from the relationship of equation 2.24 through an efficient recursive way (Tsagris et al., 2014). The process is to use an initial value of σ^2 to find a positive root of μ from equation (2.23) then insert the value in equation 2.24 to obtain an adjusted value of σ^2. Repeat the process until there is a negligible change in the log-likelihood values.

2.5 Related distributions

1. The distribution of Y becomes half normal-distribution when $\mu = 0$ (Bland, 2005). It is a fold with zero mean at the mean of an ordinary normal distribution.

   (a) We get the pdf by replacing $\mu = 0$ in equation (2.2),

$$\frac{1}{\sqrt{2\pi\sigma^2}}\left(e^{-\frac{1}{2\sigma^2}y^2}+e^{-\frac{1}{2\sigma^2}y^2}\right)=\sqrt{\frac{2}{\pi\sigma^2}}e^{-\frac{1}{2\sigma^2}y^2}\ for\ Y>0$$

(b) The mean of half-normal distribution is,

$$\mu_Y=E\left(Y\right)=\int_0^\infty yf\left(y\right)dy=\sigma\sqrt{\frac{2}{\pi}}$$

(c) The variance of the distribution is,

$$Var\left(Y\right)=\sigma^2\left(1-\frac{2}{\pi}\right)$$

(d) The cumulative distribution function,

$$F_Y=\int_0^y\frac{1}{\sigma}\sqrt{\frac{2}{\pi}}e^{-\frac{y}{2\sigma^2}}dy$$

$$=erf\left(\frac{y}{\sigma\sqrt{2}}\right)$$

(e) The median is given by $\sigma\sqrt{2}erf^{-1}\left(\frac{1}{2}\right)$

(f) The unknown parameter σ can be estimated via maximum likelihood which gives, $\hat{\sigma}=\sqrt{\frac{1}{n}\sum_{i=1}^n y_i^2}$ and the bias equals to,
$b\equiv E\left[\left(\hat{\sigma}_{mle}-\sigma\right)\right]=-\frac{\sigma}{4n}$

(g) The half-normal distribution corresponds to a zero-mean normal distribution truncated from below at zero.
If Y has a half-normal distribution, then $\left(\frac{Y}{\sigma^2}\right)$ random variable has a chi-distribution with 1 degree of freedom.
Half-normal distribution is a specific example of a generalized gamma distribution with $d=1,\ p=2,\ a=\sqrt{2}\sigma$.

2. If Y has folded normal distribution, then $\left(\frac{Y}{\sigma^2}\right)$ random variable has a non-central Chi-squared distribution with 1 degree of freedom and non-centrality parameter being $\left(\frac{\mu}{\sigma}\right)^2$.

3. The folded normal distribution can be perceived as the limit of the folded

non-standardized t distribution as the degrees of freedom approaches infinity (Psarakis and Panaretoes, 1990). The folded non-standardized t distribution is the distribution of the absolute values of the non-standardized t distribution of v degrees of freedom.

$$g\left(y\right)=\frac{\Gamma\frac{v+1}{2}}{\Gamma\frac{v}{2}\sqrt{v\pi\sigma^{2}}}\left\{\left[1+\frac{1}{2}\frac{(y-\mu)^{2}}{\sigma^{2}}\right]^{-\frac{v+1}{2}}+\left[1+\frac{1}{2}\frac{(y+\mu)^{2}}{\sigma^{2}}\right]^{-\frac{v+1}{2}}\right\}$$

4. The uni-variate folded normal can be extended to bi-variate folded normal distribution as developed by (Psarakis and Panaretos, 2001) and more generally to multivariate folded normal distribution introduced by (Chakraborty and Chatterjee, 2013).

Chapter 3

Methods of constructing confidence intervals

Definition

In statistics, interval estimation is the use of sample data to calculate an interval of possible values of an unknown population parameter such as mean and variance (Neyman, 1937). The most prevalent forms of interval estimation are: confidence intervals (a frequentist method), and credible intervals (a Bayesian method). Other forms include: likelihood intervals (a likelihood Ratio method), pivotal quantity intervals, and fiducial intervals (a fiducial method). Here, we focus on the confidence interval estimation method.

Let x_{ig} denote the difference between angle measurements at visit follow-up and immediately post-operation for all $i = 1, 2..., n_g$ and both treatment groups $g = 1, 2$ for Magnesium and Titanium screws respectively. We assume that x_{ig} is normally distributed with mean μ_g and variance σ_g^2 . Since angle differences between time point in either direction are undesirable, the absolute value $y_{ig} = \mid x_{ig} \mid$ or the squared value $y_{ig}^2 = x_{ig}^2$ of the x_{ig} are the values of interest. Thus we are interested in two random variable $y_g, g = 1, 2$. The hypothesis of interest is

$$H_0 \colon E(y_2) = E(y_1) \quad \text{vs.} \quad H_1 \colon E(y_2) \neq E(y_1) \,. \tag{3.1}$$

The main aim is the construction of a confidence interval for the estimand $\theta = E(y_2) - E(y_1)$ from observed sample data.

3.1 The standard t-test

A standard t-test is a parametric test that compares the means of two independent groups to establish whether there is a statistical proof that the associated population means differ significantly or not (Watters and Boslaugh). When the population variances are assumed to be similar $\sigma_1^2 = \sigma_2^2$, the confidence interval is calculated as;

$$\bar{y}_2 - \bar{y}_1 \pm t \times s_p \sqrt{\frac{1}{n_1} + \frac{1}{n_2}} \tag{3.2}$$

with $df = n_1 + n_2 - 2$ and

$$s_p = \sqrt{\frac{(n_1 - 1)\, s_1^2 + (n_2 - 1)\, s_2^2}{n_1 + n_2 - 2}}\ .$$

When the assumption that the population variances are unequal $\sigma_1^2 \neq \sigma_2^2$, the confidence interval is calculated as;

$$\bar{y}_2 - \bar{y}_1 \pm t \times \sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}} \tag{3.3}$$

with

$$df = \frac{\left(\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}\right)^2}{\frac{1}{n_1-1}\left(\frac{s_1^2}{n_1}\right)^2 + \frac{1}{n_2-1}\left(\frac{s_2^2}{n_2}\right)^2}\ .$$

3.1.1 Limitation of t-test method

The t-test for independent groups requires that within each group, the variable of interest to be approximately normally distributed (Lumley et al., 2002). The graphical evaluation to test whether the normality assumption for a folded normal random variable holds, is possible through a Q-Q plot and a histogram of a standardized folded normal random variable. A Q-Q plot assesses the normality of a random variable by investigating the correlation between a given sample and the normal distribution. Standardization is the process of placing different values of a random variable on the same scale. The standardized folded normal random variable is, $y_{standardized} = \frac{y_i - \mu_y}{\sigma_y}$. In Figure 3.1, we note that most of the points do not fall along the reference line; hence we cannot assume normality. Figure 3.2 shows that the standardized variable of interest portrays a heavily skewed distribution.

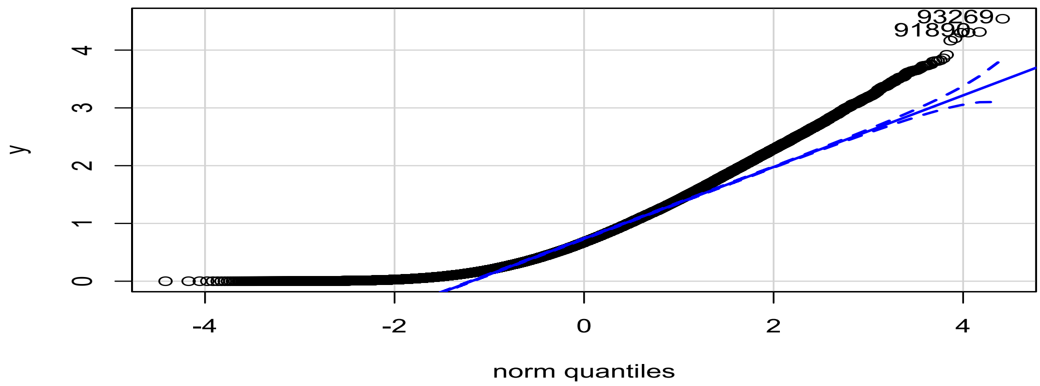


Figure 3.1: A Q-Q plot for a simulated folded normal random variable.

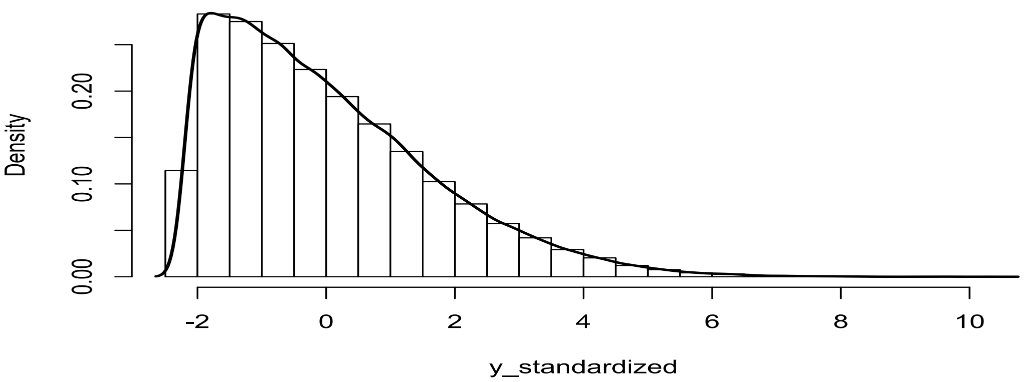


Figure 3.2: The histogram for a standardized simulated folded normal random variable.

It is evident from the graphs that a folded normal random variable violates the normality assumption. Consequently, it reduces the t test's power, therefore not reliable to construct the confidence interval for comparing the means of two independent folded normal distributions. An R code function for the graphical presentation is presented in the appendix. We therefore, explore other methods of constructing an appropriate confidence interval for comparing two independent folded normal random variables.

3.2 The Delta method

The delta method approximates means, variances and co-variances of functions of random variables with known mean and variance. It uses Taylor series expansion to derive variation around a point (Rothmann and Tsou, 2003). In particular, the method is helpful in finding the mean and variance of a test statistic in hypothesis testing. To derive an asymptotically valid confidence interval at confidence level $1-\alpha$, the multivariate delta method theorem 4.6 (Ziegler and Vens, 2011) is useful as stated below.

Multivariate Delta Method theorem

" Consider an estimator $\hat{\beta}$ for β_0 that is asymptotically normally distributed in detail, $\hat{\beta} \overset{a}{\sim} N\left(\beta_0, var\left(\hat{\beta}_0\right)\right)$. We assume that a transformation function $\xi = v\left(\hat{\beta}\right)$ of β is continuously differentiable with respect to β in a neighborhood of β_0. The estimator $\hat{\xi} = v\left(\hat{\beta}\right)$ of $\xi_0 = v\left(\beta_0\right)$ is asymptotically normal, precisely;

$$\hat{\xi} \overset{a}{\sim} N\left(\xi_0, \frac{\partial \xi\left(\beta_0\right)}{\partial \beta'} var\left(\beta_0\right) \frac{\partial \xi\left(\beta_0\right)'}{\partial \beta}\right).$$

The covariance matrix of ξ is estimated by replacing β_0 with $\hat{\beta}$.

Proof: If we admit that $v\left(\beta\right)$ can be expanded in a Taylor series around $v\left(\beta_0\right)$, we obtain $\sqrt{n}\left(v\left(\hat{\beta}\right) - v\left(\beta_0\right)\right) \overset{a.s.}{=} \left(\partial v\left(\beta_0\right)/\partial \beta'\right)\sqrt{n}\left(\hat{\beta} - \beta_0\right)$. The left side is thus asymptotically equivalent to a linear function of a random vector of which we know its asymptotic normal distribution, and the covariance matrix can be

obtained using standard calculation rules for covariance matrices.
The inversion of the idea of the multivariate delta method leads to the minimum distance estimation (MDE) approach. Specifically we consider the case that $\beta = \beta(\kappa)$ in some function of a parameter vector $\kappa \in K \subset \mathrm{IR}^q$, $q \leq p$. Regularity conditions include that κ is first order identifiable, i.e., $\beta(\kappa_1) = \beta(\kappa_2) \Rightarrow \kappa_1 \overset{a.s.}{=} \kappa_2$ and that the number of restrictions does not exceed the dimensions of β . "

With the assumption that x_{ig} is normally distributed with mean μ_g and variance σ_g^2 then, $\bar{x}_g \sim N\left(\mu_g, \frac{\sigma_g^2}{n_g}\right)$. We consider an estimator θ for μ_g that is asymptotically normally distributed with $g(\theta)$ as the function of θ. If the MLE of θ is $\bar{x}_g$ then, MLE of $g(\theta)$ is $g(\bar{x}_g)$. So we let $g(\theta) = \mid \theta \mid$ in order to construct an asymptotically confidence interval at confidence level $1-\alpha$ of the estimand $\mid \mu_2 \mid - \mid \mu_1 \mid$.

If $\mid \theta \mid \neq 0$ we directly apply the delta method as g is differentiable at θ (Zhanxiong, 2018). The limiting distribution is

$$\sqrt{n}\left(\mid \bar{x}_g \mid - \mid \theta \mid\right) \overset{a}{\sim} N\Bigg(\mid \mu_g \mid,\ \sigma^2 \left[g\prime(\theta)\right]^2 \Bigg).$$

On the other hand if $\mid \theta \mid = 0$ we cannot apply delta method because g is not differentiable at 0. A direct calculation is only expedient for $x_{ig} \geq 0$ (Zhanxiong, 2018).

$$p\left[\sqrt{n} \mid \bar{x}_g \mid \leq x_{ig}\right] = p\left[-x_{ig} \leq \sqrt{n}\ \bar{x}_g \leq x_{ig}\right]$$
$$= p\left[\sqrt{n}\ \bar{x}_g \leq x_{ig}\right] - p\left[\sqrt{n}\bar{x}_g < -x_{ig}\right].$$

If $x_{ig} < 0$ then clearly $p\left[\sqrt{n}\ \bar{x}_g \leq x_{ig}\right] = 0$.
Figure 3.3 clearly shows the discontinuity at 0 of the resultant distribution for the difference of two simulated folded normal random variable. An R code is available at the appendix for the figure.
The non-differentiability of g at $\mid \theta \mid = 0$ is limiting factor of the delta method. We therefore, consider the method unreliable to derive a valid confidence interval for the difference of the means of two independent folded normal random variables.

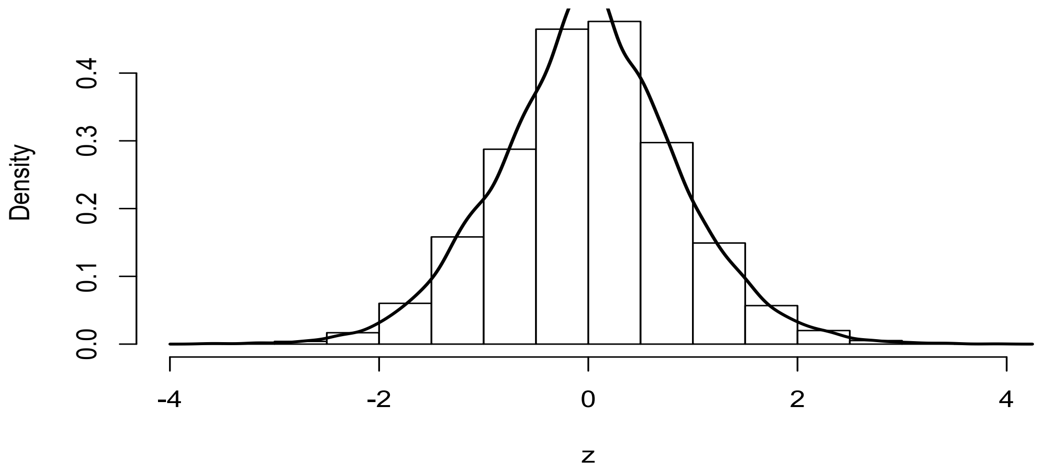


Figure 3.3: The histogram for the difference of two simulated folded normal random variable.

The exact method might be a better method to consider as described next.

3.3 The Exact Method

3.3.1 The density

We derive the density of the difference of two independent folded normal random variable. Let $f_{Y_1}(y_1)$ be a distribution function of Y_1 for $Y_1 \geq 0$, and $f_{Y_2}(y_2)$ of Y_2 for $Y_2 \geq 0$. We assume Y_1 and Y_2 are independent folded normally distributed random variables. Also, let $Z = Y_1 - Y_2$. The pdf of Z by the CDF technique is,

$$F_Z(z) = P(Y_1 - Y_2 \leq z) = \iint\limits_{Y_1 - Y_2 \leq Z} f_{Y_1,Y_2}(y_1, y_2)\, dy_1 dy_2$$

The random variable Z can be positive or negative. The region of integration if $Z > 0$, is $Y_1 \geq Y_2$ and if $Z < 0$, is $Y_1 < Y_2$.

The CDF of Z becomes,

$$F_Z(z)\begin{cases}\int_0^\infty\int_0^{z+y_2} f_{Y_1,Y_2}(y_1,y_2)\,dy_1dy_2, & \text{if } Z>0\\ \int_{-z}^\infty\int_0^{z+y_2} f_{Y_1,Y_2}(y_1,y_2)\,dy_1dy_2, & \text{if } Z<0\end{cases}$$

The pdf of Z, $f_Z(z)=\frac{dF_Z(z)}{dz}$ is achieved using Leibniz Rule for differentiation under the integral sign (Flanders, 1973).

Leibniz Rule: It states that for an integral of the form

$$H(x)=\int_{b(x)}^{a(x)} g(x,t)\,dt$$

where $-\infty<a(x),b(x)<\infty$, the derivative is expressible as,

$$\frac{dH(x)}{dx}=g(x,b(x))\frac{db(x)}{dx}-g(x,a(x))\frac{da(x)}{dx}+\int_{b(x)}^{a(x)}\frac{\partial g(x,t)}{\partial x}dt$$

The pdf of Z is simplified to,

$$f_Z(z)=\begin{cases}\int_0^\infty f_{Y_1,Y_2}(z+y_2,y_2)\,dy_2, & Z\geq 0\\ \int_{-z}^\infty f_{Y_1,Y_2}(z+y_2,y_2)\,dy_2, & Z\leq 0\end{cases}$$

Since Y_1 and Y_2 are independent, we simplify $f_Z(z)$ using convolution theorem (Pogány and Nadarajah, 2013).

Convolution theorem: If X_1 and X_2 are continous, independent, with pdf $f_{X_1}(x_1)$ and $f_{X_2}(x_2)$ respectively, and $X=X_1-X_2$ then the convolution formulae is

$$f_X(x)=\int_{-\infty}^{\infty} f_{X_1}(x+x_2)\times f_{X_2}(x_2)\,dx_2\ .$$

Therefore,

$$f_Z(z)=\begin{cases}\int_0^\infty f_{Y_1}(z+y_2)\times f_{Y_2}(y_2)\,dy_2, & Z\geq 0\\ \int_{-z}^\infty f_{Y_1}(z+y_2)\times f_{Y_2}(y_2)\,dy_2, & Z\leq 0\end{cases}$$

The two independent random variables $Y_1 \sim FN\left(\mu_1, \sigma_1^2\right)$ and $Y_2 \sim FN\left(\mu_2, \sigma_2^2\right)$ are given as,

$$f_{Y_1}\left(y_1\right) = \frac{1}{\sqrt{2\pi\sigma_1^2}}\left(e^{-\frac{\left(y_1-\mu_1\right)^2}{2\sigma_1^2}} + e^{-\frac{\left(y_1+\mu_1\right)^2}{2\sigma_1^2}}\right) \tag{3.4}$$

$$f_{Y_2}\left(y_2\right) = \frac{1}{\sqrt{2\pi\sigma_2^2}}\left(e^{-\frac{\left(y_2-\mu_2\right)^2}{2\sigma_2^2}} + e^{-\frac{\left(y_2+\mu_2\right)^2}{2\sigma_2^2}}\right) \tag{3.5}$$

The $f_Z\left(z\right)$ for $Z > 0$, follows the steps below.

$$\begin{aligned} f_Z\left(z\right) = \int_0^{\infty} &\frac{1}{\sqrt{2\pi\sigma_1^2}}\left(e^{-\frac{\left(\left(z+y_2\right)-\mu_1\right)^2}{2\sigma_1^2}} + e^{-\frac{\left(\left(z+y_2\right)+\mu_1\right)^2}{2\sigma_1^2}}\right) \times \\ &\frac{1}{\sqrt{2\pi\sigma_2^2}}\left(e^{-\frac{\left(y_2-\mu_2\right)^2}{2\sigma_2^2}} + e^{-\frac{\left(y_2+\mu_2\right)^2}{2\sigma_2^2}}\right) dy_2 \end{aligned} \tag{3.6}$$

Expanding terms of the exponents to get,
$\left(\left(z+y_2\right)-\mu_1\right)^2 = z^2+2zy_2+y_2^2-2z\mu_1-2y_2\mu_1+\mu_1^2$, $\left(\left(z+y_2\right)+\mu_1\right)^2 = z^2+2zy_2+y_2^2+2z\mu_1+2y_2\mu_1+\mu_1^2$, $\left(y_2-\mu_2\right)^2 = y_2^2-2y_2\mu_2+\mu_2^2$ and $\left(y_2+\mu_2\right)^2 = y_2^2+2y_2\mu_2+\mu_2^2$.

We replace the expansions of the terms from exponents to get,

$$\begin{aligned} = \frac{1}{2\pi\sigma_1^2\sigma_2^2}\int_0^{\infty} &\left(e^{-\frac{1}{2\sigma_1^2}\left(z^2+2zy_2+y_2^2-2z\mu_1-2y_2\mu_1+\mu_1^2\right)} + e^{-\frac{1}{2\sigma_1^2}\left(z^2+2zy_2+y_2^2+2z\mu_1+2y_2\mu_1+\mu_1^2\right)}\right) \times \\ &\left(e^{-\frac{1}{2\sigma_2^2}\left(y_2^2-2y_2\mu_2+\mu_2\right)} + e^{-\frac{1}{2\sigma_2^2}\left(y_2^2+2y_2\mu_2+\mu_2^2\right)}\right) dy_2 \end{aligned} \tag{3.7}$$

Expanding the integral of Equation (3.7) leads to,

$$= \frac{1}{2\pi\sigma_1^2\sigma_2^2}\int_0^{\infty}\left(e^{-\frac{1}{2\sigma_1^2}\left(z^2+2zy_2+y_2^2-2z\mu_1-2y_2\mu_1+\mu_1^2\right)}+e^{-\frac{1}{2\sigma_1^2}\left(z^2+2zy_2+y_2^2+2z\mu_1+2y_2\mu_1+\mu_1^2\right)}\right)\times \left(e^{-\frac{1}{2\sigma_2^2}\left(y_2^2-2y_2\mu_2+\mu_2\right)}\right)dy_2+\frac{1}{2\pi\sigma_1^2\sigma_2^2}\int_0^{\infty}\left(e^{-\frac{1}{2\sigma_2^2}\left(y_2^2+2y_2\mu_2+\mu_2^2\right)}\right)\times \left(e^{-\frac{1}{2\sigma_1^2}\left(z^2+2zy_2+y_2^2-2z\mu_1-2y_2\mu_1+\mu_1^2\right)}+e^{-\frac{1}{2\sigma_1^2}\left(z^2+2zy_2+y_2^2+2z\mu_1+2y_2\mu_1+\mu_1^2\right)}\right)dy_2 \tag{3.8}$$

Further, we expand Equation (3.8) to get,

$$\begin{aligned}=&\frac{1}{2\pi\sigma_1^2\sigma_2^2}\underbrace{\int_0^{\infty}\left(e^{-\frac{1}{2\sigma_1^2}\left(z^2+2zy_2+y_2^2-2z\mu_1-2y_2\mu_1+\mu_1^2\right)}\right)\times\left(e^{-\frac{1}{2\sigma_2^2}\left(y_2^2-2y_2\mu_2+\mu_2^2\right)}\right)}_{1^{st}\text{ part}}dy_2+\\ &\frac{1}{2\pi\sigma_1^2\sigma_2^2}\underbrace{\int_0^{\infty}\left(e^{-\frac{1}{2\sigma_1^2}\left(z^2+2zy_2+y_2^2+2z\mu_1+2y_2\mu_1+\mu_1^2\right)}\right)\times\left(e^{-\frac{1}{2\sigma_2^2}\left(y_2^2-2y_2\mu_2+\mu_2^2\right)}\right)}_{2^{st}\text{ part}}dy_2+\\ &\frac{1}{2\pi\sigma_1^2\sigma_2^2}\underbrace{\int_0^{\infty}\left(e^{-\frac{1}{2\sigma_1^2}\left(z^2+2zy_2+y_2^2-2z\mu_1-2y_2\mu_1+\mu_1^2\right)}\right)\times\left(e^{-\frac{1}{2\sigma_2^2}\left(y_2^2+2y_2\mu_2+\mu_2^2\right)}\right)}_{3^{rd}\text{ part}}dy_2+\\ &\frac{1}{2\pi\sigma_1^2\sigma_2^2}\underbrace{\int_0^{\infty}\left(e^{-\frac{1}{2\sigma_1^2}\left(z^2+2zy_2+y_2^2+2z\mu_1+2y_2\mu_1+\mu_1^2\right)}\right)\times\left(e^{-\frac{1}{2\sigma_2^2}\left(y_2^2+2y_2\mu_2+\mu_2^2\right)}\right)}_{4^{th}\text{ part}}dy_2\end{aligned} \tag{3.9}$$

Integrating the parts of Equation (3.9), we get series of solutions,
The first part;

$$\begin{aligned}&= \frac{e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\left(z^2-2z\mu_1+\mu_1^2\right)+\sigma_1^2\mu_2^2\right]}}{2\pi\sigma_1^2\sigma_2^2}\left[-\frac{\sigma_1^2\sigma_2^2e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\left(2zy_2+y_2^2-2y_2\mu_1\right)+\sigma_1^2\left(y_2^2-2y_2\mu_2\right)\right]}}{\sigma_2^2\left(z+y_2-\mu_1\right)+\sigma_1^2\left(y_2-\mu_2\right)}\right]_0^{\infty}\\ &= \frac{1}{2\pi}\left\{\frac{e^{-\left[\frac{(z-\mu_1)^2}{2\sigma_1^2}+\frac{\mu_2^2}{2\sigma_2^2}\right]}}{\sigma_2^2\left(z-\mu_1\right)-\sigma_1^2\mu_2}\right\}\end{aligned} \tag{3.10}$$

The second part;

$$= \frac{e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\left(z^2+2z\mu_1+\mu_1^2\right)+\sigma_1^2\mu_2^2\right]}}{2\pi\sigma_1^2\sigma_2^2}\left[-\frac{\sigma_1^2\sigma_2^2 e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\left(2zy_2+y_2^2+2y_2\mu_1\right)+\sigma_1^2\left(y_2^2-2y_2\mu_2\right)\right]}}{\sigma_2^2\left(z+y_2+\mu_1\right)+\sigma_1^2\left(y_2-\mu_2\right)}\right]_0^\infty$$
$$= \frac{1}{2\pi}\left\{\frac{e^{-\left[\frac{(z+\mu_1)^2}{2\sigma_1^2}+\frac{\mu_2^2}{2\sigma_2^2}\right]}}{\sigma_2^2\left(z+\mu_1\right)-\sigma_1^2\mu_2}\right\} \tag{3.11}$$

The third part,

$$= \frac{e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\left(z^2-2z\mu_1+\mu_1^2\right)+\sigma_1^2\mu_2^2\right]}}{2\pi\sigma_1^2\sigma_2^2}\left[-\frac{\sigma_1^2\sigma_2^2 e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\left(2zy_2+y_2^2-2y_2\mu_1\right)+\sigma_1^2\left(y_2^2+2y_2\mu_2\right)\right]}}{\sigma_2^2\left(z+y_2-\mu_1\right)+\sigma_1^2\left(y_2+\mu_2\right)}\right]_0^\infty$$
$$= \frac{1}{2\pi}\left\{\frac{e^{-\left[\frac{(z-\mu_1)^2}{2\sigma_1^2}+\frac{\mu_2^2}{2\sigma_2^2}\right]}}{\sigma_2^2\left(z-\mu_1\right)+\sigma_1^2\mu_2}\right\} \tag{3.12}$$

The fourth part,

$$= \frac{e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\left(z^2+2z\mu_1+\mu_1^2\right)+\sigma_1^2\mu_2^2\right]}}{2\pi\sigma_1^2\sigma_2^2}\left[-\frac{\sigma_1^2\sigma_2^2 e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\left(2zy_2+y_2^2+2y_2\mu_1\right)+\sigma_1^2\left(y_2^2+2y_2\mu_2\right)\right]}}{\sigma_2^2\left(z+y_2+\mu_1\right)+\sigma_1^2\left(y_2+\mu_2\right)}\right]_0^\infty$$
$$= \frac{1}{2\pi}\left\{\frac{e^{-\left[\frac{(z+\mu_1)^2}{2\sigma_1^2}+\frac{\mu_2^2}{2\sigma_2^2}\right]}}{\sigma_2^2\left(z+\mu_1\right)+\sigma_1^2\mu_2}\right\} \tag{3.13}$$

Combining Equations (3.10), (3.11), (3.12) and (3.13) $f_Z(z)$ for $Z \geq 0$ becomes,

$$\begin{aligned} f_Z(z) =& \frac{1}{2\pi}\left[\frac{e^{-\left[\frac{(z-\mu_1)^2}{2\sigma_1^2}+\frac{\mu_2^2}{2\sigma_2^2}\right]}}{\sigma_2^2\left(z-\mu_1\right)-\sigma_1^2\mu_2}+\frac{e^{-\left[\frac{(z+\mu_1)^2}{2\sigma_1^2}+\frac{\mu_2^2}{2\sigma_2^2}\right]}}{\sigma_2^2\left(z+\mu_1\right)-\sigma_1^2\mu_2}\right]+ \\ & \frac{1}{2\pi}\left[\frac{e^{-\left[\frac{(z-\mu_1)^2}{2\sigma_1^2}+\frac{\mu_2^2}{2\sigma_2^2}\right]}}{\sigma_2^2\left(z-\mu_1\right)+\sigma_1^2\mu_2}+\frac{e^{-\left[\frac{(z+\mu_1)^2}{2\sigma_1^2}+\frac{\mu_2^2}{2\sigma_2^2}\right]}}{\sigma_2^2\left(z+\mu_1\right)+\sigma_1^2\mu_2}\right] \end{aligned} \tag{3.14}$$

The $f_Z(z)$ for $Z < 0$ is given by,

$$f_Z(z) = \int_{-z}^{\infty} \frac{1}{\sqrt{2\pi\sigma_1^2}} \left(e^{-\frac{((z+y_2)-\mu_1)^2}{2\sigma_1^2}} + e^{-\frac{((z+y_2)+\mu_1)^2}{2\sigma_1^2}} \right) \times \frac{1}{\sqrt{2\pi\sigma_2^2}} \left(e^{-\frac{(y_2-\mu_1)^2}{2\sigma_2^2}} + e^{-\frac{(y_2+\mu_2)^2}{2\sigma_2^2}} \right) dy_2 \tag{3.15}$$

We follow the same steps for integrating Equation (3.6) using the limits $(-z, \infty)$. We obtain a series of solutions;
The first part;

$$\begin{aligned}
&= \frac{e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\left(z^2-2z\mu_1+\mu_1^2\right)+\sigma_1^2\mu_2^2\right]}}{2\pi\sigma_1^2\sigma_2^2} \left[-\frac{\sigma_1^2\sigma_2^2 e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\left(2zy_2+y_2^2-2y_2\mu_1\right)+\sigma_1^2\left(y_2^2-2y_2\mu_2\right)\right]}}{\sigma_2^2\left(z+y_2-\mu_1\right)+\sigma_1^2\left(y_2-\mu_2\right)} \right]_{-z}^{\infty} \\
&= \frac{1}{2\pi}\left\{ \frac{1}{\sigma_1^2\left(-z-\mu_2\right)-\sigma_2^2\mu_1} e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\mu_1^2+\sigma_1^2\left(z^2+2z\mu_2^2+\mu_2^2\right)\right]} \right\} \\
&= \frac{1}{2\pi}\left\{ \frac{e^{-\left[\frac{\mu_1^2}{2\sigma_1^2}+\frac{(z+\mu_2)^2}{2\sigma_2^2}\right]}}{\sigma_1^2\left(-z-\mu_2\right)-\sigma_2^2\mu_1} \right\}
\end{aligned} \tag{3.16}$$

The second part;

$$\begin{aligned}
&= \frac{e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\left(z^2+2z\mu_1+\mu_1^2\right)+\sigma_1^2\mu_2^2\right]}}{2\pi\sigma_1^2\sigma_2^2} \left[-\frac{\sigma_1^2\sigma_2^2 e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\left(2zy_2+y_2^2+2y_2\mu_1\right)+\sigma_1^2\left(y_2^2-2y_2\mu_2\right)\right]}}{\sigma_2^2\left(z+y_2+\mu_1\right)+\sigma_1^2\left(y_2-\mu_2\right)} \right]_{-z}^{\infty} \\
&= \frac{1}{2\pi}\left\{ \frac{1}{\sigma_1^2\left(-z-\mu_2\right)+\sigma_2^2\mu_1} e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\mu_1^2+\sigma_1^2\left(z^2+2z\mu_2^2+\mu_2^2\right)\right]} \right\} \\
&= \frac{1}{2\pi}\left\{ \frac{e^{-\left[\frac{\mu_1^2}{2\sigma_1^2}+\frac{(z+\mu_2)^2}{2\sigma_2^2}\right]}}{\sigma_1^2\left(-z-\mu_2\right)+\sigma_2^2\mu_1} \right\}
\end{aligned} \tag{3.17}$$

The third part;

$$
\begin{aligned}
&= \frac{e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\left(z^2-2z\mu_1+\mu_1^2\right)+\sigma_1^2\mu_2^2\right]}}{2\pi\sigma_1^2\sigma_2^2}\left[-\frac{\sigma_1^2\sigma_2^2 e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\left(2zy_2+y_2^2-2y_2\mu_1\right)+\sigma_1^2\left(y_2^2+2y_2\mu_2\right)\right]}}{\sigma_2^2\left(z+y_2-\mu_1\right)+\sigma_1^2\left(y_2+\mu_2\right)}\right]_{-z}^{\infty} \\
&= \frac{1}{2\pi}\left\{\frac{1}{\sigma_1^2\left(-z+\mu_2\right)-\sigma_2^2\mu_1} e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\mu_1^2+\sigma_1^2\left(z^2-2z\mu_2^2+\mu_2^2\right)\right]}\right\} \\
&= \frac{1}{2\pi}\left\{\frac{e^{-\left[\frac{\mu_1^2}{2\sigma_1^2}+\frac{(z-\mu_2)^2}{2\sigma_2^2}\right]}}{\sigma_1^2\left(-z+\mu_2\right)-\sigma_2^2\mu_1}\right\}
\end{aligned}
\tag{3.18}
$$

The fourth part;

$$
\begin{aligned}
&= \frac{e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\left(z^2+2z\mu_1+\mu_1^2\right)+\sigma_1^2\mu_2^2\right]}}{2\pi\sigma_1^2\sigma_2^2}\left[-\frac{\sigma_1^2\sigma_2^2 e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\left(2zy_2+y_2^2+2y_2\mu_1\right)+\sigma_1^2\left(y_2^2+2y_2\mu_2\right)\right]}}{\sigma_2^2\left(z+y_2+\mu_1\right)+\sigma_1^2\left(y_2+\mu_2\right)}\right]_{-z}^{\infty} \\
&= \frac{1}{2\pi}\left\{\frac{1}{\sigma_1^2\left(-z+\mu_2\right)+\sigma_2^2\mu_1} e^{-\frac{1}{2\sigma_1^2\sigma_2^2}\left[\sigma_2^2\mu_1^2+\sigma_1^2\left(z^2-2z\mu_2^2+\mu_2^2\right)\right]}\right\} \\
&= \frac{1}{2\pi}\left\{\frac{e^{-\left[\frac{\mu_1^2}{2\sigma_1^2}+\frac{(z-\mu_2)^2}{2\sigma_2^2}\right]}}{\sigma_1^2\left(-z+\mu_2\right)+\sigma_2^2\mu_1}\right\}
\end{aligned}
\tag{3.19}
$$

Combining Equations (3.16), (3.17), (3.18) and (3.19) $f_Z\left(z\right) for Z \leq 0$ becomes,

$$
\begin{aligned}
f_Z\left(z\right) =& \frac{1}{2\pi}\left[\frac{e^{-\left[\frac{\mu_1^2}{2\sigma_1^2}+\frac{(z+\mu_2)^2}{2\sigma_2^2}\right]}}{\sigma_1^2\left(-z-\mu_2\right)-\sigma_2^2\mu_1}+\frac{e^{-\left[\frac{\mu_1^2}{2\sigma_1^2}+\frac{(z+\mu_2)^2}{2\sigma_2^2}\right]}}{\sigma_1^2\left(-z-\mu_2\right)+\sigma_2^2\mu_1}\right]+ \\
& \frac{1}{2\pi}\left[\frac{e^{-\left[\frac{\mu_1^2}{2\sigma_1^2}+\frac{(z-\mu_2)^2}{2\sigma_2^2}\right]}}{\sigma_1^2\left(-z+\mu_2\right)-\sigma_2^2\mu_1}+\frac{e^{-\left[\frac{\mu_1^2}{2\sigma_1^2}+\frac{(z-\mu_2)^2}{2\sigma_2^2}\right]}}{\sigma_1^2\left(-z+\mu_2\right)+\sigma_2^2\mu_1}\right]
\end{aligned}
\tag{3.20}
$$

Re-arranging Equation (3.20) we get,

$$f_Z(z) = \frac{1}{2\pi}\left[\frac{e^{-\left[\frac{\mu_1^2}{2\sigma_1^2}+\frac{(z-\mu_2)^2}{2\sigma_2^2}\right]}}{\sigma_1^2(-z+\mu_2)+\sigma_2^2\mu_1} + \frac{e^{-\left[\frac{\mu_1^2}{2\sigma_1^2}+\frac{(z+\mu_2)^2}{2\sigma_2^2}\right]}}{\sigma_1^2(-z-\mu_2)+\sigma_2^2\mu_1}\right] + \frac{1}{2\pi}\left[\frac{e^{-\left[\frac{\mu_1^2}{2\sigma_1^2}+\frac{(z-\mu_2)^2}{2\sigma_2^2}\right]}}{\sigma_1^2(-z+\mu_2)-\sigma_2^2\mu_1} + \frac{e^{-\left[\frac{\mu_1^2}{2\sigma_1^2}+\frac{(z+\mu_2)^2}{2\sigma_2^2}\right]}}{\sigma_1^2(-z-\mu_2)-\sigma_2^2\mu_1}\right] \tag{3.21}$$

Conclusion: The pdf of the difference of two independent folded normal random variable $f_Z(z)$, has two distributions for two cases.

$$f_Z(z) = \begin{cases} \frac{1}{2\pi}\left[\frac{e^{-\left[\frac{(z-\mu_1)^2}{2\sigma_1^2}+\frac{\mu_2^2}{2\sigma_2^2}\right]}}{\sigma_2^2(z-\mu_1)-\sigma_1^2\mu_2} + \frac{e^{-\left[\frac{(z+\mu_1)^2}{2\sigma_1^2}+\frac{\mu_2^2}{2\sigma_2^2}\right]}}{\sigma_2^2(z+\mu_1)-\sigma_1^2\mu_2}\right] + \\ \frac{1}{2\pi}\left[\frac{e^{-\left[\frac{(z-\mu_1)^2}{2\sigma_1^2}+\frac{\mu_2^2}{2\sigma_2^2}\right]}}{\sigma_2^2(z-\mu_1)+\sigma_1^2\mu_2} + \frac{e^{-\left[\frac{(z+\mu_1)^2}{2\sigma_1^2}+\frac{\mu_2^2}{2\sigma_2^2}\right]}}{\sigma_2^2(z+\mu_1)+\sigma_1^2\mu_2}\right], & for\ Z > 0 \\ \\ \frac{1}{2\pi}\left[\frac{e^{-\left[\frac{\mu_1^2}{2\sigma_1^2}+\frac{(z-\mu_2)^2}{2\sigma_2^2}\right]}}{\sigma_1^2(-z+\mu_2)+\sigma_2^2\mu_1} + \frac{e^{-\left[\frac{\mu_1^2}{2\sigma_1^2}+\frac{(z+\mu_2)^2}{2\sigma_2^2}\right]}}{\sigma_1^2(-z-\mu_2)+\sigma_2^2\mu_1}\right] + \\ \frac{1}{2\pi}\left[\frac{e^{-\left[\frac{\mu_1^2}{2\sigma_1^2}+\frac{(z-\mu_2)^2}{2\sigma_2^2}\right]}}{\sigma_1^2(-z+\mu_2)-\sigma_2^2\mu_1} + \frac{e^{-\left[\frac{\mu_1^2}{2\sigma_1^2}+\frac{(z+\mu_2)^2}{2\sigma_2^2}\right]}}{\sigma_1^2(-z-\mu_2)-\sigma_2^2\mu_1}\right], & for\ Z < 0 \end{cases} \tag{3.22}$$

3.3.2 Mean

We obtain the mean in a closed form.

$$\begin{aligned}
\mu_Z &= E(Z) = E(Y_1 - Y_2) \\
&= E(Y_1) - E(Y_2) \\
E(Y_1) &= \mu_1 \left[1 - 2\Phi\left(-\frac{\mu_1}{\sigma_1}\right)\right] + \sigma_1 \sqrt{\frac{2}{\pi}}\ e^{-\mu_1^2/2\sigma_1^2} = \mu_{Y_1} \\
E(Y_2) &= \mu_2 \left[1 - 2\Phi\left(-\frac{\mu_2}{\sigma_2}\right)\right] + \sigma_2 \sqrt{\frac{2}{\pi}}\ e^{-\mu_2^2/2\sigma_2^2} = \mu_{Y_2} \\
\mu_Z &= \mu_{Y_1} - \mu_{Y_2}
\end{aligned} \tag{3.23}$$

3.3.3 Variance

$$\begin{aligned}
\sigma_Z^2 &= Var(Z) = Var(Y_1 - Y_2) \\
&= Var(Y_1) + Var(Y_2) \\
Var(Y_1) &= \sigma_1^2 + \mu_1^2 - \mu_{Y_1}^2 = \sigma_{Y_1}^2 \\
Var(Y_2) &= \sigma_2^2 + \mu_2^2 - \mu_{Y_2}^2 = \sigma_{Y_2}^2 \\
\sigma_Z^2 &= \sigma_1^2 + \sigma_2^2 + \mu_1^2 + \mu_2^2 - \left(\mu_{Y_1}^2 + \mu_{Y_2}^2\right)
\end{aligned} \tag{3.24}$$

3.3.4 Confidence interval

A valid Confidence interval for $\mu_Z = \mu_{Y_1} - \mu_{Y_2}$ with variance heterogeneity,

$$\bar{y}_2 - \bar{y}_1 \pm q_{1-\frac{\alpha}{2}} \sqrt{\frac{\hat{\sigma}_{Y_1}^2}{n_1} + \frac{\hat{\sigma}_{Y_2}^2}{n_2}} \tag{3.25}$$

Assuming variance homogeneity $\sigma_{Y_1}^2 = \sigma_{Y_2}^2$,

$$\bar{y}_2 - \bar{y}_1 \pm q_{1-\frac{\alpha}{2}} \hat{\sigma}_Y \sqrt{\frac{1}{n_1} + \frac{1}{n_2}} \tag{3.26}$$

Where q is the quantile from the pdf of the difference of two independent folded normal distribution and $\hat{\sigma}$ is estimated from the absolute values, i.e.,

$$\hat{\sigma}_Y^2 = \frac{(n_1 - 1)\,\hat{\sigma}_{Y_1}^2 + (n_2 - 1)\,\hat{\sigma}_{Y_2}^2}{n_1 + n_2 - 2} \tag{3.27}$$

It is vital to emphasize that the standard table for quantiles for the pdf of the difference of two independent folded normal is currently unavailable in popular statistics software. However, it is possible to use empirical quantiles generated through a simulation of the pdf difference. We can consider developing an R software package that calculates the quantiles for the pdf of the difference between two independent folded normal random variables as future research work. An R function code for the pdf and cdf of the distribution difference is attached in the appendix, which can be useful for the package development and empirical quantile calculation.

3.4 The ratio of two Chi-Square Variables

The simplest approach is to reformulate the hypothesis of Equation (3.1) using the ratio of the centered squared random variables, i.e.,

$$H_0' \colon \frac{\mu_{2,2}}{\mu_{2,1}} = \frac{E\big((x_2-\mu_2)^2\big)}{E\big((x_1-\mu_1)^2\big)} = 1 \quad \text{vs.} \quad H_1' \colon \frac{\mu_{2,2}}{\mu_{2,1}} = \frac{E\big((x_2-\mu_2)^2\big)}{E\big((x_1-\mu_1)^2\big)} \neq 1\,, \tag{3.28}$$

with $\mu_{2,g}$ denoting the second central moment of x_g of group g. In fact, under the assumptions from above,

$$Z_g = \sum_{i=1}^{n_g} \left(\frac{x_{ig}-\bar{x}_g}{\sigma_g}\right)^2 = \frac{1}{\sigma_g^2} \sum_{i=1}^{n_g} \big(x_{ig}-\bar{x}_g\big)^2$$

is centrally χ^2 distributed with $n_g - 1$ degrees of freedom because μ_g is estimated by $\bar{x}_g$. Below we use the notation $s_g^2 = \frac{1}{n_g-1}\sum_{i=1}^{n_g}\big(x_{ig}-\bar{x}_g\big)^2$. The ratio

$$F = \frac{Z_1/(n_1-1)}{Z_2/(n_2-1)} = \frac{\frac{1}{(n_1-1)\sigma_1^2}\sum_{i=1}^{n_1}\big(x_{i1}-\mu_1\big)^2}{\frac{1}{(n_2-1)\sigma_2^2}\sum_{i=1}^{n_2}\big(x_{i2}-\mu_2\big)^2} = \frac{\sigma_2^2}{\sigma_1^2}\,\frac{s_1^2}{s_2^2} \tag{3.29}$$

is therefore $F_{n_2-1}^{n_1-1}$ distributed, i.e., F distributed with $n_1 - 1$ and $n_2 - 1$ degrees of freedom (Kim, 2006). With $q_l = F_{n_2-1}^{n_1-1}(\alpha/2)$ and $q_u = F_{n_2-1}^{n_1-1}(1-\alpha/2) = \frac{1}{F_{n_1-1}^{n_2-1}(\alpha/2)}$ denoting the lower and upper quantiles of the $F_{n_2-1}^{n_1-1}$ distribution, hence a $1-\alpha$

confidence interval for σ_2^2/σ_1^2 is given by:

$$q_l \leq \frac{\sigma_2^2 s_1^2}{\sigma_1^2 s_2^2} \leq q_u \tag{3.30}$$

$$\frac{s_2^2}{s_1^2}\, q_l \leq \frac{\sigma_2^2}{\sigma_1^2} \leq \frac{s_2^2}{s_1^2}\, q_u \tag{3.31}$$

$$\frac{s_2^2}{s_1^2}\, q_l \leq \frac{E\big((x_2-\mu_2)^2\big)}{E\big((x_1-\mu_1)^2\big)} \leq \frac{s_2^2}{s_1^2}\, q_u \tag{3.32}$$

The confidence interval can be calculated easily from the `var.test` function within the `stats` package in R. One crucial aspect is the definition of the non-inferiority margin in the case of the two ratios. If the non-inferiority margin is formulated as $E(y_2) - E(y_1) \leq \delta$, there is no direct relationship to the estimand of Equation (3.32). In addition, the interpretation of a difference is generally simpler than the interpretation of a ratio, in this case, the ratio of two squared functions. A confidence interval for the difference of two independent χ^2 distributions might therefore be simpler. Finally, a bootstrap approach might be the simplest in terms of interpretation. Both approaches will be described below.

3.5 The difference of two Chi-Square distribution

Klar (2015) provided the density for the difference of two independent gamma distributed random variables, denoted as gamma difference distribution (GDD). In detail, for two independent variables $X_g \sim \Gamma(\alpha_g, \beta_g)$, $g = 1, 2$ with $\alpha_g > 0$, $\beta_g > 0$ the difference $Z = X_1 - X_2$ follows a GDD with parameters $\alpha_1, \beta_1, \alpha_2, \beta_2$. With the use of Whittaker's W function, the density of the GDD can be written as

$$f(z) = \begin{cases} \frac{\tilde{c}}{\Gamma(\alpha_1)} z^{(\alpha_1+\alpha_2)/2-1} e^{((\beta_2-\beta_1)/2)z} W_{(\alpha_1-\alpha_2)/2,(1-\alpha_1-\alpha_2)/2}\big((\beta_1+\beta_2)z\big) & z > 0\,, \\ \frac{\tilde{c}}{\Gamma(\alpha_2)} (-z)^{(\alpha_1+\alpha_2)/2-1} e^{((\beta_2-\beta_1)/2)(-z)} W_{(\alpha_2-\alpha_1)/2,(1-\alpha_1-\alpha_2)/2}\big((\beta_1+\beta_2)(-z)\big) & z < 0\,, \end{cases} \tag{3.33}$$

where $\Gamma(\cdot)$ denotes the gamma function and

$$\tilde{c} = \frac{\beta_1^{\alpha_1}\,\beta_2^{\alpha_2}}{(\beta_1+\beta_2)^{(\alpha_1+\alpha_2)/2}}\,.$$

The Whittaker's W function is a special solution to the Whittaker equation. Whittaker's equation is a modified version of the hypergeometric confluent equation to make the formulas concerning the solutions more symetric (Parmar, 2013). It has a regular single point at 0 and irregular single point at ∞. It is given by,

$$\frac{d^2w}{dz^2} + \left(\frac{-1}{4} + \frac{\kappa}{z} + \frac{\frac{1}{4}-\mu^2}{z^2}\right) w = 0.$$

The Whittaker's W function is given by,

$$W_{\kappa,\mu}\,(z) = exp\left(\frac{-z}{2}\right) z^{\mu+\frac{1}{2}}\; U_{\mu-\kappa+\frac{1}{2},1+2\mu,z}$$

with $\kappa = \frac{1}{2}b - a$, $\mu = \frac{1}{2}b - \frac{1}{2}$, U is the Tricomi's function and z are points on a z plane $(-\infty, 0)$ where b, a are points on an x-y plane.
In the application from above, $X_g \sim \chi^2_{n_g-1} = \Gamma(\frac{n_g-1}{2}, \frac{1}{2})$ so that the density reduces to

$$f(z) = \begin{cases} \frac{\tilde{c}}{\Gamma(\frac{n_1-1}{2})} z^{(n_1+n_2)/2-2} W_{(n_1-n_2)/4,(4-n_1-n_2)/4}(z) & z > 0\,, \\ \frac{\tilde{c}}{\Gamma(\frac{n_2-1}{2})} (-z)^{(n_1+n_2)/2-2} W_{(n_2-n_1)/4,(4-n_1-n_2)/4}(-z) & z < 0\,, \end{cases} \tag{3.34}$$

with $\tilde{c} = 2^{1-(n_1+n_2)/2}$.
To determine the $1-\alpha$ confidence interval for Z, the quantile needs to be determined for the lower and upper $\alpha/2$ quantile of the distribution of Equation (3.34). This can be obtained by a point halving algorithm, such as `updown` from the `stats` package, in conjunction with numeric integration, as implemented in `integral`, and a pre-defined Whittaker W function, as implemented in `whittakerW` from the `fAsianOptions` in R.

The non-inferiority margin can be easily transferred to the confidence interval described in this section. The non-inferiority margin is $E(y_2) - E(y_1) \leq \delta$. If the squared of absolute values are considered, it is plausible to assume a squared non-inferiority margin, such that $E\big((x_2-\mu_2)^2\big)-E\big((x_1-\mu_1)^2\big)\leq\delta^2$. If means are identical, it is reasonable to assume variance homogeneity between study groups so that the non-inferiority margin increases by the assumed σ, if it has to be formulated in terms of $E(X_2)-E(X_1)\leq\sigma\delta^2$.

3.6 Bootstrapping method

Bootstrapping is a test that utilizes random sampling with replacement and assigns measures of accuracy, such as confidence interval to sample estimates. We use the method as an alternative statistical inference when parametric inference requires complicated formulas to calculate standard errors. We evaluate the parametric and the non-parametric bootstraps to estimate confidence intervals for two absolute differences. Since sample sizes may be different for groups $g=1$ and 2, we propose to use a group-specific bootstrap. With the notation from the definition section, we perform the non-parametric bootstrap as follows:

Step 1 Set bootstrap counter to $b=1$

Step 2 Draw n_g subjects with replacement from the original n_g subjects. Note that resampling is done within groups $g=1,2$. This approach leads to bootstrapped group-specific sample sizes identical to the original group-specific sample sizes.

Step 3 Calculate the relevant statistics from the bootstrap sample. These are

1. $\bar{y}_1^{(b)}$, $\bar{y}_2^{(b)}$ and diffmeanabs$^{(b)}=\bar{y}_2^{(b)}-\bar{y}_1^{(b)}$.
2. $s_1^{2^{(b)}}=\left(\frac{1}{n_1-1}\sum_{i=1}^{n}\left(d_{i1}-\bar{d}_1^{(b)}\right)^2\right)^{(b)}$, $s_2^{2^{(b)}}=\left(\frac{1}{n_2-1}\sum_{i=1}^{n}\left(d_{i2}-\bar{d}_2^{(b)}\right)^2\right)^{(b)}$, which are the empirical variances of the bootstrap samples.
3. ratiovars$^{(b)}=s_2^{2^{(b)}}/s_1^{2^{(b)}}$.
4. diffvars$^{(b)}=s_2^{2^{(b)}}-s_1^{2^{(b)}}$.
5. The corrected means, i.e., $\bar{D}_1^{(b)}=\bar{y}_1^{(b)}-\widehat{E(Y)}^{(b)}=\bar{y}_1^{(b)}-\bar{x}_1^{(b)}\big(1-2\Phi\big(-\frac{\bar{x}_1^{(b)}}{s_1^{(b)}}\big)\big)-s_1^{(b)}\sqrt{2/\pi}\exp\left(-\bar{x}_1^{2^{(b)}}/(2s_1^{2^{(b)}})\right)$ and $\bar{D}_2^{(b)}$ as well as their difference $\bar{D}_1^{(b)}-\bar{D}_2^{(b)}$.

6. The corrected means under the assumption that the individual means equal 0, i.e., $\bar{D}*_1^{(b)} = \bar{y}_1^{(b)} - \widehat{E(Y*)}^{(b)} = \bar{y}_1^{(b)} - s_1^{(b)}\sqrt{2/\pi}$ and $\bar{D}*_2^{(b)}$ and their difference $\bar{D}*_2^{(b)} - \bar{D}*_1^{(b)}$.

Step 4 Do step 2 and step 3 B times, such as $B = 10,000$ in order to obtain the bootstrap distribution for the relevant statistics calculated in step 2.

Step 5 The non-parametric bootstrap confidence interval is given by the lower and upper 2.5% quantiles of the bootstrap distribution for the parameters of interest, such as diffmeanabs and ratiosqdiffabs.

Step 6 The parametric bootstrap confidence interval is obtained using the standard form of the confidence interval. The mean and the variance of the bootstrapped parameter of interest are obtained, say m and s^2, and the parametric bootstrap confidence interval is obtained as $m \pm z_{1-\alpha/2}s$ for the parameters of interest.

The use of the bootstrap confidence interval permits the use of a non-inferiority margin dependent on the difference of the means of the absolute values of the group-specific differences.
For simulations, it is important to define the true mean difference, and it might well be appropriate to use the mean from the folded normal as starting point, which depends on the mean and the variance of the underlying normal distribution and is provided by,

$$E(Y) = \mu\left[1 - 2\Phi\left(-\frac{\mu}{\sigma}\right)\right] + \sigma\sqrt{\frac{2}{\pi}}\, e^{-\mu^2/2\sigma^2} = \mu_Y.$$

In this thesis, simulation studies assuming true underlying folded normal distribution parameters are left as a future extension to the work. The focus presently is to implement the above methods of constructing the confidence intervals to a real data set.

Chapter 4

Application to real data

We present real-life data to illustrate the application and performance of the ratio of two Chi-square, the difference of two Chi-square distribution and bootstrap methods explored in the previous chapter.

4.1 Results

The results of Table 4.1 depicts that the variance ratio of two chi-square random variables from group 1 and 2 is 1.5765. The ratio deviates by 0.5765 from 1, which gives more robust evidence of unequal group variances. However, the p-value of F test is 0.3721 which is greater than 5% significance level leading to the conclusion that there is no significant difference between the two variances of the groups. Therefore, we are 95% confident that the variance ratio between Magnesium and Titanium group is between 0.5709 and 4.3533.

Table 4.1: Summary of 95% confidence level for the ratio of two chi-square variables.

Method	Group	Mean	Variance	Var ratio	95%CI_low	95%CI_up	Conf_width	p value
2 Chi ratio	Mg	12.1765	426.1544	1.5765	0.5709	4.3534	3.7824	0.3721
	Ti	10.7059	671.8456					

The Table 4.2, shows both non-parametric and parametric results of the bootstrap method. We observe that there is a negligible difference of outcomes between the parametric and non-parametric bootstrap approach. We are 95% confidence that the mean difference of the two groups is approximately between -2.1 and 1.3. The bootstrap method permits a non inferiority margin δ of -0.411.

Table 4.2: Summary of 95% confidence level for bootstrap method.

Method	**Mean**	**Variance**	**95%CI_low**	**95%CI_up**	**Conf_width**
Non-parametric	—	—	-2.1176	1.3529	3.4706
Parametric	-0.4059	0.8990	-2.1287	1.3169	3.4456

To illustrate the non-reliability of the delta method, we plot a histogram of the real data for the distributional difference of the absolute values of magnesium group and Titanium group. We note the discontinuity at 0 of the distribution in Figure 4.1, which clearly explains the non-differentiability of the function of the estimand $\mid \mu_2 \mid - \mid \mu_1 \mid$ when the estimator is 0.

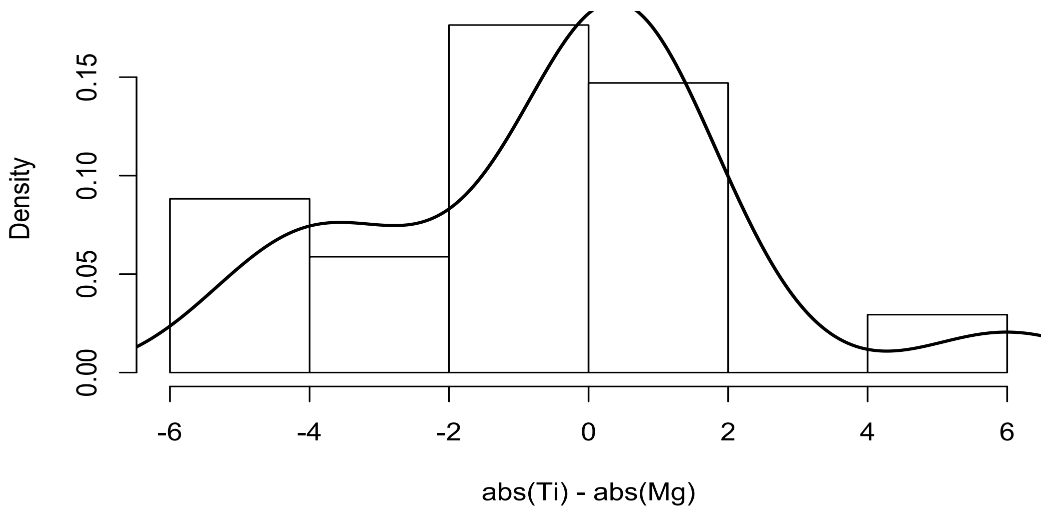


Figure 4.1: The histogram for the difference between the absolute HVA of Mg and Ti random variable.

The difference of two chi-square distribution is a complex function due to the Whittaker's W function, whose solution is a complex number. The expected confidence interval, therefore, is of complex numbers. Computing the Whittaker function of the real data is time-consuming, which affects the general performance of the method.

Chapter 5

Discussion and conclusion

The thesis constructed four approaches to calculate the confidence interval to compare two independent folded normally distributed random variables which are applicable to establish the stability of a surgery for the treatment of Hallux Valgus and judging the non-inferiority of the two treatments administered. The confidence interval for the ratio of two chi-square random variable is straightforward, easy to calculate and not time-consuming. Bootstrapping method allows a straightforward way to derive the confidence interval for the mean of two absolute differences and is asymptotically more accurate than the standard interval obtained from samples that assume normality (Islam and Begum, 2018). It is an appropriate way to ascertain the stability of the results. However, the method is time-consuming and requires large computer storage to perform the computations when the bootstrap sample and bootstrap repetition B, is immense.

The difference between the two chi-square distributions method to obtain a confidence interval is not straightforward, and the computations are computer-intensive due to the Whittaker function. We did not apply the exact method to the real data due to the unavailability of satandard quantile table for the pdf of the difference of two independent folded normal random variables in the popular statistical softwares. Additionally, the complexity of the pdf difference made it challenging to come up with the emeprical quantiles. Judging by δ of the bootstrap method, we establish non-inferiority for the new surgical procedure that uses biodegradable magnesium alloy screw compared to the surgical procedure that uses standard titanium screw fixation for the treatment of HV deformity. In conclusion, the methods are promising, and we recommend them for use to compare other practical data that require the use of folded normal distribution.

One of the shortcomings of this study was the small sample size of the variable of interest, which may have produced results biased to small sample sizeed datasets only. Secondly, the computer intensive computations of the Whitteker W function for the difference of two chi squared RVs approach made it challenging to produce results of real data application. Closely related to that was the insufficient computer storage space to carry out immense simulation study for all the methods. Additionally, some methods such as bootstrapping was time consuming and it required long awaited hours to produce results. Finally, the uavailability of standard table for quantiles of the pdf for the difference of two independent folded normal distribution limited the application of exact method.

There is a large potential space to extend research on this study. Simulations to establish coverage properties of the methods discussed are needed. A great deal of work needs to be completed on the exact approach to generate the empirical quantiles. For future research purposes, we can consider developing an R software package to produce standard quantiles for use when dealing with the distribution for the difference of two independent folded normal random variables. Further, we can incorporate the ratio of two chi-square and the difference of two chi-square methods into the parametric bootstrapping conducted. More can be done on the difference between the two chi-square distributions based on the complexity of Whittaker's W function. In addition, if percent changes of the HVA are a reasonable metric, one can consider analyzing the absolute value data in the log-scale. Also, If the sign of the difference between early post-operation and late followup for HV angels is also clinically relevant, repeat the analysis without taking absolute values, of course adjusting your analytic approach. This study focused on one continuous outcome variable HVA utilizing the uni-variate version of folded normal distribution. Therefore, the model can be extended to be able to incorporate another outcome variable such IMA to use the bi-variate version of the folded normal distribution. Finally, likelihood based CIs, bayesian approach for non-inferiority assesment and the BC_α (is likely to perform better than the basic approach) can be considered too for future research.

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Appendix A

R codes

A.1 Exploratory data analysis

```
#set working directory
setwd("C:\\users\\Shiphrah Sarah\\OneDrive\\R codes\\HV DATA")
# importing the Excel data file
library(readxl)
mydata = read_excel("HV_Study_Data.xlsx", col_types="numeric",
range=cell_cols("Q:R"))
# Extracting magnesium group data
#Group 1
Mg_data<-as.data.frame(mydata[1:17,], drop=FALSE)
Mg_data
#extracting titanium group data
#Group 2
Ti_data<-as.data.frame(mydata[18:34,], drop=FALSE)
Ti_data
# sample size
n1<-nrow(Mg_data)
n2<-nrow(Ti_data)
# calculating the difference of the HVA for both groups
Mg_data_difference<-apply(Mg_data, 1, diff)
```

```
Ti_data_difference<-apply(Ti_data, 1, diff)
# calculating absolute difference of HVA for both groups
Mg_data_absolute<-abs(apply(Mg_data, 1, diff))
Ti_data_absolute<-abs(apply(Ti_data, 1, diff))
# Exploratory data analysis
# descriptive statistics of absolute difference for both groups
summary(Mg_data_absolute)
summary(Ti_data_absolute)
# violin plot
mg<-rep("Mg", 17) # creating a vector for Mg
ti<-rep("Ti", 17) # creating a vector for Ti
a<-c(mg,ti) # combining the Group vectors
b<-c(Mg_data_absolute, Ti_data_absolute) # a vector of absolute values
absHVA<-cbind.data.frame(a,b) # creating a data frame of absolute values
# renaming the data frame columns
names(absHVA)[1]="GROUP"
names(absHVA)[2]="VALUES"
library(ggplot2)
# creating a data summary for violin plot
dataaa_summary<-function(absHVA){
mean<-mean(absHVA)
yminn<-mean-sd(absHVA)
ymaxx<-mean+sd(absHVA)
return(c(y=mean, ymin=yminn, ymax=ymaxx))
}
# the plott
violin<-(ggplot(data=absHVA, aes(x=GROUP,y=VALUES))
+geom_violin(trim = FALSE)
+geom_boxplot(width=0.1, fill="white")+stat_boxplot(geom = "errorbar",width=0.1)
+labs(x="Group", y="Absolute HVA"))
violin+theme_classic()+stat_summary(fun.data = dataaa_summary)
```

A.2 Properties of a folded normal RV

```
# generating a random variable
set.seed(110) # for reproducibility
#generating folded normal random variable
y<-abs(rnorm(100000, mean = 0, sd=1))

# Q-Q plot
library("car")
qqPlot(y, ylab = "y")
# standardizing a folded normal random variable
y_mean<-mean(y) # mean of y
y_variance<-var(y) # variance of y
#true mean of y
y_true_mean<-(sqrt(s1)* sqrt(2/pi) * exp(-m1^2/(2*s1))
+m1 * (1 - 2 * pnorm(-m1/sqrt(s1))))
# true variance of y
y_true_variance<-s1+m1^2-(y_true_mean)^2

#Histogram
# a distributional histogram for y
hist(y, col = "white", xlab="y",)
# standardized absolute values y_standardized<-(y-y_true_mean)/y_true_variance
# a distributional histogram for absolute standardized values
Histo<-hist(y_standardized, freq = FALSE, main = NULL, col="white")
lines(density(y_standardized), lwd=2)

#The resultant distribution for the difference of two folded normal RV
set.seed(111)
y_1<-abs(rnorm(10000, mean = 0, sd = 1)) # group 1 absolute random variable
set.seed(112)
y_2<-abs(rnorm(10000, mean = 0, sd = 1)) # group 2 absolute random variable
z<-y_2-y_1 # difference between y2 and y1
```

```
hist(z, freq = FALSE, main = NULL, col = "white")
lines(density(z), lwd=2)
```

A.3 Functions for the difference of two independent folded normal RV

```
# pdf
pdf_absdiff <- function(tvalue, mean_y1, meam_y2, sd) {
mean_y1_tidle <- (1 / sqrt(2)) * (mean_y1 - mean_y2) # rotated mean_y1
mean_y2_tidle <- (1 / sqrt(2)) * (mean_y1 + mean_y2) # rotated mean_y2
cy1min <- -tvalue / (sd * sqrt(2)) - mean_y1_tidle / sd
cy2min <- -tvalue / (sd * sqrt(2)) - mean_y2_tidle / sd
cy2plus <- tvalue / (sd * sqrt(2)) - mean_y2_tidle / sd
cy1plus <- tvalue / (sd * sqrt(2)) - mean_y1_tidle / sd
sol <- ifelse(
tvalue > 0,
(1 / (sd * sqrt(2))) * (
pnorm(cy2min) * dnorm(cy1min) - (1 - pnorm(cy1min)) * dnorm(cy2min) +
(1 - pnorm(cy2plus)) * dnorm(cy1plus) -
pnorm(cy1plus) * dnorm(cy2plus) +
dnorm(cy2min) + dnorm(cy2plus)
),
(1 / (sd * sqrt(2))) * (
pnorm(cy2plus) * dnorm(cy1min) + pnorm(cy1plus) * dnorm(cy1min) +
(1 - pnorm(cy2min)) * dnorm(cy1plus) +
(1 - pnorm(cy1min)) * dnorm(cy2plus)
)
)
return(sol)
}
```

```
# mean
mean_absnormal <- function(mean_y1, sd){
return(sd * sqrt(2/pi) * exp(-mean_y1^2/(2*sigma^2))
+ mean_y1 * (1 - 2 * pnorm(-mean_y1/sd)))
}
means_absdiff <- function(mean_y1, mean_y2, sd){
return(mean_absnormal(mean_y1, sd) - mean_absnormal(mean_y2, sd))
}

# Variance
variance_absdiff <- function(mean_y1, mean_y2, sd){
mean_absy1 <- mean_absnormal(mean_y1, sd)
mean_absy2 <- mean_absnormal(mean_y2, sd)
return(mean_absy1^2 + mean_absy2^2 + 2*sigma^2 - mean_y1^2 - mean_y2^2)
}

# cdf
cdf_absdiff <- function(tvalue, mean_y1, mean_y2, sigma) {
mean_y1_tidle <- (1 / sqrt(2)) * (mean_y1 - mean_y2) # rotated mean_x
mean_y2_tidle <- (1 / sqrt(2)) * (mean_y2 + mean_y2) # rotated mean_y
cy1min <- -tvalue / (sd * sqrt(2)) - mean_y1_tidle / sd
cy2min <- -tvalue / (sd * sqrt(2)) - mean_y2_tidle / sd
cy2plus <- tvalue / (sd * sqrt(2)) - mean_y2_tidle / sd
cy1plus <- tvalue / (sd * sqrt(2)) - mean_y1_tidle / sd
sol <- ifelse(
tvalue > 0,
(1 - pnorm(cy1min)) * pnorm(cy2min) + pnorm(cy1plus) * (1 - pnorm(cy2plus))
+pnorm(cy2plus) - pnorm(cy2min),
pnorm(cy1plus) * (1 - pnorm(cy2min)) + (1 - pnorm(cy1min)) * pnorm(cy2plus)
)
return(sol)
}
```

A.4 Application to real data

```
# Ratio of two chi-square RV
# chi square random variable
chi_Mg_data<-(Mg_data_absolute)^2
chi_Ti_data<-(Ti_data_absolute)^2
chi_Mg_mean<-mean(chi_Mg_data_diff) # mean of group 1
chi_Mg_var<-var(chi_Mg_data_diff) # variance of group 1
chi_Ti_mean<-mean(chi_Ti_data_diff) # mean of group 2
chi_Ti_var<-var(chi_Ti_data_diff) # variance of group 2
# variance test
f_test<-var.test(chi_Ti_data_diff, chi_Mg_data_diff,
alternative = "two.sided", conf.level = 0.95)
# extracting specific values
f_test$estimate
f_test$conf.int
f_test$p.value

# Bootstrap method
set.seed(202027)# for reproducibility
B <- 10000 # the number of bootstrap samples
# bootstrap samples
d1<-matrix( sample(Mg_data_difference, size = B*n1,
replace = TRUE), ncol = B, nrow = n1)
d2<-matrix( sample(Ti_data_difference, size = B*n2,
replace = TRUE), ncol = B, nrow = n2)
# check to make sure they are not empty!
d1[1:5,1:5]
d2[1:5,1:5]
#absolute difference of the bootstrap samples
y1<-abs(d1)
y2<-abs(d2)
#check if they are absolute values!
```

```
y1[1:5,1:5]
y2[1:5,1:5]
# calculating relevant statistics from bootstrap samples
# mean of the absolute bootstrap samples
y1_bar<-colMeans(y1)
y2_bar<-colMeans(y2)
y_bar_diff<-y2_bar-y1_bar # mean diff of the means of abs bootstrap samples
# empirical variances of the bootstrap samples
library(resample)
d1_var<-colVars(d1)
d2_var<-colVars(d2)
# variance of the absolute bootstrap samples
D1_varr<-colVars(y1)
D2_varr<-colVars(y2)
# variance ratio of the bootstrap samples and absolute bootstrap samples
d_var_ratio<-d2_var/d1_var
D_varr_ratio<-D2_varr/D1_varr
d_var_diff<-d2_var-d1_var #variance difference of the bootstrap samples
# the corrected means of the bootstrap samples
d1_bar<-colMeans(d1)
d2_bar<-colMeans(d2)
Dd1_bar<-y1_bar-(sqrt(d1_var)* sqrt(2/pi) * exp(-d1_bar^2/(2*d1_var)) +
d1_bar * (1 - 2 * pnorm(-d1_bar/sqrt(d1_var))))
Dd2_bar<-y2_bar-(sqrt(d2_var)* sqrt(2/pi) * exp(-d2_bar^2/(2*d2_var)) +
d2_bar * (1 - 2 * pnorm(-d2_bar/sqrt(d2_var))))
Dd_bar_diff<-Dd2_bar-Dd1_bar
# correlated mean assuming that the means of the bootstrap samples=0
Dstar1_bar<-y1_bar-(sqrt(d1_var)*sqrt(2/pi))
Dstar2_bar<-y2_bar-(sqrt(d2_var)*sqrt(2/pi))
Dstar_bar_diff<-Dstar2_bar-Dstar1_bar
# non-parametric confidence interval
quantile(y_bar_diff, probs=c(0.025, 0.975))
# parametric confidence interval
```

```
z=qnorm(0.05/2,lower.tail = F)
m<-mean(y_bar_diff) # mean
s<-sd(y_bar_diff) # sd
lcl.b<-m-z*s # upper limit
ucl.b<-m+z*s # lower limit
cw.b<-ucl.b-lcl.b # confidence width
```

plot for the difference of absolute values between group 1 and 2

```
# the difference of absolute values
diff<-Ti_data_absolute-Mg_data_absolute
hist(diff, freq = F, main = NULL, xlab = "abs(Ti) - abs(Mg)",
col = "white", breaks = 7)
lines(density(diff), lwd=2)
```

The difference of two chi-square distribution

library(fAsianOptions)# to load whittaker function
chi_diff<- ch_Ti_data-chi_Mg_data # The difference of 2 chi-square RV
# Whittaker function
W=whittakerW(x=chi_diff, kappa = (n1-n2)/4, mu=(4-n1-n2)/4)
# The pff of the difference of two chi square distribution
# distribution for Z>0
chi_dist_diff1<-function(Z){((2$^{(1-(n1-n2)/2)}$)/(gamma((n1-1)/2)))*
$Z^{(((n1+n2)/2)-2)}$*W*Z}
# distribution for Z<0
chi_dist_diff2<-function(D){(2$^{(1-(n1-n2)/2)}$)/(gamma((n2-1)/2))*
$(-Z)^{(((n1+n2)/2)-2)}$*W*(-Z)}
library(elliptic) # complex number package
library(pracma) # complex number package
integrates complex function
since chi_dist_diff is asymptotic in nature any interval chosen gives quantile
myintegrate(chi_dist_diff1, lower, upper) # upper quantile
myintegrate(chi_dist_diff2, lower, upper) # lower quantile