Umbilicocerebral ratio: potential implications of inversing the cerebroplacental ratio

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INTRODUCTION

Increased cerebral blood flow in response to hypoxia is a well-defined regulatory mechanism in humans[1]. Fetuses show a similar response to hypoxia by reducing the impedance to flow in the cerebral arteries[2]. Investigation of such an effect in growth-restricted fetuses is commonly performed using the middle cerebral artery Doppler. However, the stand-alone accuracy of middle cerebral artery Doppler for the prediction of adverse outcomes appears limited in late-onset fetal growth restriction and the addition of umbilical artery Doppler improves this accuracy[3]. The ratio of middle-cerebral artery pulsatility index to umbilical artery pulsatility index is called the cerebroplacental ratio (CPR) and has been associated with increased rates of intrapartum complications in both growth restricted and appropriately grown fetuses[4-6].

More recently, a secondary analysis of the TRUFFLE (Trial of Randomized Umbilical and Fetal Flow in Europe) study has suggested that the umbilicocerebral ratio (UCR), which is calculated by inversing the CPR, is a better predictor of survival without neurodevelopmental impairment at two years of age in fetuses with early-onset growth restriction[7]. The conclusion was drawn from a logistic regression analysis with the following results. The odds of neurodevelopmental impairment was associated with UCR Z-score at enrolment (odds ratio: 0.88, 95% confidence interval: 0.78-0.99, p=0.04) while the CPR Z-score at enrolment showed an insignificant association (odds ratio: 1.58, 95% confidence interval: 0.92-2.71, p=0.10). The last UCR and CPR values recorded before delivery or the delta of two measurements did not show a significant relationship. The Z-scores for UCR were calculated using ranges reported in a cross-sectional study[8]. Acharya *et al.* have recently published longitudinal reference ranges for UCR and referred to the better performance of UCR compared to CPR without specifying the context[9]. There is a substantive published literature on CPR and its potential benefits and shortcomings. Moreover, the adoption of CPR into clinical practice has been slow so far, which is likely due to the controversy about its clinical utility[10]. Before committing to further research on UCR, we believe that it is important to discuss potential merits of inversing CPR. In this opinion piece, we will investigate the potential implications of reversing the CPR. We used a cohort of near term 7758 appropriately grown and 1405 small for gestational age fetuses to demonstrate the potential effects of inversing the ratio.

The effect of inversion on the distribution of ratios

In fetuses near-term the CPR has a normal distribution with light tails (Figure 1a). The symmetric nature of the distribution means that the values above and below the mean are distributed evenly, as are the number of fetuses above and below the critical thresholds (i.e. 95% confidence intervals). The light tails also support the assertion that the CPR has a normal distribution in near-term fetuses with a percentage of outliers within expected values. Figure 1a demonstrates the histogram of CPR of 7758 appropriately grown fetuses with fitted density plots. Visual inspection suggests a symmetrical, Gaussian distribution and the quantile plot confirms this assumption (Figure 1a). Inversing the ratio has a major impact on the distribution of the variable. When we calculated the UCR, the distribution changes to a highly skewed and heavy tail distribution (Figure 1b). Visual inspection of the UCR histogram reveals a right-skewed distribution and heavy tails (Figure 1b). The quantile plot also demonstrates that the distribution is non-normal. Although the reference ranges recently published by Acharya et al. took the distribution of UCR into account, the older study by Arduini et al. did not transform the UCR in their regression analyses[8,9]. In these circumstances, the residuals are likely to be non-normally distributed; this would cause biased estimation of the coefficients. Figures 2a and 2b present the distribution of both CPR and UCR in 1405 small for gestational age fetuses at the same gestation, respectively. We note the normal distribution of CPR (Figure 2a) and skewed distribution of UCR (Figure 2b)

Interpretation of standardized measurements with different distributions

Z-scores are mostly used to describe variables from a normal distribution. Although it is possible to use Z-scores to describe non-normal distributions as long as they are symmetrical, it is less common. In a symmetrical distribution, the number of patients above or below a certain ±Z score is similar. Moreover, the numbers of outliers are within expected ranges in a light-tailed distribution. The use of Z-scores for heavily skewed distributions is discouraged due to challenges with its interpretation above and below the mean. Figure 3 demonstrates the density plot of both CPR and UCR Z-scores from a population of small-for-gestational age fetuses with similar distribution characteristics to their raw values. Furthermore, the same pattern was seen in preterm small-for-gestational age fetuses (below

32 weeks' gestation) as well (Figure 4). CPR has symmetric distribution, while UCR has a skewed distribution. This has been confirmed in a recent publication.

Similar to the raw values of UCR, the Z scores also have a heavy-tailed, positively skewed distribution and the number of outliers is increased compared to CPR Z-scores (Table 1). A similar effect is also observed in the values reported by Stampalija et al [7]. The upper interquantile range (Quartile 3 – Quartile 2) of CPR Z-score is 0.4 compared to 2.5 for UCR Z-score, suggesting a skewed distribution. Moreover, the Euclidian distance between Z-scores corresponding to the same patients also increase at the abnormal end of the spectrum when we inverse the ratio. It is important to appreciate that the interpretation of Z-scores changes with the inversion, making a one-to-one comparison of CPR and UCR using Z-scores problematic. In addition to problems with interpretation, these changes also create difficulties with the statistical analysis[11].

The impact of outliers and variable distribution on logistic regression analyses

Logistic regression is one the most common forms of statictial analysis due to the binary nature of most studied outcomes in our field. Although logistic regression does not make any assumptions about the distribution of a predictive variable, there are some assumptions of logistic regression, which are often overlooked. Whenever we include a continuous variable in a logistic regression model such as CPR, it is best to check whether linearity to the log odds assumption holds. While linear regression assumes a linear relationship between the predictor and the outcome variable, logistic regression assumes linearity of the log odds; this assumption can be checked with the Box-Tidwell test. Violation of linearity to the log odds assumption will cause the estimate not to be reliable across the range of tested continuous variable. Moreover, the estimates in logistic regression can be affected by the outliers, given that they are shown to be influential[12,13]. The increased number of outliers and the change of distribution of UCR can cause inaccuracies in the results of the logistic regression.

We performed the Box-Tidwell test for a logistic regression model predicting emergency cesarean section with CPR and UCR in a population of small-for-gestational age fetuses. Similar to previously published studies, the CPR model confirmed that the linearity to the log odds assumption holds ($p=0.839$)[4]. However, the UCR model violated the assumption

(p=0.022), indicating that UCR should not be incorporated into the model on a continuous scale. When we categorized the two variables using the same critical threshold (Z score -1.644 and 1.644 for CPR and UCR, respectively), the resulting model accuracies were 78.9% (95% confidence interval: 76.6 to 0.81) and 76.2% (95% confidence interval: 73.8 to 78.4%) for the CPR and UCR models, respectively. The Bayesian analysis revealed a high posterior probability (>99.9%) of a slight drop in accuracy (mean: 2.7%) with the use of UCR Z-score. The increased number of outliers in UCR is likely to be the cause of such a change in accuracy. Given the fact that the two variables contain essentially the same information, any change in statistical significance or model accuracies are likely to be either Type I or Type II errors, depending on the design and studied outcome. Moreover, modelling of UCR requires special attention due to its distribution structure and problems with interpretation of standardized measures.

Conclusion

Inversing the CPR has a major effect on its distribution and interpretation of the resulting UCR variable. The analysis of UCR and its comparison with CPR have statistical caveats to consider. We see no convincing reason to pursue the use of UCR over CPR, given the substantial existing literature on CPR and the statistical challenges arising from the use of UCR.

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Figure legends

Figure 1. The distribution histogram and corresponding quantile plots of cerebroplacental (1a, 1b) and umbilicocerebral ratio (1c, 1d) of 7758 appropriate for gestational age fetuses above 35 weeks' gestation. The distribution of cerebroplacental ratio is symmetrical with light tails (skewness: 0.55, kurtosis: 0.28) and the quantile plot suggest a normal distribution. The umbilicocerebral ratio of the same population shows a heavily skewed distribution with heavy tails (skewness: 1.38, kurtosis: 4.72). The quantile plot suggests a non-normal heavily skewed distribution.

Figure 2. The distribution histogram and corresponding quantile plots of cerebroplacental (2a, 2b) and umbilicocerebral ratio (2c, 2d) of 1405 small for gestational age fetuses above 35 weeks' gestation.

Figure 3. The density plots of cerebroplacental ratio and umbilicocerebral ratio Z-scores of 1405 small-for-gestational age fetuses. The dashed black and grey lines demonstrate the critical thresholds (Z-scores -1.96 and 1.96, respectively). Inversing the cerebroplacental ratio results increases the number of outliers.

Figure 4. The distribution histogram and corresponding quantile plots of cerebroplacental (4a, 4b) and umbilicocerebral ratio (4c, 5d) of 288 small for gestational age preterm (<32 weeks' gestation) fetuses.

Table 1. The effect of inversing the cerebroplacental ratio on the number of women above or below the critical thresholds in a population of 1405 small-for-gestational age near-term and 288 preterm fetuses.

Inversing the ratio significantly changes the number of women past the critical thresholds (p value < $1x10^{-12}$). The skewed distribution of umbilicocerebral ratio changes the interpretation of Z-scores and makes direct comparison of umbilicocerebral and cerebroplacental ratio impossible. Z-scores were calculated using linear equations obtained from a population of 7758 appropriate for gestational age fetuses for near-term fetuses.

Near term	**UCR Z-score > 1.96**	**UCR Z-score < 1.96**	**p value***
Near term			
CPR Z-score < -1.96	134 (9.5)	0 (0.0)	<.001
CPR Z-score > -1.96	71 (5.1)	1200 (85.4)	
<32 weeks' gestation			
CPR Z-score < -1.96	12 (4.2)	0 (0.0)	<.001
CPR Z-score > -1.96	68 (23.6)	208 (72.2)	

The values represent the number (%)

*McNemar's chi-squared test

CPR: cerebroplacental ratio, UCR: umbilicocerebral ratio

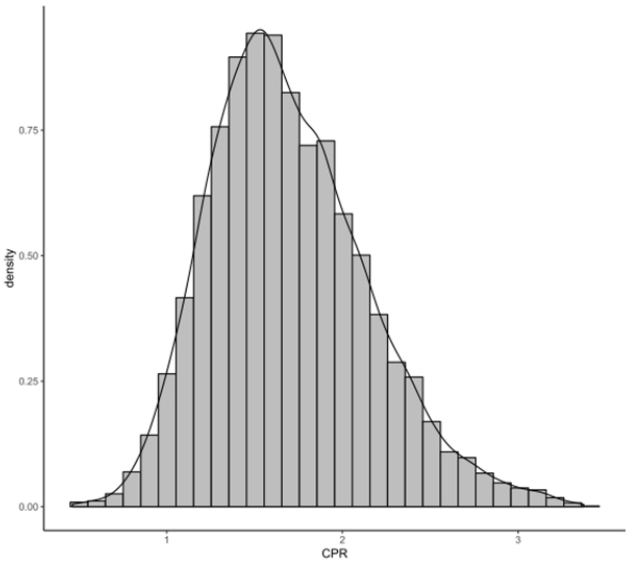
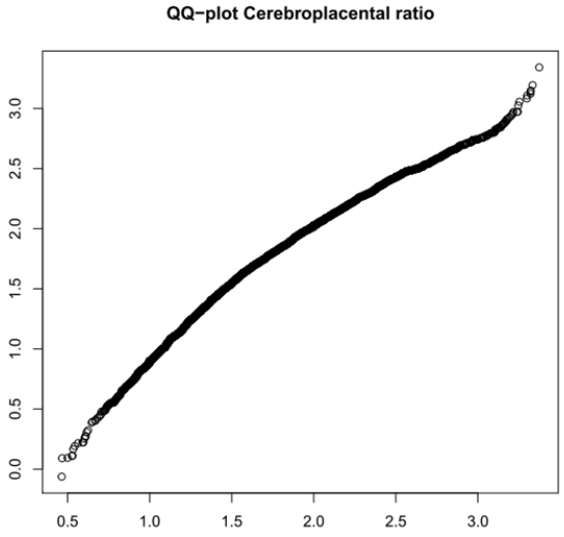


Figure 1a



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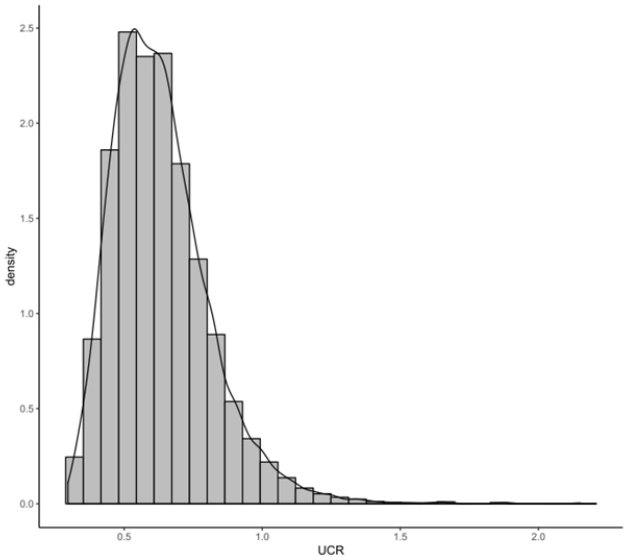


Figure 1c

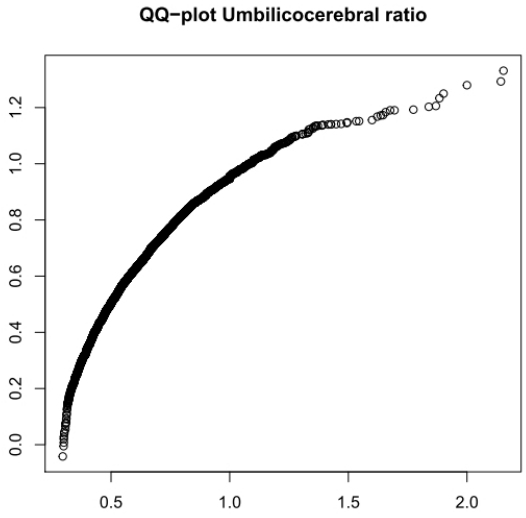


Figure 1d

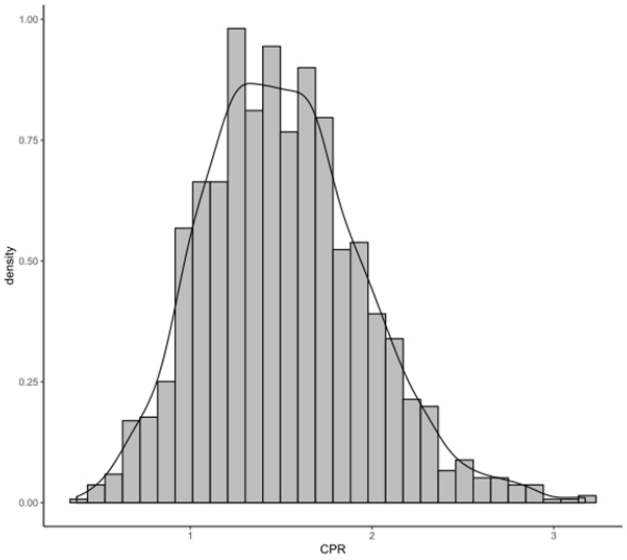


Figure 2a

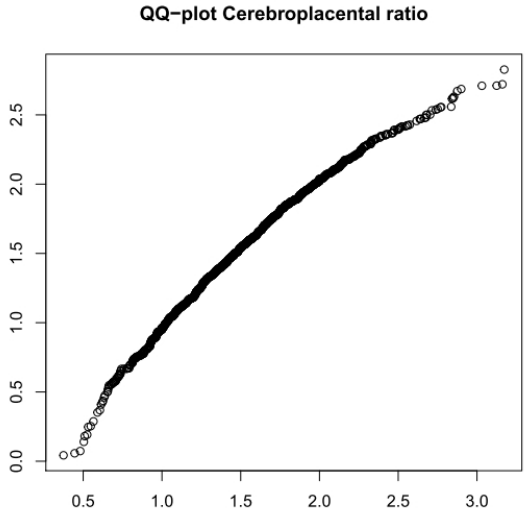
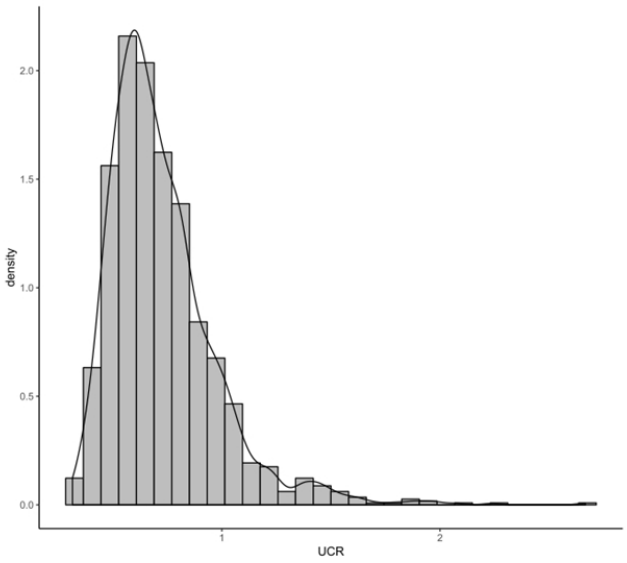


Figure 2b



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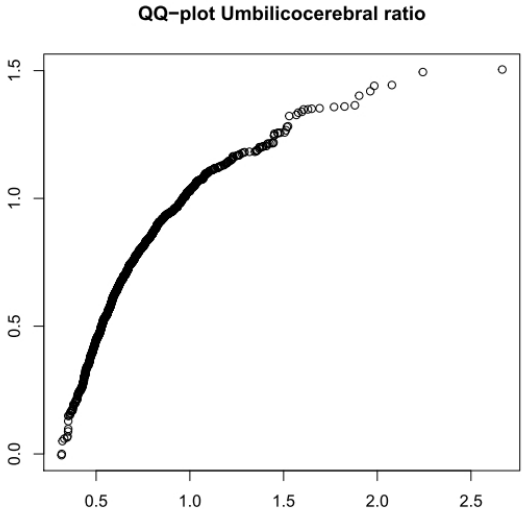

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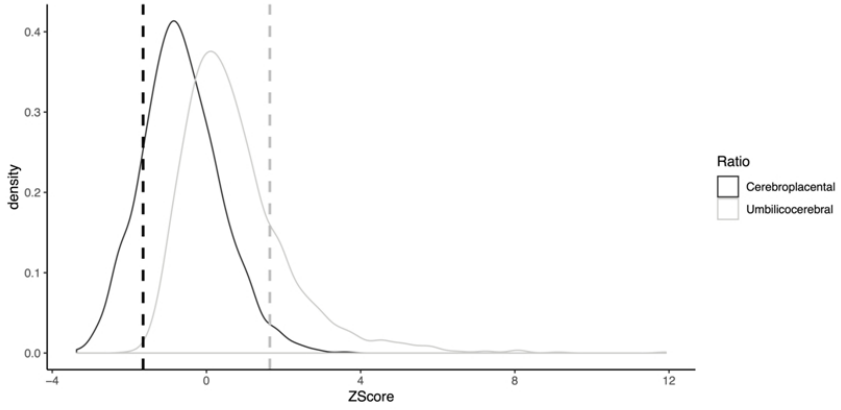


Figure 3

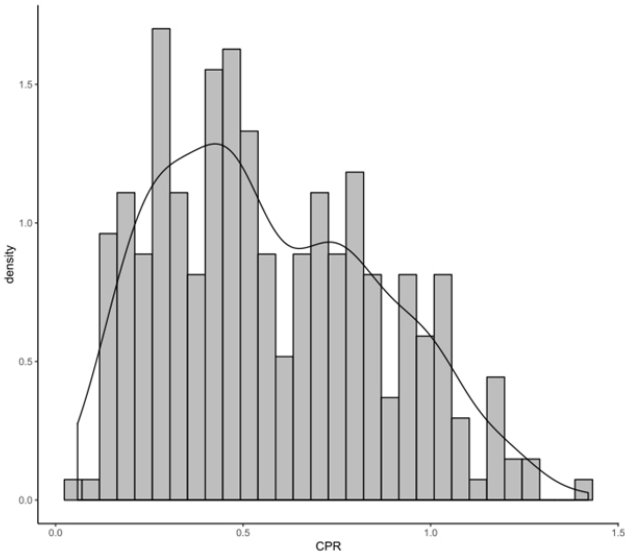


Figure 4a

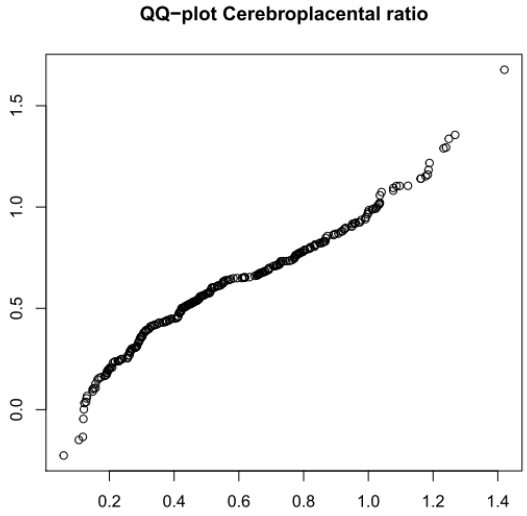
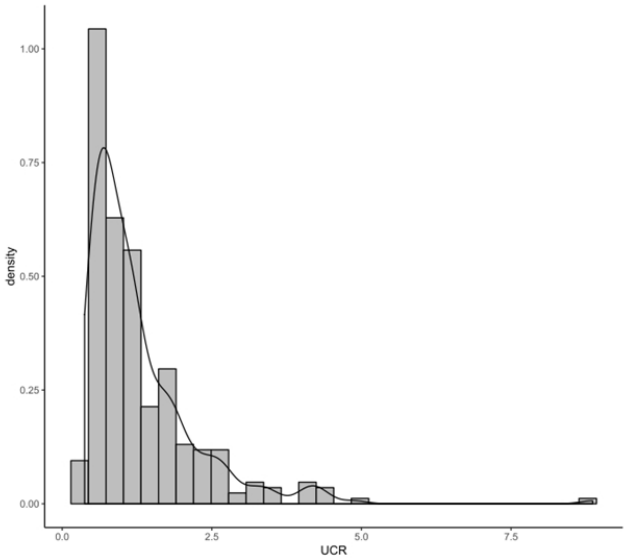


Figure 4b



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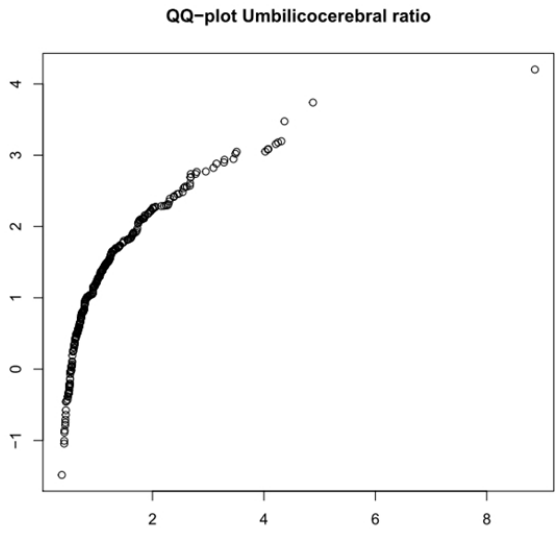

Figure 4d