Correlation of Transcutaneous Bilirubin & Total Serum Bilirubin in Neonates

INTRODUCTION

After being born many babies nearly 50 percent to 60 percent of full-term babies and 80 percent of those born prematurely may develop Jaundice, a yellowing of skin color, due to an excess buildup of the chemical Bilirubin . During pregnancy, the mother's liver removes bilirubin for the baby, but after birth the baby's liver may not be functioning fully to remove the excess bilirubin, causing hyperbilirubin or jaundice. If Jaundice is not detected early enough or not treated at all it lead to permanent damage from a condition called kernicterus. Kernicterus is a type of brain damage that is a result from the high levels of bilirubin in a baby's blood. The damage caused to the brain can cause deafness, delayed development or a form of cerebral palsy.

MOTIVATION

Traditionally bilirubin levels are measured by Total Serum Bilirubin (TSB) via periodic blood samples which may be taken every hour using the heel stick method which is painful experience for the newborn and stressful parents. Heel sticks also require multiple heating of the heel to increase blood flow in the area and repeated heel sticks can cause bruising or worse. As the heel stick method if done improperly or done too much it can cause difficulties walking later in life. In addition, this method of testing and retesting is a time consuming process, which delays the care of patients causing undue stress to newborns and parents. However a less intrusive and cost effective method is to use a handheld device called the jaundice meter such as the Konica Minolta JM-103 that measures Trans-Cutaneous Bilirubin (TCB) via a light. From previous studies TCB has been shown to be a reliable alternative to TSB sampling and a consistent method

to monitor and identify newborns that are at risk of developing jaundice.

ISSUES TO ADDRESS

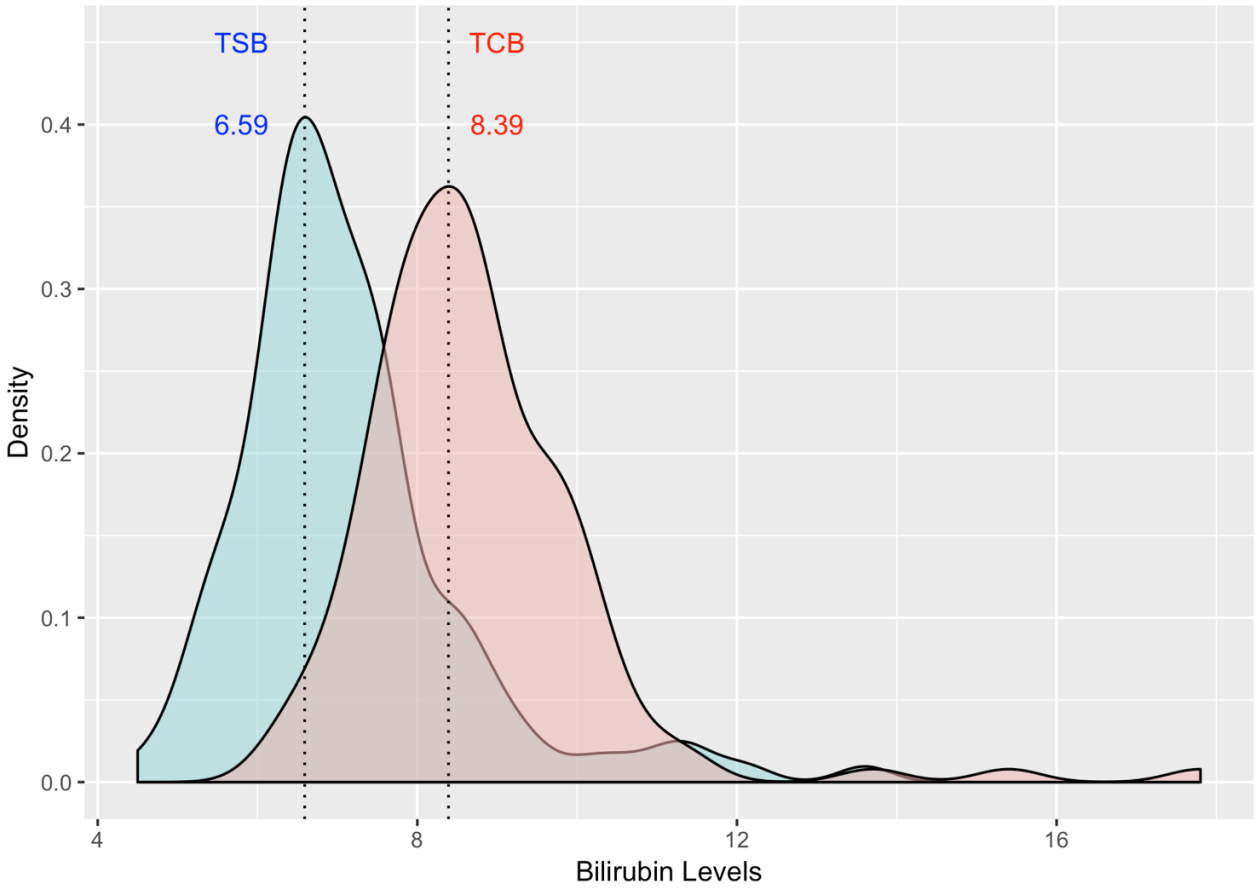
1. Is TCB correlated to TSB, If so to what extent and is TCB measurements an acceptable method for detecting hyperbilirubinemia over TSB sampling methods.

2. Our the TSB & TCB levels in neonates correlated to birth weight or gender of the baby.

DATA COLLECTION

The data was collected from 126 neonates born at Riverside County Regional Medical Center between January 1st and June 30th 2014 and who also met the inclusion criteria. The criteria for the study is that the baby was born at term, greater than 36 and 42 weeks of gestation. TSB & TCB were both measured after the first day of life thus at the 24 hour mark after birth.

VISULIZATION OF TSB & TCB



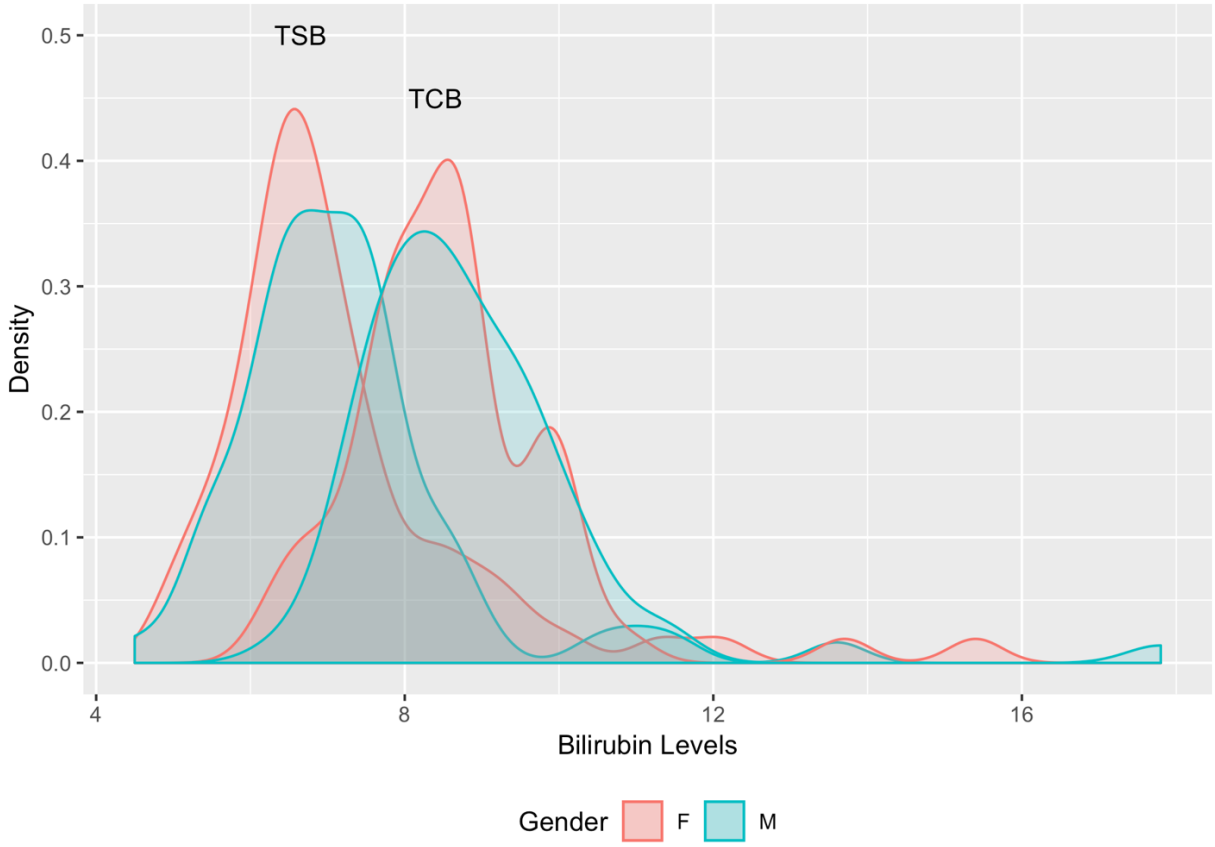
Two Sample Paired T-Test

Test statistic	df	P value	Alternative hypothesis
-17.56	125	1.509e-35 * * *	two.sided

Kolmogorov Smirnov Test

Test statistic	P value	Alternative hypothesis
0.5873	0 * * *	two-sided

From the density plots TSB & TCB appear to have different distributions with different centers, the two sample paired t-test confirms this along with the Kolmogorov Simonov test.



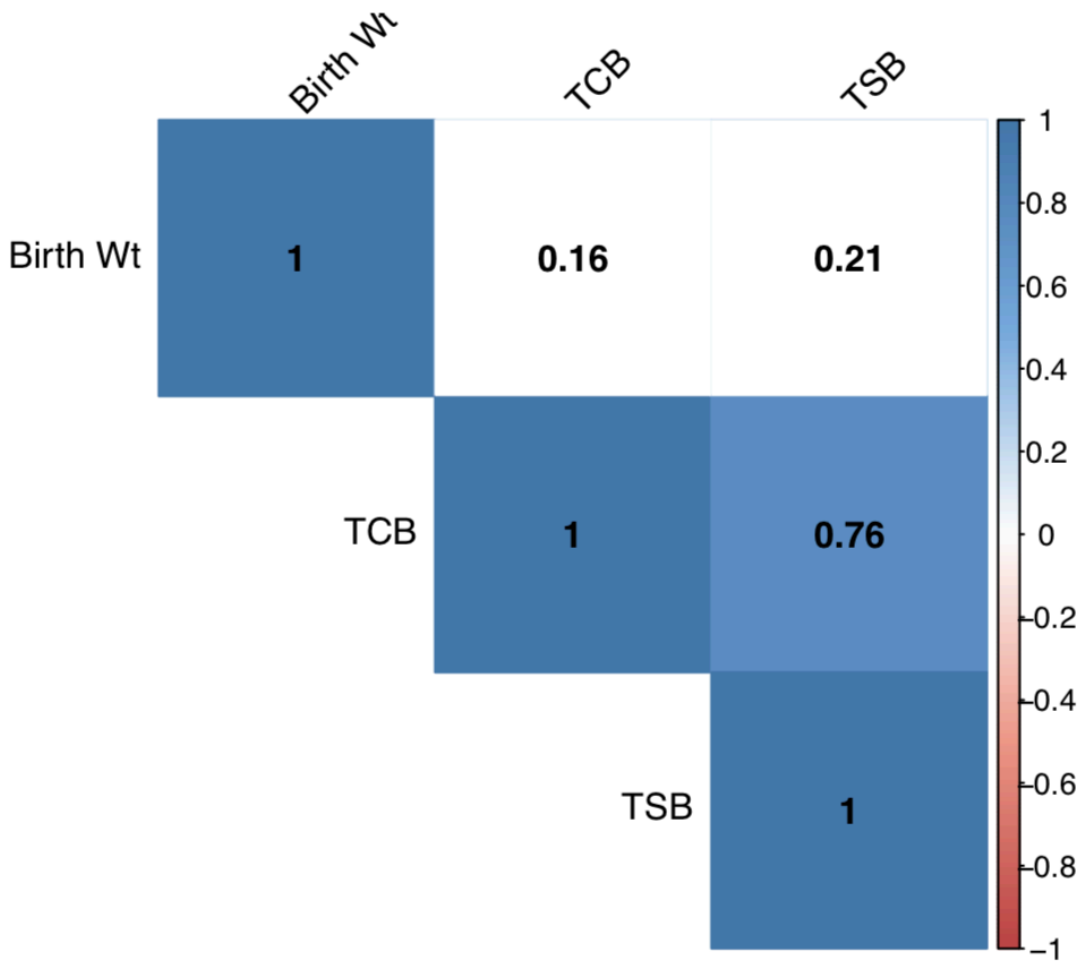
T-Test: Male TCB & Female TCB

Test statistic	df	P value	Alternative hypothesis	mean of x	mean of y
0.5025	123.3	0.6162	two.sided	8.802	8.665

T-Test: Male TSB & Female TSB

Test statistic	df	P value	Alternative hypothesis	mean of x	mean of y
0.6174	123.8	0.5381	two.sided	7.217	7.058

CORRELATION PLOT



TSB & TCB

Test statistic	df	P value	Alternative hypothesis	cor
13.18	124	2.498e-25 * * *	two.sided	0.7637

TSB & Birth Weight

Test statistic	df	P value	Alternative hypothesis	cor
2.339	124	0.02093 *	two.sided	0.2056

TCB & Birth Weight

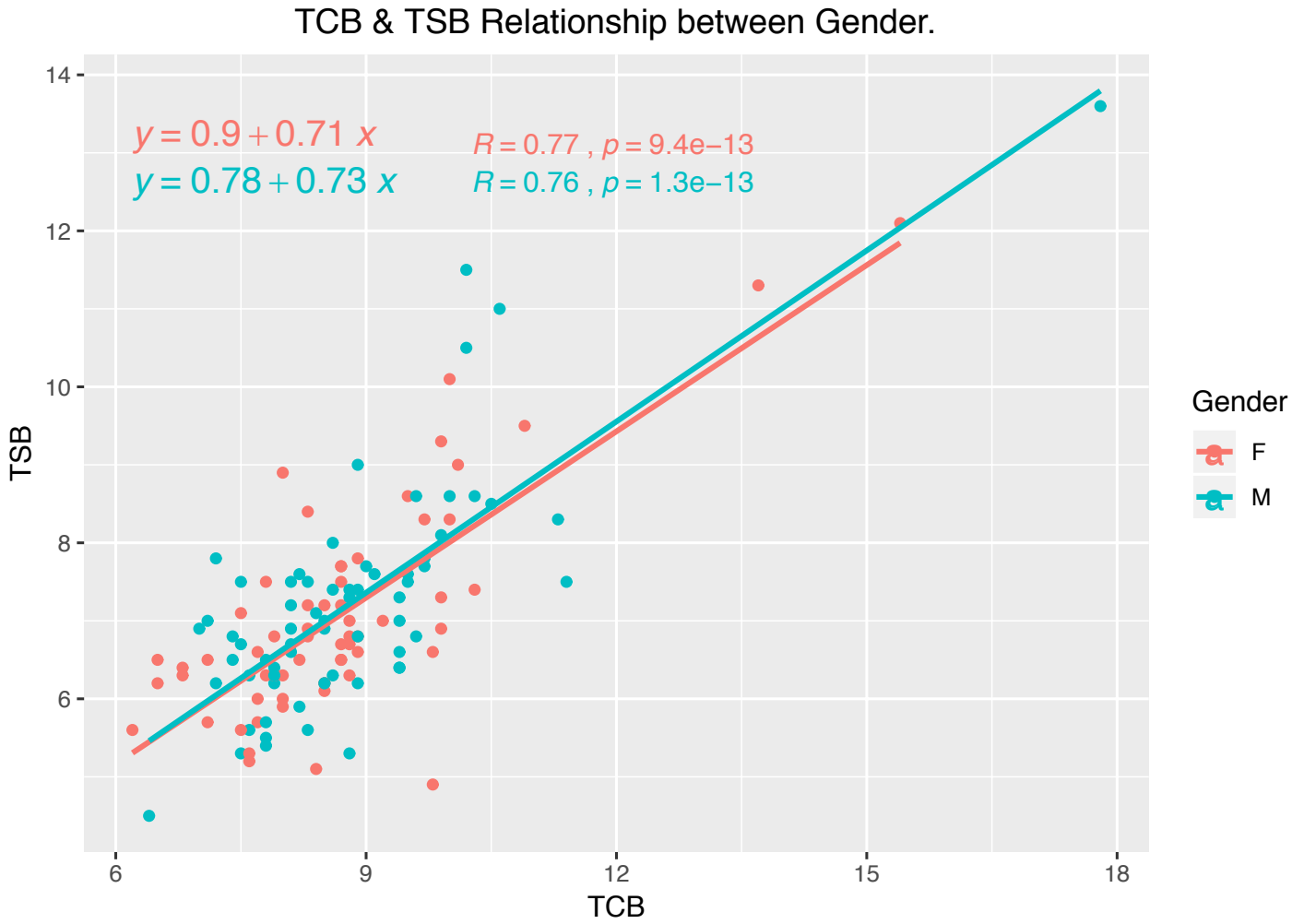
Test statistic	df	P value	Alternative hypothesis	cor
1.791	124	0.07574	two.sided	0.1588

The correlation plot shows that TCB & TCB have a strong positive linear relationship with r = 0.76, however birth weight has very low relationship with both TSB & TCB.

STATISTICAL MODEL

To address both issues as stated above we will use a simple linear model as we want to use TCB levels as an alternative to predict TSB levels. For example the full model will follow the form:

TCB = TSB + Birth Weight + Gender


TCB & TSB Relationship between Gender.
y = 0.9 + 0.71 x
y = 0.78 + 0.73 x
R = 0.77 , p = 9.4e−13
R = 0.76 , p = 1.3e−13
TSB
TCB
Gender
F
M
14
12
10
8
6
6
9
12
15
18

Full Model

```
Call:
glm(formula = TSB ~ TCB + `Birth Wt` + Gender, family = gaussian(),
    data = T_Data)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-2.8784  -0.6590  -0.0361   0.5471   3.1984

Coefficients:
              Estimate Std. Error t value Pr(>|t|)
(Intercept) -0.1406109  0.8198483  -0.172    0.864
TCB          0.7092992  0.0555158  12.777   <2e-16 ***
`Birth Wt`   0.0003242  0.0002252   1.440    0.153
GenderM      0.0287057  0.1676977   0.171    0.864
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for gaussian family taken to be 0.867408)

    Null deviance: 258.55  on 125  degrees of freedom
Residual deviance: 105.82  on 122  degrees of freedom
AIC: 345.58
```

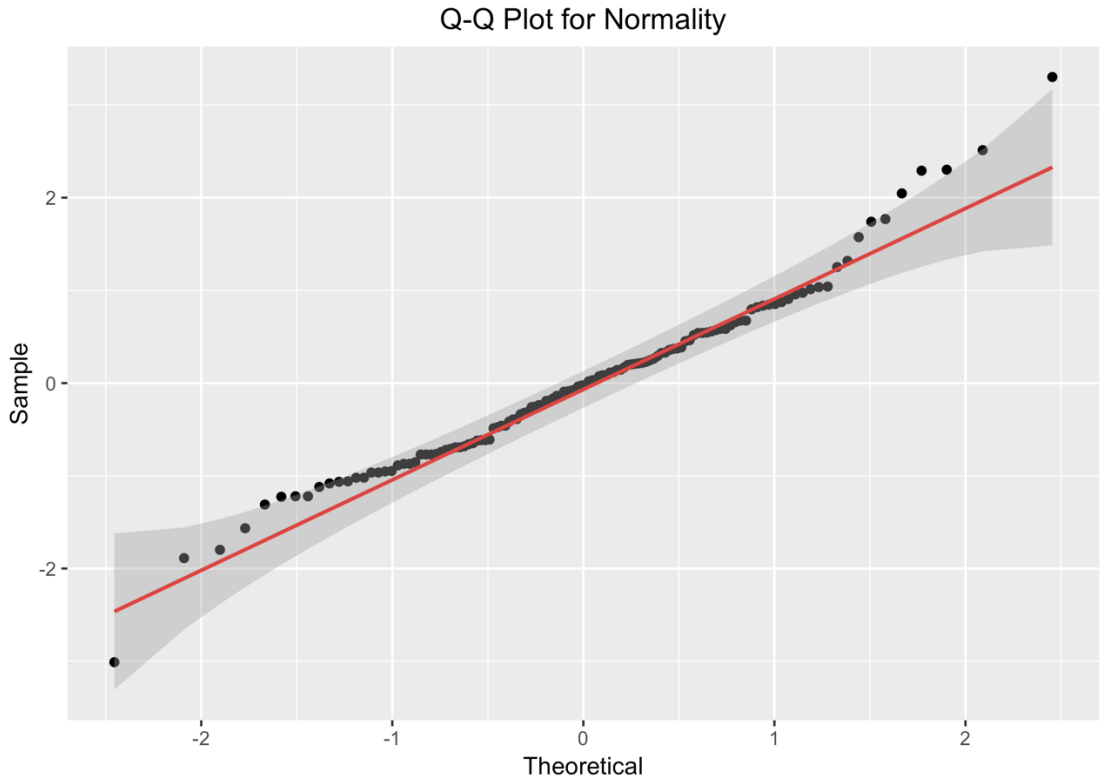
Once fitting the full model TSB is the only significant term in the model, but birth weight and gender are not significant terms in the model. Thus I removed both birth weight and gender from the model and refit the model in the following form:

TCB ~ TSB

```
Call:
glm(formula = TSB ~ TCB, family = gaussian(), data = T_Data)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-3.0097  -0.6763  -0.0230   0.5410   3.3013

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  0.82897    0.48625   1.705   0.0907 .
TCB          0.72252    0.05484  13.175   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for gaussian family taken to be 0.8688208)

    Null deviance: 258.55  on 125  degrees of freedom
Residual deviance: 107.73  on 124  degrees of freedom
AIC: 343.84
```

The model still shows that TCB is significant, however the intercept of the model is insignificant. Despite these cause for concern we must check the multiple assumptions of the model, such as normality of the errors and equal variance. Let us first check the normality assumption.

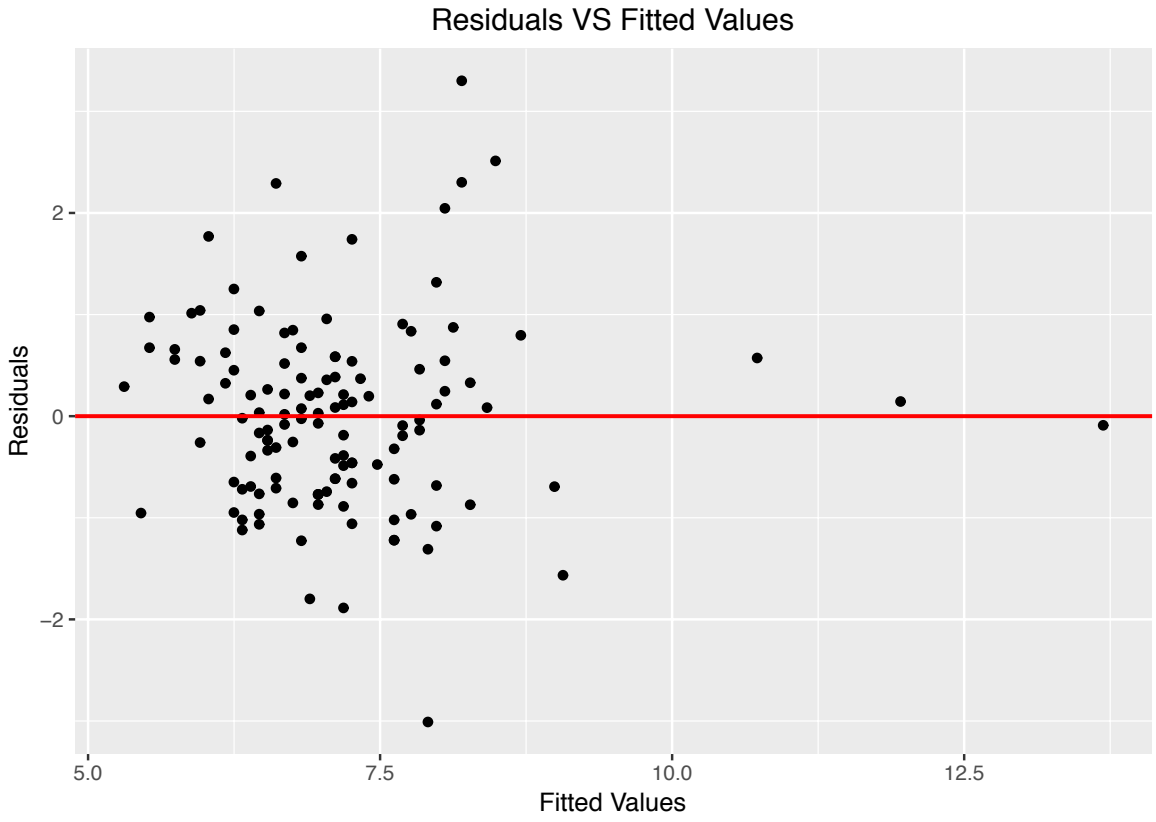
Normality Assumption



Test statistic	P value
0.972	0.01023 *

At alpha = 0.05 we have significant evidence to conclude that the errors for model 1 are not normally distributed as also seen in the Q-Q plot as points on the right tail begin to fall beyond the 95% confidence bands.

Equal Variance Assumption



Test statistic	df	P value
1.933	1	0.1644

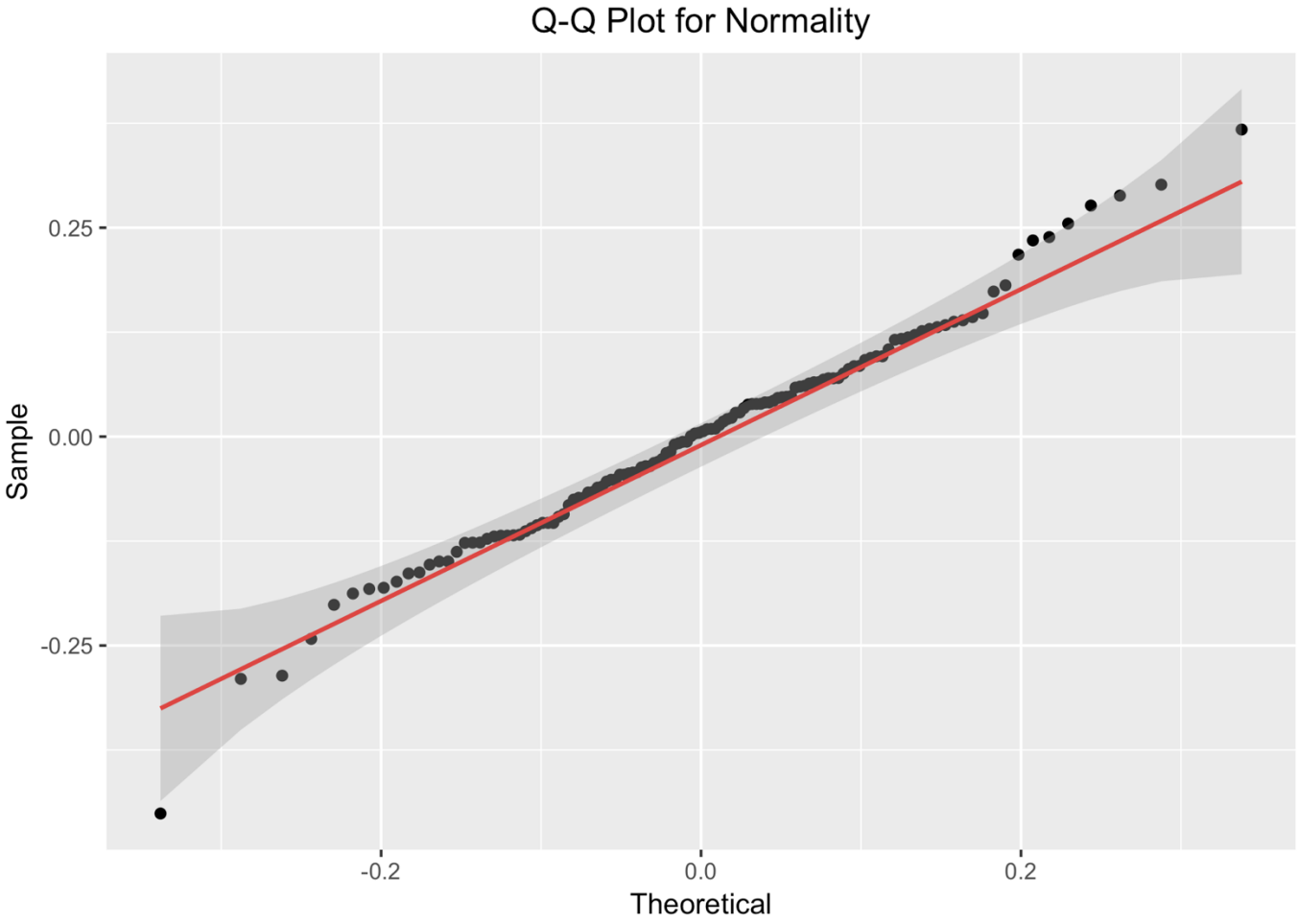
The equal variance assumption at alpha = 0.05 is satisfied, however the equality assumption was violated thus in the following model I apply a log transformation to the response variable TSB to solve the normality violation.

Log(TSB) ~ TCB

```
Call:
glm(formula = log(TSB) ~ TCB, family = gaussian(), data = T_Data)

Deviance Residuals:
     Min        1Q    Median        3Q       Max
-0.45105  -0.09013   0.00546   0.07004   0.36746

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  1.19254    0.06694   17.82   <2e-16 ***
TCB          0.08650    0.00755   11.46   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for gaussian family taken to be 0.01646546)

    Null deviance: 4.2035  on 125  degrees of freedom
Residual deviance: 2.0417  on 124  degrees of freedom
AIC: -155.86
```

After fitting the new model with a log transformation to TSB both the intercept and TCB become significant in the model. The next step is to check if the model is valid and whether or not the log transformation had resolved the normality violation in the previous model.

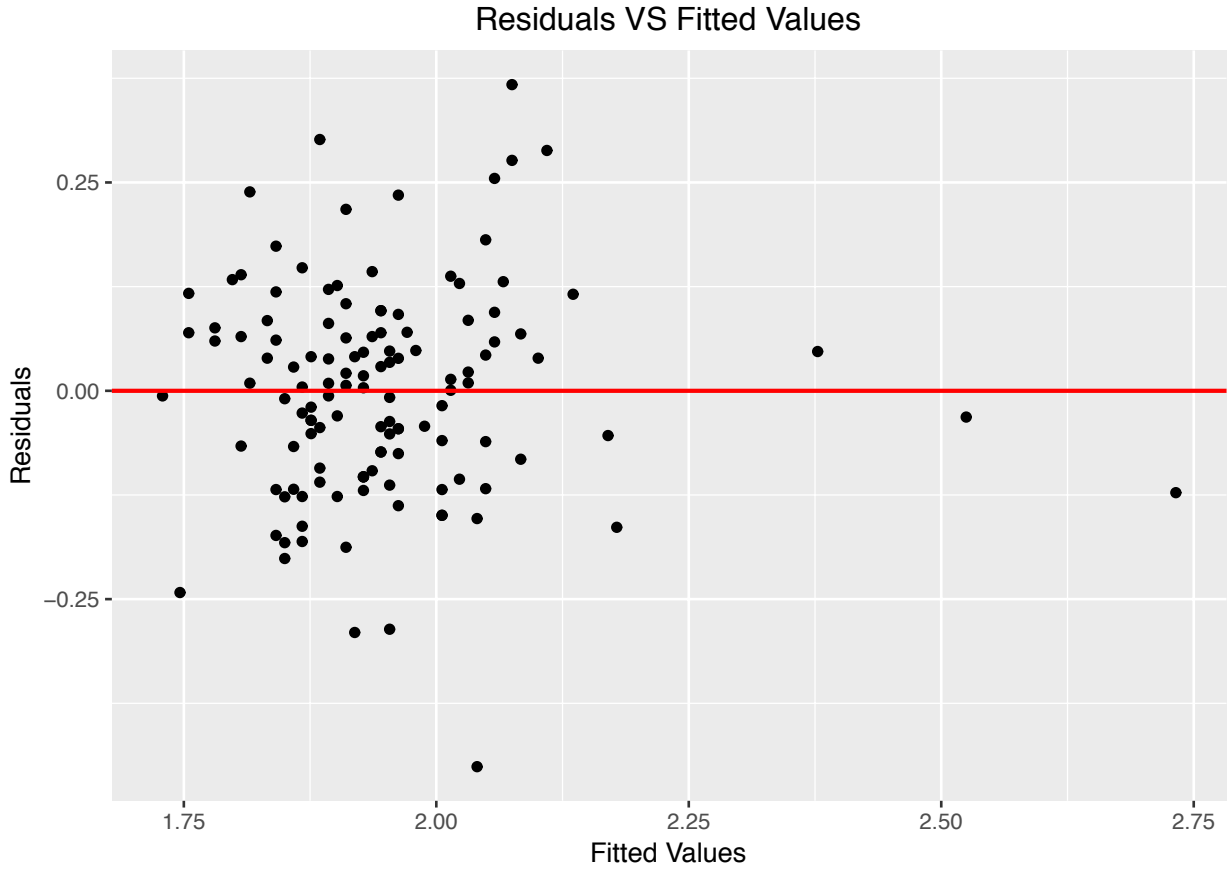
Normality Assumption



Test statistic	P value
0.987	0.2736

After applying the log transformation it indeed resolved the issue of normality of our errors, next we go ahead and check the equal variance assumption.

Equal Variance Assumption



Test statistic	df	P value
0.6207	1	0.4308

Applying the log transformation to TSB also satisfies the equal variance assumption. Thus the model above is a valid model and can be used to predict TSB levels reliably using TCB as the independent variable. Next we perform a few model comparisons to evaluate the improvement between the two models.

10 FOLD CROSS VALIDATION

Model 2: TSB ~ TCB

- Delta: 0.8774399 0.8762413

Model 3: log(TSB) ~ TCB

- Delta: 0.01674727 0.01671932

```
Analysis of Deviance Table

Model 1: log(TSB) ~ TCB
Model 2: log(TSB) ~ TCB + `Birth Wt` + Gender
  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
1       124     2.0417
2       122     2.0121  2 0.029593   0.4077
```

Insignificant

Thus the reduced model performs better than than the full model.

CONCLUSION

Let's first address the first issue of testing the strength of correlation between TSB, TCB, birth weight, and gender the most significantly correlated variables are TSB and TCB with a Pearson correlation coefficient of r = 0.76. While birth weight & TSB have a weak correlation of r = 0.21 and birth weight & TCB fair no better as it has a weaker correlation of r = 0.16. We then build a full model of the form TSB ~ TCB + Birth Weight + Gender, when checking what predictor variables are significant in the model TCB was the only significant variable. Next we remove birth weight and gender from the model due these variables not contributing anything to the model and refit the model with TSB ~ TCB. Once we checked the model's adequacy the normality assumption fails and the equal variance assumption is satisfied. To resolve the issue of non-normality we apply a log transformation to the response variable TSB and refit the model with the form log(TSB) ~ TCB. When checking the assumptions of the new model both the normality and equal variance assumptions are satisfied and the model is valid for us to use in prediction. Comparing the original model with the log transformed model using 10 fold cross validation the original model has a delta of 0.8762 and the transformed model has a delta of 0.0167, a significant improvement in model performance. The Akaike information criterion or AIC also shows major model improvements from 343.84 to -115.86. Thus TCB is a reliable more cost effective and less intrusive method of monitoring bilirubin levels in newborns.