8-Modelling

Description of model development.

0.1 Univariable association of candidate predictors with EOS

Below is a univariable logistic regression showing the univariable association between each candidate predictor and the outcome of EOS. The results are pooled across all imputed datasets.

N.B. To make interpretation easier, birth weight has been converted to kilograms, respiratory rate and heart rate have been divided by 5 (i.e. 5 breaths per minute), and "activity" has been collapsed into "alert", "lethargic", or "other".

```
## # A tibble: 17 x 7
##    predictor              beta    SE    OR   LCL   UCL     p
##    <fct>                 <dbl> <dbl> <dbl> <dbl> <dbl> <dbl>
##  1 pi_gest               0.067 0.026 1.07  1.02   1.12 0.009
##  2 et_bw                 0.131 0.087 1.14  0.961  1.35 0.133
##  3 oh_matfeveryes        1.79  0.544 5.99  2.06  17.4  0.001
##  4 oh_offliquoryes       0.707 0.208 2.03  1.35   3.05 0.001
##  5 co_promyes            0.391 0.173 1.48  1.05   2.08 0.024
##  6 et_gruntyes           0.203 0.132 1.23  0.945  1.59 0.126
##  7 et_rr                 0.093 0.022 1.10  1.05   1.14 0
##  8 et_hr                 0.047 0.019 1.05  1.01   1.09 0.012
##  9 et_temp               0.886 0.087 2.42  2.04   2.88 0
## 10 oe_activitylethargic  0.395 0.162 1.48  1.08   2.04 0.015
## 11 oe_activityother      1.05  0.25  2.86  1.75   4.67 0
## 12 oe_nasalflareyes      0.29  0.126 1.34  1.04   1.71 0.021
## 13 oe_retractionsyes     0.417 0.124 1.52  1.19   1.93 0.001
## 14 oe_gruntyes           0.346 0.155 1.41  1.04   1.92 0.025
## 15 oe_wobmild           -0.207 0.197 0.813 0.552  1.20 0.293
## 16 oe_wobmoderate        0.345 0.146 1.41  1.06   1.88 0.018
## 17 oe_wobsevere          0.674 0.217 1.96  1.28   3.00 0.002
```

0.2 Model selection

0.2.1 Randomly select a single imputed dataset

To facilitate comparison between models, we randomly select a single imputed dataset (from the 40 imputations) and use this imputation throughout model selection.

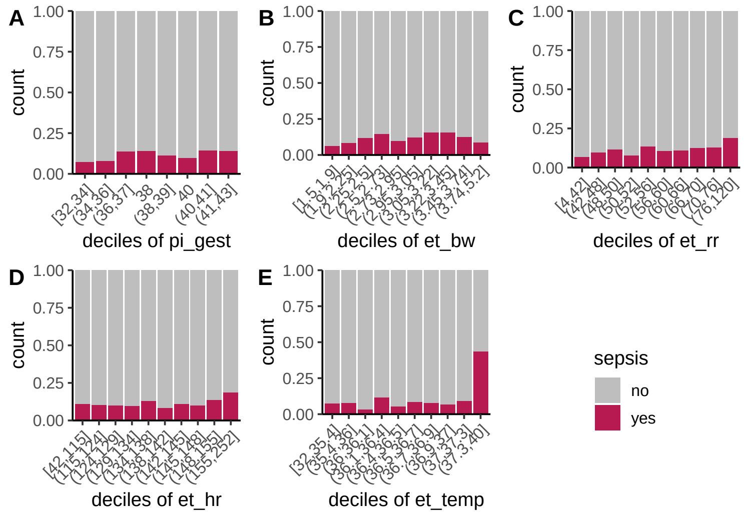
```r
set.seed(37)
rand <- floor(runif(1, min = 1, max = 30))
rand
```

```
## [1] 16
```

```r
si <- as_tibble(complete(imp, rand))
```

0.2.2 Assess linearity assumption

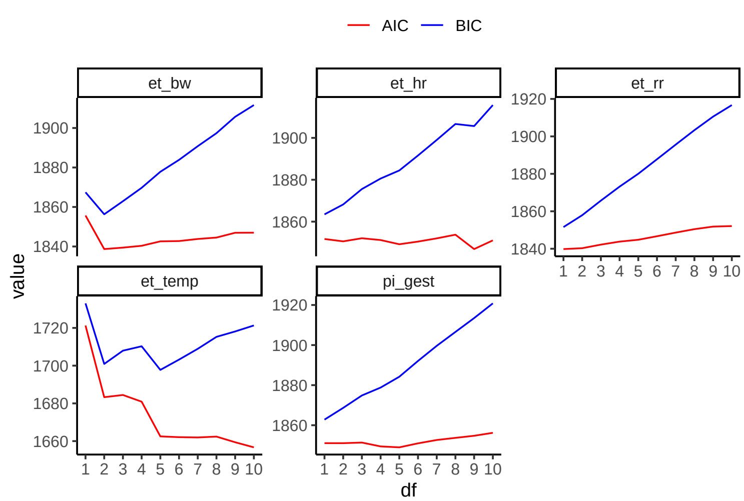
0.2.2.1 Histograms We first assessed the linearity assumption – that the outcome of sepsis is modelled by a linear combination of predictors – graphically, by plotting histograms of the proportion of included neonates with sepsis per decile of each continuous predictor.



If the relationship between the predictor and the probability of EOS were linear, we would expect the proportion of cases of sepsis to increase or decrease at a constant rate across deciles. Therefore, the above figure suggests some non-linearity for all continuous candidate predictors but most pronounced for temperature.

0.2.2.2 Splines We explored non-linear effects of continuous predictors by fitting univariable logistic regression models to predict the outcome of sepsis and modelling each continuous predictor as a natural cubic spline (NCS) function with varying degrees of freedom from 1 (linear) to 10.

We plotted the AIC and BIC of these models for each predictor to visually determine the optimal degrees of freedom for the NCS function.



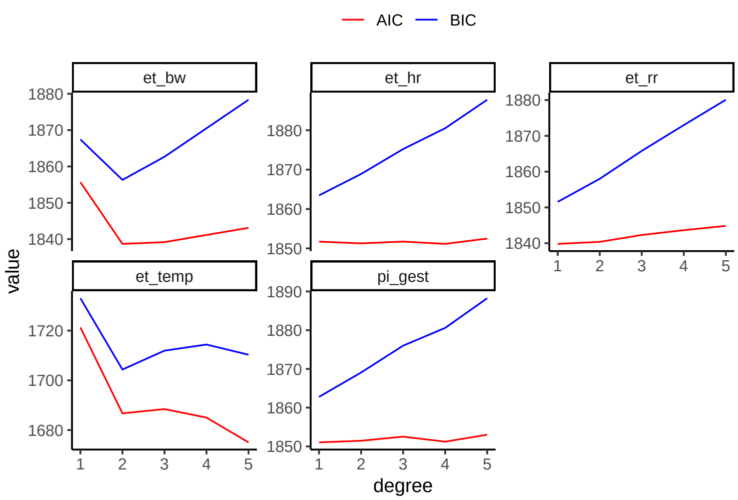
The above figure shows that the AIC and BIC increased monotonically or remained approximately constant across all degrees of freedom for heart rate, respiratory rate and gestational age. This suggests that using the untransformed predictor (i.e. assuming linearity) resulted in a better model than defining these predictors with natural cubic splines.

However, for birth weight, minimum values for AIC and BIC were determined by a natural cubic spline with 2 degrees of freedom (top left panel, above). Similarly, for temperature, the BIC was minimal for natural cubic splines with 2 or 5 degrees of freedom before increasing monotonically. The AIC had minima at 5 or 7 degrees of freedom (bottom left panel, above).

The above figure suggests that transforming birth weight using a natural cubic spline with 2 degrees of freedom and transforming temperature using a natural cubic spline with 5 degrees of freedom produced the optimal univariable models of the natural cubic spline transformations explored.

0.2.2.3 Polynomials We further explored non-linear effects by modelling each continuous predictor with polynomial transformations instead of natural cubic spline functions.

Again, we plotted the AIC and BIC of these models for each predictor to visually determine the optimal degree of polynomial.



The above figure shows that the AIC and BIC increased monotonically or remained approximately constant across all degrees of polynomials for heart rate, respiratory rate and gestational age. This suggests that using the untransformed predictor (i.e. assuming linearity) resulted in a better model than transforming these predictors with polynomial functions.

However, for birth weight, minimum values for AIC and BIC were determined by a second-degree polynomial (top left panel, above). Similarly, for temperature, the BIC was minimal for a second-degree polynomial and the AIC was minimal for a second-degree or fifth-degree polynomial (bottom left panel, above).

The above figure suggests that transforming birth weight and temperature using a second-degree polynomial produced the optimal univariable models of the polynomial transformations explored.

0.2.2.4 Univariable models with non-linear transformations - birth weight Based on the above results, we fit a univariable model to predict early-onset sepsis with birth weight modelled as a natural cubic spline with 2 degrees of freedom.

Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
ns(et__bw, df = 2)				
ns(et__bw, df = 2)1	1.5	0.468	0.62, 2.5	0.001
ns(et__bw, df = 2)2	-1.4	0.555	-2.5, -0.34	0.013

```
##  50%
## 2.95
```

While both components of the spline were significant, their coefficients were unstable with large SEs.

Thus, we subsequently modelled birth weight as a second-degree polynomial.

Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
et__bw				
et__bw	5.7	3.70	-1.6, 13	0.13
et__bw^2	-16	4.03	-24, -8.4	<0.001

This model suffered similar numerical issues. Adding random noise did not improve estimations in either the natural cubic spline or polynomial models:

Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
ns(et__bw__noise, df = 2)				
ns(et__bw__noise, df = 2)1	1.6	0.496	0.67, 2.6	0.001
ns(et__bw__noise, df = 2)2	-1.4	0.569	-2.5, -0.31	0.016

Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
et__bw__noise				
et__bw__noise	5.5	3.69	-1.8, 13	0.14
et__bw__noise^2	-16	4.02	-24, -8.2	<0.001

Therefore, birth weight was assumed to be linear in subsequent models.

0.2.2.5 Univariable models with non-linear transformations - temperature Based on the above results, we fit a univariable model to predict early-onset sepsis with temperature modelled as a natural cubic spline with 5 degrees of freedom and with 2 degrees of freedom.

Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
ns(et__temp, df = 5)				
ns(et__temp, df = 5)1	-1.1	1.24	-3.4, 1.8	0.4
ns(et__temp, df = 5)2	-2.3	1.32	-4.7, 0.86	0.088
ns(et__temp, df = 5)3	2.3	0.713	1.0, 3.9	0.001
ns(et__temp, df = 5)4	-0.93	2.80	-6.2, 5.6	0.7
ns(et__temp, df = 5)5	3.3	0.805	1.8, 5.1	<0.001

```
##  20%  40%  60%  80%
## 36.0 36.4 36.7 37.0
```

Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
ns(et__temp, df = 2)				
ns(et__temp, df = 2)1	-1.4	1.36	-4.0, 1.4	0.3
ns(et__temp, df = 2)2	5.1	0.428	4.3, 6.0	<0.001

```
##  50%
## 36.5
```

Similar numerical issues were encountered for these models as were encountered when fitting non-linear functions of birth weight.

Again, we subsequently modelled temperature as a second-degree polynomial and tried adding random noise, neither of which produced satisfactory models.

Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
et_temp				
et_temp	28	3.13	22, 34	<0.001
et_temp^2	19	2.89	14, 25	<0.001

Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
ns(et_temp_noise, df = 2)				
ns(et_temp_noise, df = 2)1	-1.5	1.41	-4.1, 1.5	0.3
ns(et_temp_noise, df = 2)2	5.2	0.436	4.3, 6.0	<0.001

Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
et_temp_noise				
et_temp_noise	27	3.13	21, 34	<0.001
et_temp_noise^2	19	2.87	13, 24	<0.001

Therefore, temperature was also assumed to be linear in subsequent models.

0.2.3 Selecting main effects

0.2.3.1 Fit full main effects model (model M1) We next fit a full main effects model to predict sepsis, including all 14 candidate predictors (those remaining after consideration of skewed predictor distributions). The AIC and BIC of this full model were the benchmark to which subsequent models were compared.

```
## sepsis ~ et_temp + et_rr + et_hr + et_bw + pi_gest + oh_matfever +
##     oh_offliquor + co_prom + et_grunt + oe_activity + oe_nasalflare +
##     oe_retractions + oe_grunt + oe_wob
```

```
##
## Call:
## glm(formula = main_form, family = "binomial", data = si)
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -2.0049  -0.4918  -0.3843  -0.2764   3.4433
##
## Coefficients:
##                       Estimate Std. Error z value Pr(>|z|)
## (Intercept)          -3.898e+01  3.200e+00 -12.181   <2e-16 ***
## et_temp               9.483e-01  8.557e-02  11.083   <2e-16 ***
## et_rr                 6.170e-02  2.712e-02   2.275   0.0229 *
## et_hr                -9.885e-04  1.947e-02  -0.051   0.9595
## et_bw                -1.276e-01  1.245e-01  -1.025   0.3054
## pi_gest               3.790e-02  3.339e-02   1.135   0.2564
## oh_matfeveryes        1.466e+00  6.247e-01   2.347   0.0189 *
## oh_offliquoryes       5.309e-01  2.279e-01   2.330   0.0198 *
## co_promyes            3.665e-01  1.904e-01   1.925   0.0542 .
## et_gruntyes          -3.046e-01  2.072e-01  -1.470   0.1416
## oe_activitylethargic  4.541e-01  1.895e-01   2.396   0.0166 *
## oe_activityother      6.914e-01  2.831e-01   2.443   0.0146 *
## oe_nasalflareyes      1.021e-01  2.388e-01   0.427   0.6690
## oe_retractionsyes     7.372e-01  3.231e-01   2.282   0.0225 *
## oe_gruntyes           1.977e-01  2.194e-01   0.901   0.3674
## oe_wobmild           -7.523e-01  3.829e-01  -1.965   0.0494 *
## oe_wobmoderate       -2.559e-01  4.182e-01  -0.612   0.5406
```

```
## oe_wobsevere          1.623e-01  5.082e-01   0.319   0.7494
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 1854.2  on 2627  degrees of freedom
## Residual deviance: 1632.0  on 2610  degrees of freedom
## AIC: 1668
##
## Number of Fisher Scoring iterations: 5
```

```
##           AIC      BIC
## [1,] 1668.045 1773.777
```

This model assumed linearity of all continuous candidate predictors and additivity at the predictor scale. The regression coefficients and SEs of each predictor in this model (estimated in the single imputed dataset) are as follows:

Characteristic	**OR**	**95% CI**	**p-value**
et_temp	2.58	2.19, 3.06	<0.001
et_rr	1.06	1.01, 1.12	0.023
et_hr	1.00	0.96, 1.04	>0.9
et_bw	0.88	0.69, 1.12	0.3
pi_gest	1.04	0.97, 1.11	0.3
oh_matfever	4.33	1.22, 14.6	0.019
oh_offliquor	1.70	1.07, 2.63	0.020
co_prom	1.44	0.98, 2.08	0.054
et_grunt	0.74	0.49, 1.11	0.14
oe_activity			
alert	1.00		
lethargic	1.57	1.08, 2.27	0.017
other	2.00	1.13, 3.43	0.015
oe_nasalflare	1.11	0.70, 1.79	0.7
oe_retractions	2.09	1.15, 4.10	0.023
oe_grunt	1.22	0.79, 1.87	0.4
oe_wob			
normal	1.00		
mild	0.47	0.21, 0.97	0.049
moderate	0.77	0.33, 1.71	0.5
severe	1.18	0.42, 3.12	0.7

The highest VIF values were for the 'moderate' and 'severe' categories of work of breathing and retractions. All other VIF values were < 5. Pearson's chi-squared test showed that these two predictors were highly correlated with each other:

```
## # A tibble: 17 x 2
##    predictor             VIF
##    <chr>               <dbl>
##  1 oe_wobmoderate       8.26
##  2 oe_retractionsyes    6.06
##  3 oe_wobsevere         5.08
##  4 oe_wobmild           3.79
##  5 oe_nasalflareyes     3.20
```

```
##   6 et_gruntyes           2.18
##   7 oe_gruntyes           1.76
##   8 et_bw                 1.63
##   9 pi_gest               1.57
##  10 et_rr                 1.45
##  11 oe_activitylethargic  1.21
##  12 et_temp               1.21
##  13 oh_offliquoryes       1.09
##  14 co_promyes            1.08
##  15 et_hr                 1.08
##  16 oe_activityother      1.05
##  17 oh_matfeveryes        1.02
```

```
##
##       normal mild moderate severe
##   no    1431  131       77      3
##   yes      0  282      537    167
```

```
##
##  Pearson's Chi-squared test
##
## data:  table(si$oe_retractions, si$oe_wob)
## X-squared = 1946.6, df = 3, p-value < 2.2e-16
```

0.2.3.2 Models M2 & M2a Next, we fit model M2 as the above full model (model M1), but without work of breathing (the predictor with the highest VIF in model M1). This model had a higher AIC compared to model M1, but a lower BIC. Removing work of breathing from the model also reduced collinearity between predictors.

```
## sepsis ~ et_temp + et_rr + et_hr + et_bw + pi_gest + oh_matfever +
##     oh_offliquor + co_prom + et_grunt + oe_activity + oe_nasalflare +
##     oe_retractions + oe_grunt
```

```
##
## Call:
## glm(formula = sepsis ~ et_temp + et_rr + et_hr + et_bw + pi_gest +
##     oh_matfever + oh_offliquor + co_prom + et_grunt + oe_activity +
##     oe_nasalflare + oe_retractions + oe_grunt, family = "binomial",
##     data = si)
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -1.9336  -0.4947  -0.3894  -0.2801   3.4162
##
## Coefficients:
##                       Estimate Std. Error z value Pr(>|z|)
## (Intercept)         -39.055288   3.193704 -12.229  < 2e-16 ***
## et_temp               0.948867   0.085225  11.134  < 2e-16 ***
## et_rr                 0.055174   0.026681   2.068  0.03865 *
## et_hr                -0.002396   0.019444  -0.123  0.90191
## et_bw                -0.121639   0.124511  -0.977  0.32860
## pi_gest               0.040054   0.033343   1.201  0.22964
```

```
## oh_matfeveryes         1.399622   0.613958   2.280  0.02263 *
## oh_offliquoryes        0.514570   0.226127   2.276  0.02287 *
## co_promyes             0.376776   0.189514   1.988  0.04680 *
## et_gruntyes           -0.246139   0.199117  -1.236  0.21640
## oe_activitylethargic   0.540164   0.181121   2.982  0.00286 **
## oe_activityother       0.746981   0.280387   2.664  0.00772 **
## oe_nasalflareyes      -0.021323   0.187648  -0.114  0.90953
## oe_retractionsyes      0.487810   0.203423   2.398  0.01648 *
## oe_gruntyes            0.344932   0.204324   1.688  0.09138 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 1854.2  on 2627  degrees of freedom
## Residual deviance: 1644.3  on 2613  degrees of freedom
## AIC: 1674.3
##
## Number of Fisher Scoring iterations: 5
```

```
##           AIC      BIC
## [1,] 1674.269 1762.379
```

```
## # A tibble: 14 x 2
##    predictor              VIF
##    <chr>                <dbl>
##  1 oe_retractionsyes     2.42
##  2 et_gruntyes           2.04
##  3 oe_nasalflareyes      2.00
##  4 et_bw                 1.63
##  5 pi_gest               1.57
##  6 oe_gruntyes           1.55
##  7 et_rr                 1.39
##  8 et_temp               1.19
##  9 oe_activitylethargic  1.13
## 10 co_promyes            1.08
## 11 oh_offliquoryes       1.08
## 12 et_hr                 1.08
## 13 oe_activityother      1.04
## 14 oh_matfeveryes        1.02
```

For comparison, model M2a instead dropped retractions from model M1. This model had a slightly improved AIC compared to model M2, but a higher BIC.

```
## sepsis ~ et_temp + et_rr + et_hr + et_bw + pi_gest + oh_matfever +
##     oh_offliquor + co_prom + et_grunt + oe_activity + oe_nasalflare +
##     oe_grunt + oe_wob
```

```
##
## Call:
## glm(formula = sepsis ~ et_temp + et_rr + et_hr + et_bw + pi_gest +
##     oh_matfever + oh_offliquor + co_prom + et_grunt + oe_activity +
##     oe_nasalflare + oe_grunt + oe_wob, family = "binomial", data = si)
```

```
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -2.0011  -0.4919  -0.3914  -0.2789   3.4686
##
## Coefficients:
##                        Estimate Std. Error z value Pr(>|z|)
## (Intercept)          -39.077480   3.201211 -12.207   <2e-16 ***
## et_temp                0.949635   0.085550  11.100   <2e-16 ***
## et_rr                  0.064783   0.026977   2.401   0.0163 *
## et_hr                  0.002098   0.019367   0.108   0.9138
## et_bw                 -0.147107   0.124356  -1.183   0.2368
## pi_gest                0.037518   0.033381   1.124   0.2610
## oh_matfeveryes         1.530361   0.626977   2.441   0.0147 *
## oh_offliquoryes        0.525994   0.227718   2.310   0.0209 *
## co_promyes             0.375810   0.190041   1.978   0.0480 *
## et_gruntyes           -0.221430   0.203837  -1.086   0.2773
## oe_activitylethargic   0.465809   0.189245   2.461   0.0138 *
## oe_activityother       0.715477   0.282140   2.536   0.0112 *
## oe_nasalflareyes       0.026152   0.234934   0.111   0.9114
## oe_gruntyes            0.159332   0.217231   0.733   0.4633
## oe_wobmild            -0.194130   0.280647  -0.692   0.4891
## oe_wobmoderate         0.412948   0.289606   1.426   0.1539
## oe_wobsevere           0.890029   0.395284   2.252   0.0243 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 1854.2  on 2627  degrees of freedom
## Residual deviance: 1637.9  on 2611  degrees of freedom
## AIC: 1671.9
##
## Number of Fisher Scoring iterations: 5
```

```
##           AIC      BIC
## [1,] 1671.938 1771.795
```

0.2.3.3 Models M3 & M4 Note that the sign of the regression coefficient for grunting at emergency triage (`et_grunt`) and nasal flaring in model M2 (above) was inconsistent with established subject knowledge of neonatal sepsis. We would expect the presence of these clinical features would increase the probability of sepsis, yet they had negative regression coefficients.

Therefore, model M3 was fitted as model M2, but without grunting at emergency triage or nasal flaring. This model had a slightly lower AIC and BIC compared to model M2.

```
## sepsis ~ et_temp + et_rr + et_hr + et_bw + pi_gest + oh_matfever +
##     oh_offliquor + co_prom + oe_activity + oe_retractions + oe_grunt
```

```
##
## Call:
## glm(formula = sepsis ~ et_temp + et_rr + et_hr + et_bw + pi_gest +
##     oh_matfever + oh_offliquor + co_prom + oe_activity + oe_retractions +
```

```
##     oe_grunt, family = "binomial", data = si)
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -1.8588  -0.4973  -0.3897  -0.2800   3.4138
##
## Coefficients:
##                        Estimate Std. Error z value Pr(>|z|)
## (Intercept)          -39.113913   3.189308 -12.264  < 2e-16 ***
## et_temp                0.952733   0.085060  11.201  < 2e-16 ***
## et_rr                  0.051336   0.025943   1.979  0.04784 *
## et_hr                 -0.001694   0.019333  -0.088  0.93020
## et_bw                 -0.121533   0.124412  -0.977  0.32864
## pi_gest                0.038105   0.033286   1.145  0.25231
## oh_matfeveryes         1.389925   0.607455   2.288  0.02213 *
## oh_offliquoryes        0.525150   0.225418   2.330  0.01982 *
## co_promyes             0.378975   0.189088   2.004  0.04505 *
## oe_activitylethargic   0.530911   0.180704   2.938  0.00330 **
## oe_activityother       0.734252   0.279597   2.626  0.00864 **
## oe_retractionsyes      0.377934   0.169782   2.226  0.02601 *
## oe_gruntyes            0.236857   0.182930   1.295  0.19539
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 1854.2  on 2627  degrees of freedom
## Residual deviance: 1645.9  on 2615  degrees of freedom
## AIC: 1671.9
##
## Number of Fisher Scoring iterations: 5
```

```
##           AIC      BIC
## [1,] 1671.881 1748.243
```

Looking at the above model, the regression coefficient for heart rate was close to zero and it was not found to be a significant predictor in the model. Therefore, heart rate was dropped from model M3 to fit model M4. This model had a lower AIC and BIC compared to model M3. Also, this model had minimal collinearity between predictors.

```
## sepsis ~ et_temp + et_rr + et_bw + pi_gest + oh_matfever + oh_offliquor +
##     co_prom + oe_activity + oe_retractions + oe_grunt
```

```
##
## Call:
## glm(formula = sepsis ~ et_temp + et_rr + et_bw + pi_gest + oh_matfever +
##     oh_offliquor + co_prom + oe_activity + oe_retractions + oe_grunt,
##     family = "binomial", data = si)
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -1.8535  -0.4976  -0.3894  -0.2801   3.4148
##
```

```
## Coefficients:
##                      Estimate Std. Error z value Pr(>|z|)
## (Intercept)         -39.10319    3.18678 -12.270  < 2e-16 ***
## et_temp               0.95124    0.08332  11.417  < 2e-16 ***
## et_rr                 0.05112    0.02583   1.979  0.04782 *
## et_bw                -0.12136    0.12438  -0.976  0.32919
## pi_gest               0.03811    0.03329   1.145  0.25223
## oh_matfeveryes        1.39284    0.60651   2.296  0.02165 *
## oh_offliquoryes       0.52515    0.22542   2.330  0.01983 *
## co_promyes            0.37945    0.18901   2.008  0.04469 *
## oe_activitylethargic  0.53159    0.18055   2.944  0.00324 **
## oe_activityother      0.73472    0.27958   2.628  0.00859 **
## oe_retractionsyes     0.37666    0.16917   2.227  0.02598 *
## oe_gruntyes           0.23714    0.18290   1.297  0.19479
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 1854.2  on 2627  degrees of freedom
## Residual deviance: 1645.9  on 2616  degrees of freedom
## AIC: 1669.9
##
## Number of Fisher Scoring iterations: 5
```

```
##           AIC      BIC
## [1,] 1669.889 1740.376
```

```
## # A tibble: 11 x 2
##    predictor              VIF
##    <chr>                <dbl>
##  1 oe_retractionsyes     1.68
##  2 et_bw                 1.62
##  3 pi_gest               1.56
##  4 et_rr                 1.31
##  5 oe_gruntyes           1.25
##  6 et_temp               1.14
##  7 oe_activitylethargic  1.12
##  8 co_promyes            1.08
##  9 oh_offliquoryes       1.08
## 10 oe_activityother      1.04
## 11 oh_matfeveryes        1.01
```

Note that two non-significant predictors were retained in the regression model (premature rupture of membranes and grunting on examination) as the sign of their regression coefficient was consistent with established knowledge and the corresponding *p*-values were reasonably small. Also, birth weight and gestational age were retained in the model despite being non-significant to test for interactions between these two predictors, as described ahead.

0.2.4 Assess additivity assumption

We then assessed the additivity assumption – that the effects of predictors can be added at the linear predictor scale (and thus multiplied at the odds scale) - by assessing for a biologically plausible interaction between birth weight and gestational age.

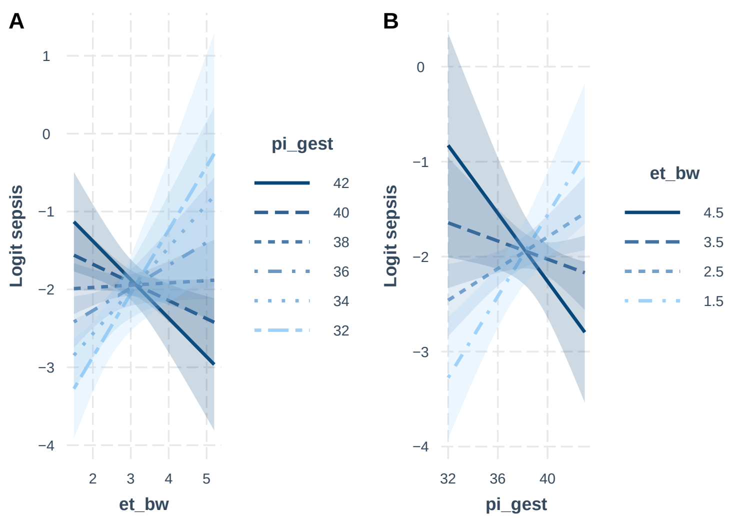
0.2.4.1 Interaction plots

There was a significant interaction between birth weight and gestational age in a logistic regression model of these two predictors predicting EOS:

```
## sepsis ~ et_bw * pi_gest

##
## Call:
## glm(formula = sepsis ~ et_bw * pi_gest, family = "binomial",
##     data = si)
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -0.6927  -0.5190  -0.5016  -0.4248   2.5739
##
## Coefficients:
##                Estimate Std. Error z value Pr(>|z|)
## (Intercept)   -17.65053    4.29516  -4.109 3.97e-05 ***
## et_bw           5.01038    1.58224   3.167 0.001542 **
## pi_gest         0.41098    0.11408   3.602 0.000315 ***
## et_bw:pi_gest  -0.13108    0.04133  -3.171 0.001517 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 1854.2  on 2627  degrees of freedom
## Residual deviance: 1836.2  on 2624  degrees of freedom
## AIC: 1844.2
##
## Number of Fisher Scoring iterations: 5
```

A plot of this interaction is shown below. Panel A shows the logit of the probability of sepsis across all values of birth weight at six selected values of gestational age. Panel B shows the same interaction but displayed across all values of gestational age at four selected values of birth weight.



At lower birth weights, those with a higher gestational age appeared to have a greater probability of sepsis compared to those with lower gestational ages (panel A, above). However, at approximately 3200 grams, this relationship reversed, after which the probability of sepsis appeared higher for those with lower gestational ages. The above figure suggests that the probability of sepsis decreased with increasing birth weight for gestational ages > 38 weeks but increased with increasing birth weight for gestational ages < 38 weeks.

This relationship can also be interpreted such that, for lower gestational ages, those with higher birth weights had a greater probability of sepsis compared to those with lower birth weights (panel B, above). For higher gestational ages (above around 38 weeks), those with a higher birth weight had the lowest probability of sepsis.

0.2.4.2 Models M5 & M5a

The interaction between birth weight and gestational age was included in the selected multivariable model M4 to produce model M5.

The main effects and the interaction term were significant for birth weight and gestational age in this model. However, the coefficients and standard errors were extreme for these terms, with large VIF values.

```
## sepsis ~ et_temp + et_rr + oh_matfever + oh_offliquor + co_prom +
##     oe_activity + oe_retractions + oe_grunt + et_bw + pi_gest +
##     et_bw:pi_gest
```

```
##
## Call:
## glm(formula = sepsis ~ et_temp + et_rr + oh_matfever + oh_offliquor +
##     co_prom + oe_activity + oe_retractions + oe_grunt + et_bw +
##     pi_gest + et_bw:pi_gest, family = "binomial", data = si)
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -1.7234  -0.4965  -0.3857  -0.2742   3.5029
##
## Coefficients:
##                       Estimate Std. Error z value Pr(>|z|)
## (Intercept)          -52.44300    5.53724  -9.471  < 2e-16 ***
## et_temp                0.95391    0.08355  11.417  < 2e-16 ***
## et_rr                  0.05285    0.02593   2.038  0.04152 *
## oh_matfeveryes         1.35358    0.60445   2.239  0.02513 *
## oh_offliquoryes        0.46816    0.22615   2.070  0.03844 *
## co_promyes             0.37102    0.18953   1.958  0.05028 .
## oe_activitylethargic   0.55685    0.18069   3.082  0.00206 **
## oe_activityother       0.69087    0.28060   2.462  0.01381 *
## oe_retractionsyes      0.40819    0.16964   2.406  0.01612 *
## oe_gruntyes            0.22821    0.18296   1.247  0.21227
## et_bw                  4.98628    1.68916   2.952  0.00316 **
## pi_gest                0.38744    0.12138   3.192  0.00141 **
## et_bw:pi_gest         -0.13384    0.04422  -3.027  0.00247 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 1854.2  on 2627  degrees of freedom
## Residual deviance: 1636.1  on 2615  degrees of freedom
## AIC: 1662.1
##
## Number of Fisher Scoring iterations: 5
```

```
##           AIC      BIC
## [1,] 1662.066 1738.427
```

```
## # A tibble: 12 x 2
##    predictor              VIF
##    <chr>                <dbl>
##  1 et_bw:pi_gest       349.
##  2 et_bw               265.
##  3 pi_gest              18.0
##  4 oe_retractionsyes     1.68
##  5 et_rr                 1.31
##  6 oe_gruntyes           1.24
##  7 et_temp               1.14
##  8 oe_activitylethargic  1.12
##  9 oh_offliquoryes       1.08
## 10 co_promyes            1.08
## 11 oe_activityother      1.04
## 12 oh_matfeveryes        1.01
```

Refitting this model but with birth weight and gestational age centred by subtracting their respective sample means from each observation greatly improved the estimates (model M5a). However, the main effects of these terms were no longer significant despite a significant interaction. This is consistent with the crossover interaction effect seen in the interaction plot shown previously.

```
## sepsis ~ et_temp + et_rr + oh_matfever + oh_offliquor + co_prom +
##     oe_activity + oe_retractions + oe_grunt + et_bw_centred +
##     pi_gest_centred + et_bw_centred:pi_gest_centred
```

```
##
## Call:
## glm(formula = sepsis ~ et_temp + et_rr + oh_matfever + oh_offliquor +
##     co_prom + oe_activity + oe_retractions + oe_grunt + et_bw_centred +
##     pi_gest_centred + et_bw_centred:pi_gest_centred, family = "binomial",
##     data = si)
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -1.7234  -0.4965  -0.3857  -0.2742   3.5029
##
## Coefficients:
##                                Estimate Std. Error z value Pr(>|z|)
## (Intercept)                   -38.00750    3.09156 -12.294  < 2e-16 ***
## et_temp                         0.95391    0.08355  11.417  < 2e-16 ***
## et_rr                           0.05285    0.02593   2.038  0.04152 *
## oh_matfeveryes                  1.35358    0.60445   2.239  0.02513 *
## oh_offliquoryes                 0.46816    0.22615   2.070  0.03844 *
## co_promyes                      0.37102    0.18953   1.958  0.05028 .
## oe_activitylethargic            0.55685    0.18069   3.082  0.00206 **
## oe_activityother                0.69087    0.28060   2.462  0.01381 *
## oe_retractionsyes               0.40819    0.16964   2.406  0.01612 *
## oe_gruntyes                     0.22821    0.18296   1.247  0.21227
## et_bw_centred                  -0.09992    0.12392  -0.806  0.42002
## pi_gest_centred                 0.00100    0.03529   0.028  0.97738
```

```
## et_bw_centred:pi_gest_centred  -0.13384    0.04422  -3.027  0.00247 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 1854.2  on 2627  degrees of freedom
## Residual deviance: 1636.1  on 2615  degrees of freedom
## AIC: 1662.1
##
## Number of Fisher Scoring iterations: 5
```

```
##           AIC      BIC
## [1,] 1662.066 1738.427
```

```
## # A tibble: 12 x 2
##    predictor                       VIF
##    <chr>                         <dbl>
##  1 oe_retractionsyes              1.68
##  2 pi_gest_centred                1.52
##  3 et_bw_centred                  1.43
##  4 et_rr                          1.31
##  5 oe_gruntyes                    1.24
##  6 et_bw_centred:pi_gest_centred  1.16
##  7 et_temp                        1.14
##  8 oe_activitylethargic           1.12
##  9 oh_offliquoryes                1.08
## 10 co_promyes                     1.08
## 11 oe_activityother               1.04
## 12 oh_matfeveryes                 1.01
```

Given that allowing for an interaction between birth weight and gestational age (model M5a) showed only minor improvements in the AIC and BIC compared to the model assuming additivity (model M4), we selected model M4 as it was the simpler model.

This decision was reinforced since the distributions of birth weight and gestational age in our cohort suggested that higher birth weights and gestational ages had a higher probability of sepsis than lower birth weights and gestational ages. This contradicted what is expected from established subject knowledge.

0.2.4.3 Models M6 and M7 Since the interaction between birth weight and gestational age was no longer included in the model, model M4 was refitted but without gestational age (model M6) as the sign of its regression coefficient contradicted established knowledge and it was not significant in model M4. This improved both the AIC and BIC compared to model M4.

```
## sepsis ~ et_temp + et_rr + et_bw + oh_matfever + oh_offliquor +
##     co_prom + oe_activity + oe_retractions + oe_grunt
```

```
##
## Call:
## glm(formula = sepsis ~ et_temp + et_rr + et_bw + oh_matfever +
##     oh_offliquor + co_prom + oe_activity + oe_retractions + oe_grunt,
##     family = "binomial", data = si)
##
```

```
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -1.8318  -0.4979  -0.3919  -0.2799   3.3984
##
## Coefficients:
##                      Estimate Std. Error z value Pr(>|z|)
## (Intercept)         -38.04494    3.04066 -12.512  < 2e-16 ***
## et_temp               0.95517    0.08323  11.476  < 2e-16 ***
## et_rr                 0.05175    0.02584   2.002  0.04525 *
## et_bw                -0.03863    0.10042  -0.385  0.70044
## oh_matfeveryes        1.37556    0.60513   2.273  0.02302 *
## oh_offliquoryes       0.53778    0.22494   2.391  0.01681 *
## co_promyes            0.37350    0.18908   1.975  0.04823 *
## oe_activitylethargic  0.54103    0.18040   2.999  0.00271 **
## oe_activityother      0.74885    0.27895   2.685  0.00726 **
## oe_retractionsyes     0.37904    0.16929   2.239  0.02515 *
## oe_gruntyes           0.23663    0.18282   1.294  0.19555
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 1854.2  on 2627  degrees of freedom
## Residual deviance: 1647.2  on 2617  degrees of freedom
## AIC: 1669.2
##
## Number of Fisher Scoring iterations: 5
```

```
##           AIC      BIC
## [1,] 1669.199 1733.813
```

Finally, in model M7, we refitted model M6 without birth weight as the p-value for this term in model M6 was large.

```
## sepsis ~ et_temp + et_rr + oh_matfever + oh_offliquor + co_prom +
##     oe_activity + oe_retractions + oe_grunt
```

```
##
## Call:
## glm(formula = sepsis ~ et_temp + et_rr + oh_matfever + oh_offliquor +
##     co_prom + oe_activity + oe_retractions + oe_grunt, family = "binomial",
##     data = si)
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -1.8461  -0.4965  -0.3929  -0.2799   3.4018
##
## Coefficients:
##                      Estimate Std. Error z value Pr(>|z|)
## (Intercept)         -37.94676    3.02862 -12.529  < 2e-16 ***
## et_temp               0.94934    0.08178  11.608  < 2e-16 ***
## et_rr                 0.05174    0.02583   2.003  0.04514 *
## oh_matfeveryes        1.38415    0.60506   2.288  0.02216 *
```

```
## oh_offliquoryes        0.53271    0.22452   2.373  0.01766 *
## co_promyes             0.37705    0.18886   1.996  0.04589 *
## oe_activitylethargic   0.54097    0.18042   2.998  0.00271 **
## oe_activityother       0.74455    0.27847   2.674  0.00750 **
## oe_retractionsyes      0.38662    0.16819   2.299  0.02152 *
## oe_gruntyes            0.23644    0.18284   1.293  0.19596
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 1854.2  on 2627  degrees of freedom
## Residual deviance: 1647.3  on 2618  degrees of freedom
## AIC: 1667.3
##
## Number of Fisher Scoring iterations: 5
```

```
##           AIC      BIC
## [1,] 1667.348 1726.087
```

```
## # A tibble: 9 x 2
##   predictor              VIF
##   <chr>                <dbl>
## 1 oe_retractionsyes     1.66
## 2 et_rr                 1.31
## 3 oe_gruntyes           1.25
## 4 oe_activitylethargic  1.12
## 5 et_temp               1.10
## 6 co_promyes            1.08
## 7 oh_offliquoryes       1.07
## 8 oe_activityother      1.04
## 9 oh_matfeveryes        1.01
```

0.2.5 Selected model

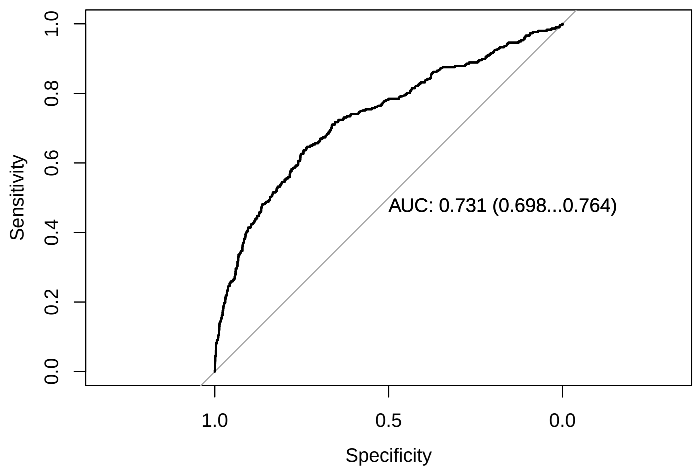
Model M7 was favoured by both the AIC and BIC and was thus selected as the optimal model. This model included 8 of the 14 candidate predictors. The regression coefficients and SEs of each predictor in this model (estimated in the single imputed dataset) are as follows:

Characteristic	**OR**	**95% CI**	**p-value**
et_temp	2.58	2.21, 3.04	<0.001
et_rr	1.05	1.00, 1.11	0.045
oh_matfever	3.99	1.17, 13.0	0.022
oh_offliquor	1.70	1.08, 2.62	0.018
co_prom	1.46	1.00, 2.09	0.046
oe_activity			
alert	1.00	—	
lethargic	1.72	1.20, 2.43	0.003
other	2.11	1.20, 3.58	0.008
oe_retractions	1.47	1.06, 2.05	0.022
oe_grunt	1.27	0.88, 1.81	0.2

0.3 Model performance

0.3.1 In the single imputed dataset

The ROC curve for the optimal model in the single imputed dataset (imputation number 16) is shown below.

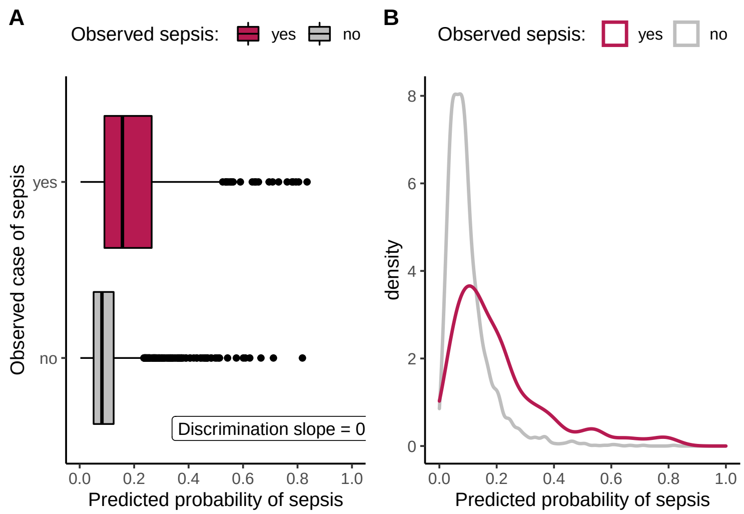


We calculated Yates' discrimination slope as the absolute difference in mean predicted probabilities between the two observed outcome groups. We obtained 95% confidence intervals using bootstrap (calculated using the normal approximation and 10,000 resamples).

```
##
## ORDINARY NONPARAMETRIC BOOTSTRAP
##
##
## Call:
## boot(data = si, statistic = yatesBootstrap, R = 10000, model = M7)
##
##
## Bootstrap Statistics :
##      original      bias    std. error
## t1* 0.1052515 0.005814652  0.01789948

## BOOTSTRAP CONFIDENCE INTERVAL CALCULATIONS
## Based on 10000 bootstrap replicates
##
## CALL :
## boot.ci(boot.out = yates, type = c("norm", "perc"))
##
## Intervals :
## Level      Normal             Percentile
## 95%   ( 0.0644,  0.1345 )   ( 0.0781,  0.1476 )
## Calculations and Intervals on Original Scale
```

A boxplot and density plot of predicted probabilities of EOS by observed outcome are shown below. On average, the predicted probability was higher for observed cases of sepsis than observed cases without sepsis. Nevertheless, there was substantial overlap in predicted probabilities, with cases of sepsis with a low predicted probability (below the median for observed cases without sepsis) and cases without sepsis with a high predicted probability (above the median for observed cases with sepsis).



Performance of the optimal model in the selected imputed dataset at various thresholds of predicted probability are shown below. We obtained 95% confidence intervals for likelihood ratios using bootstrap (calculated using the empirical method and 10,000 resamples).

```
## $best
##      obs
## pred   yes   no
##   yes  192  617
##   no   105 1714
##
## $`0.8`
##      obs
## pred   yes   no
##   yes  239 1311
##   no    58 1020
##
## $`0.85`
##      obs
## pred   yes   no
##   yes  251 1448
##   no    46  883
##
## $`0.9`
##      obs
## pred   yes   no
##   yes  268 1816
##   no    29  515
##
## $`0.95`
##      obs
## pred   yes   no
##   yes  283 2068
##   no    14  263
```

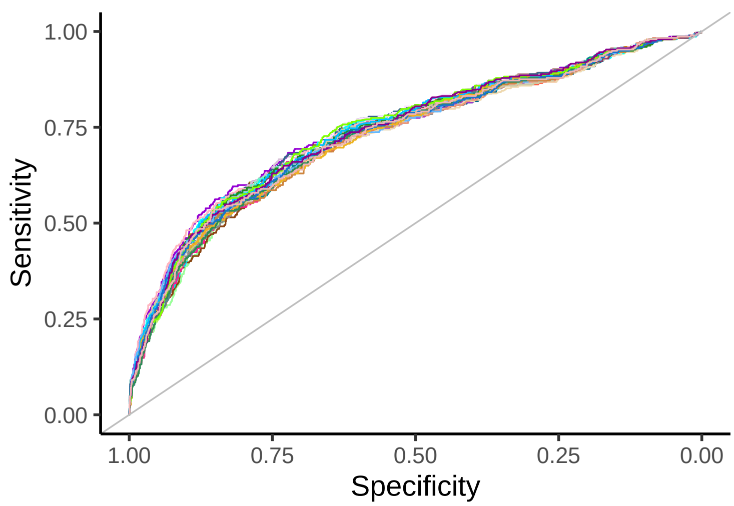
```
## # A tibble: 5 x 19
```

```
##   thres  sens sens.lcl sens.ucl  spec spec.lcl spec.ucl   PPV PPV.lcl PPV.ucl
##   <dbl> <dbl>    <dbl>    <dbl> <dbl>    <dbl>    <dbl> <dbl>   <dbl>   <dbl>
## 1 0.121  64.6     58.9     70.1  73.5     71.7     75.3  23.7    20.8    26.8
## 2 0.075  80.5     75.5     84.8  43.8     41.7     45.8  15.4    13.7    17.3
## 3 0.067  84.5     79.9     88.4  37.9     35.9     39.9  14.8    13.1    16.6
## 4 0.047  90.2     86.3     93.4  22.1     20.4     23.8  12.9    11.5    14.4
## 5 0.034  95.3     92.2     97.4  11.3     10       12.6  12      10.7    13.4
##     NPV NPV.lcl NPV.ucl   PLR PLR.lcl PLR.ucl   NLR NLR.lcl NLR.ucl
##   <dbl>   <dbl>   <dbl> <dbl>   <dbl>   <dbl> <dbl>   <dbl>   <dbl>
## 1  94.2    93.1    95.3  2.44   1.58     2.88 0.481   0.402   0.595
## 2  94.6    93.1    95.9  1.43   1.04     1.57 0.446   0.378   0.547
## 3  95      93.5    96.4  1.36   1.21     1.59 0.409   0.219   0.476
## 4  94.7    92.4    96.4  1.16   0.9      1.22 0.442   0.334   0.632
## 5  94.9    91.7    97.2  1.07   0.976    1.12 0.418   0.265   0.592
```

The 'optimal' classification threshold according to Youden's J statistic was 0.1206428.

0.3.2 Pooled across all imputed datasets

The ROC curve for the optimal model in each of the 40 multiply imputed datasets is shown below.



We then applied Rubin's rules to get the pooled AUC across all imputed datasets.

```
##            auc       lcl       ucl
## [1,] 0.7364804 0.7009544 0.7720063
```

The pooled AUC across the imputed datasets was 0.736 (95% CI 0.701-0.772%).

Finally, we estimated the regression coefficients and odds ratios for the optimal model, pooled across all imputed datasets:

```
## # A tibble: 10 x 7
##    predictor               beta    SE    OR   lcl   ucl p.value
##    <chr>                  <dbl> <dbl> <dbl> <dbl> <dbl>   <dbl>
##  1 (Intercept)          -39.4   3.52   0     0     0      0
##  2 et_temp                0.987 0.095  2.68  2.23  3.23   0
```

```
##  3 et_rr                 0.055 0.026  1.06  1     1.11  0.0373
##  4 oh_matfeveryes        1.44  0.612  4.21  1.27 14.0   0.0189
##  5 oh_offliquoryes       0.543 0.228  1.72  1.1   2.69  0.0174
##  6 co_promyes            0.36  0.192  1.43  0.98  2.09  0.0612
##  7 oe_activitylethargic  0.586 0.184  1.8   1.25  2.58  0.0015
##  8 oe_activityother      0.84  0.286  2.32  1.32  4.06  0.0033
##  9 oe_retractionsyes     0.406 0.172  1.5   1.07  2.1   0.0187
## 10 oe_gruntyes           0.179 0.186  1.2   0.83  1.72  0.337
```