Charactersing effect of anaemia on mortality in severe malaria

Contents

Background

This looks at the severe malaria legacy dataset from MORU

The contributions of the different studies:

```
# Whole dataset
table(Leg_data$studyID)
```

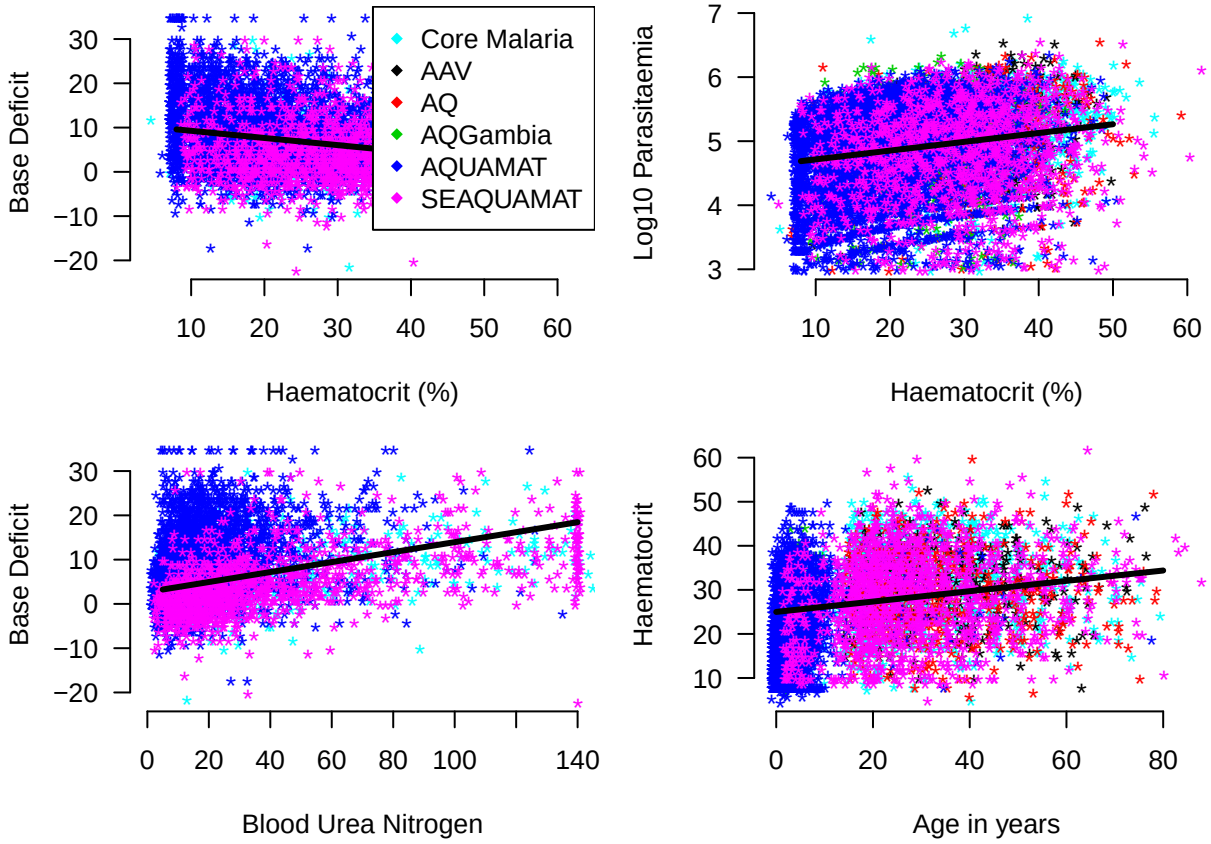
```
##
##          AAV           AQ     AQGambia      AQUAMAT Core Malaria
##          370          560          579         5494         1121
##    SEAQUAMAT
##         1461
```

```
# in the complete dataset (all variables recorded)
table(Complete_Leg_data$studyID)
```

```
##
##      AQUAMAT Core Malaria    SEAQUAMAT
##         3779          359         1090
```

Exploratory analysis

Let's look at the key predictive variables. We use a random effects term to model differences between studies.



Predictive value of anaemia on death adjusting for confounders

Before fitting the more complex GAM models we explore the standard glm (logistic regression) models.

```
mod_full = glmer(outcome ~ HCT + LPAR + AgeInYear + BUN + BD + drug + (1 | studyID),
                 data=Complete_Leg_data, family=binomial)
```

```
## Warning in checkConv(attr(opt, "derivs"), opt$par, ctrl = control
## $checkConv, : unable to evaluate scaled gradient
```

```
## Warning in checkConv(attr(opt, "derivs"), opt$par, ctrl = control
## $checkConv, : Model failed to converge: degenerate Hessian with 1 negative
## eigenvalues
```

```
summary(mod_full)
```

```
## Warning in vcov.merMod(object, use.hessian = use.hessian): variance-covariance matrix computed from
## not positive definite or contains NA values: falling back to var-cov estimated from RX
```

```
## Warning in vcov.merMod(object, correlation = correlation, sigm = sig): variance-covariance matrix co
## not positive definite or contains NA values: falling back to var-cov estimated from RX
```

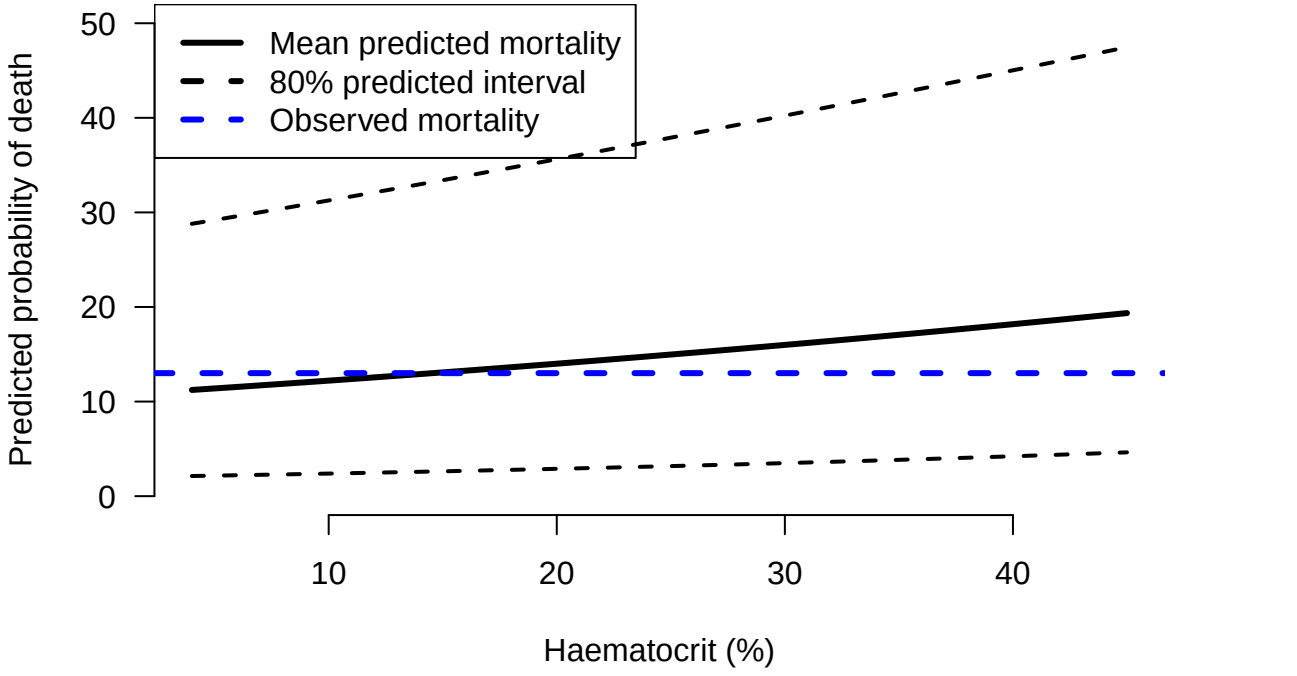
```
## Generalized linear mixed model fit by maximum likelihood (Laplace
##   Approximation) [glmerMod]
```

```
##  Family: binomial  ( logit )
## Formula:
## outcome ~ HCT + LPAR + AgeInYear + BUN + BD + drug + (1 | studyID)
##    Data: Complete_Leg_data
##
##      AIC      BIC   logLik deviance df.resid
##   3199.6   3278.3  -1587.8   3175.6     5216
##
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -2.7825 -0.3409 -0.2313 -0.1633 10.1058
##
## Random effects:
##  Groups  Name        Variance Std.Dev.
##  studyID (Intercept) 0.07967  0.2823
## Number of obs: 5228, groups:  studyID, 3
##
## Fixed effects:
##                     Estimate Std. Error z value Pr(>|z|)
## (Intercept)      -1.850e+01  5.664e+02  -0.033  0.97394
## HCT               1.960e-02  5.471e-03   3.583  0.00034 ***
## LPAR              1.855e-02  6.719e-02   0.276  0.78247
## AgeInYear         2.186e-02  4.343e-03   5.033 4.83e-07 ***
## BUN               1.166e-02  1.694e-03   6.882 5.89e-12 ***
## BD                1.361e-01  6.944e-03  19.601  < 2e-16 ***
## drugArtesunate    1.404e+01  5.664e+02   0.025  0.98022
## drugChloroquine   1.610e+01  5.664e+02   0.028  0.97733
## drugLumefantrine -1.034e+00  4.187e+03   0.000  0.99980
## drugNAC          -5.245e+00  8.479e+03  -0.001  0.99951
## drugQuinine       1.438e+01  5.664e+02   0.025  0.97975
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##             (Intr) HCT    LPAR   AgInYr BUN    BD     drgArt drgChl drgLmf
## HCT          0.000
## LPAR        -0.001 -0.172
## AgeInYear    0.000 -0.183  0.030
## BUN          0.000  0.064 -0.050 -0.189
## BD           0.000  0.263 -0.135  0.120 -0.263
## drugArtesnt -1.000  0.000  0.000  0.000  0.000  0.000
## drugChlorqn -1.000  0.000  0.000  0.000  0.000  0.000  1.000
## drugLmfntrn -0.135  0.000  0.000  0.000  0.000  0.000  0.135  0.135
## drugNAC     -0.067  0.000  0.000  0.000  0.000  0.000  0.067  0.067  0.009
## drugQuinine -1.000  0.000  0.000  0.000  0.000  0.000  1.000  1.000  0.135
##             drgNAC
## HCT
## LPAR
## AgeInYear
## BUN
## BD
## drugArtesnt
## drugChlorqn
## drugLmfntrn
```

```
## drugNAC
## drugQuinine  0.067
## convergence code: 0
## unable to evaluate scaled gradient
## Model failed to converge: degenerate  Hessian with 1 negative eigenvalues
```

Now let's make counterfactual predictions of anaemia on death for the patients in the database. The way to interpret this 'counterfactual' plot is as follows: suppose that every individual in the dataset was assigned (as in a intervention) a specific haematocrit X, what would the resulting per patient probability of death be. Here we summarise these probabilities by the predicted mean probability of death and 80% predictive intervals.

```
overall_mortality = 100*mean(Complete_Leg_data$outcome)
par(las=1, bty='n')
x_hcts = seq(4,45, by=.5)
probs = array(dim = c(3, length(x_hcts)))
for(i in 1:length(x_hcts)){
  mydata = Complete_Leg_data
  mydata$HCT=x_hcts[i]
  ys = 100*predict(mod_full, newdata = mydata, re.form=NA, type='response')
  probs[2,i] = mean(ys)
  probs[c(1,3),i] = quantile(ys, probs=c(0.1,0.9))
}
plot(x_hcts,probs[2,], xlim=c(4,45), ylab='Predicted probability of death',
     xlab='Haematocrit (%)', ylim=c(0,50), lty=1, lwd=3, type='l')
lines(x_hcts, probs[1,], lty=2, lwd=2)
lines(x_hcts, probs[3,], lty=2, lwd=2)
abline(h=overall_mortality, lwd=3, col='blue',lty=2)
legend('topleft', col=c('black','black','blue'), lwd=3, lty=c(1,2,2),
       legend = c('Mean predicted mortality', '80% predicted interval','Observed mortality'))
```



More complex GAM model

The GAM model allows for non-linear relationships between certain variables and the outcome.

Here we fit as non-linear the effect of age and haematocrit on mortality.

```
mod_full_GAM = gam(outcome ~ s(HCT,AgeInYear) + LPAR + BUN + BD,
               data=Complete_Leg_data, family=binomial)
summary(mod_full_GAM)
```

```
##
## Family: binomial
## Link function: logit
##
## Formula:
## outcome ~ s(HCT, AgeInYear) + LPAR + BUN + BD
##
## Parametric coefficients:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept) -3.706458   0.332187 -11.158  < 2e-16 ***
## LPAR        -0.003305   0.067265  -0.049    0.961
## BUN          0.010038   0.001720   5.838 5.29e-09 ***
## BD           0.140822   0.007133  19.742  < 2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Approximate significance of smooth terms:
##                     edf Ref.df Chi.sq p-value
## s(HCT,AgeInYear) 6.522   9.09  131.3  <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## R-sq.(adj) =  0.202   Deviance explained = 21.4%
## UBRE = -0.38846  Scale est. = 1         n = 5228
```

Now we compute the corresponding counterfactual probabilities of death for the dataset for all values of the haematocrit:

```
overall_mortality = 100*mean(Complete_Leg_data$outcome)
par(las=1, bty='n')
x_hcts = seq(4,45, by=.5)
probs = array(dim = c(3, length(x_hcts)))
for(i in 1:length(x_hcts)){
  mydata = Complete_Leg_data
  mydata$HCT=x_hcts[i]
  ys = 100*predict(mod_full_GAM, newdata = mydata, re.form=NA, type='response')
  probs[2,i] = mean(ys)
  probs[c(1,3),i] = quantile(ys, probs=c(0.1,0.9))
}
```

We see that the effect of haematocrit on mortality is non-linear under this model: below 20 is protective, above 20 plateaus out:

```
par(las=1, bty='n')
plot(x_hcts,probs[2,], xlim=c(4,45), ylab='Predicted probability of death',
     xlab='Haematocrit (%)', ylim=c(0,40), lty=1, lwd=3, type='l')
lines(x_hcts, probs[1,], lty=2, lwd=2)
```

```
lines(x_hcts, probs[3,], lty=2, lwd=2)
abline(h=overall_mortality, lwd=3, col='blue',lty=2)
legend('topleft', col=c('black','black','blue'), lwd=3, lty=c(1,2,2),
       legend = c('Mean predicted mortality', '80% predicted interval','Observed mortality'))
```