Charactersing effect of anaemia on mortality in severe malaria

Contents

Background

This looks at the severe malaria legacy dataset from MORU

Imputation of missing variables

Quite a lot of the important covariates are missing in the older studies. We use linear regression to estimate these unknown variables:

- Mising base deficit is imputed using bicarbonate (if available) else using respiratory rate
- Missing Blood urea nitrogen is imputed using creatinine

Impute base deficit from bicarbonate

```
BD_and_bicarbonate = !is.na(Leg_data$BD) & !is.na(Leg_data$bicarbonate)
print(paste('We have ', sum(BD_and_bicarbonate), 'observations for both bicarbonate and base deficit'))
```

```
## [1] "We have  5067 observations for both bicarbonate and base deficit"
```

```
mod_impute1 = lmer(BD ~ bicarbonate + (1 | studyID) + (1 | country), data= Leg_data[BD_and_bicarbonate,]
missing_BD = is.na(Leg_data$BD)
Available_Bicarbonate = !is.na(Leg_data$bicarbonate)
print(paste(sum(missing_BD & Available_Bicarbonate), 'observations will now be imputed'))
```

```
## [1] "309 observations will now be imputed"
```

```
# impute with model
Leg_data$BD[missing_BD & Available_Bicarbonate] = predict(mod_impute1,newdata=Leg_data[missing_BD & Ava
```

Impute base deficit from lactate

```
BD_and_lactate = !is.na(Leg_data$BD) & !is.na(Leg_data$lactate)
print(paste('We have ', sum(BD_and_lactate), 'observations for both lactate and base deficit'))
```

```
## [1] "We have  632 observations for both lactate and base deficit"
```

```
if(length(unique(Leg_data$studyID[BD_and_lactate]))==1){
  mod_impute2 = lm(BD ~ lactate, data= Leg_data[BD_and_lactate,])
} else {
  mod_impute2 = lmer(BD ~ lactate + (1 | studyID), data= Leg_data[BD_and_lactate,])
}
missing_BD = is.na(Leg_data$BD)
Available_Lactate = !is.na(Leg_data$lactate)
print(paste(sum(missing_BD & Available_Lactate), 'observations will now be imputed'))
```

```
## [1] "722 observations will now be imputed"
```

```
# impute with model
Leg_data$BD[missing_BD & Available_Lactate] = predict(mod_impute2,newdata=Leg_data[missing_BD & Availabl
```

Impute base deficit from respiratory rate

```
BD_and_rr = !is.na(Leg_data$BD) & !is.na(Leg_data$rr)
print(paste('We have ', sum(BD_and_rr), 'observations for both resp rate and base deficit'))
```

```
## [1] "We have  7572 observations for both resp rate and base deficit"
```

```
mod_impute3 = lmer(BD ~ rr + (1 | studyID), data= Leg_data[BD_and_rr,])
missing_BD = is.na(Leg_data$BD)
Available_rr = !is.na(Leg_data$rr)
print(paste(sum(missing_BD & Available_rr), 'observations will now be imputed'))
```

```
## [1] "1650 observations will now be imputed"
```

```
Leg_data$BD[missing_BD & Available_rr] = predict(mod_impute3,newdata=Leg_data[missing_BD & Available_rr
```

Impute blood urea nitrogen from creatinine:

```
BUN_and_cr = !is.na(Leg_data$BUN) & !is.na(Leg_data$creatinine)
print(paste('We have ', sum(BUN_and_cr), 'observations for both blood urea nitrogen and creatinine'))
```

```
## [1] "We have  1453 observations for both blood urea nitrogen and creatinine"
```

```
mod_impute4 = lmer(BUN ~ creatinine + (1 | studyID), data= Leg_data[BUN_and_cr,])
missing_BUN = is.na(Leg_data$BUN)
Available_cr = !is.na(Leg_data$creatinine)
print(paste(sum(missing_BUN & Available_cr), 'observations will now be imputed'))
```

```
## [1] "679 observations will now be imputed"
```

```
Leg_data$BUN[missing_BUN & Available_cr] = predict(mod_impute4,newdata=Leg_data[missing_BUN & Available_
```

Resulting data we can now use: The contributions of the different studies:

```
vars_interest = c('outcome','HCT','LPAR_pct','BD','BUN','poedema',
                  'convulsions','coma','AgeInYear','drug_class')
complete_cases = apply(Leg_data[,vars_interest], 1, function(x) sum(is.na(x))) == 0
Complete_Leg_data = Leg_data[complete_cases,] # for the model fitting
Complete_Leg_data$studyID = as.factor(as.character(Complete_Leg_data$studyID))
# Whole dataset
table(Leg_data$studyID)
```

```
##
##          AAV           AQ     AQGambia      AQUAMAT Core Malaria
##          370          560          579         5494         1122
##    SEAQUAMAT
```

```
##         1461
```

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

```
##
##          AAV           AQ     AQGambia      AQUAMAT Core Malaria
##          214          150          168         3666          657
##    SEAQUAMAT
##         1333
```

```
Complete_Leg_data$drug_AS = 0
Complete_Leg_data$drug_AS[Complete_Leg_data$drug_class=='artemisinin']=1

# remove infinite log parasitaemias
ind_keep = !(is.infinite(Complete_Leg_data$LPAR_pct) | is.nan(Complete_Leg_data$LPAR_pct))
Complete_Leg_data = Complete_Leg_data[ind_keep,]
```

Exploratory analysis

```
for(s in unique(Complete_Leg_data$studyID)){
  print(paste(s, ', mortality of:', round(100*mean(Complete_Leg_data$outcome[Complete_Leg_data$studyID==
}
```

```
## [1] "Core Malaria , mortality of: 23 %"
## [1] "AQGambia , mortality of: 12 %"
## [1] "AAV , mortality of: 12 %"
## [1] "SEAQUAMAT , mortality of: 18 %"
## [1] "AQUAMAT , mortality of: 9 %"
## [1] "AQ , mortality of: 23 %"
```

```
for(s in unique(Complete_Leg_data$studyID)){
  print(paste0(s, ', ages:', round(quantile(Complete_Leg_data$AgeInYear[Complete_Leg_data$studyID==s], p
}
```

```
## [1] "Core Malaria, ages:1Core Malaria, ages:27Core Malaria, ages:75"
## [1] "AQGambia, ages:1AQGambia, ages:4AQGambia, ages:9"
## [1] "AAV, ages:15AAV, ages:34AAV, ages:77"
## [1] "SEAQUAMAT, ages:2SEAQUAMAT, ages:25SEAQUAMAT, ages:87"
## [1] "AQUAMAT, ages:0AQUAMAT, ages:2AQUAMAT, ages:78"
## [1] "AQ, ages:15AQ, ages:30AQ, ages:74"
```

```
for(s in unique(Complete_Leg_data$studyID)){
  print(s)
  print(table(Complete_Leg_data$drug[Complete_Leg_data$studyID==s]))
}
```

```
## [1] "Core Malaria"
##
##  Amodiaquine   Artemether   Artesunate  Chloroquine Lumefantrine
##            0           11          368            2            0
##   Mefloquine          NAC      Quinine
##            7            6          262
## [1] "AQGambia"
##
```

```
##  Amodiaquine   Artemether   Artesunate  Chloroquine Lumefantrine
##            0           82            0            0            0
##   Mefloquine          NAC      Quinine
##            0            0           86
## [1] "AAV"
##
##  Amodiaquine   Artemether   Artesunate  Chloroquine Lumefantrine
##            0          102          112            0            0
##   Mefloquine          NAC      Quinine
##            0            0            0
## [1] "SEAQUAMAT"
##
##  Amodiaquine   Artemether   Artesunate  Chloroquine Lumefantrine
##            0            0          645            0            0
##   Mefloquine          NAC      Quinine
##            0            0          628
## [1] "AQUAMAT"
##
##  Amodiaquine   Artemether   Artesunate  Chloroquine Lumefantrine
##            0            0         1837            0            0
##   Mefloquine          NAC      Quinine
##            0            0         1818
## [1] "AQ"
##
##  Amodiaquine   Artemether   Artesunate  Chloroquine Lumefantrine
##            0           73            0            0            0
##   Mefloquine          NAC      Quinine
##            0            0           77
```

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

```
## Linear mixed model fit by REML ['lmerMod']
## Formula: BD ~ HCT + (1 | studyID/country)
##    Data: Complete_Leg_data
##
## REML criterion at convergence: 40261.9
##
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -4.4421 -0.6612 -0.1488  0.5224  4.7209
##
## Random effects:
##  Groups          Name        Variance Std.Dev.
##  country:studyID (Intercept)  2.6525  1.6286
##  studyID         (Intercept)  0.8373  0.9151
##  Residual                    41.8947  6.4726
## Number of obs: 6116, groups:  country:studyID, 18; studyID, 6
##
## Fixed effects:
##              Estimate Std. Error t value
## (Intercept) 10.339058   0.653393   15.82
## HCT         -0.133548   0.009699  -13.77
##
## Correlation of Fixed Effects:
##     (Intr)
```

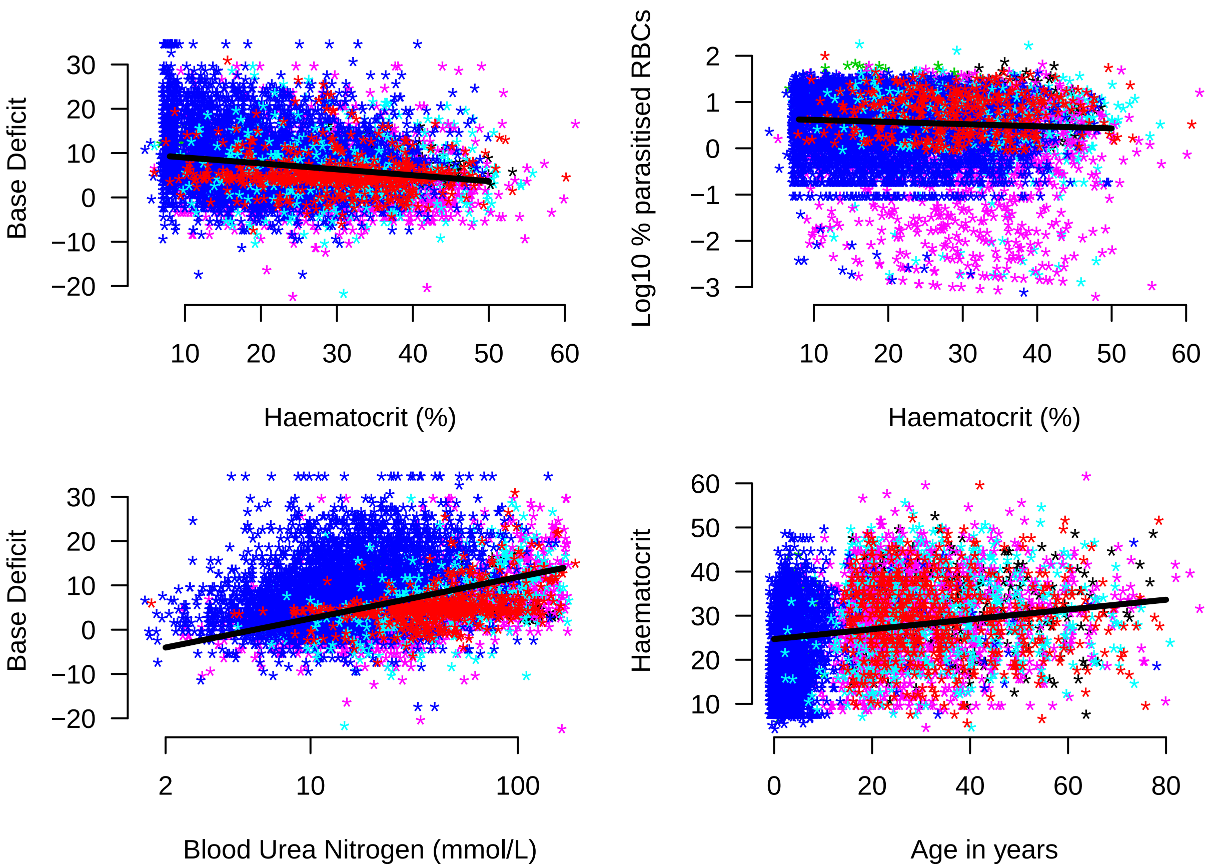
```
## HCT -0.394
```

```
## Linear mixed model fit by REML ['lmerMod']
## Formula: LPAR_pct ~ HCT + (1 | studyID/country)
##    Data: Complete_Leg_data
##
## REML criterion at convergence: 13822.9
##
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -4.7144 -0.5555  0.1598  0.7265  2.4355
##
## Random effects:
##  Groups          Name        Variance Std.Dev.
##  country:studyID (Intercept) 0.00946  0.09726
##  studyID         (Intercept) 0.07496  0.27379
##  Residual                    0.55564  0.74541
## Number of obs: 6116, groups:  country:studyID, 18; studyID, 6
##
## Fixed effects:
##              Estimate Std. Error t value
## (Intercept)  0.659944   0.121244   5.443
## HCT         -0.004579   0.001116  -4.105
##
## Correlation of Fixed Effects:
##     (Intr)
## HCT -0.251
```

```
## Linear mixed model fit by REML ['lmerMod']
## Formula: BD ~ log10(BUN) + (1 | studyID/country)
##    Data: Complete_Leg_data
##
## REML criterion at convergence: 39236.2
##
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -5.6063 -0.6369 -0.1041  0.5191  5.0754
##
## Random effects:
##  Groups          Name        Variance Std.Dev.
##  country:studyID (Intercept)  2.876   1.696
##  studyID         (Intercept)  6.858   2.619
##  Residual                    35.405   5.950
## Number of obs: 6116, groups:  country:studyID, 18; studyID, 6
##
## Fixed effects:
##             Estimate Std. Error t value
## (Intercept)  -6.8409     1.2574   -5.44
## log10(BUN)    9.3530     0.2559   36.55
##
## Correlation of Fixed Effects:
##            (Intr)
## log10(BUN) -0.293
```

```
## Linear mixed model fit by REML ['lmerMod']
```

```
## Formula: HCT ~ AgeInYear + (1 | studyID/country)
##    Data: Complete_Leg_data
##
## REML criterion at convergence: 43534.9
##
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -3.1004 -0.7399 -0.0515  0.6927  3.5627
##
## Random effects:
##  Groups          Name        Variance Std.Dev.
##  country:studyID (Intercept)  5.722   2.392
##  studyID         (Intercept)  7.322   2.706
##  Residual                    71.467   8.454
## Number of obs: 6116, groups:  country:studyID, 18; studyID, 6
##
## Fixed effects:
##             Estimate Std. Error t value
## (Intercept) 24.69246    1.36141  18.137
## AgeInYear    0.11159    0.01159   9.626
##
## Correlation of Fixed Effects:
##           (Intr)
## AgeInYear -0.185
```

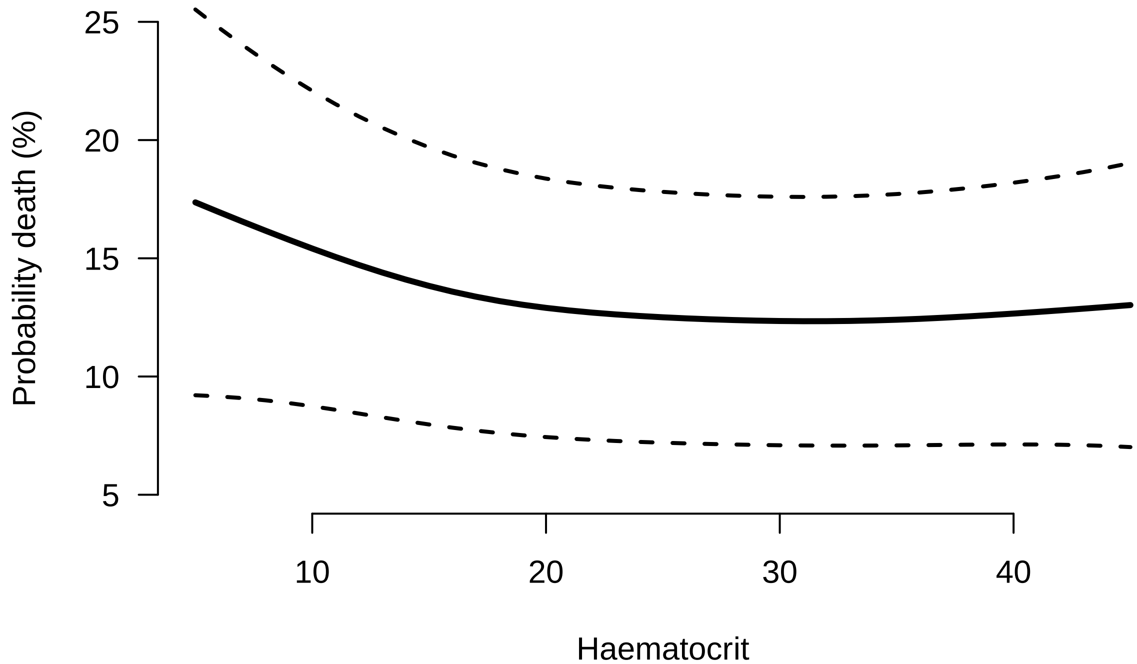


If we look at the relationship between haematocrit and death:

```r
par(las=1, bty='n')
Complete_Leg_data$country=as.factor(Complete_Leg_data$country)
modHCT=gam(outcome ~ s(HCT) + s(studyID, bs='re') + s(country, bs='re'),data = Complete_Leg_data, famil
summary(modHCT)
```

```
##
## Family: binomial
## Link function: logit
##
## Formula:
## outcome ~ s(HCT) + s(studyID, bs = "re") + s(country, bs = "re")
##
## Parametric coefficients:
##             Estimate Std. Error z value Pr(>|z|)
## (Intercept)  -1.8865     0.2397   -7.87 3.54e-15 ***
## ---
## 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)      2.304  2.922   5.482 0.15478
## s(studyID)  3.611  5.000 314.182 0.00361 **
## s(country) 10.766 14.000 162.027 0.01464 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## R-sq.(adj) =  0.0484   Deviance explained = 5.99%
## UBRE = -0.25846  Scale est. = 1         n = 6116
```

```r
preds = predict(modHCT, newdata = data.frame(HCT=5:45, studyID='AQ', country='Thailand', country=1),
                        exclude = c("s(country)","s(studyID)"), type='response', se.fit=T)
plot(5:45, 100*preds$fit, ylab='Probability death (%)', xlab='Haematocrit',
     type='l', lwd=3,ylim = c(5,25))
lines(5:45, 100*preds$fit + 100*2*preds$se.fit, lty=2,lwd=2)
lines(5:45, 100*preds$fit - 100*2*preds$se.fit,lty=2,lwd=2)
```



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_GLM = glmer(outcome ~ HCT + LPAR_pct + AgeInYear + coma + convulsions +
                       poedema + log10(BUN) + BD + drug_AS +
                       (1 | studyID) + (1 | country),
                     data = Complete_Leg_data, family=binomial)
```

```
## Warning in checkConv(attr(opt, "derivs"), opt$par, ctrl = control
## $checkConv, : Model failed to converge with max|grad| = 0.00101495 (tol =
## 0.001, component 1)
```

```
summary(mod_full_GLM)
```

```
## Generalized linear mixed model fit by maximum likelihood (Laplace
##   Approximation) [glmerMod]
##  Family: binomial  ( logit )
## Formula:
## outcome ~ HCT + LPAR_pct + AgeInYear + coma + convulsions + poedema +
##     log10(BUN) + BD + drug_AS + (1 | studyID) + (1 | country)
##    Data: Complete_Leg_data
##
##      AIC      BIC   logLik deviance df.resid
##   3459.7   3540.3  -1717.8   3435.7     6104
##
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -3.9034 -0.3324 -0.1914 -0.1076 15.4072
##
## Random effects:
##  Groups   Name        Variance  Std.Dev.
```

```
##  country (Intercept) 1.501e-01 3.875e-01
##  studyID (Intercept) 1.919e-09 4.381e-05
## Number of obs: 6116, groups:  country, 15; studyID, 6
##
## Fixed effects:
##               Estimate Std. Error z value Pr(>|z|)
## (Intercept)  -7.000057   0.306929 -22.807  < 2e-16 ***
## HCT           0.016441   0.005284   3.111 0.001863 **
## LPAR_pct     -0.001281   0.060471  -0.021 0.983095
## AgeInYear     0.013715   0.003840   3.571 0.000355 ***
## coma          1.338046   0.100906  13.260  < 2e-16 ***
## convulsions1  0.513532   0.116864   4.394 1.11e-05 ***
## poedema1      0.543720   0.385373   1.411 0.158276
## log10(BUN)    1.778368   0.166012  10.712  < 2e-16 ***
## BD            0.121719   0.007183  16.944  < 2e-16 ***
## drug_AS      -0.343604   0.090337  -3.804 0.000143 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##             (Intr) HCT    LPAR_p AgInYr coma   cnvls1 poedm1 l10(BU BD
## HCT         -0.483
## LPAR_pct    -0.041  0.030
## AgeInYear    0.039 -0.178  0.001
## coma        -0.163 -0.027  0.075  0.000
## convulsins1 -0.133 -0.073  0.017  0.108 -0.220
## poedema1    -0.004 -0.005 -0.006 -0.048  0.027  0.000
## log10(BUN)  -0.700  0.064 -0.047 -0.245 -0.014  0.103  0.006
## BD          -0.148  0.199 -0.180  0.135 -0.024  0.024 -0.008 -0.262
## drug_AS     -0.091 -0.012 -0.024 -0.022  0.007  0.004 -0.025 -0.044 -0.020
## convergence code: 0
## Model failed to converge with max|grad| = 0.00101495 (tol = 0.001, component 1)
```

Now let's make counterfactual predictions of anaemia on death for the patients in the database.

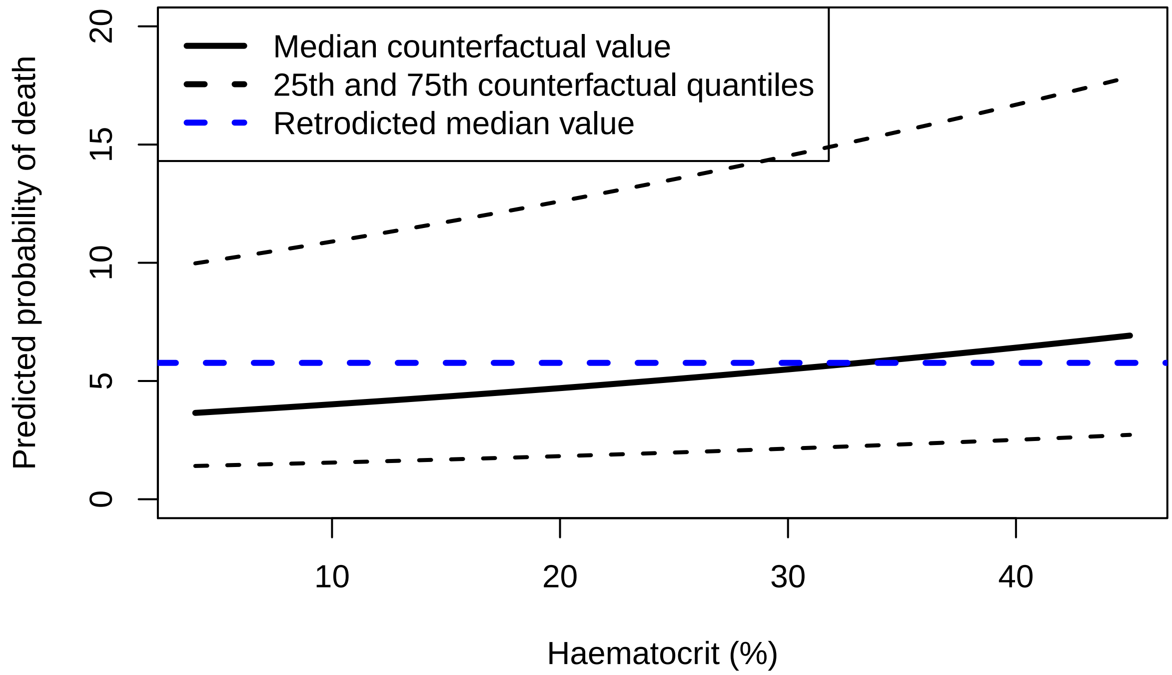
```
myquantiles = c(0.25,0.5,0.75) # this is 50% predictive interval

overall_median_mortality = median(100*predict(mod_full_GLM, type='response'))
par(las=1, bty='n')
x_hcts = seq(4,45, by=1)
probs_lin = 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_GLM, newdata = mydata, re.form=NA, type='response')
  probs_lin[,i] = quantile(ys, probs=myquantiles)
}
```

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.

```
plot(x_hcts,probs_lin[2,], xlim=c(4,45), ylab='Predicted probability of death',
     xlab='Haematocrit (%)', ylim=c(0,20), lty=1, lwd=3, type='l')
lines(x_hcts, probs_lin[1,], lty=2, lwd=2)
```

```
lines(x_hcts, probs_lin[3,], lty=2, lwd=2)
abline(h=overall_median_mortality, lwd=3, col='blue',lty=2)
legend('topleft', col=c('black','black','blue'), lwd=3, lty=c(1,2,2),
       legend = c('Median counterfactual value', '25th and 75th counterfactual quantiles','Retrodicted r
```



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. We add a random effect term for the studyID We should also be doing this for the study site…

```
mod_full_GAM = gam(outcome ~ s(HCT,AgeInYear) + LPAR_pct  + coma + convulsions +
                     poedema + log10(BUN) + BD + drug_AS +
                     s(studyID, bs='re') + s(country, bs='re'),
                   data=Complete_Leg_data, family=binomial)
summary(mod_full_GAM)
```

```
##
## Family: binomial
## Link function: logit
##
## Formula:
## outcome ~ s(HCT, AgeInYear) + LPAR_pct + coma + convulsions +
##     poedema + log10(BUN) + BD + drug_AS + s(studyID, bs = "re") +
##     s(country, bs = "re")
##
## Parametric coefficients:
##               Estimate Std. Error z value Pr(>|z|)
## (Intercept)  -6.327660   0.270379 -23.403  < 2e-16 ***
## LPAR_pct      0.001763   0.060455   0.029 0.976734
## coma          1.330823   0.100889  13.191  < 2e-16 ***
```

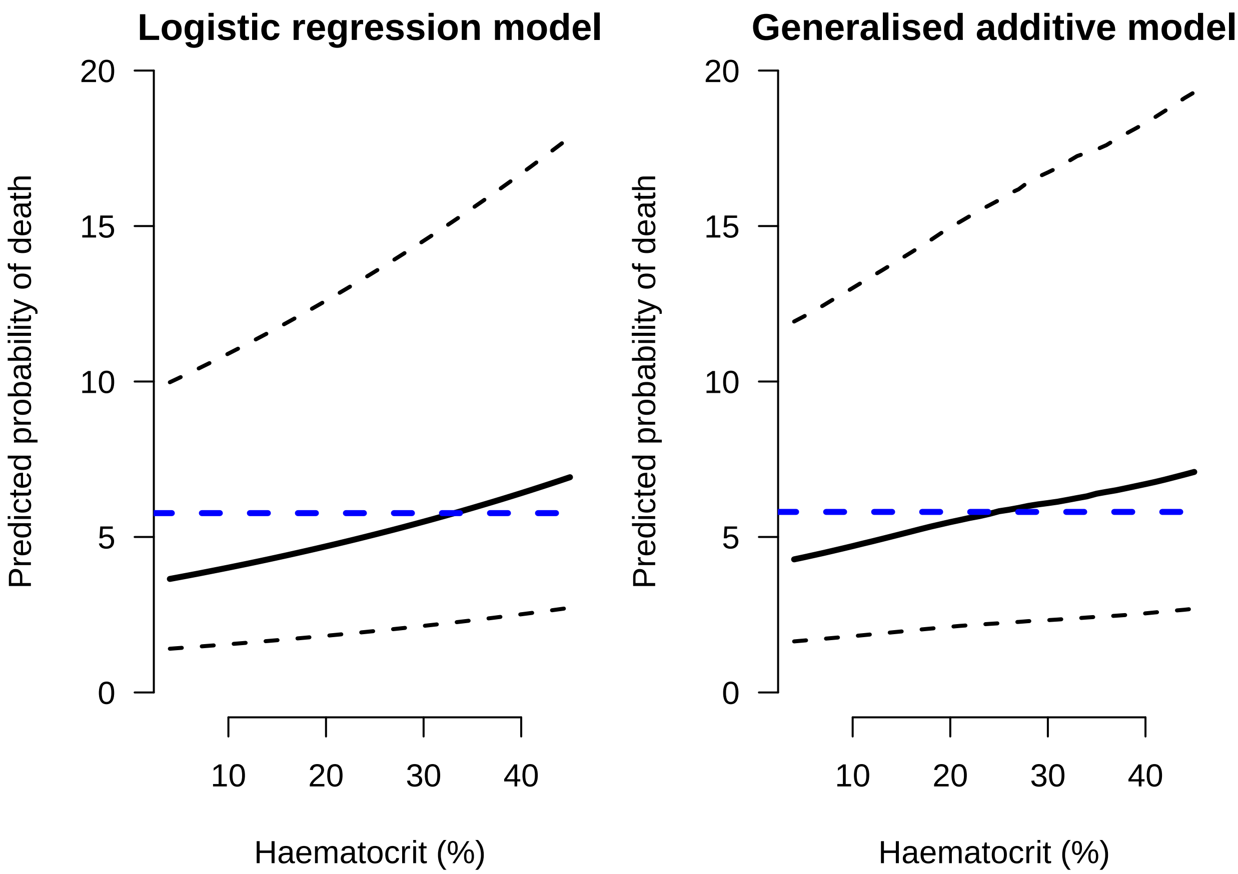
```
## convulsions1  0.534702   0.117347   4.557  5.2e-06 ***
## poedema1      0.547874   0.384141   1.426 0.153801
## log10(BUN)    1.701427   0.170554   9.976  < 2e-16 ***
## BD            0.123330   0.007331  16.824  < 2e-16 ***
## drug_AS      -0.343908   0.090360  -3.806 0.000141 ***
## ---
## Signif. 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) 5.486902  7.664 33.629 3.61e-05 ***
## s(studyID)       0.004287  5.000  0.003    0.495
## s(country)       9.944672 14.000 74.600 2.80e-15 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## R-sq.(adj) =   0.27   Deviance explained = 29.1%
## UBRE = -0.43785  Scale est. = 1         n = 6116
```

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

```r
overall_median_mortalityGAM = median(100*predict(mod_full_GAM, type='response'))
par(las=1, bty='n')
probs_gam = 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, type='response')
  probs_gam[,i] = quantile(ys, probs=myquantiles)
}
```

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

```r
#
par(las=1, mfrow=c(1,2), bty='n', mar=c(4,4,1,1))
### Plot the standard logistic regression model
plot(x_hcts,probs_lin[2,], xlim=c(4,45), ylab='Predicted probability of death',
     xlab='Haematocrit (%)', ylim=c(0,20), lty=1, lwd=3, type='l')
lines(x_hcts, probs_lin[1,], lty=2, lwd=2)
lines(x_hcts, probs_lin[3,], lty=2, lwd=2)
abline(h=overall_median_mortality, lwd=3, col='blue',lty=2)
title('Logistic regression model')
### And now the GAM model
plot(x_hcts,probs_gam[2,], xlim=c(4,45), ylab='Predicted probability of death',
     xlab='Haematocrit (%)', ylim=c(0,20), lty=1, lwd=3, type='l')
lines(x_hcts, probs_gam[1,], lty=2, lwd=2)
lines(x_hcts, probs_gam[3,], lty=2, lwd=2)
abline(h=overall_median_mortalityGAM, lwd=3, col='blue',lty=2)
title('Generalised additive model')
```



Model comparison

Which model is better fit in terms of AIC

```r
print(AIC(mod_full_GAM, mod_full_GLM))
```

```
##                    df      AIC
## mod_full_GAM 23.43586 3438.101
## mod_full_GLM 12.00000 3459.687
```

And in terms of deviance

```r
print(list(mod_full_GLM = deviance(mod_full_GLM), mod_full_GAM=deviance(mod_full_GAM)))
```

```
## $mod_full_GLM
## [1] 3400.304
##
## $mod_full_GAM
## [1] 3391.229
```