Charactersing effect of anaemia on mortality in severe malaria

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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],
}
```

```
## [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"
##
##  Artemether  Artesunate Chloroquine  Mefloquine         NAC     Quinine
##          11         368           2           7           6         262
## [1] "AQGambia"
##
## Artemether    Quinine
##         82         86
## [1] "AAV"
##
## Artemether Artesunate
##        102        112
## [1] "SEAQUAMAT"
##
## Artesunate    Quinine
##        645        628
## [1] "AQUAMAT"
##
## Artesunate    Quinine
##       1837       1818
## [1] "AQ"
##
## Artemether    Quinine
##         73         77
```

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

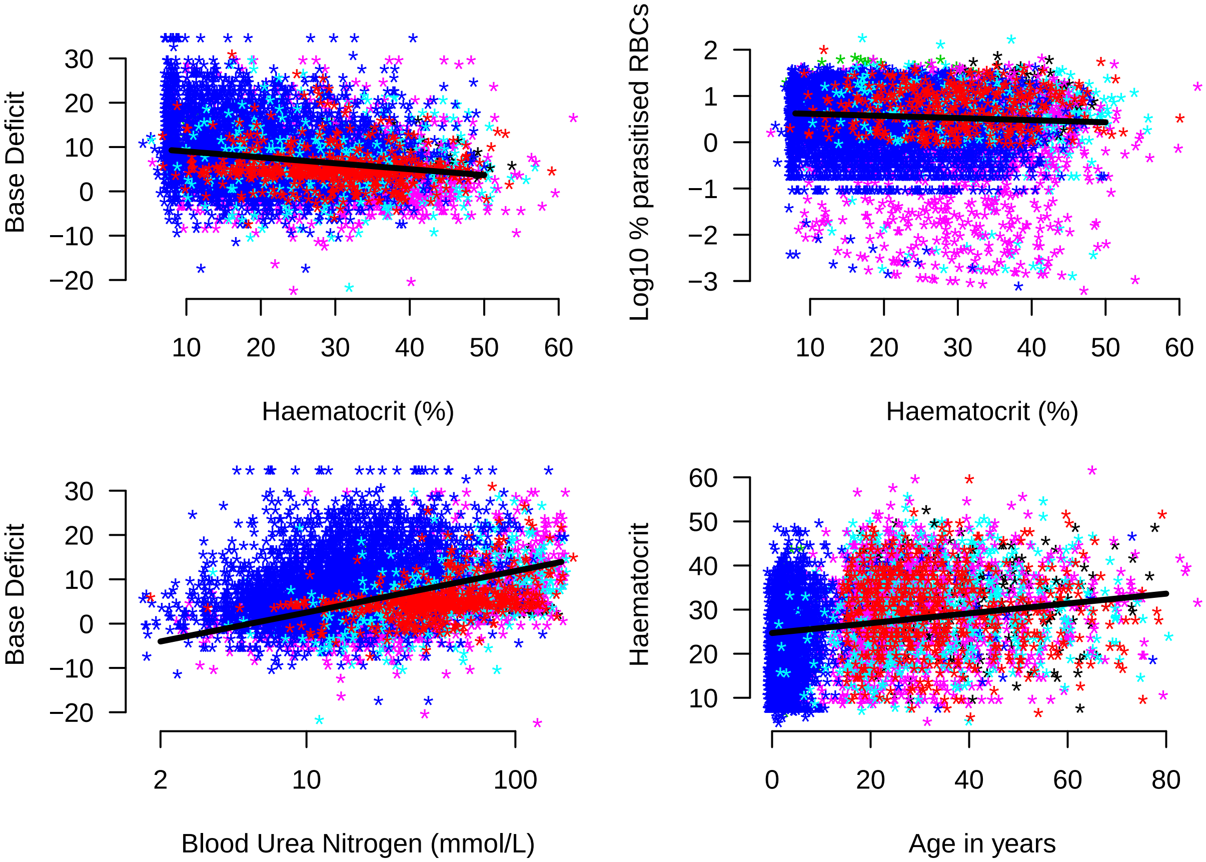
```
## Linear mixed model fit by REML ['lmerMod']
## Formula: BD ~ HCT + (1 | studyID/country)
##    Data: Complete_Leg_data
##
## REML criterion at convergence: 40261.9
##
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -4.4421 -0.6612 -0.1488  0.5224  4.7209
##
## Random effects:
##  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
```



Predictive value of anaemia on death adjusting for confounders

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

```
Complete_Leg_data$country=as.factor(Complete_Leg_data$country)
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| = 0.00216998 (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
##   3460.3   3540.9  -1718.2   3436.3     6104
##
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -3.8745 -0.3319 -0.1918 -0.1083 15.4981
##
## Random effects:
##  Groups  Name        Variance  Std.Dev.
##  country (Intercept) 1.419e-01 3.767e-01
##  studyID (Intercept) 2.272e-09 4.766e-05
## Number of obs: 6116, groups:  country, 16; studyID, 6
##
## Fixed effects:
##               Estimate Std. Error z value Pr(>|z|)
## (Intercept)  -6.983607   0.303116 -23.039  < 2e-16 ***
## HCT           0.016434   0.005280   3.113 0.001854 **
## LPAR_pct      0.001461   0.060471   0.024 0.980728
## AgeInYear     0.013550   0.003816   3.551 0.000384 ***
## coma          1.347163   0.100988  13.340  < 2e-16 ***
## convulsions1  0.503538   0.116981   4.304 1.67e-05 ***
## poedema1      0.544303   0.385069   1.414 0.157503
## log10(BUN)    1.779846   0.165792  10.735  < 2e-16 ***
## BD            0.121095   0.007202  16.813  < 2e-16 ***
## drug_AS      -0.343889   0.090333  -3.807 0.000141 ***
## ---
## 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         -0.487
## LPAR_pct    -0.046  0.030
## AgeInYear    0.053 -0.182  0.003
## coma        -0.173 -0.028  0.077  0.001
## convulsins1 -0.125 -0.072  0.015  0.107 -0.224
## poedema1    -0.003 -0.005 -0.006 -0.049  0.027  0.000
## log10(BUN)  -0.705  0.063 -0.045 -0.253 -0.010  0.098  0.006
## BD          -0.143  0.199 -0.183  0.138 -0.031  0.030 -0.008 -0.265
## drug_AS     -0.092 -0.012 -0.024 -0.022  0.007  0.003 -0.025 -0.044 -0.021
## convergence code: 0
## Model failed to converge with max|grad| = 0.00216998 (tol = 0.001, component 1)
```

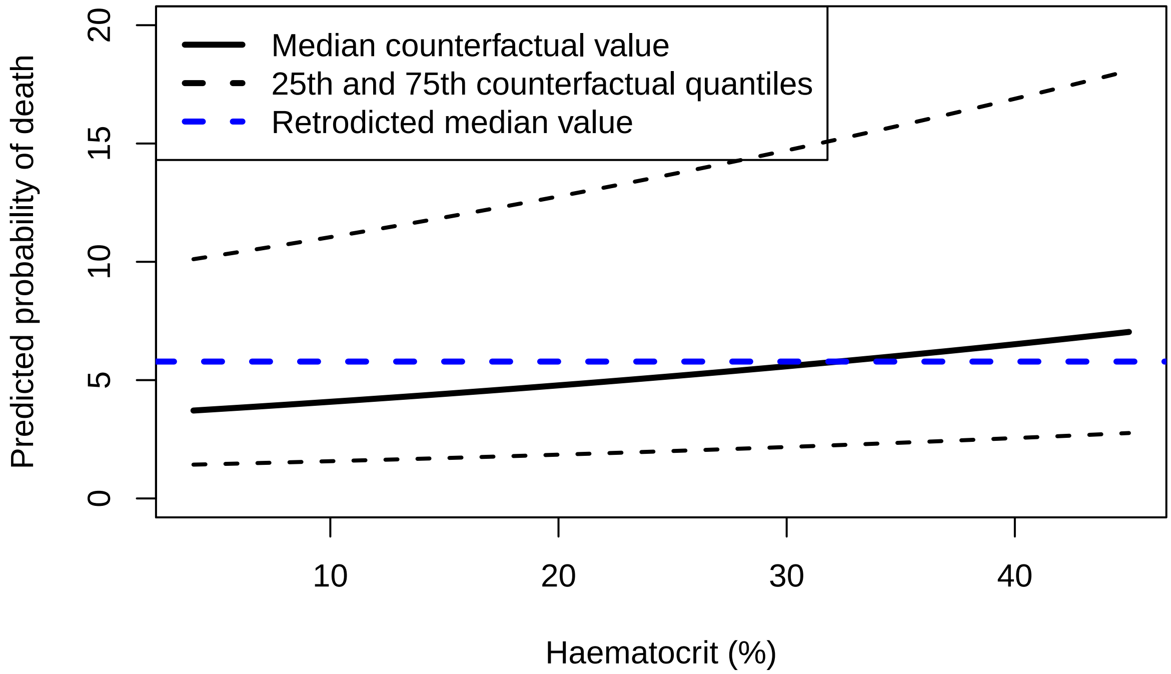
Now let's make counterfactual predictions of anaemia on death for the patients in the database.

```
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
```



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)
```

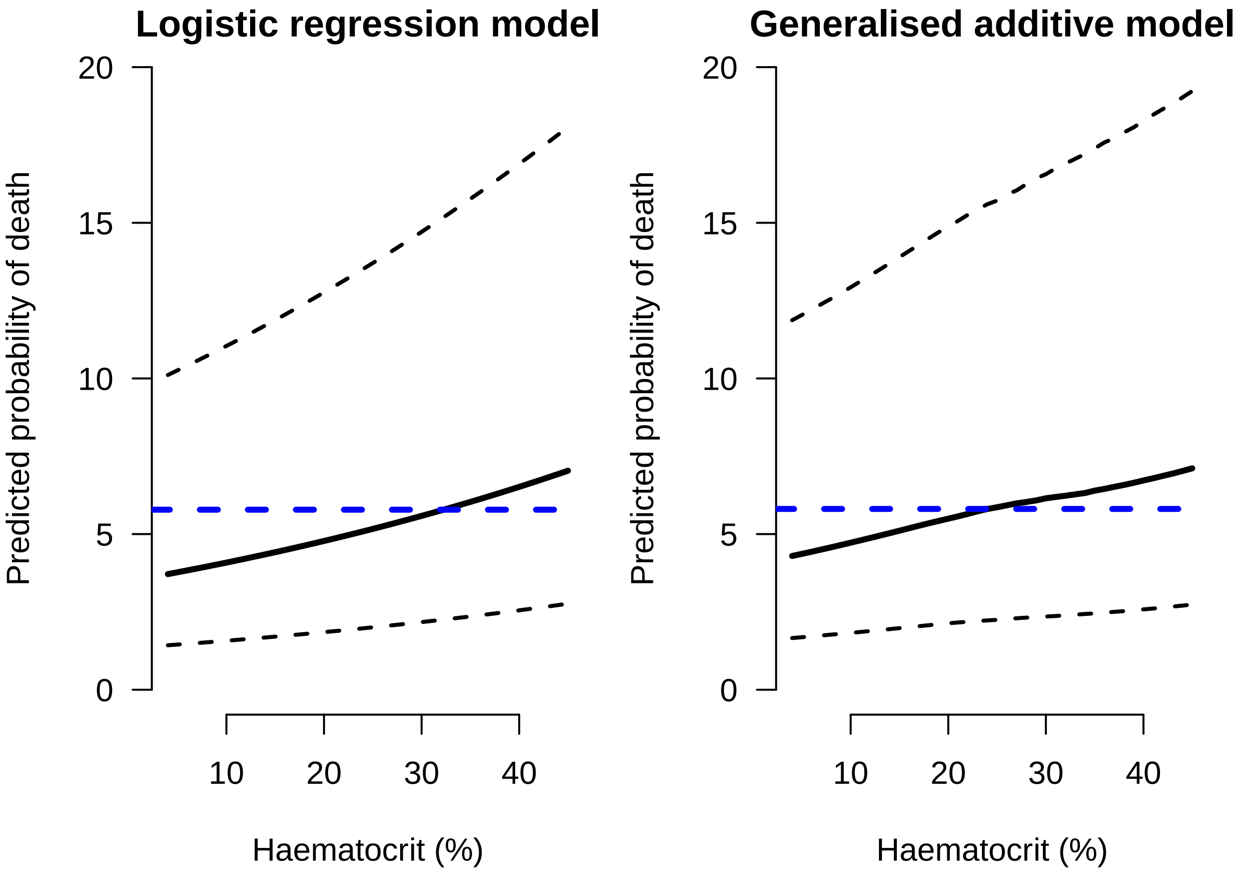
```
##
## Family: binomial
## Link function: logit
##
## Formula:
## outcome ~ s(HCT, AgeInYear) + LPAR_pct + coma + convulsions +
##     poedema + log10(BUN) + BD + drug_AS + s(studyID, bs = "re") +
##     s(country, bs = "re")
##
## Parametric coefficients:
##               Estimate Std. Error z value Pr(>|z|)
## (Intercept)  -6.313364   0.269592 -23.418  < 2e-16 ***
## LPAR_pct      0.005387   0.060503   0.089 0.929055
## coma          1.341020   0.100997  13.278  < 2e-16 ***
## convulsions1  0.523154   0.117424   4.455 8.38e-06 ***
## poedema1      0.553081   0.384188   1.440 0.149977
## log10(BUN)    1.704622   0.170398  10.004  < 2e-16 ***
## BD            0.122630   0.007348  16.688  < 2e-16 ***
## drug_AS      -0.343192   0.090443  -3.795 0.000148 ***
## ---
## 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)  5.3258  7.429 32.471 4.8e-05 ***
## s(studyID)        0.1912  5.000  0.198   0.407
## s(country)       10.4166 15.000 75.283 6.9e-15 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## R-sq.(adj) =   0.27   Deviance explained = 29.1%
## UBRE = -0.43766  Scale est. = 1         n = 6116
```

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

```
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:

```
#
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

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

```
##                    df      AIC
## mod_full_GAM 23.93359 3439.294
## mod_full_GLM 12.00000 3460.312
```

And in terms of deviance

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

```
## $mod_full_GLM
## [1] 3400.247
##
## $mod_full_GAM
## [1] 3391.427
```