TTE Modeling History

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30 July, 2018

Contents

1 Preamble

```
##====================================== PREAMBLE ======================================##
script.version <- "V2"      #
script.status  <- "DRAFT"   #
set.seed(11626)             # reproducibility
##------------------------------------------------------------------------------------##

## DIRECTORIES ----
project.dir <- file.path("",'pmx_bip','PMx_Playground','gbenitez',
                         "other_projects",  'PostDoc_project_ISoP', '2018_TTE')
data.dir <-file.path(project.dir,"DATA")
nm.dir <-file.path(project.dir, 'NONMEM')
setwd(nm.dir)

## Study specific terms
proj.no        <- "TTE_tutorial"
analysis.type  <- "TTE"
mod.type       <- 'Base'
run.log        <- "TTE_runlog.csv" # run record name
diagnostics    <- "VisualizeRunTTE_base.Rmd" # run diagnostics
hazVPC         <- "VisualizeRunTTE_hazard.Rmd" # run hazard based vpc

## Define path for figure output:
fig.dir <- file.path(nm.dir,
                     paste0("Modelling_history_plots_",mod.type,"_",script.version), "")
knitr::opts_chunk$set(fig.path = fig.dir, dev = c('pdf', 'png'),
                      fig.align = 'center', fig.height = 9, fig.width = 16,
                      out.width = '0.95\\linewidth')
##========================================================================================##

load("/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/DATA/ProjectDataSph
```

2 Objectives

1. Develop a base time to event model for AZ Cediranib data, ProjectDataSphere # 78
2. Assess the impact of cateogical and continuous covariates on the hazard.

3 Base hazard model runs

3.0.1 Run 1 : Exponential hazard

```
##------------------------------------ Run notes  ------------------------------------##
# Rationale:   Simplest hazard model to test
# Question:    Will an exponential hazard describe this data?
##------------------------------------------------------------------------------------##
show.mod(1, nm.dir) # print model
```

```
## ;; 1. Based on:
## ;; 2. Description:
## ;;    TTE model
## ;; 3. Label:
## ;;    exponential hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;; 6. Interindividual variability:
## ;;    LAMBDA
## ;; 7. Interoccasion variability:
## ;; 8. Residual variability:
## ;; 9. Estimation:
## ;;    LAPLACE
##
##
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
##
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
##
## $PROBLEM    Base TTE model - Project DataSphere # 78
##
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVE
##
## ;-------------------------------------------------------data description
## ; ID, subject identifier
## ; TIME, in years
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
## ; CENS, censored event, 0 = no, 1 = yes
## ; MAXT, last recorded event per patient (either death or censor)
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
## ; GENDER, bianry covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
```

```
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
## ; OSTIM, observed time in days to event or censor time
##
## ;-----------------------------------------------------
##
## $DATA    ../../DATA/ProjectDataSphere78_tte_V2.csv IGNORE=@
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time, ignored for estimation
## ;IGNORE=(STIME.EQ.0) ;; observed time, ignore for simulation
## ;Sim_end
##
## $SUBROUTINE ADVAN=6 TOL=9
## $MODEL      COMP=(HAZARD)
##
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##  LAMBDA = THETA(1) * EXP(ETA(1))
##
## ;;================================ DIFFERENTIAL EQUATIONS ================================
## ; Typical Value exponential hazard h0(t) = lambda
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = LAMBDA
##
## DADT(1) = LAMBDA
##
## ;;================================= MODEL FIT ================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;-----------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;-----------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX= LAMBDA
##  HAZNOW= BASEX
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
```

```
## ;;================================= RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================= SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES ====================================
##
## $THETA
## (0, 0.2) ; lambda
##
## $OMEGA
## 0  FIX   ; place holder
##
## ;;============================== ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9  NSIG=3 MSFO=msfb_1
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
## ;Sim_end
## ;;================================= TABLES ================================
##
## ;Sim_start : add/remove for simulation
## $TABLE NOPRINT ONEHEADER FILE=mytab1
## ID TIME DV EVID MDV PRED CHZ SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALB
## ;Sim_end
```

```
##
## $TABLE NOAPPEND ONEHEADER NOPRINT FILE=sdtab1
## ID TIME SUR EVID
##
## $TABLE NOAPPEND ONEHEADER NOPRINT FILE=patab1
## ID LAMBDA ETAS(1:LAST)
##
## ;$TABLE NOAPPEND ONEHEADER NOPRINT FILE=catab1
## ;ID NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL
## NULL
```

3.0.1.1 Run summary

```
##  [1] "-------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run1/run1
##  [4] ""
##  [5] "Successful minimization                                          [    OK   ]   "
##  [6] "No rounding errors                                               [    OK   ]   "
##  [7] "No zero gradients                                                [    OK   ]   "
##  [8] "No final zero gradients                                          [    OK   ]   "
##  [9] "Hessian not reset                                                [    OK   ]   "
## [10] "No parameter near boundary                                       [    OK   ]   "
## [11] "Covariance step                                                  [    OK   ]   "
## [12] ""
## [13] "Condition number                                                 [    OK   ]   "
## [14] "Correlations                                                     [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:00"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   31.2"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   0.11"
## [19] ""
## [20] "Objective function value: 1037.8336"
## [21] ""
## [22] "Condition number: 1"
## [23] ""
## [24] "Number of observation records: 690"
## [25] "Number of individuals: 690"
## [26] ""
## [27] "         THETA               OMEGA      SIGMA    "
## [28] "lambda  0.3156  (0.05953)                         "
## [29] ""
## [30] "The relative standard errors for omega and sigma are reported on the approximate"
## [31] "standard deviation scale (SE/variance estimate)/2."
## [32] "-------------------------------------------------------------------------"
```

3.0.1.2 Diagnostic plots

3.0.1.3 Evaluation of run 1

- an exponential hazard does not describe this data (supported by diagnostics)

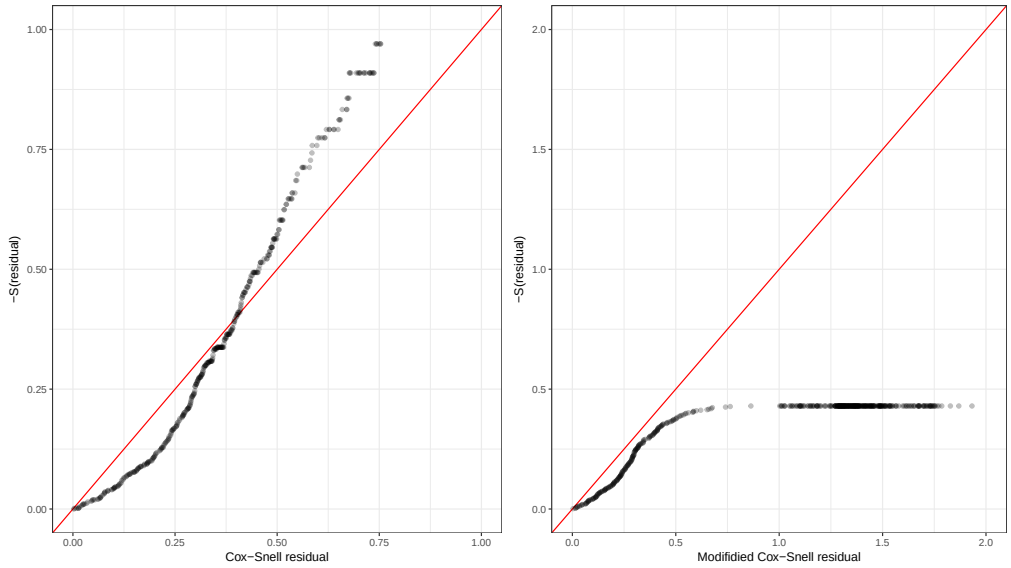


Figure 1: Residual-based diagnostics

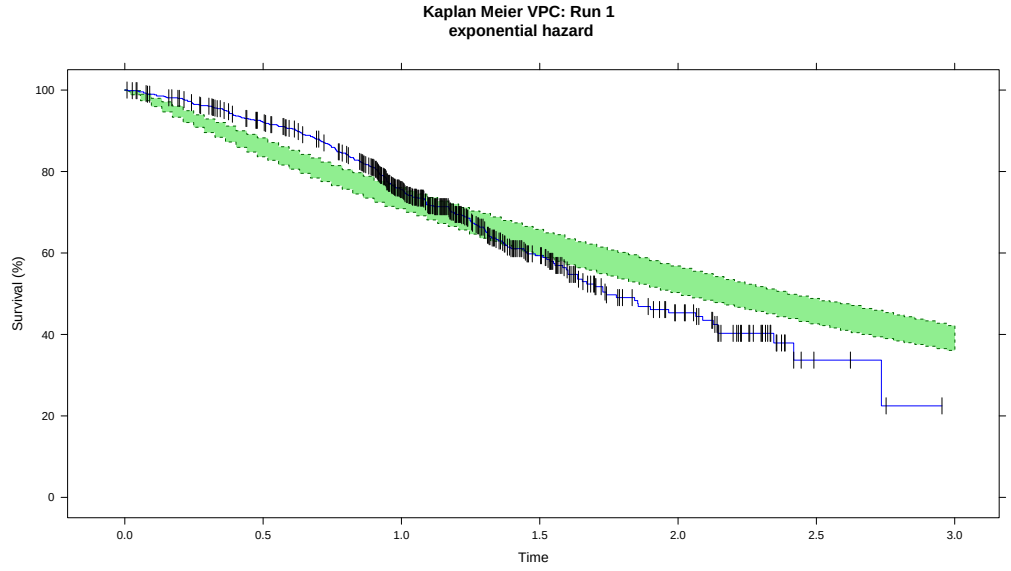


Figure 2: Simulation-based diagnostic: Kaplan Meier plot

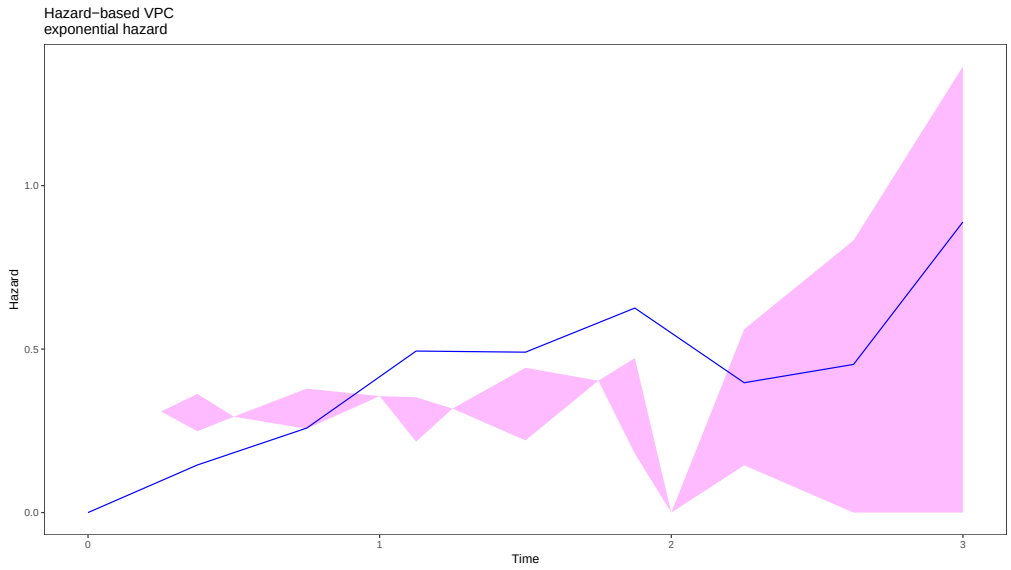


Figure 3: Simulation-based diagnostic: Hazard based VPC

3.0.2 Run 2: Gompertz hazard

```
##=================================== Run notes  ====================================##
# Rationale:   Test models with increasing complexity
# Question:    Will a Gompertz hazard describe this data?
##-----------------------------------------------------------------------------------##
show.mod(2, nm.dir) # print model
```

```
## ;; 1. Based on: 1
## ;; 2. Description:
## ;;    TTE model
## ;; 3. Label:
## ;;    Gompertz hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;; 6. Interindividual variability:
## ;; 7. Interoccasion variability:
## ;; 8. Residual variability:
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    Base TTE model - Project DataSphere # 78
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVE
##
## ;-------------------------------------------------------data description
##
## ; ID, subject identifier
##
## ; TIME, in years
##
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
##
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
##
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
##
## ; CENS, censored event, 0 = no, 1 = yes
##
## ; MAXT, last recorded event per patient (either death or censor)
##
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
##
## ; GENDER, bianry covariate (0=male,1=female)
##
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
##
## ; BLAGE, categorical, age group in years
##
```

```
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
##
## ; BLALB, continuous, ALB test values at baseline
##
## ; BLALP, continuous, ALP test values at baseline
##
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
##
## ; OSTIM, observed time in days to event or censor time
##
## ;-----------------------------------------------------
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2.csv IGNORE=@
##
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
## ;IGNORE=(STIME.EQ.0) ;; observed time, ignore for simulation
##
## ;Sim_end
## $SUBROUTINE ADVAN=6 TOL=9
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##  LAMBDA = THETA(1) * EXP(ETA(1))
##  DELTA = THETA(2)
##
## ;;================================ DIFFERENTIAL EQUATIONS ================================
## ; Typical Value Gompertz hazard h0(t) = lambda * exp(delta*t)
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = LAMBDA * EXP(DELTA*(T+DEL))
##
## DADT(1) = BASE
##
## ;;================================ MODEL FIT ================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
```

```
##  DELX = 1E-6
##  BASEX= LAMBDA * EXP(DELTA*(TIME+DELX))
##  HAZNOW= BASEX
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================ RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================ SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================ INITIAL ESTIMATES ====================================
##
## $THETA  (0,0.316) ; lambda
## (0.2)    ;delta
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_2
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
```

```
##
## ;;================================ TABLES ================================
##
## ;Sim_start : add/remove for simulation
## $TABLE      NOPRINT ONEHEADER FILE=mytab2 ID TIME DV EVID MDV PRED CHZ
##             SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTI
## ;Sim_end
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab2 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab2 ID LAMBDA
##             ETAS(1:LAST)
## ;$TABLE NOAPPEND ONEHEADER NOPRINT FILE=catab
##
## ;ID NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL

## NULL
```

3.0.2.1 Run summary

```
##  [1] "-------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run2/run2
##  [4] ""
##  [5] "Successful minimization                                        [    OK   ]   "
##  [6] "No rounding errors                                             [    OK   ]   "
##  [7] "No zero gradients                                              [    OK   ]   "
##  [8] "No final zero gradients                                        [    OK   ]   "
##  [9] "Hessian not reset                                              [    OK   ]   "
## [10] "No parameter near boundary                                     [    OK   ]   "
## [11] "Covariance step                                                [    OK   ]   "
## [12] ""
## [13] "Condition number                                               [    OK   ]   "
## [14] "Correlations                                                   [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:08"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   39"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   0.22"
## [19] ""
## [20] "Objective function value: 991.7985"
## [21] ""
## [22] "Condition number: 8.54"
## [23] ""
## [24] "Number of observation records: 690"
## [25] "Number of individuals: 690"
## [26] ""
## [27] "         THETA              OMEGA      SIGMA    "
## [28] "lambda  0.1707  (0.1059)                        "
## [29] " delta  0.7818  (0.1297)                        "
## [30] ""
## [31] "The relative standard errors for omega and sigma are reported on the approximate"
## [32] "standard deviation scale (SE/variance estimate)/2."
## [33] "-------------------------------------------------------------------------"
```

3.0.2.2 Diagnostic plots

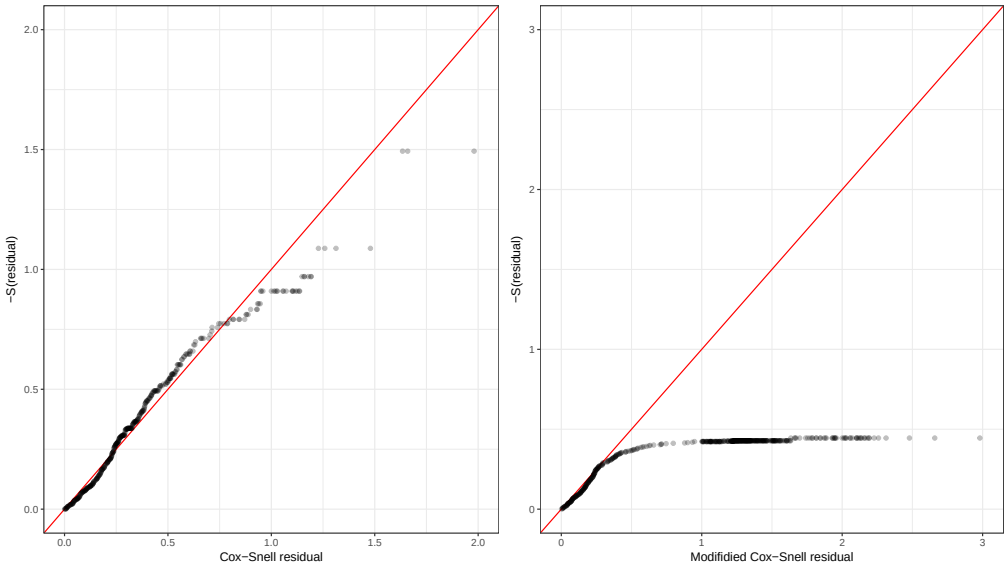


Figure 4: Residual-based diagnostics

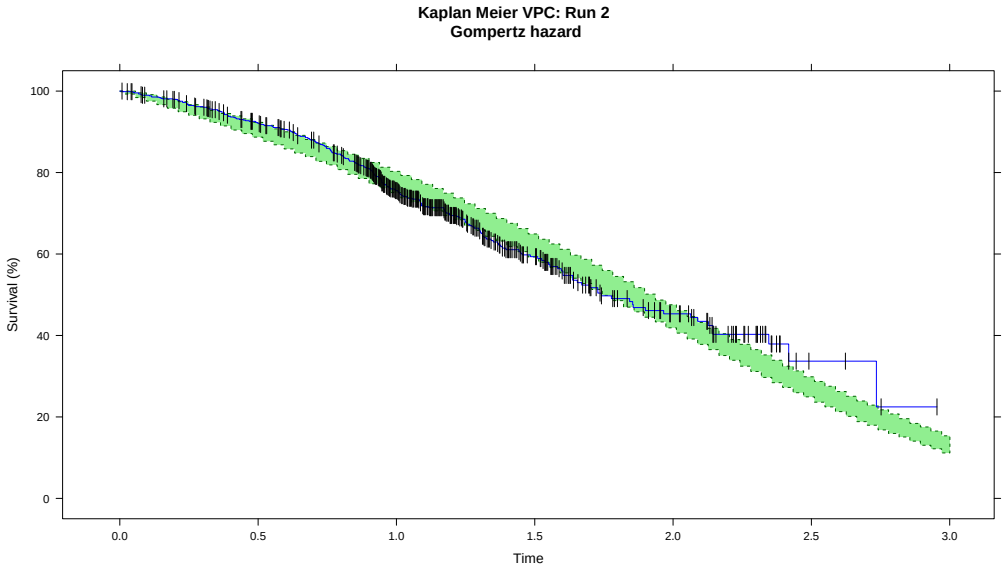


Figure 5: Simulation-based diagnostic

3.0.2.3 Evaluation of run 2

- Gompertz hazard better caputures the trend of the data up to 2 years (supported by KM VPC and hbVPC) as compared to exponential hazard

- Deviations seen in Cox-Snell residuals support the hazard is inapproriate

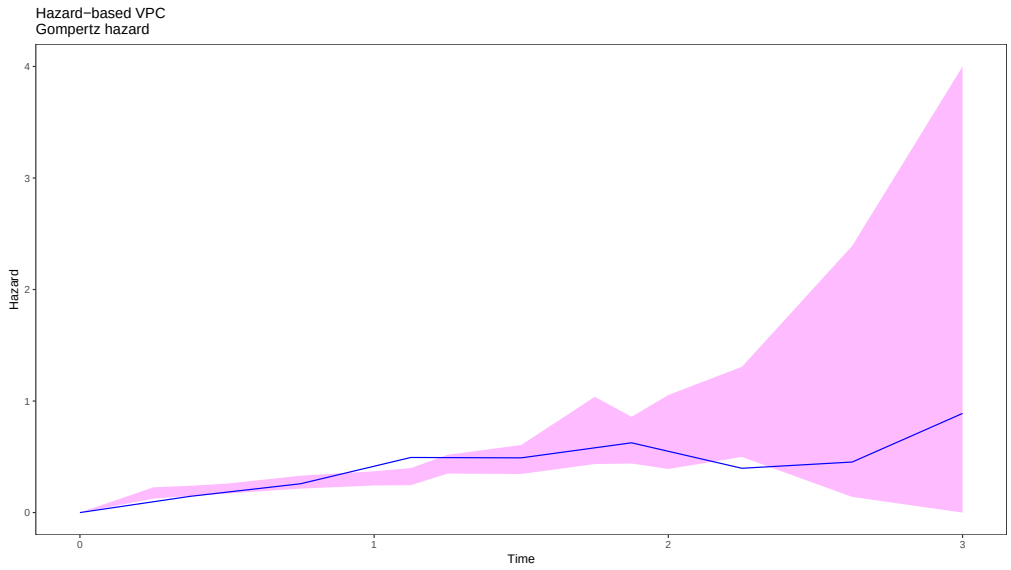


Figure 6: Simulation-based diagnostic: Hazard based VPC

3.0.3 Run 3 - Weibull hazard

```
##------------------------------------ Run notes  ------------------------------------##
# Rationale:   Test models with increasing complexity
# Question:    Will a Weibull hazard describe this data?
##------------------------------------------------------------------------------------##
show.mod(3, nm.dir) # print model
```

```
## ;; 1. Based on: 2
## ;; 2. Description:
## ;;    TTE model
## ;; 3. Label:
## ;;    Weibull hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;; 6. Interindividual variability:
## ;; 7. Interoccasion variability:
## ;; 8. Residual variability:
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    Base TTE model - Project DataSphere # 78
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVE
##
## ;-----------------------------------------------------data description
## ; ID, subject identifier
## ; TIME, in years
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
## ; CENS, censored event, 0 = no, 1 = yes
## ; MAXT, last recorded event per patient (either death or censor)
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
## ; GENDER, bianry covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
## ; OSTIM, observed time in days to event or censor time
## ;-------------------------------------------------
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2.csv IGNORE=@
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
## ;IGNORE=(STIME.EQ.0) ;; observed time, ignore for simulation
## ;Sim_end
```

```
##
## $SUBROUTINE ADVAN=6 TOL=6
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##  LAMBDA = THETA(1) * EXP(ETA(1))
##  GAMMA = THETA(2)
##
## ;;================================ DIFFERENTIAL EQUATIONS ================================
## ; Typical Value Weibull hazard h0(t) = lambda*gamma*t^(gamma-1)
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = (LAMBDA*GAMMA)*(LAMBDA*(T+DEL))**(GAMMA-1)
##
## DADT(1) = BASE
##
## ;;================================ MODEL FIT ================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=(LAMBDA*GAMMA)*(LAMBDA*(TIME+DELX))**(GAMMA-1)
##  HAZNOW= BASEX
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================ RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
```

```
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================= SIMULATION ========================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES ==================================
##
## $THETA  (0,0.171) ; lambda
##  (0, 0.2) ; gamma
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_3
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
##
## ;;================================= TABLES ================================
##
## $TABLE      NOPRINT ONEHEADER FILE=mytab3 ID TIME DV EVID MDV PRED CHZ
##             SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTI
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab3 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab3 ID LAMBDA
##             ETAS(1:LAST)
## ;$TABLE NOAPPEND ONEHEADER NOPRINT FILE=catab
##
## ;ID NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL

## NULL
```

3.0.3.1 Run summary

```
##  [1] "-------------------------------------------------------------------------"
##  [2] ""
```

```
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run3/run3
##  [4] ""
##  [5] "Successful minimization                                              [    OK   ]   "
##  [6] "No rounding errors                                                   [    OK   ]   "
##  [7] "No zero gradients                                                    [    OK   ]   "
##  [8] "No final zero gradients                                              [    OK   ]   "
##  [9] "Hessian not reset                                                    [    OK   ]   "
## [10] "No parameter near boundary                                           [    OK   ]   "
## [11] "Covariance step                                                      [    OK   ]   "
## [12] ""
## [13] "Condition number                                                     [    OK   ]   "
## [14] "Correlations                                                         [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:11"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   44.39"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   0.67"
## [19] ""
## [20] "Objective function value: 979.5856"
## [21] ""
## [22] "Condition number: 3.943"
## [23] ""
## [24] "Number of observation records: 690"
## [25] "Number of individuals: 690"
## [26] ""
## [27] "         THETA               OMEGA      SIGMA    "
## [28] "lambda  0.4379  (0.05053)                        "
## [29] " gamma    1.59  (0.05795)                        "
## [30] ""
## [31] "The relative standard errors for omega and sigma are reported on the approximate"
## [32] "standard deviation scale (SE/variance estimate)/2."
## [33] "-------------------------------------------------------------------------------"
```

3.0.3.2 Diagnostic plots

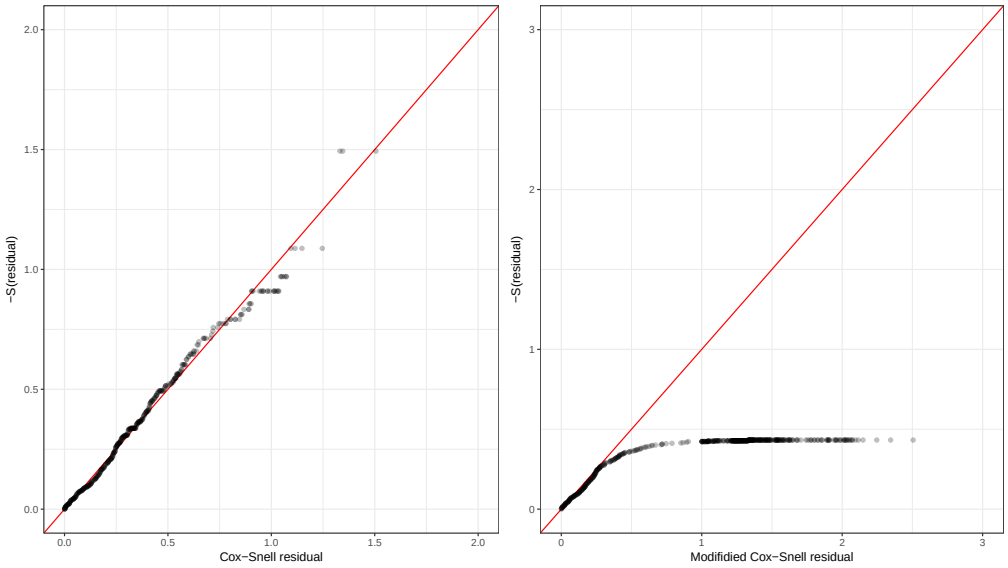


Figure 7: Residual-based diagnostics

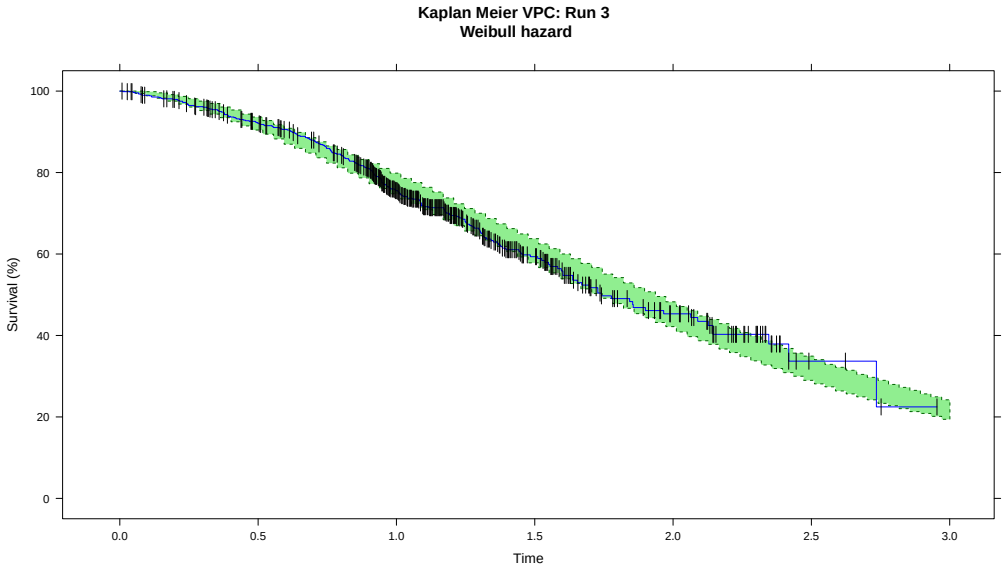


Figure 8: Simulation-based diagnostic

3.0.3.3 Evaluation of run 3

- Weibull hazard describes the trend of the data fairly well (supported by KM VPC, hbVPC & Cox-Snell residuals)
- The modified Cox-Snell residual appear to be uninformative; they do not show an improved fit to the data when other diagnostics do.

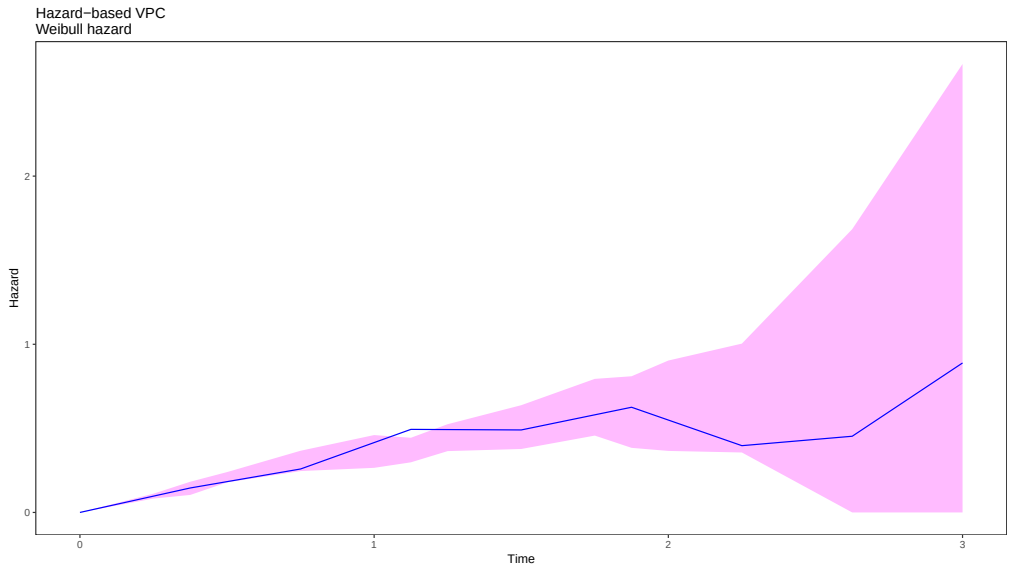


Figure 9: Simulation-based diagnostic: Hazard based VPC

3.0.4 Run 4 - Log-logistic hazard

```
##------------------------------------ Run notes  ------------------------------------##
# Rationale:   Test models with increasing complexity
# Question:    Will a log logistic hazard describe this data?
##------------------------------------------------------------------------------------##
show.mod(4, nm.dir) # print model
```

```
## ;; 1. Based on: 3
## ;; 2. Description:
## ;;    TTE model
## ;; 3. Label:
## ;;    log-logistic hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;; 6. Interindividual variability:
## ;; 7. Interoccasion variability:
## ;; 8. Residual variability:
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    Base TTE model - Project DataSphere # 78
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVE
##
## ;-----------------------------------------------------data description
## ; ID, subject identifier
## ; TIME, in years
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
## ; CENS, censored event, 0 = no, 1 = yes
## ; MAXT, last recorded event per patient (either death or censor)
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
## ; GENDER, bianry covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
## ; OSTIM, observed time in days to event or censor time
##
## ;-----------------------------------------------------
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2.csv IGNORE=@
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
## ;IGNORE=(STIME.EQ.0) ;; observed time, ignore for simulation
```

```
##
## ;Sim_end
## $SUBROUTINE ADVAN=6 TOL=9
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ==========================
## $PK
##  DELTA = THETA(1)* EXP(ETA(1))
##  GAMMA = THETA(2)
##
## ;;================================ DIFFERENTIAL EQUATIONS ==================================
## ; Typical Value Log-logistic hazard,  h0(t) = exp(delta) kt^(k-1) / (1+ exp(delta)*t^k), where k = g
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = EXP(DELTA)*GAMMA*(T+DEL)**(GAMMA-1) / (1 + EXP(DELTA)*(T+DEL)**GAMMA)
##
## DADT(1) = BASE
##
## ;;================================ MODEL FIT ================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=EXP(DELTA)*GAMMA*(TIME+DELX)**(GAMMA-1) / (1 + EXP(DELTA)*(TIME+DELX)**GAMMA)
##  HAZNOW= BASEX
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================ RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
```

```
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================= SIMULATION ========================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES ==================================
##
## $THETA  (0.2) ; delta
##  (0,1) ; gamma
## $OMEGA  0  FIX  ; place holder
## ;;============================= ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_4
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
##
## ;;================================= TABLES ================================
## $TABLE      NOPRINT ONEHEADER FILE=mytab4 ID TIME DV EVID MDV PRED CHZ
##             SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTI
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab4 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab4 ID DELTA GAMMA
##             ETAS(1:LAST)
## ;$TABLE NOAPPEND ONEHEADER NOPRINT FILE=catab
##
## ;ID NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL

## NULL
```

3.0.4.1 Run summary

```
##  [1] "-------------------------------------------------------------------------"
##  [2] ""
```

```
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run4/run4
##  [4] ""
##  [5] "Successful minimization                                              [    OK   ]   "
##  [6] "No rounding errors                                                   [    OK   ]   "
##  [7] "No zero gradients                                                    [    OK   ]   "
##  [8] "No final zero gradients                                              [    OK   ]   "
##  [9] "Hessian not reset                                                    [    OK   ]   "
## [10] "No parameter near boundary                                           [    OK   ]   "
## [11] "Covariance step                                                      [    OK   ]   "
## [12] ""
## [13] "Condition number                                                     [    OK   ]   "
## [14] "Correlations                                                         [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:04"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   39.55"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   1.4"
## [19] ""
## [20] "Objective function value: 982.6190"
## [21] ""
## [22] "Condition number: 1.758"
## [23] ""
## [24] "Number of observation records: 690"
## [25] "Number of individuals: 690"
## [26] ""
## [27] "        THETA               OMEGA      SIGMA    "
## [28] "delta  -1.137  (0.07126)                        "
## [29] "gamma   1.831  (0.06489)                        "
## [30] ""
## [31] "The relative standard errors for omega and sigma are reported on the approximate"
## [32] "standard deviation scale (SE/variance estimate)/2."
## [33] "-------------------------------------------------------------------------------"
```

3.0.4.2 Diagnostic plots

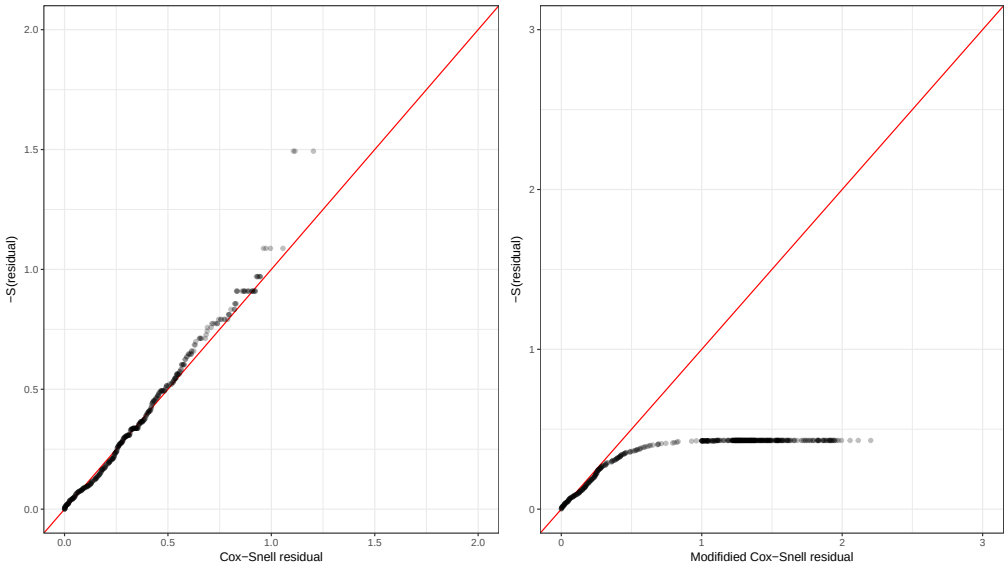


Figure 10: Residual-based diagnostics

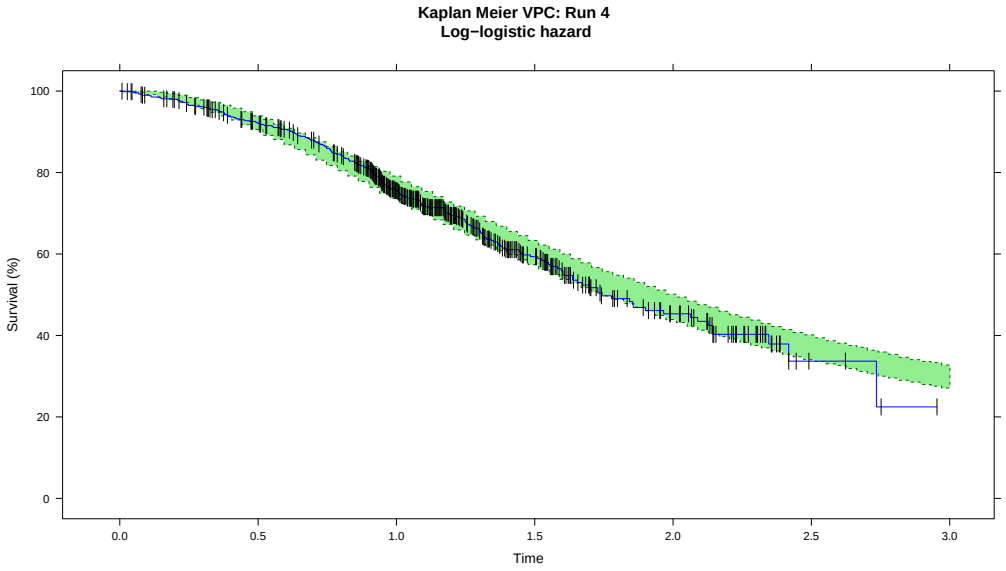


Figure 11: Simulation-based diagnostic

3.0.4.3 Evaluation of run 4

- The log-logistic describes the trend of the data fairly well (supported by KM VPC, hbVPC & Cox-Snell residuals)
- dOFV = 3.033 compared to run 3 (Weibull model, same # of parameters)

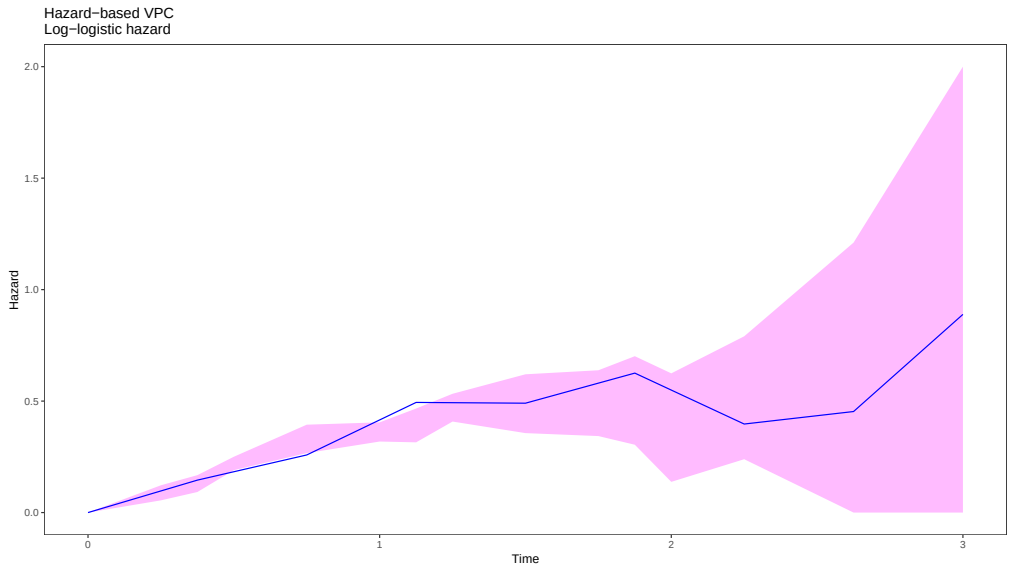


Figure 12: Simulation-based diagnostic: Hazard based VPC

4 Sensitivity analysis - exclude subjects missing LDH

4.0.5 Run 5 - Weibull Hazard (ignore patients missing LDH data)

```
##===================================== Run notes  ======================================##
# Rationale:   Model data for subjects with baseline LDH data
# Question:    How will excluding this subjects influence parameter estimation?
##-------------------------------------------------------------------------------------##
# next.mod(3,5,nm.dir)
show.mod(5, nm.dir) # print model
```

```
## ;; 1. Based on: 3
## ;; 2. Description:
## ;;    TTE model
## ;; 3. Label:
## ;;    Weibull hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;; 6. Interindividual variability:
## ;; 7. Interoccasion variability:
## ;; 8. Residual variability:
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    Base TTE model - Project DataSphere # 78
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM
## ;-----------------------------------------------------data description
##
## ; ID, subject identifier
##
## ; TIME, in years
##
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
##
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
##
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
##
## ; CENS, censored event, 0 = no, 1 = yes
##
## ; MAXT, last recorded event per patient (either death or censor)
##
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
##
## ; GENDER, bianry covariate (0=male,1=female)
##
```

```
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
##
## ; BLAGE, categorical, age group in years
##
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
##
## ; BLALB, continuous, ALB test values at baseline
##
## ; BLALP, continuous, ALP test values at baseline
##
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
##
## ; OSTIM, observed time in days to event or censor time
##
## ;-----------------------------------------------------
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2.csv IGNORE=@
## IGNORE(NOLDH.EQ.1) ; 24 patients missing LDH data
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
## ;IGNORE=(STIME.EQ.0) ;; observed time, ignore for simulation
## ;Sim_end
## $SUBROUTINE ADVAN=6 TOL=6
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##  LAMBDA = THETA(1) * EXP(ETA(1))
##  GAMMA = THETA(2)
##
## ;;================================ DIFFERENTIAL EQUATIONS ================================
## ; Typical Value Weibull hazard h0(t) = lambda*gamma*t^(gamma-1)
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = (LAMBDA*GAMMA)*(LAMBDA*(T+DEL))**(GAMMA-1)
##
## DADT(1) = BASE
##
## ;;================================ MODEL FIT ================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;-----------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
```

```
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=(LAMBDA*GAMMA)*(LAMBDA*(TIME+DELX))**(GAMMA-1)
##  HAZNOW= BASEX
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================= RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================= SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES =====================================
##
## $THETA  (0,0.438) ; lambda
##  (0,1.59) ; gamma
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_5
```

```
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
##
## ;;================================ TABLES ================================
## $TABLE      NOPRINT ONEHEADER FILE=mytab5 ID TIME DV EVID MDV PRED CHZ BASE BASEX
##             SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab5 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab5 ID LAMBDA
##             ETAS(1:LAST)
## ;$TABLE NOAPPEND ONEHEADER NOPRINT FILE=catab
##
## ;ID NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL

## NULL
```

4.0.5.1 Run summary

```
##  [1] "------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run5/run5
##  [4] ""
##  [5] "Successful minimization                                        [    OK   ]   "
##  [6] "No rounding errors                                             [    OK   ]   "
##  [7] "No zero gradients                                              [    OK   ]   "
##  [8] "No final zero gradients                                        [    OK   ]   "
##  [9] "Hessian not reset                                              [    OK   ]   "
## [10] "No parameter near boundary                                     [    OK   ]   "
## [11] "Covariance step                                                [    OK   ]   "
## [12] ""
## [13] "Condition number                                               [    OK   ]   "
## [14] "Correlations                                                   [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:17"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   44.61"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   0.68"
## [19] ""
## [20] "Objective function value: 940.9514"
## [21] ""
## [22] "Condition number: 4.01"
## [23] ""
## [24] "Number of observation records: 666"
## [25] "Number of individuals: 666"
## [26] ""
## [27] "         THETA              OMEGA      SIGMA    "
## [28] "lambda  0.4347  (0.0513)                        "
## [29] " gamma    1.61  (0.0595)                        "
## [30] ""
## [31] "The relative standard errors for omega and sigma are reported on the approximate"
## [32] "standard deviation scale (SE/variance estimate)/2."
## [33] "------------------------------------------------------------------------"
```

4.0.5.2 Diagnostic plots

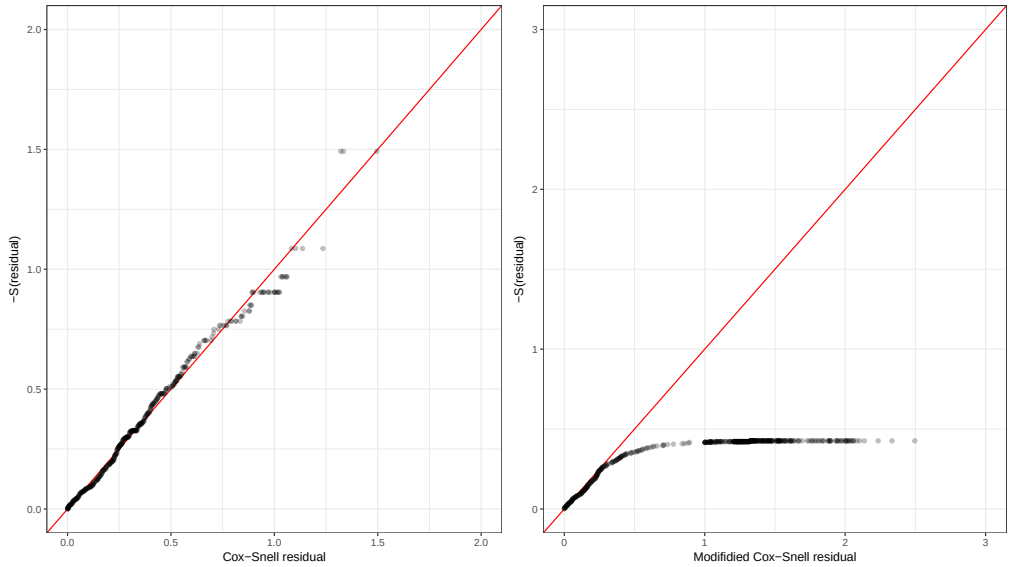


Figure 13: Residual-based diagnostics

- zero reference line (red) ; mean residuals (green diamond)

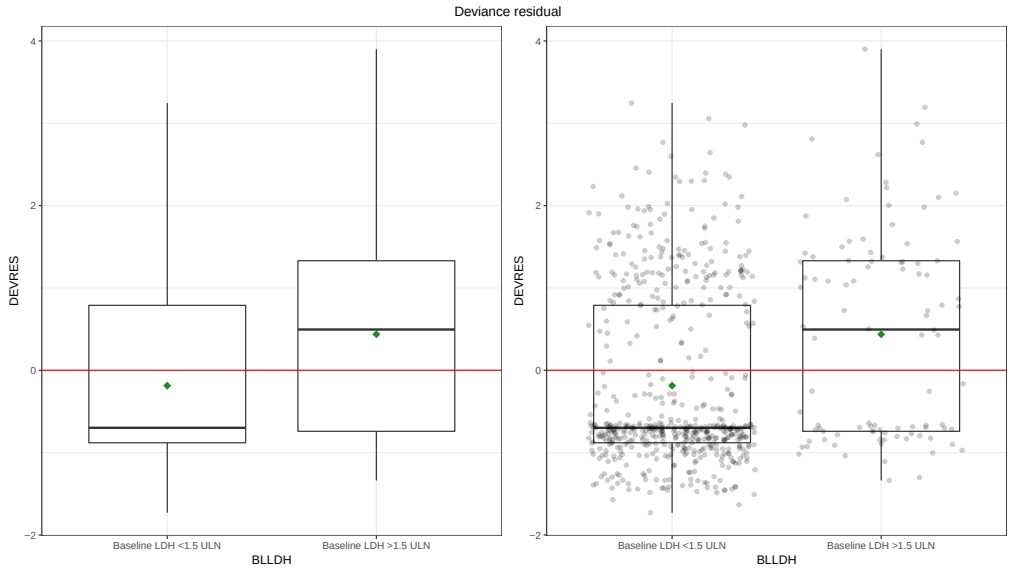


Figure 14: Residual-based diagnostics - Deviance plot

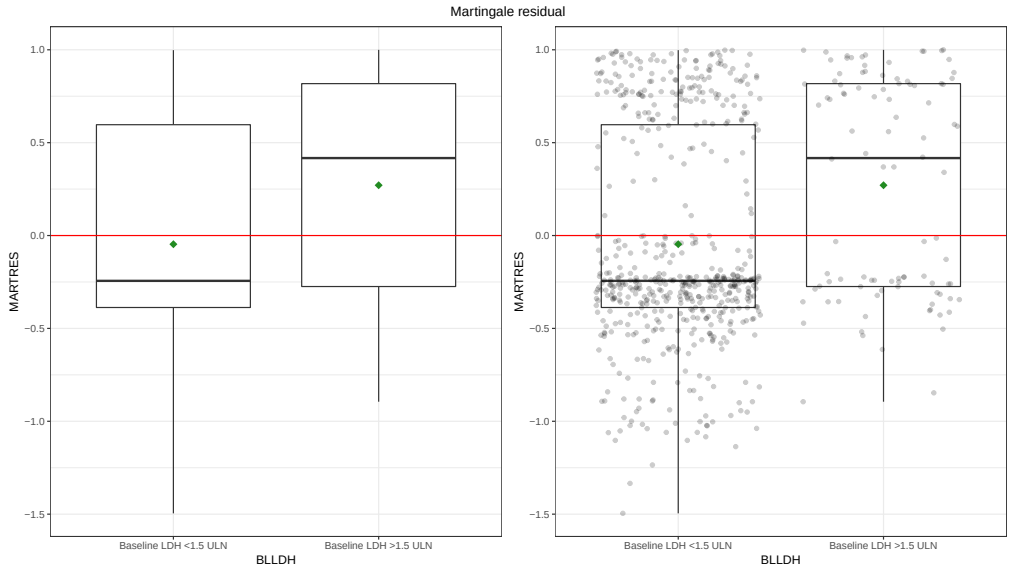


Figure 15: Residual-based diagnostics - Martingale plot

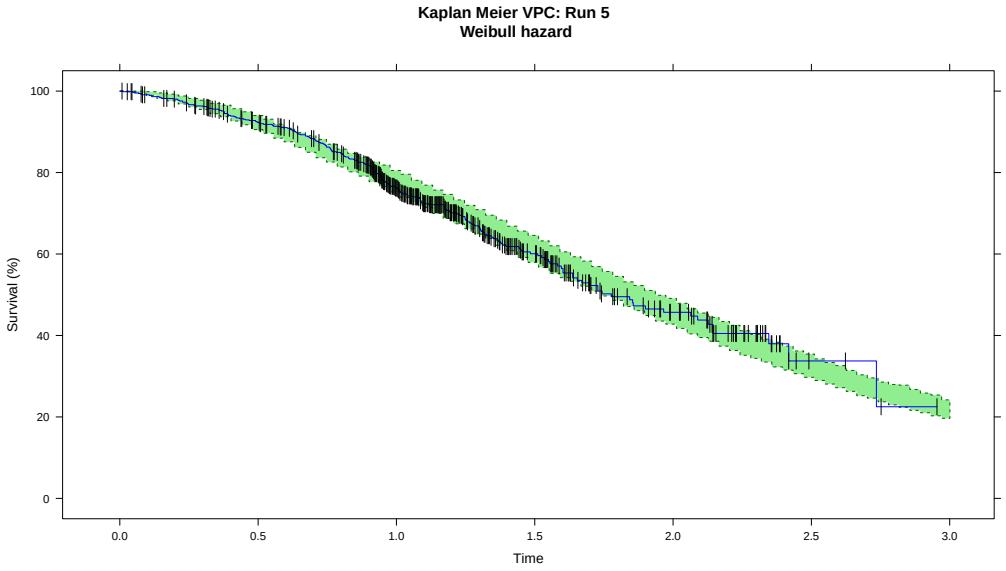


Figure 16: Simulation-based diagnostic

4.0.5.3 Evaluation of run 5

- Similar final estimates for lambda (run3: 0.4379, run5: 0.4347) and gamma (run3: 1.59, run5: 1.61)
- base diagnositcs (KM VPC, hbVPC and Cox-Snell residuals) do not appear to be impacted

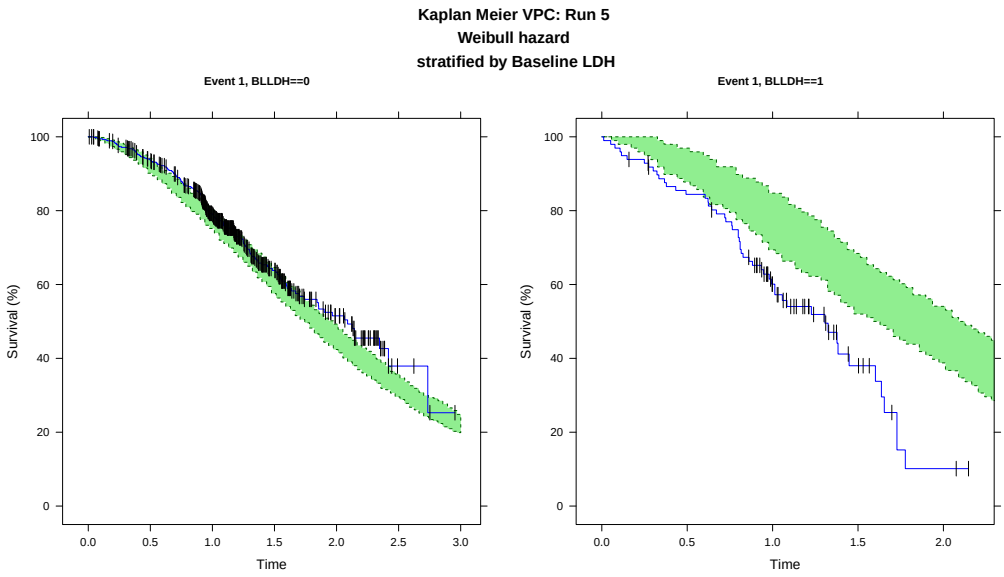


Figure 17: Simulation-based diagnostic - stratified by baseline LDH

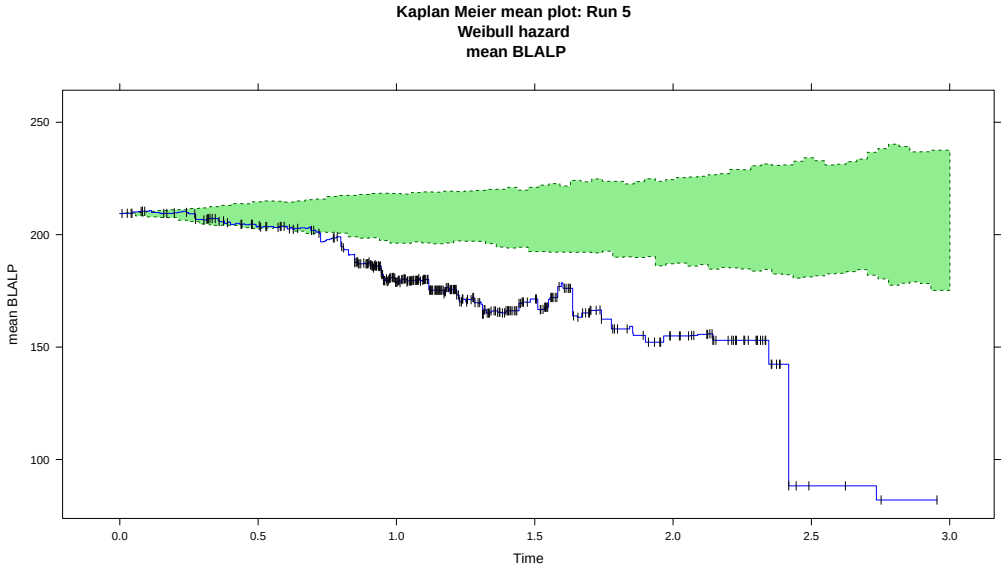


Figure 18: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

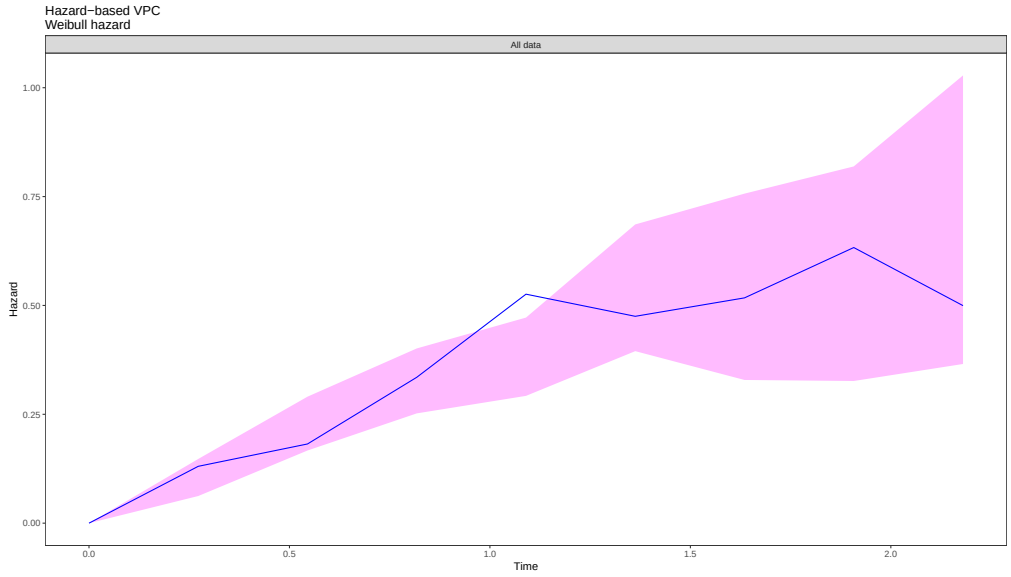


Figure 19: Simulation-based diagnostic: Hazard based VPC

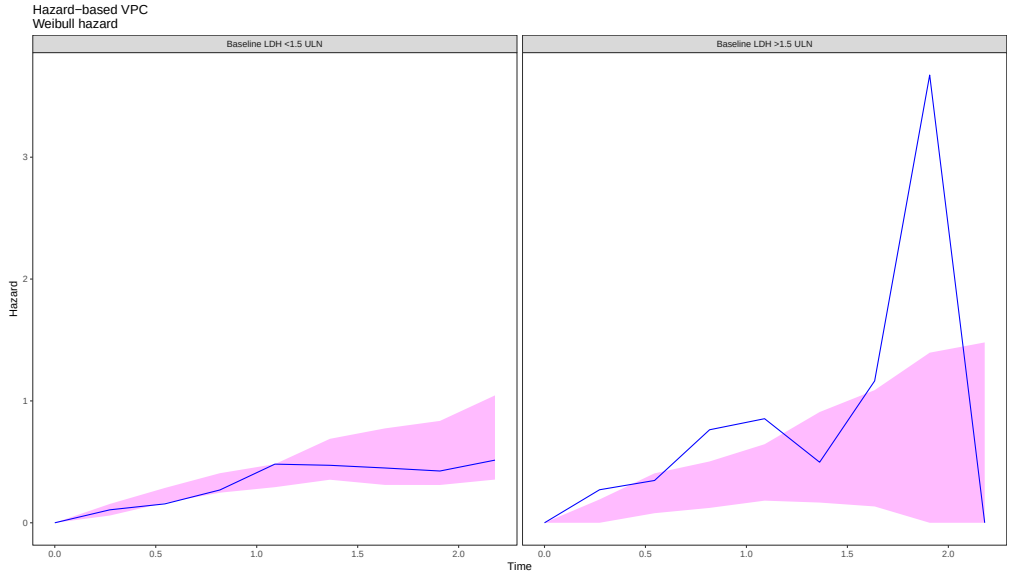


Figure 20: Simulation-based diagnostic: Hazard based VPC

4.0.6 Run 6 - Log-logistic hazard (ignore patients missing LDH data)

```
##===================================== Run notes  ======================================##
# Rationale:   Test models with increasing complexity
# Question:    How will excluding this subjects influence parameter estimation?
##-------------------------------------------------------------------------------------##
# next.mod(4,6,nm.dir)
show.mod(6, nm.dir) # print model
```

```
## ;; 1. Based on: 4
## ;; 2. Description:
## ;;    TTE model
## ;; 3. Label:
## ;;    log-logistic hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;; 6. Interindividual variability:
## ;; 7. Interoccasion variability:
## ;; 8. Residual variability:
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    Base TTE model - Project DataSphere # 78
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM
## ;-----------------------------------------------------data description
##
## ; ID, subject identifier
##
## ; TIME, in years
##
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
##
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
##
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
##
## ; CENS, censored event, 0 = no, 1 = yes
##
## ; MAXT, last recorded event per patient (either death or censor)
##
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
##
## ; GENDER, bianry covariate (0=male,1=female)
##
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
##
## ; BLAGE, categorical, age group in years
```

```
##
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
##
## ; BLALB, continuous, ALB test values at baseline
##
## ; BLALP, continuous, ALP test values at baseline
##
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
##
## ; OSTIM, observed time in days to event or censor time
##
## ;-----------------------------------------------------
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2.csv IGNORE=@
##
## IGNORE(NOLDH.EQ.1) ; 24 patients missing LDH data
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
## ;IGNORE=(STIME.EQ.0) ;; observed time, ignore for simulation
##
## ;Sim_end
## $SUBROUTINE ADVAN=6 TOL=9
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##  DELTA = THETA(1)* EXP(ETA(1))
##  GAMMA = THETA(2)
##
## ;;================================ DIFFERENTIAL EQUATIONS ================================
## ; Typical Value Log-logistic hazard,  h0(t) = exp(delta) kt^(k-1) / (1+ exp(delta)*t^k), where k = g
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = EXP(DELTA)*GAMMA*(T+DEL)**(GAMMA-1) / (1 + EXP(DELTA)*(T+DEL)**GAMMA)
##
## DADT(1) = BASE
##
## ;;================================ MODEL FIT ================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
```

```
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=EXP(DELTA)*GAMMA*(TIME+DELX)**(GAMMA-1) / (1 + EXP(DELTA)*(TIME+DELX)**GAMMA)
##  HAZNOW= BASEX
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================= RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================= SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES =====================================
##
## $THETA  -1.14 ; delta
##  (0,1.83) ; gamma
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_6
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
```

```
##
## ;Sim_end
##
## ;;================================ TABLES ================================
## $TABLE      NOPRINT ONEHEADER FILE=mytab6 ID TIME DV EVID MDV PRED CHZ
##             SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab6 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab6 ID DELTA GAMMA
##             ETAS(1:LAST)
## ;$TABLE NOAPPEND ONEHEADER NOPRINT FILE=catab
##
## ;ID NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL

## NULL
```

4.0.6.1 Run summary

```
##  [1] "------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run6/run6
##  [4] ""
##  [5] "Successful minimization                                          [    OK   ]   "
##  [6] "No rounding errors                                               [    OK   ]   "
##  [7] "No zero gradients                                                [    OK   ]   "
##  [8] "No final zero gradients                                          [    OK   ]   "
##  [9] "Hessian not reset                                                [    OK   ]   "
## [10] "No parameter near boundary                                       [    OK   ]   "
## [11] "Covariance step                                                  [    OK   ]   "
## [12] ""
## [13] "Condition number                                                 [    OK   ]   "
## [14] "Correlations                                                     [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:09"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   33.8"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   1.33"
## [19] ""
## [20] "Objective function value: 944.1242"
## [21] ""
## [22] "Condition number: 1.828"
## [23] ""
## [24] "Number of observation records: 666"
## [25] "Number of individuals: 666"
## [26] ""
## [27] "       THETA               OMEGA      SIGMA    "
## [28] "delta  -1.17  (0.07111)                        "
## [29] "gamma  1.851  (0.06659)                        "
## [30] ""
## [31] "The relative standard errors for omega and sigma are reported on the approximate"
## [32] "standard deviation scale (SE/variance estimate)/2."
## [33] "------------------------------------------------------------------------"
```

4.0.6.2 Diagnostic plots

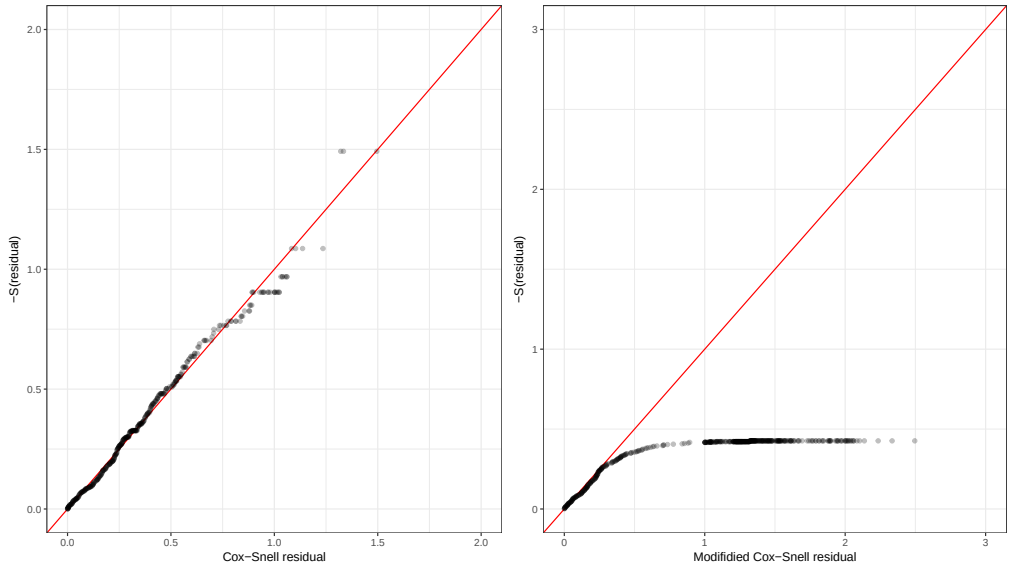


Figure 21: Residual-based diagnostics

- zero reference line (red) ; mean residuals (green diamond)

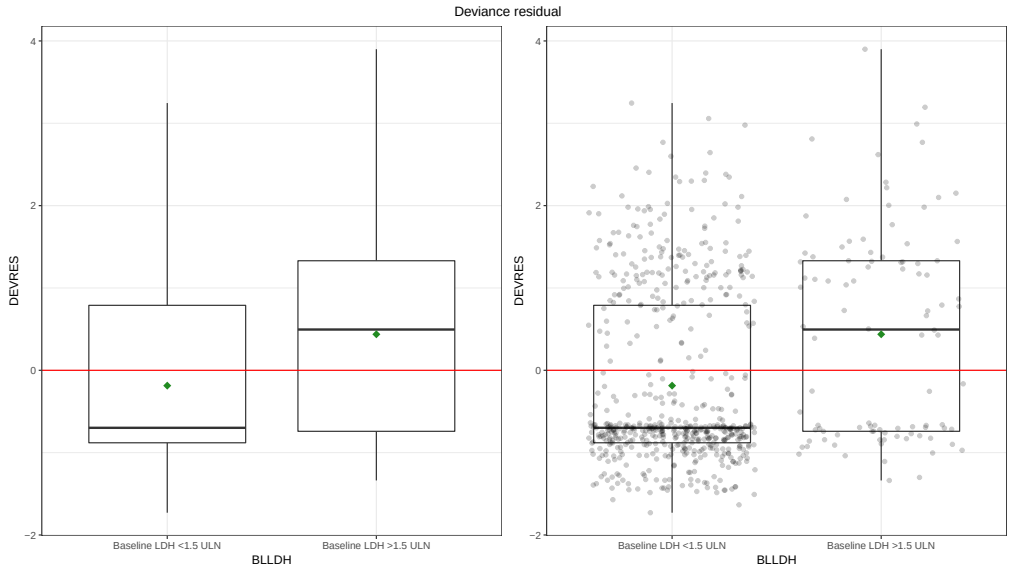


Figure 22: Residual-based diagnostics - Deviance plot

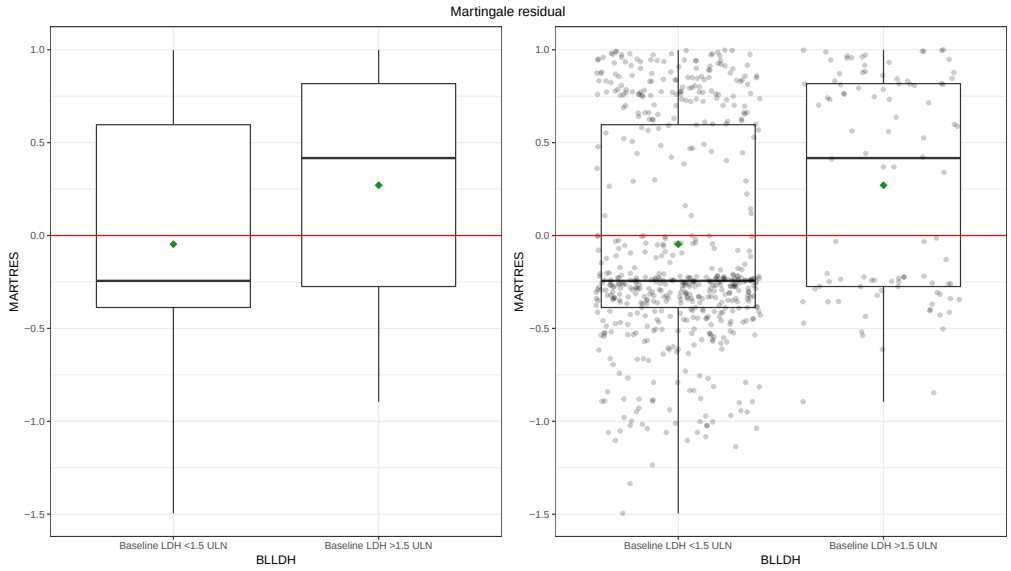


Figure 23: Residual-based diagnostics - Martingale plot

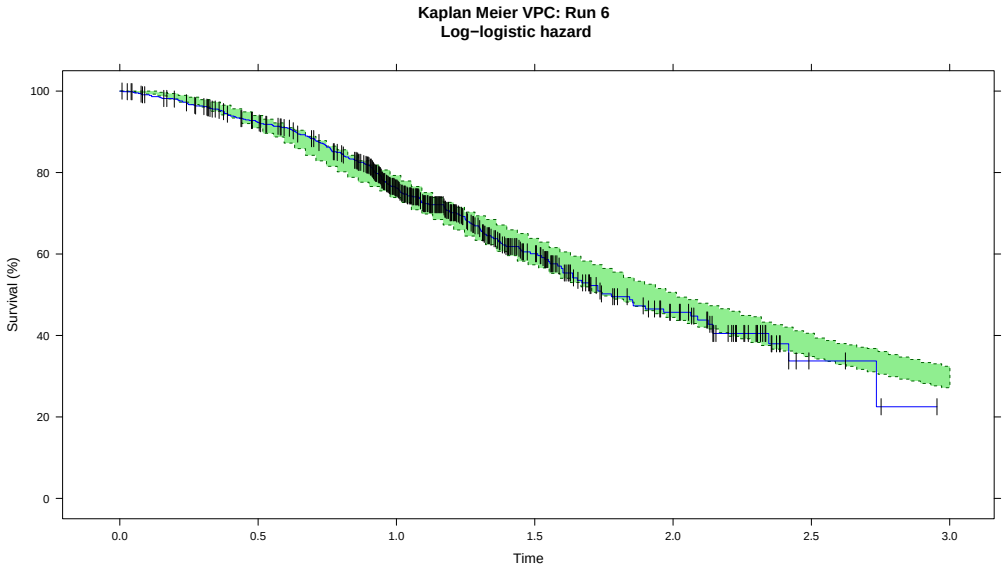


Figure 24: Simulation-based diagnostic

4.0.6.3 Evaluation of run 6

- Similar final estimate for delta (run4: -1.137, run6: -1.17) and gamma (run4: 1.831, run6: 1.851)
- base diagnositcs (KM VPC, hbVPC and Cox-Snell residuals) do not appear to be impacted

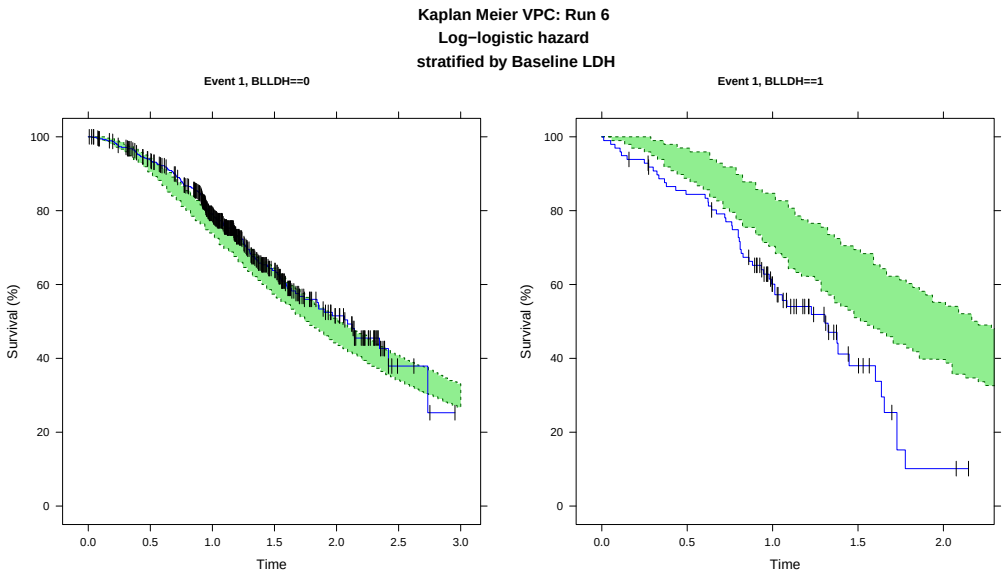


Figure 25: Simulation-based diagnostic - stratified by baseline LDH

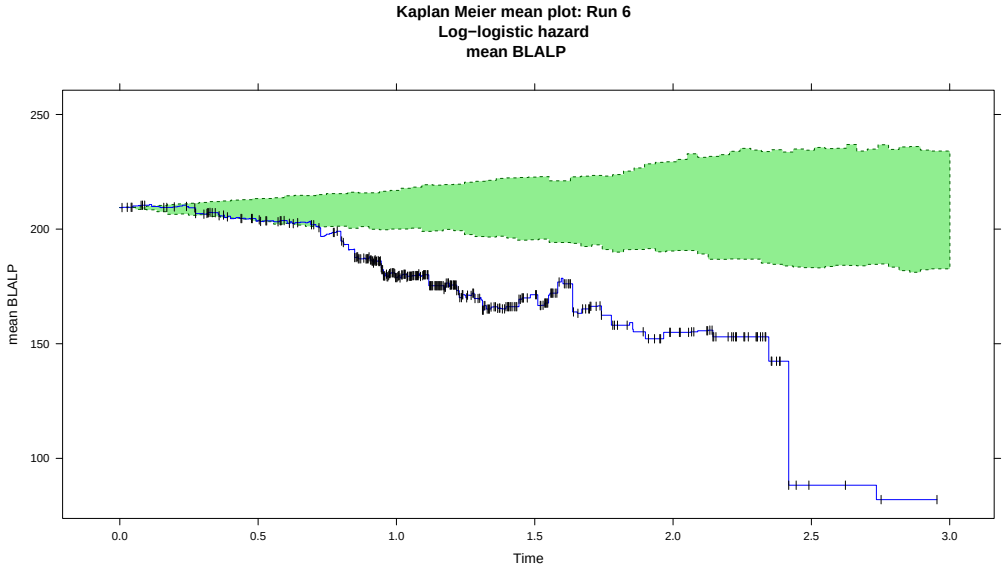


Figure 26: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

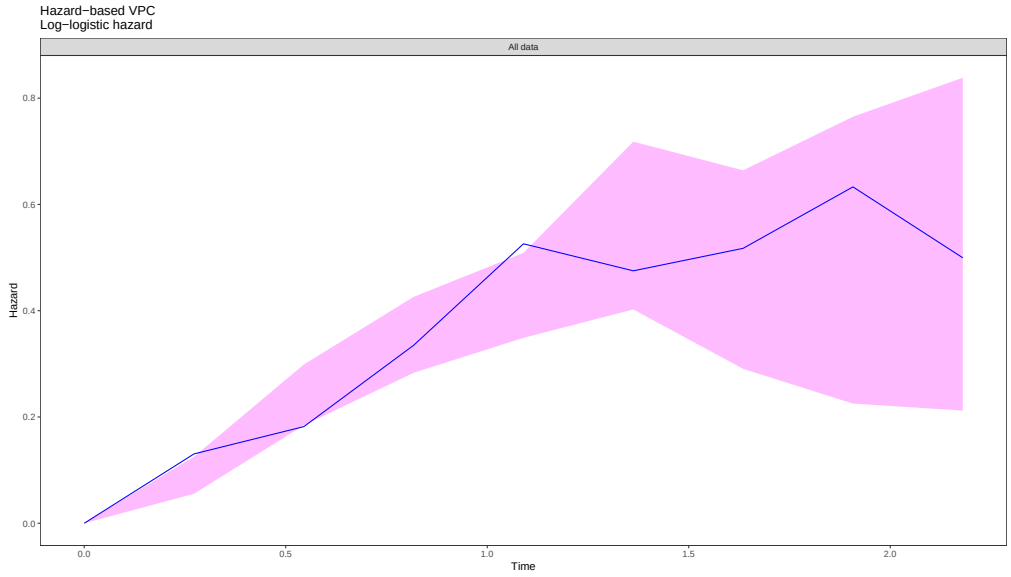


Figure 27: Simulation-based diagnostic: Hazard based VPC

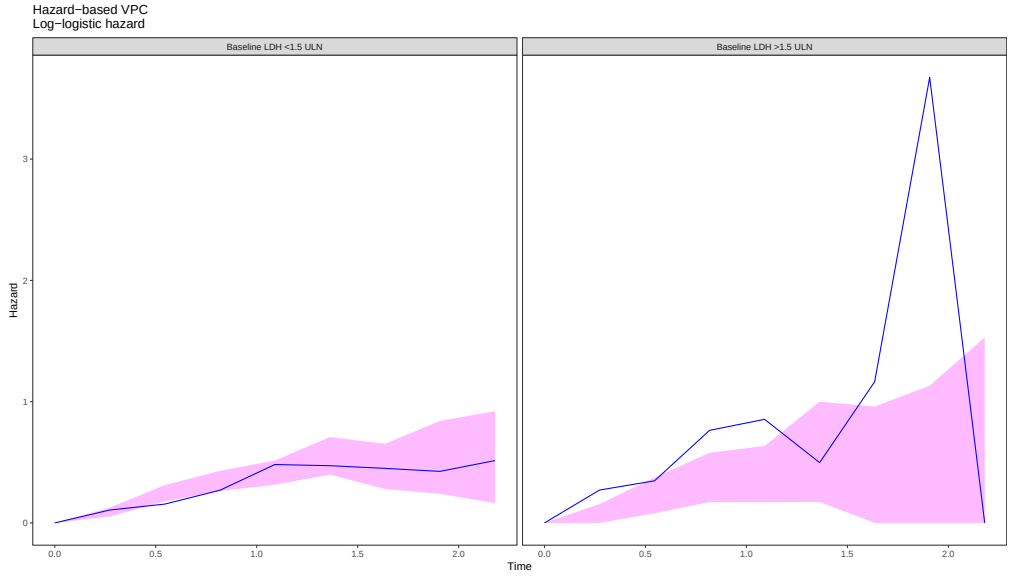


Figure 28: Simulation-based diagnostic: Hazard based VPC

5 Explore covariate relationships

5.0.7 Baseline alkaline phosphatase level test (ALP test) - continuous

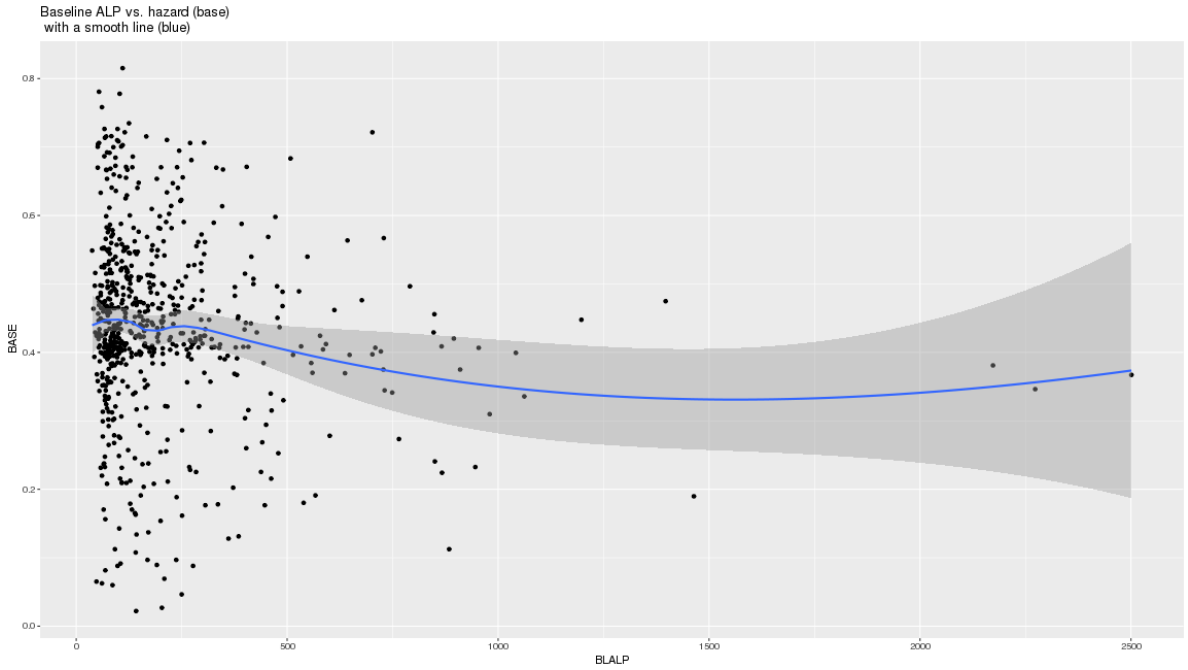
```
## Emax model, baseline ALP (inital estimates) discuss with JF
mytab <- read.mytab.tte(5, nm.dir)
patab <- read.patab(5, nm.dir) ; head(patab)
```

```
##   ID  LAMBDA ETA1
## 1  1 0.43466    0
## 2  2 0.43466    0
## 3  3 0.43466    0
## 4  4 0.43466    0
## 5  5 0.43466    0
## 6  6 0.43466    0
```

```
dat_in5 <- merge(mytab,patab)

dat_in5.1 <- dat_in5 %>% select(ID, TIME, DV, BASE, LAMBDA, BLALP, BLLDH)  %>%
                     mutate(logBLALP = log(BLALP)) %>%
                     mutate(LDH = factor(BLLDH, levels =c(0,1),
                            labels=c('baseline LDH \n within normal range', 'baseline LDH \n > 1.5 ULN'
```

```
##   ID  TIME DV    BASE  LAMBDA BLALP BLLDH logBLALP
## 1  1 2.491  0 0.73468 0.43466   125     0 4.828314
## 2  2 1.700  0 0.58190 0.43466   195     0 5.273000
## 3  3 1.448  0 0.52763 0.43466    67     0 4.204693
## 4  4 2.735  1 0.77779 0.43466   103     0 4.634729
## 5  5 2.445  0 0.72637 0.43466    67     0 4.204693
## 6  6 2.333  0 0.70588 0.43466   270     0 5.598422
##                                   LDH
## 1 baseline LDH \n within normal range
## 2 baseline LDH \n within normal range
## 3 baseline LDH \n within normal range
## 4 baseline LDH \n within normal range
## 5 baseline LDH \n within normal range
## 6 baseline LDH \n within normal range
```

```
pl.base <- ggplot(dat_in5.1, aes(y=BASE, x=BLALP)) + geom_point() +   geom_smooth()

pl.base + ggtitle('Baseline ALP vs. hazard (base) \n with a smooth line (blue)')
```

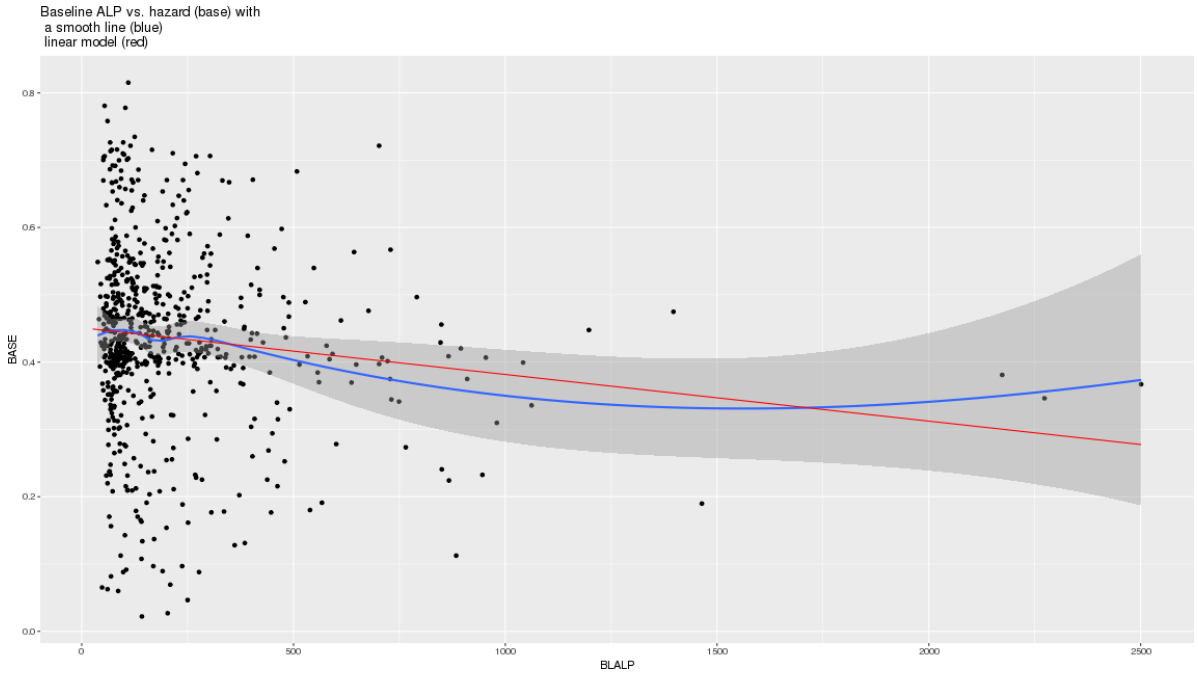



```
# no IIV on lambda --> single value of lambda for the entire population

# vector for data prediction
pred <- with(dat_in5.1,data.frame(BLALP=seq(26,max(BLALP,na.rm=TRUE),5)))

# linear model

lnr.mod <- lm(BASE ~ BLALP, data=dat_in5.1)
summary(lnr.mod)
```

```
##
## Call:
## lm(formula = BASE ~ BLALP, data = dat_in5.1)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -0.41898 -0.04863 -0.00260  0.07363  0.37192
##
## Coefficients:
##               Estimate Std. Error t value Pr(>|t|)
## (Intercept)  4.509e-01  6.927e-03  65.100  < 2e-16 ***
## BLALP       -6.933e-05  2.191e-05  -3.165  0.00162 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.1339 on 664 degrees of freedom
## Multiple R-squared:  0.01486,    Adjusted R-squared:  0.01338
## F-statistic: 10.02 on 1 and 664 DF,  p-value: 0.001622
```

```
pred_alp_lnr =within(pred,{
    PRED = predict(lnr.mod,newdata=pred)
    })
```

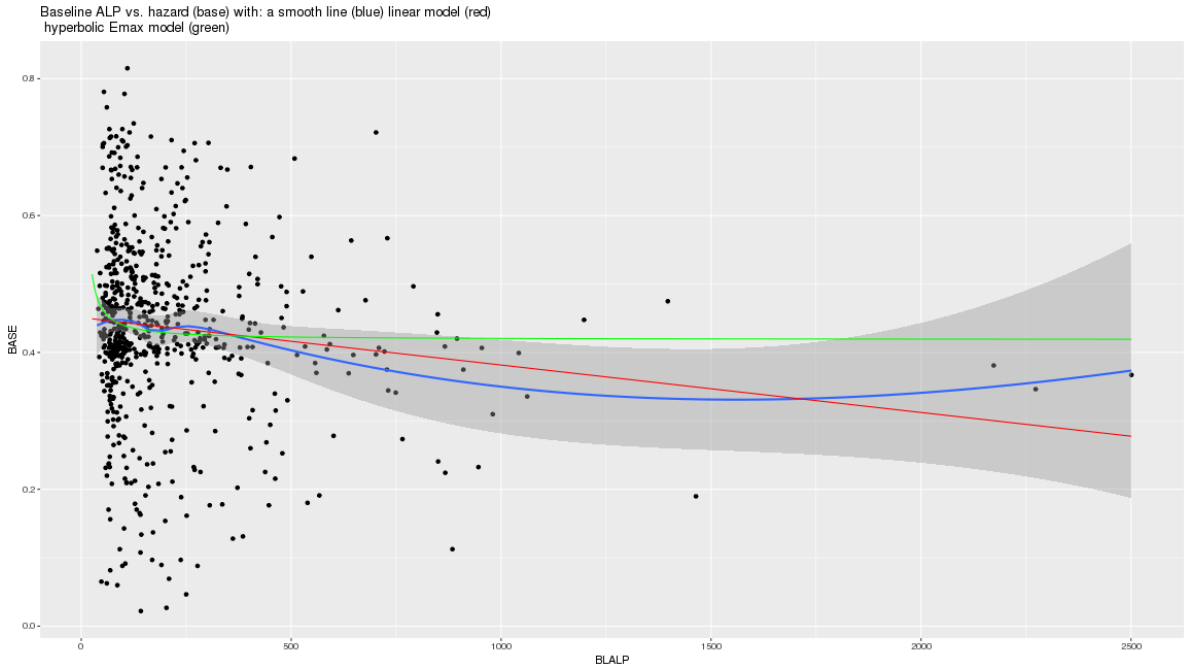
```
pl.base + geom_line(data=pred_alp_lnr, aes(x=BLALP, y=PRED), color='red')+
   ggtitle('Baseline ALP vs. hazard (base) with \n a smooth line (blue) \n linear model (red)')
```



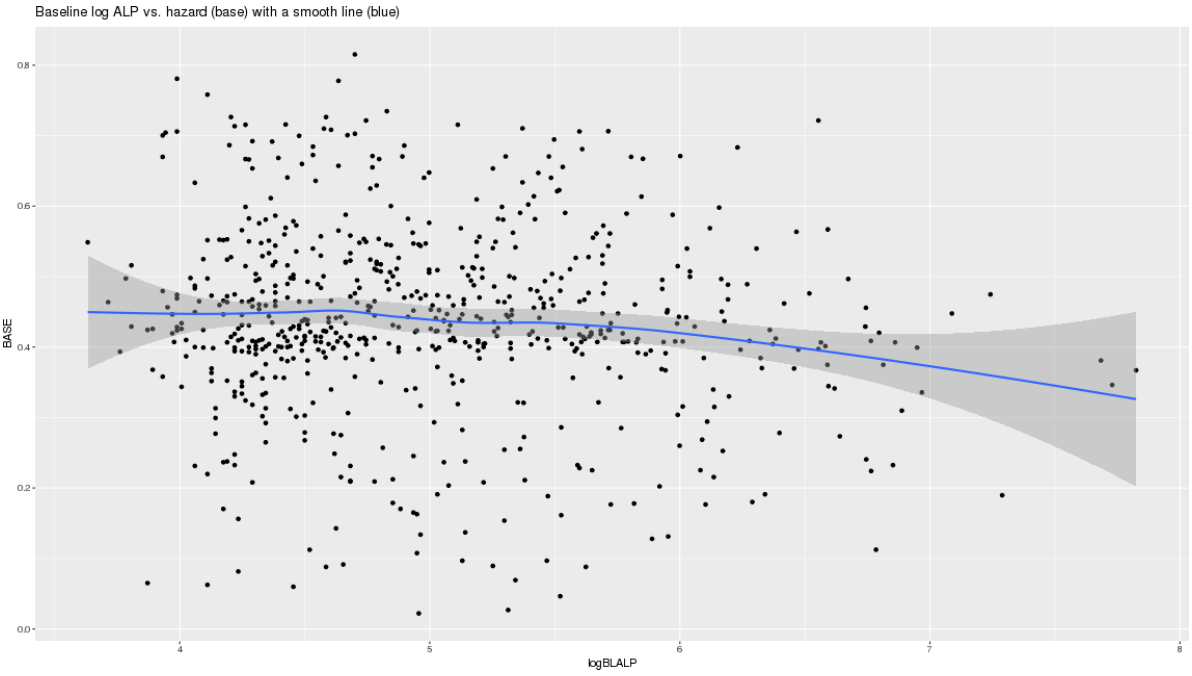

```
# Emax model
emax.mod <- nls(BASE ~ EMAX*BLALP/(EC50+BLALP),data=dat_in5.1,start=list(EC50=50,EMAX=100))
summary(emax.mod)
```

```
##
## Formula: BASE ~ EMAX * BLALP/(EC50 + BLALP)
##
## Parameters:
##       Estimate Std. Error t value Pr(>|t|)
## EC50 -4.841495   2.116826  -2.287   0.0225 *
## EMAX  0.418487   0.009516  43.978   <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.1345 on 664 degrees of freedom
##
## Number of iterations to convergence: 6
## Achieved convergence tolerance: 1.347e-06
```

```
pred_alp_emax =within(pred,{
    PRED = predict(emax.mod,newdata=pred)
    })

pl.base + geom_line(data=pred_alp_lnr, aes(x=BLALP, y=PRED), color='red')+
   geom_line(data=pred_alp_emax, aes(x=BLALP, y=PRED), color='green')+
   ggtitle('Baseline ALP vs. hazard (base) with: a smooth line (blue) linear model (red) \n hyperbolic
```




```
# log transformed ALP
pl.base.log <- ggplot(dat_in5.1, aes(x=logBLALP, y=BASE)) + geom_point() +   geom_smooth()
pl.base.log + ggtitle('Baseline log ALP vs. hazard (base) with a smooth line (blue)')
```

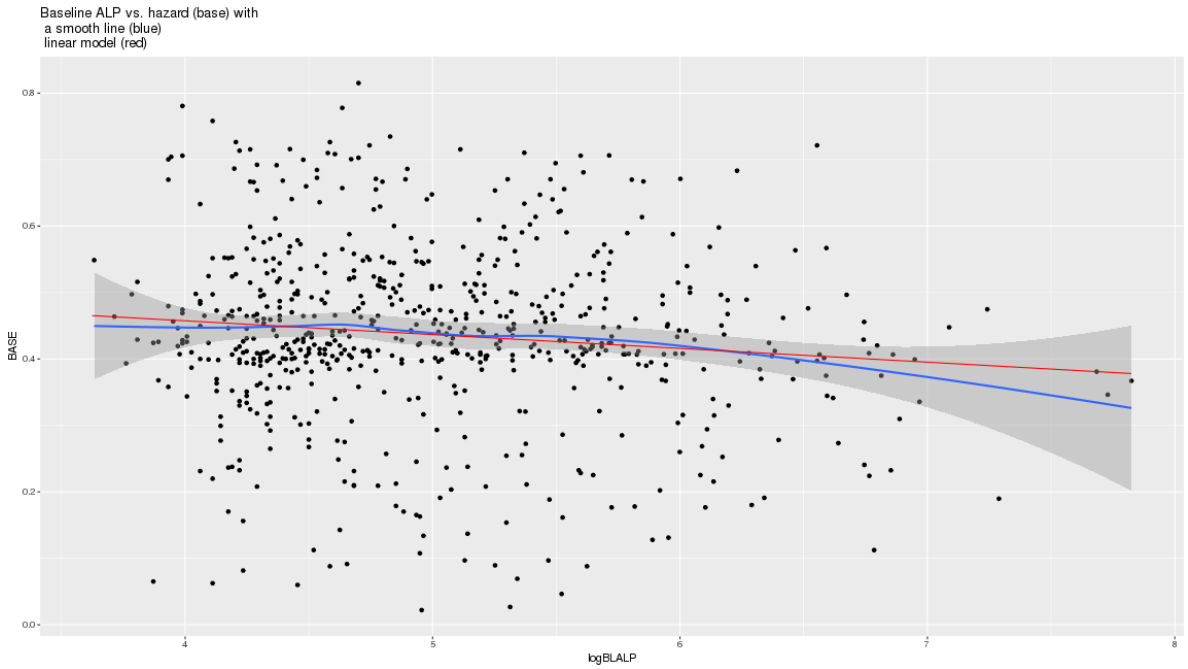



```
# vector for data prediction
log.pred <- with(dat_in5.1,data.frame(logBLALP=seq(3.624,max(logBLALP,na.rm=TRUE),0.01)))

# linear model
log.lnr.mod <- lm(BASE ~ logBLALP, data=dat_in5.1)
summary(log.lnr.mod)
```

```
##
```

```
## Call:
## lm(formula = BASE ~ logBLALP, data = dat_in5.1)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -0.41549 -0.05256 -0.00254  0.07313  0.37233
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept)  0.540420   0.035352  15.287  < 2e-16 ***
## logBLALP    -0.020747   0.006976  -2.974  0.00305 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.1341 on 664 degrees of freedom
## Multiple R-squared:  0.01315,    Adjusted R-squared:  0.01166
## F-statistic: 8.845 on 1 and 664 DF,  p-value: 0.003045
```

```
pred_alp_log.lnr =within(log.pred,{
    PRED = predict(log.lnr.mod,newdata=log.pred)
    })

pl.base.log + geom_line(data=pred_alp_log.lnr, aes(x=logBLALP, y=PRED), color='red')+
   ggtitle('Baseline ALP vs. hazard (base) with \n a smooth line (blue) \n linear model (red)')
```

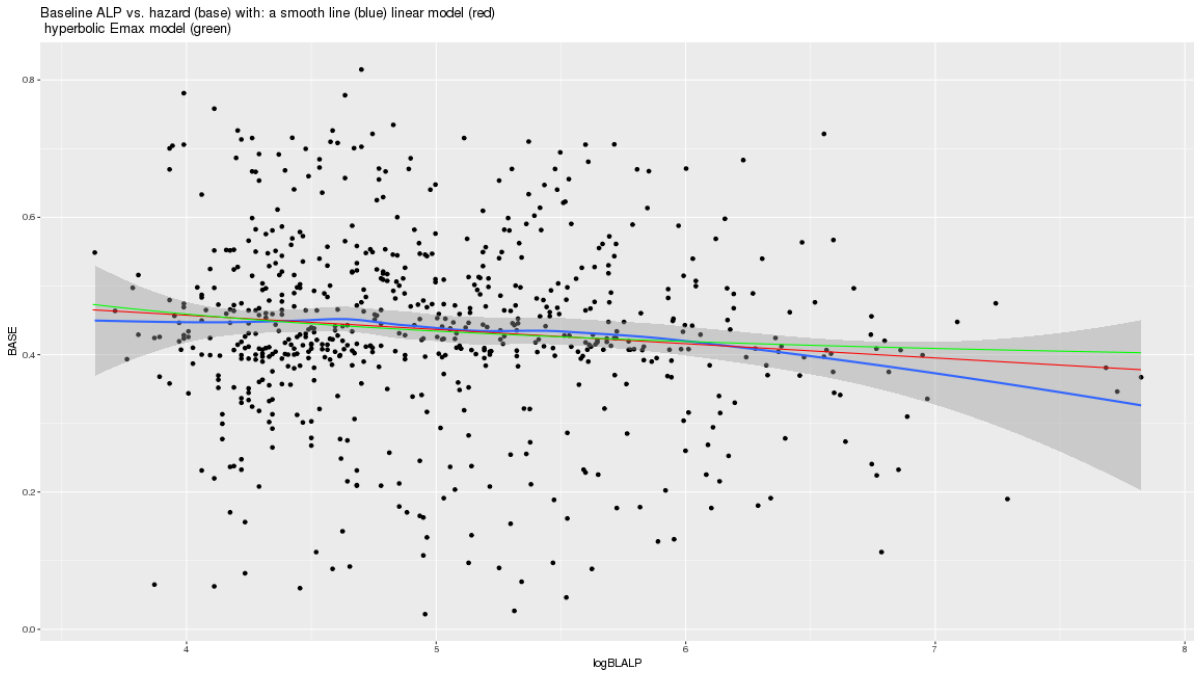



```
# Emax model
emax.mod.log <- nls(BASE ~ EMAX*logBLALP/(EC50+logBLALP),data=dat_in5.1,start=list(EC50=180,EMAX=100))
summary(emax.mod.log)
```

```
##
## Formula: BASE ~ EMAX * logBLALP/(EC50 + logBLALP)
##
## Parameters:
```

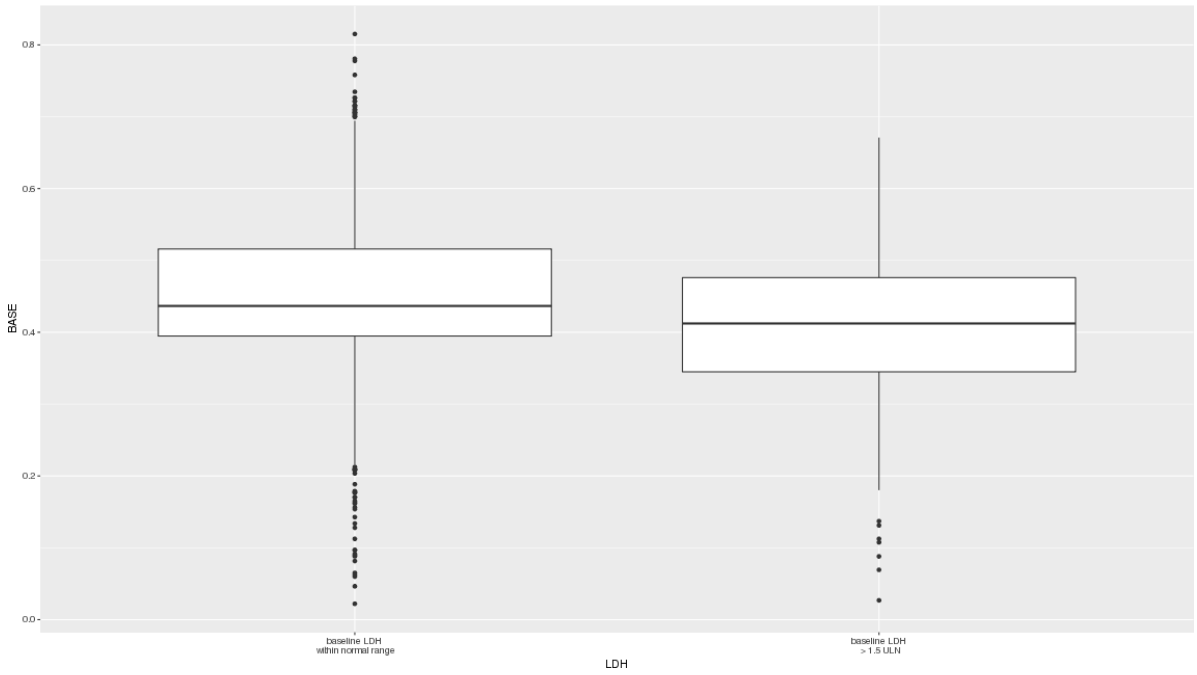
```
##      Estimate Std. Error t value Pr(>|t|)
## EC50 -0.88871    0.28354  -3.134   0.0018 **
## EMAX  0.35711    0.02592  13.778   <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.1343 on 664 degrees of freedom
##
## Number of iterations to convergence: 6
## Achieved convergence tolerance: 7.073e-06
```

```
logpred_alp_emax =within(log.pred,{
    PRED = predict(emax.mod.log,newdata=log.pred)
    })

pl.base.log + geom_line(data=pred_alp_log.lnr, aes(x=logBLALP, y=PRED), color='red')+
              geom_line(data=logpred_alp_emax, aes(x=logBLALP, y=PRED), color='green')+
              ggtitle('Baseline ALP vs. hazard (base) with: a smooth line (blue) linear model (red) \n
```



5.0.8 Baseline lactate dehydrogenase level test (LDH test) - categorical

```
ggplot(dat_in5.1, aes(LDH, BASE))+ geom_boxplot()
```


0.8
0.6
0.4
0.2
0.0
BASE
baseline LDH
within normal range
baseline LDH
> 1.5 ULN
LDH

Moving ahead: Subjects with missing baseline LDH will be excluded. Covariate effects will be tested on runs 5 & 6.

6 Proportional hazards model development (base model 5)

6.0.9 Run 7 - Weibull Hazard + LDH effect + baseline ALP (linear on BASE)

```
##=================================== Run notes  ====================================##
# Evidence:    Residuals plot show a trend with baseline LDH & ALP
# Question:    What effect do baseline LDH & ALP have on the baseline hazard
##-------------------------------------------------------------------------------------##
# next.mod(5,7,nm.dir)
show.mod(7, nm.dir) # print model
```

```
## ;; 1. Based on: 5
## ;; 2. Description:
## ;;    Covariate TTE model
## ;; 3. Label:
## ;;    Weibull hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;;     linear model (BL ALP), linear model (BL LDH)
## ;; 6. Interindividual variability:
## ;;    NA
## ;; 7. Interoccasion variability:
## ;;    NA
## ;; 8. Residual variability:
## ;;    NA
## ;; 9. Estimation:
## ;;    LAPLACE
##
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
##
##
## $PROBLEM    Base TTE model - Project DataSphere # 78 - no missing LDH
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM
## ;-----------------------------------------------------data description
## ; ID, subject identifier
## ; TIME, in years
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
## ; CENS, censored event, 0 = no, 1 = yes
## ; MAXT, last recorded event per patient (either death or censor)
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
```

```
## ; GENDER, bianry covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
## ; OSTIM, observed time in days to event or censor time
## ;-----------------------------------------------------
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2.csv IGNORE=@
##
## IGNORE(NOLDH.EQ.1) ; 24 patients missing BL_LDH data
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
##
## ;IGNORE=(STIME.EQ.0) ;; observed time, ignore for simulation
##
## ;Sim_end
## $SUBROUTINE ADVAN=13 TOL=6
## $MODEL      COMP=(HAZARD)
##
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##  LAMBDA = THETA(1) * EXP(ETA(1))
##  GAMMA = THETA(2)
##  SLP1 = THETA(3)
##  SLP2 = THETA(4)
##
##
##
## ;;================================ DIFFERENTIAL EQUATIONS ================================
## ; Typical Value Weibull hazard h0(t) = lambda*gamma*t^(gamma-1)
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## ALP = SLP1*BLALP     ; baseline ALP effect
## LDH = SLP2*BLLDH ; effect of LDH > 1.5 ULN
##
## BASE = (LAMBDA*GAMMA)*(LAMBDA*(T+DEL))**(GAMMA-1)
##
## DADT(1) = BASE * EXP(ALP + LDH)
## ;;================================ MODEL FIT ================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;-----------------------------
```

```
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=(LAMBDA*GAMMA)*(LAMBDA*(TIME+DELX))**(GAMMA-1)
##  ALPX = SLP1*BLALP   ; baseline ALP effect
##  LDHX = SLP2*BLLDH   ; effect of LDH > 1.5 ULN
##  HAZNOW= BASEX * EXP(ALPX + LDHX)
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================= RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================= SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES =====================================
##
## $THETA  (0,0.435) ; lambda
##  (0,1.61) ; gamma
```

```
## (0.01); slope1 ALP
## (0.01) ; slope2  LDH
##
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ==============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_7
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
##
## ;;================================ TABLES ================================
## $TABLE      NOPRINT ONEHEADER FILE=mytab7 ID TIME DV EVID MDV PRED CHZ
##             SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE
##          BASE BASEX LAMBDA GAMMA SLP1 SLP2
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab7 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab7 ID LAMBDA SLP1 SLP2 GAMMA BASE BASEX
##             ETAS(1:LAST)

## NULL
```

6.0.9.1 Run summary

```
##  [1] "------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run7/run7
##  [4] ""
##  [5] "Successful minimization                                        [    OK   ]   "
##  [6] "No rounding errors                                             [    OK   ]   "
##  [7] "No zero gradients                                              [    OK   ]   "
##  [8] "No final zero gradients                                        [    OK   ]   "
##  [9] "Hessian not reset                                              [    OK   ]   "
## [10] "No parameter near boundary                                     [    OK   ]   "
## [11] "Covariance step                                                [    OK   ]   "
## [12] ""
## [13] "Condition number                                               [    OK   ]   "
## [14] "Correlations                                                   [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                 0:01:49"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   80.55"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   2.55"
## [19] ""
## [20] "Objective function value: 896.5627"
## [21] ""
## [22] "Condition number: 8.969"
## [23] ""
## [24] "Number of observation records: 666"
## [25] "Number of individuals: 666"
## [26] ""
## [27] "                 THETA               OMEGA      SIGMA    "
## [28] "     lambda      0.368  (0.06134)                          "
```

```
## [29] "      gamma      1.685  (0.06098)                        "
## [30] " slope1 ALP  0.0009807   (0.1592)                        "
## [31] "slope2  LDH     0.5927   (0.2687)                        "
## [32] ""
## [33] "The relative standard errors for omega and sigma are reported on the approximate"
## [34] "standard deviation scale (SE/variance estimate)/2."
## [35] "-----------------------------------------------------------------------"
```

6.0.9.2 Diagnostic plots

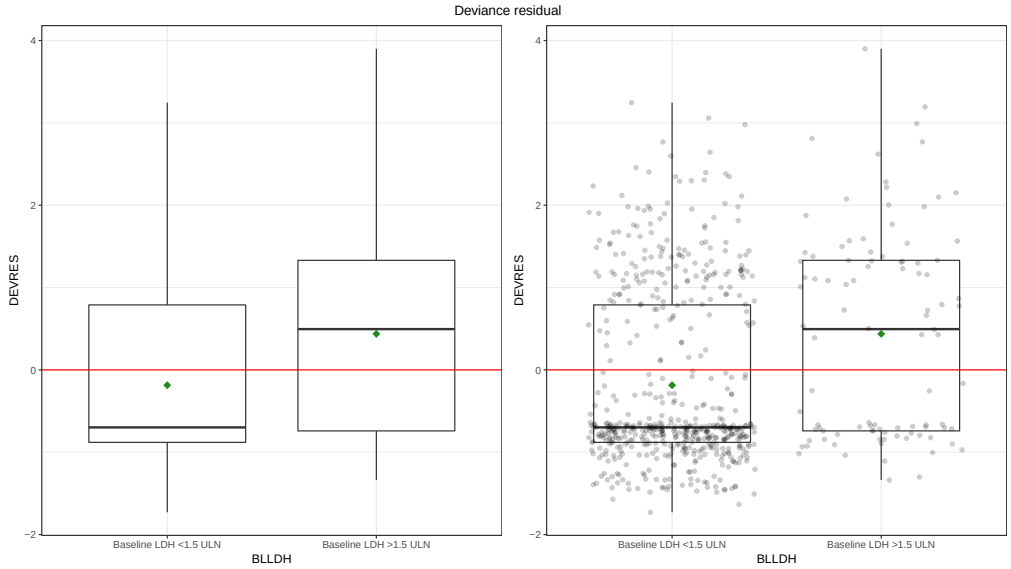


Figure 29: Residual-based diagnostics - Deviance plot

- zero reference line (red) ; mean residuals (green diamond)

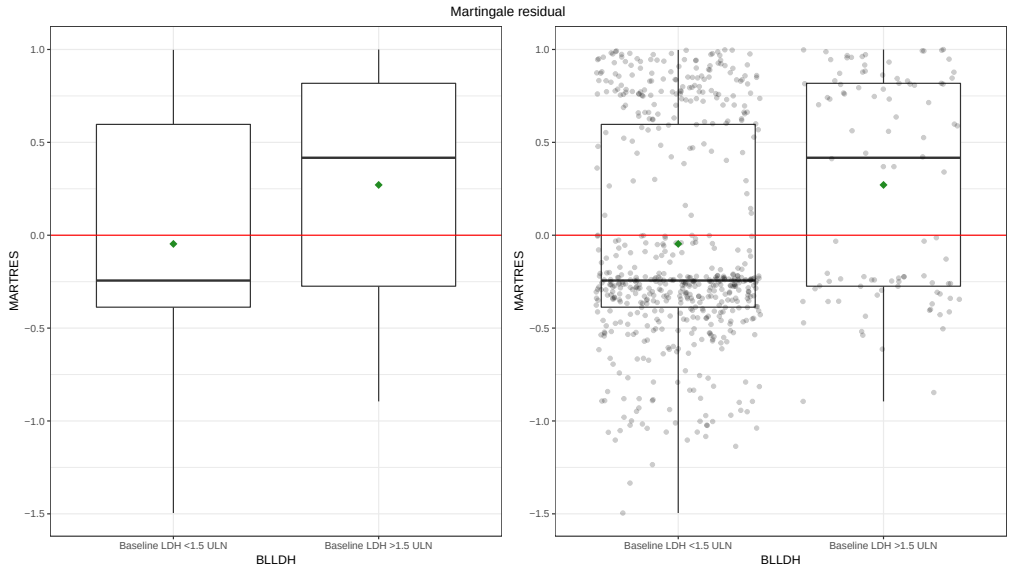
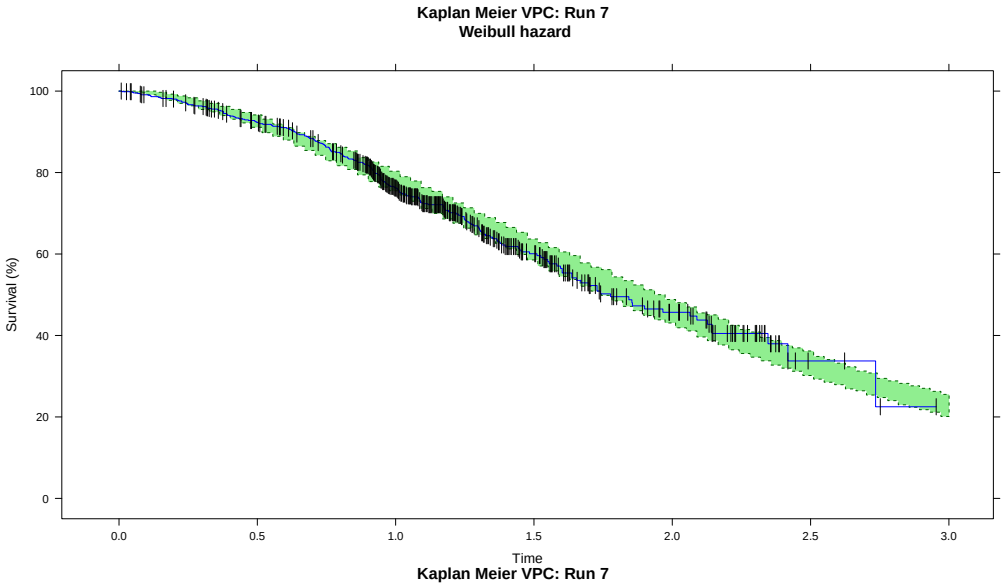
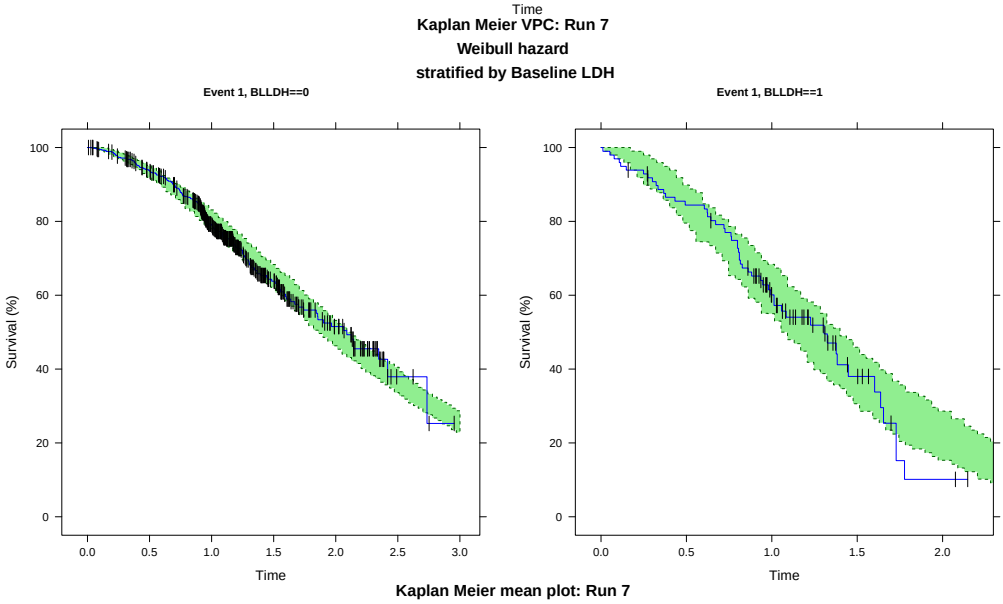
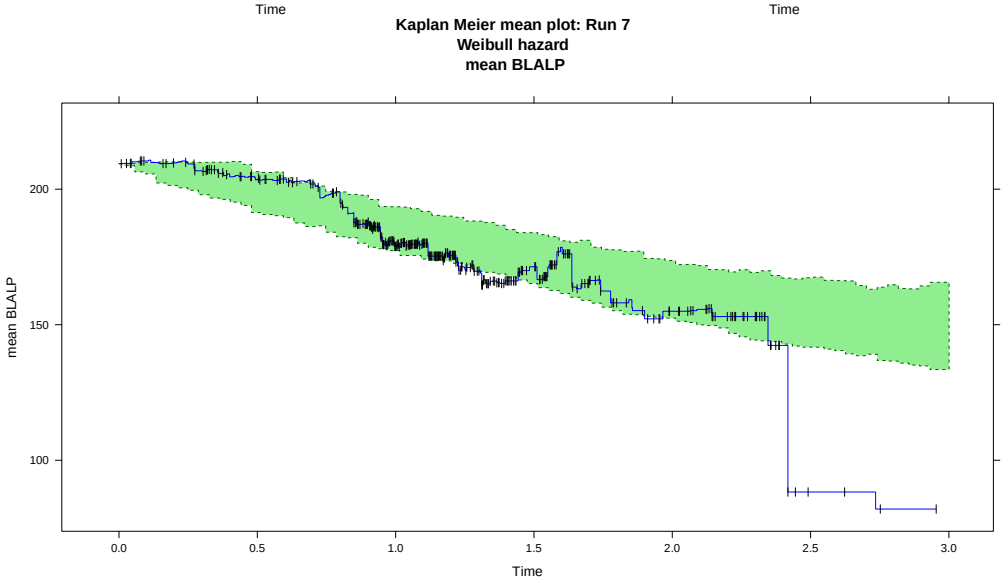


Figure 30: Residual-based diagnostics - Martingale plot


Kaplan Meier VPC: Run 7
Weibull hazard
Survival (%)
Time


Kaplan Meier VPC: Run 7
Weibull hazard
stratified by Baseline LDH
Event 1, BLLDH==0
Event 1, BLLDH==1
Survival (%)
Time


Kaplan Meier mean plot: Run 7
Weibull hazard
mean BLALP
mean BLALP
Time

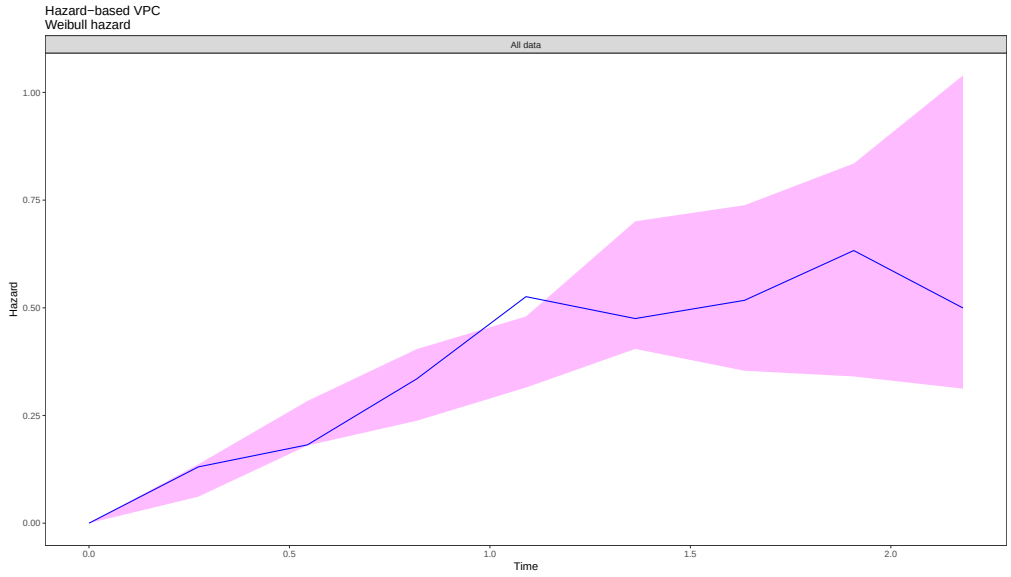


Figure 31: Simulation-based diagnostic: Hazard based VPC

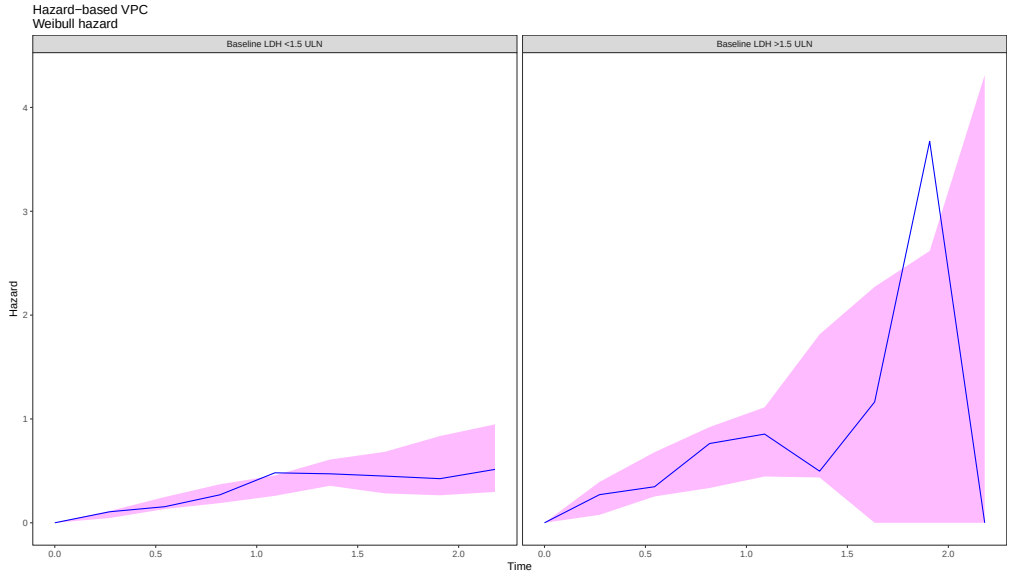


Figure 32: Simulation-based diagnostic: Hazard based VPC

6.0.10 Run 8 - Weibull Hazard + log baseline ALP & LDH effect (on BASE)

```
##==================================== Run notes  ====================================##
# Evidence:    Residuals plot show a trend with baseline LDH & ALP
# Question:    What effect does baseline LDH have on the baseline hazard
# Based on:    5
# Description: log linear models for BLALP and BLLDH
##-------------------------------------------------------------------------------------##
# next.mod(7,8,nm.dir)
show.mod(8, nm.dir) # print model
```

```
## ;; 1. Based on: 5
## ;; 2. Description:
## ;;    Covariate TTE model
## ;; 3. Label:
## ;;    Weibull hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;;     log linear model (log BL ALP), linear model (BL LDH)
## ;; 6. Interindividual variability:
## ;;    NA
## ;; 7. Interoccasion variability:
## ;;    NA
## ;; 8. Residual variability:
## ;;    NA
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    Base TTE model - Project DataSphere # 78 - no missing LDH
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM LOGBLALP
## ;-----------------------------------------------------data description
## ; ID, subject identifier
## ; TIME, in years
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
## ; CENS, censored event, 0 = no, 1 = yes
## ; MAXT, last recorded event per patient (either death or censor)
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
## ; GENDER, bianry covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
## ; OSTIM, observed time in days to event or censor time
```

```
## ; LOGBLALP, log (BLLDH)
## ;-----------------------------------------------------
##
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2.csv IGNORE=@
##
## IGNORE(NOLDH.EQ.1); 24 patients missing BL_LDH data
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
##
## ;IGNORE=(STIME.EQ.0) ; observed time, ignore for simulation
##
## ;Sim_end
## $SUBROUTINE ADVAN=13 TOL=6
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##
##  LAMBDA = THETA(1) * EXP(ETA(1))
##  GAMMA = THETA(2)
##  SLP1 = THETA(3)
##  SLP2 = THETA(4)
##
##
##
## ;;================================ DIFFERENTIAL EQUATIONS ================================
## ; Typical Value Weibull hazard h0(t) = lambda*gamma*t^(gamma-1)
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## ALP = SLP1*LOGBLALP      ; baseline ALP effect
## LDH = SLP2*BLLDH ; effect of LDH > 1.5 ULN
##
## BASE = (LAMBDA*GAMMA)*(LAMBDA*(T+DEL))**(GAMMA-1)
##
## DADT(1) = BASE * EXP(ALP + LDH)
## ;;================================ MODEL FIT ================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;-------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;-------------------------------
```

```
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=(LAMBDA*GAMMA)*(LAMBDA*(TIME+DELX))**(GAMMA-1)
##  ALPX = SLP1*LOGBLALP    ; baseline ALP effect
##  LDHX = SLP2*BLLDH   ; effect of LDH > 1.5 ULN
##  HAZNOW= BASEX * EXP(ALPX + LDHX)
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================ RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================ SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================ INITIAL ESTIMATES ====================================
##
## $THETA  (0,0.435) ; lambda
##  (0,1.61) ; gamma
##  0.009 ; slope1 ALP
##  0.5 ; slope2  LDH
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
```

```
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_8
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
##
## ;;================================ TABLES ================================
## $TABLE      NOPRINT ONEHEADER FILE=mytab8 ID TIME DV EVID MDV PRED CHZ
##             SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE BASE
##             BASEX LAMBDA GAMMA SLP1 SLP2 BLWHOSTAT BLALB BLALP
##             BLWHOLEVEL OSTIM
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab8 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab8 ID LAMBDA SLP1 SLP2
##             GAMMA BASE BASEX ETAS(1:LAST)
```

```
## NULL
```

6.0.10.1 Run summary

```
##  [1] "------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run8/run8
##  [4] ""
##  [5] "Successful minimization                                        [    OK   ]   "
##  [6] "No rounding errors                                             [    OK   ]   "
##  [7] "No zero gradients                                              [    OK   ]   "
##  [8] "No final zero gradients                                        [    OK   ]   "
##  [9] "Hessian not reset                                              [    OK   ]   "
## [10] "No parameter near boundary                                     [    OK   ]   "
## [11] "Covariance step                                                [    OK   ]   "
## [12] ""
## [13] "Condition number                                               [    OK   ]   "
## [14] "Correlations                                                   [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:22"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   54.69"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   2.52"
## [19] ""
## [20] "Objective function value: 892.0642"
## [21] ""
## [22] "Condition number: 250.3"
## [23] ""
## [24] "Number of observation records: 666"
## [25] "Number of individuals: 666"
## [26] ""
## [27] "              THETA               OMEGA      SIGMA    "
## [28] "     lambda  0.1005   (0.2818)                         "
## [29] "      gamma   1.678  (0.06044)                         "
## [30] " slope1 ALP  0.4735   (0.1881)                         "
## [31] "slope2  LDH  0.4618   (0.3478)                         "
## [32] ""
## [33] "The relative standard errors for omega and sigma are reported on the approximate"
## [34] "standard deviation scale (SE/variance estimate)/2."
## [35] "------------------------------------------------------------------------"
```

6.0.10.2 Diagnostic plots

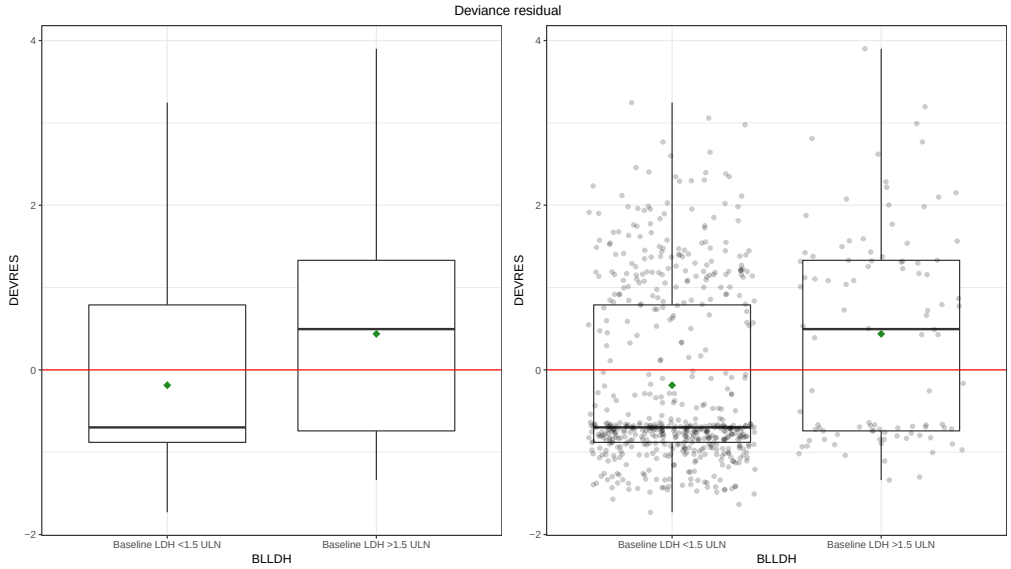


Figure 33: Residual-based diagnostics - Deviance plot

- zero reference line (red) ; mean residuals (green diamond)

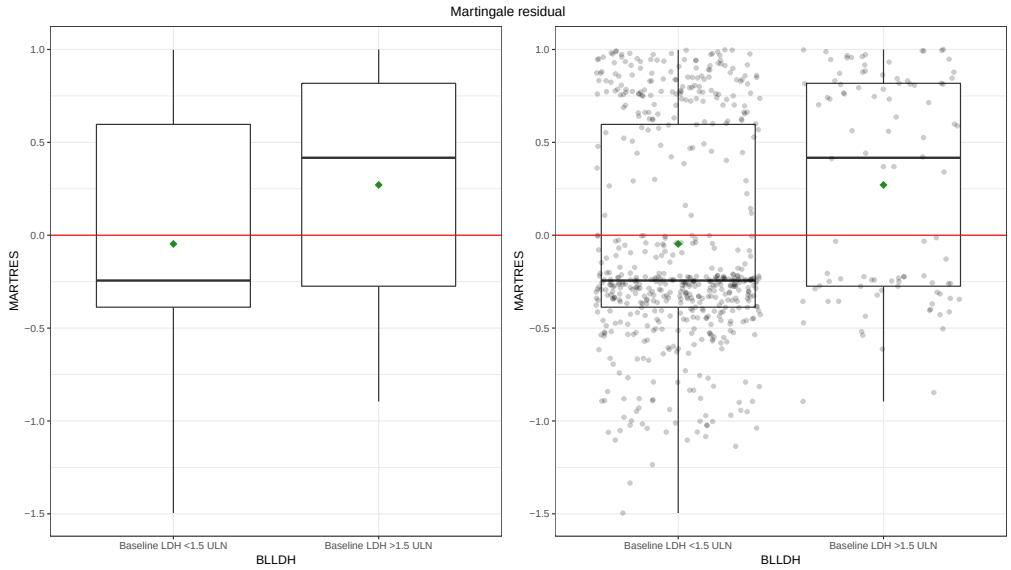


Figure 34: Residual-based diagnostics - Martingale plot

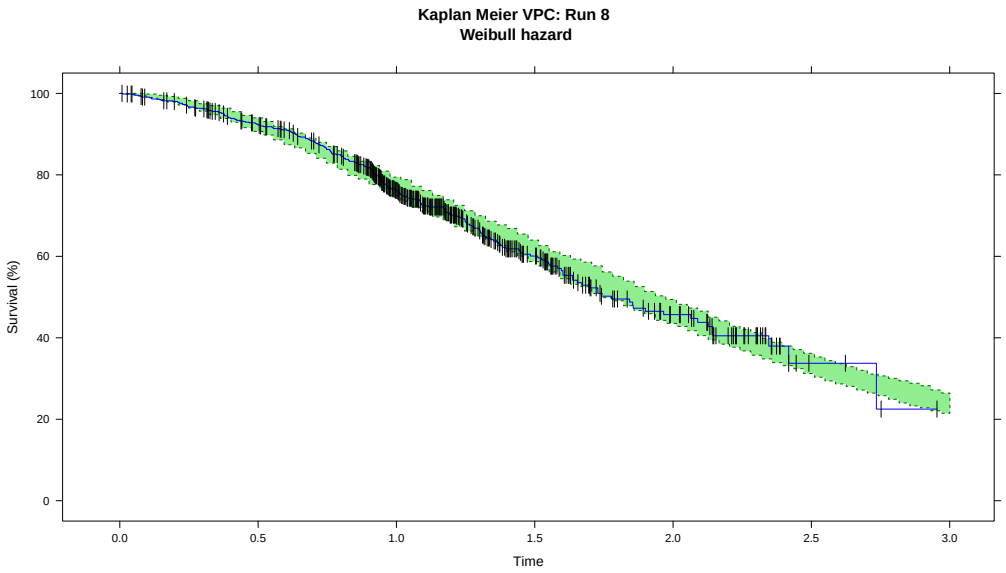


Figure 35: Simulation-based diagnostic

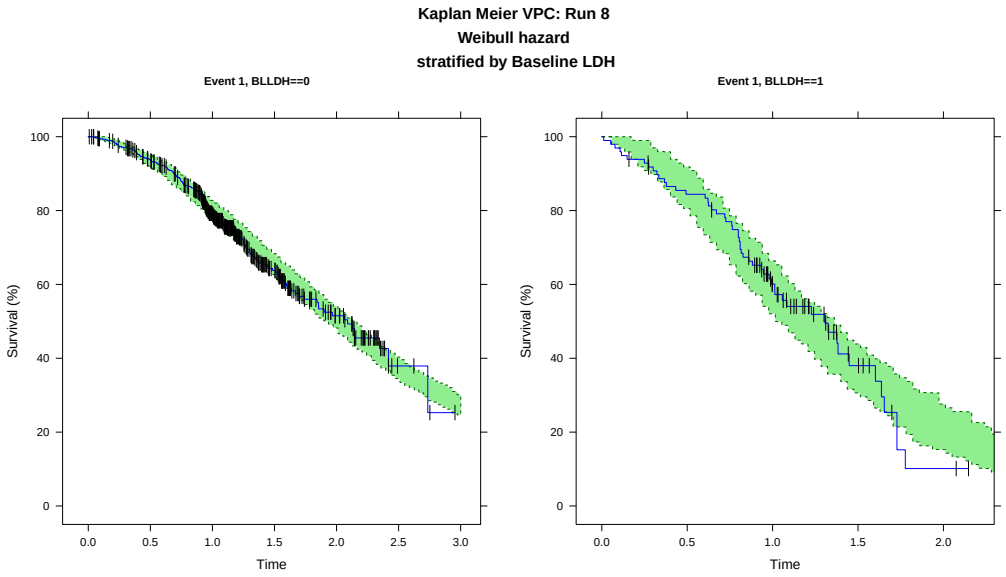


Figure 36: Simulation-based diagnostic - stratified by baseline LDH

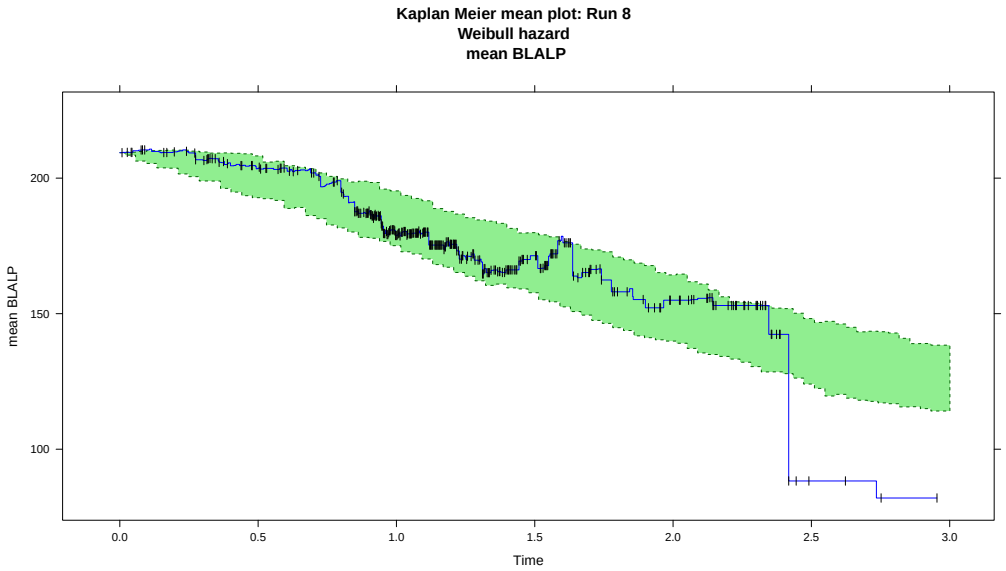


Figure 37: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

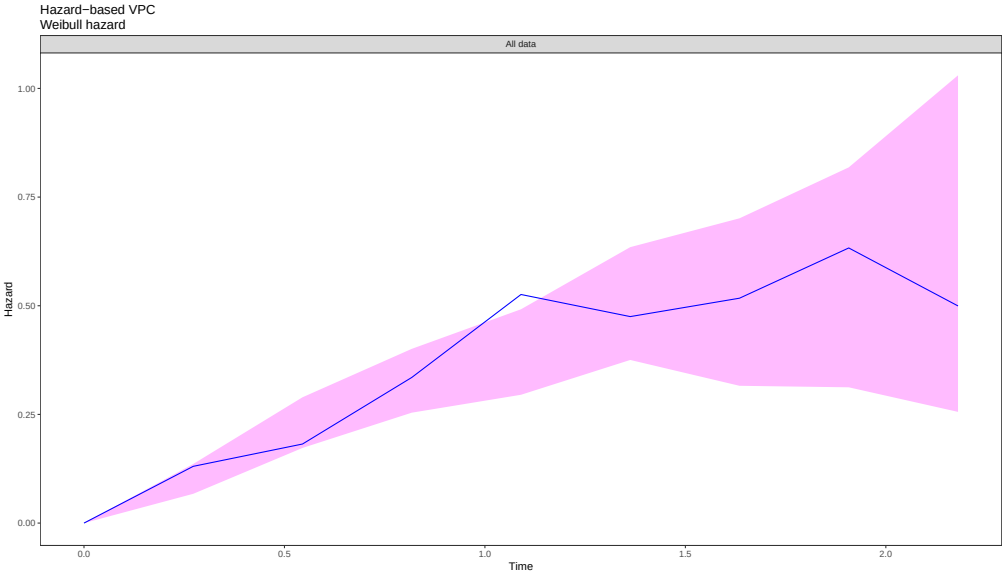


Figure 38: Simulation-based diagnostic: Hazard based VPC

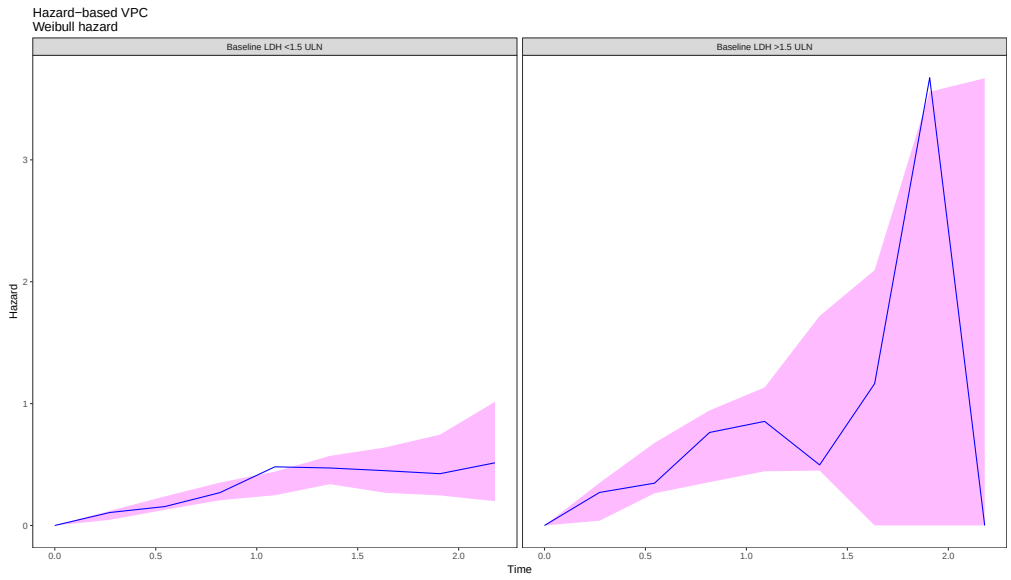


Figure 39: Simulation-based diagnostic: Hazard based VPC

7 Proportional hazards model development (base model 6)

7.0.11 Run 9 - Log-logistic Hazard + LDH effect + baseline ALP (on BASE)

```
##=================================== Run notes  ====================================##
# Evidence:    Residuals plot show a trend with baseline LDH & ALP
# Question:    What effect does baseline LDH have on the baseline hazard
# Based on:    6
# Description: linear models for BLALP and BLLDH
##-----------------------------------------------------------------------------------##
# next.mod(6,9,nm.dir)
show.mod(9, nm.dir) # print model
```

```
## ;; 1. Based on: 6
## ;; 2. Description:
## ;;    Covariate TTE model
## ;; 3. Label:
## ;;    log-logistic hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;;     linear model (BL ALP), linear model (BL LDH)
## ;; 6. Interindividual variability:
## ;; 7. Interoccasion variability:
## ;; 8. Residual variability:
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    TTE model - Project DataSphere # 78
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM
## ;-------------------------------------------------------data description
## ; ID, subject identifier
## ; TIME, in years
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
## ; CENS, censored event, 0 = no, 1 = yes
## ; MAXT, last recorded event per patient (either death or censor)
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
## ; GENDER, bianry covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
## ; OSTIM, observed time in days to event or censor time
```

```
## ;----------------------------------------------------
##
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2.csv IGNORE=@
##
## IGNORE(NOLDH.EQ.1) ; 24 patients missing LDH data
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
## ;IGNORE=(STIME.EQ.0) ;; observed time, ignore for simulation
##
## ;Sim_end
## $SUBROUTINE ADVAN=13 TOL=9
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##  DELTA = THETA(1)* EXP(ETA(1))
##  GAMMA = THETA(2)
##  SLP1 = THETA(3)
##  SLP2 = THETA(4)
## ;;================================= DIFFERENTIAL EQUATIONS ==================================
## ; Typical Value Log-logistic hazard,  h0(t) = exp(delta) kt^(k-1) / (1+ exp(delta)*t^k), where k = g
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## ALP = SLP1*BLALP     ; baseline ALP effect
## LDH = SLP2*BLLDH ; effect of LDH > 1.5 ULN
## BASE = EXP(DELTA)*GAMMA*(T+DEL)**(GAMMA-1) / (1 + EXP(DELTA)*(T+DEL)**GAMMA)
##
## DADT(1) = BASE * EXP(ALP + LDH)
##
## ;;================================= MODEL FIT ===================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=EXP(DELTA)*GAMMA*(TIME+DELX)**(GAMMA-1) / (1 + EXP(DELTA)*(TIME+DELX)**GAMMA)
##  ALPX = SLP1*BLALP   ; baseline ALP effect
##  LDHX = SLP2*BLLDH   ; effect of LDH > 1.5 ULN
##  HAZNOW= BASEX * EXP(ALPX + LDHX)
```

```
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================ RESIDUALS CALCULATIONS ================================
## ;where events DV = 1 and censoring DV = 0
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================ SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================ INITIAL ESTIMATES ====================================
##
## $THETA  -1.17 ; delta
##  (0,1.85) ; gamma
##  (0.01); slope1 ALP
## (0.01) ; slope2  LDH
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_9
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
## ;Sim_end
##
## ;;================================ TABLES ================================
## $TABLE      NOPRINT ONEHEADER FILE=mytab9 ID TIME DV EVID MDV PRED CHZ
##             SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE
```

```
##          BASE BASEX DELTA GAMMA SLP1 SLP2
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab9 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab9 ID DELTA GAMMA
##             ETAS(1:LAST)
```

```
## NULL
```

7.0.11.1 Run summary

```
##  [1] "-----------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run9/run9
##  [4] ""
##  [5] "Successful minimization                                          [    OK   ]   "
##  [6] "No rounding errors                                               [    OK   ]   "
##  [7] "No zero gradients                                                [    OK   ]   "
##  [8] "No final zero gradients                                          [    OK   ]   "
##  [9] "Hessian not reset                                                [    OK   ]   "
## [10] "No parameter near boundary                                       [    OK   ]   "
## [11] "Covariance step                                                  [    OK   ]   "
## [12] ""
## [13] "Condition number                                                 [    OK   ]   "
## [14] "Correlations                                                     [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:51"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   77.13"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   4.02"
## [19] ""
## [20] "Objective function value: 899.6654"
## [21] ""
## [22] "Condition number: 5.695"
## [23] ""
## [24] "Number of observation records: 666"
## [25] "Number of individuals: 666"
## [26] ""
## [27] "                 THETA               OMEGA      SIGMA    "
## [28] "      delta     -1.562  (0.06398)                         "
## [29] "      gamma      1.865  (0.06627)                         "
## [30] " slope1 ALP  0.0009866   (0.1578)                         "
## [31] "slope2  LDH     0.5819   (0.2735)                         "
## [32] ""
## [33] "The relative standard errors for omega and sigma are reported on the approximate"
## [34] "standard deviation scale (SE/variance estimate)/2."
## [35] "-----------------------------------------------------------------------"
```

7.0.11.2 Diagnostic plots

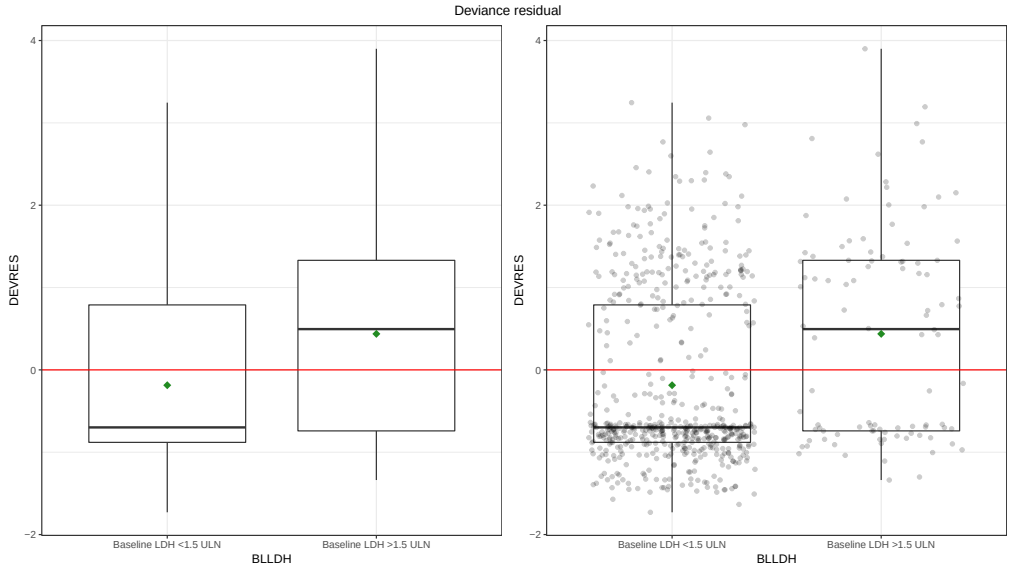


Figure 40: Residual-based diagnostics - Deviance plot

- zero reference line (red) ; mean residuals (green diamond)

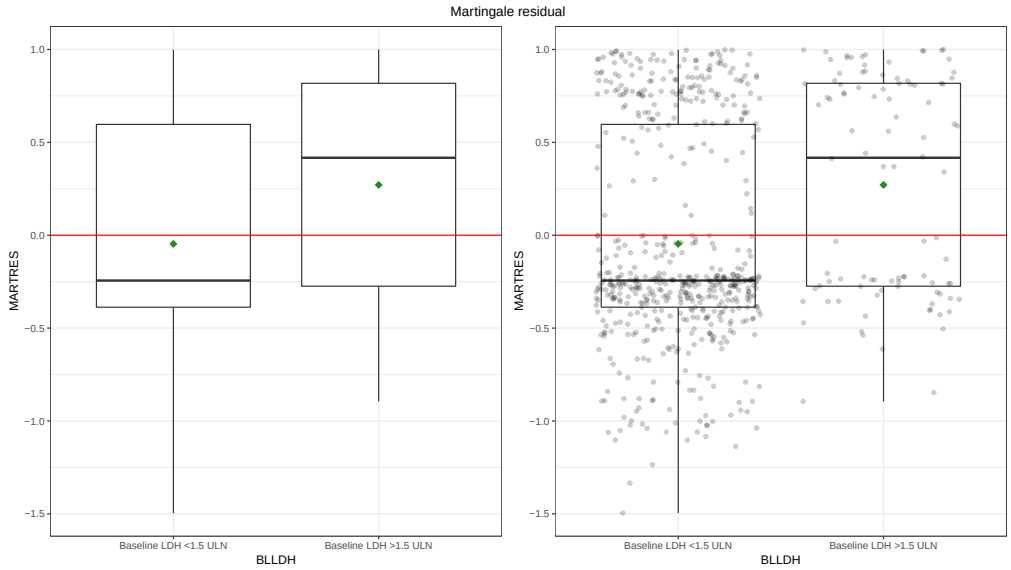
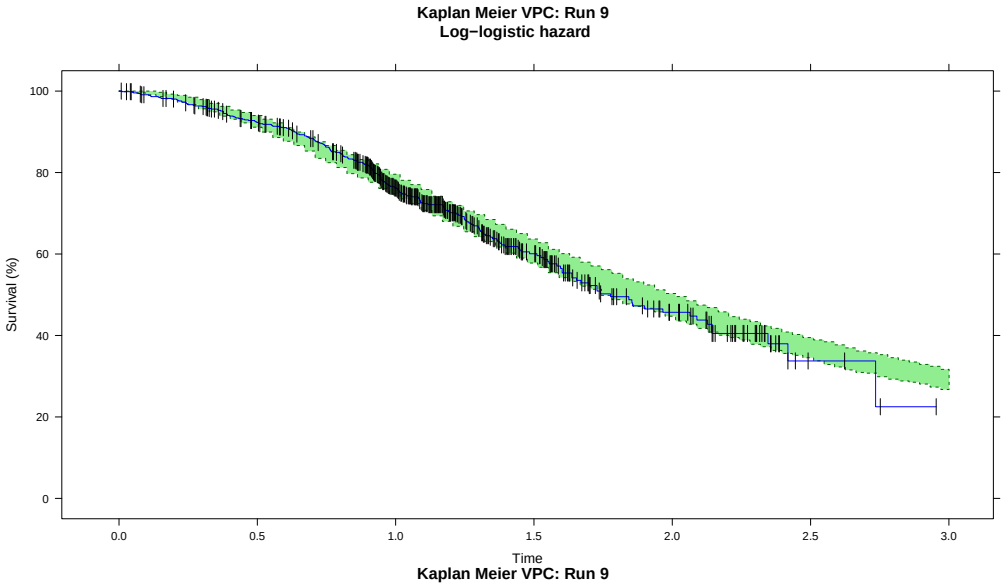
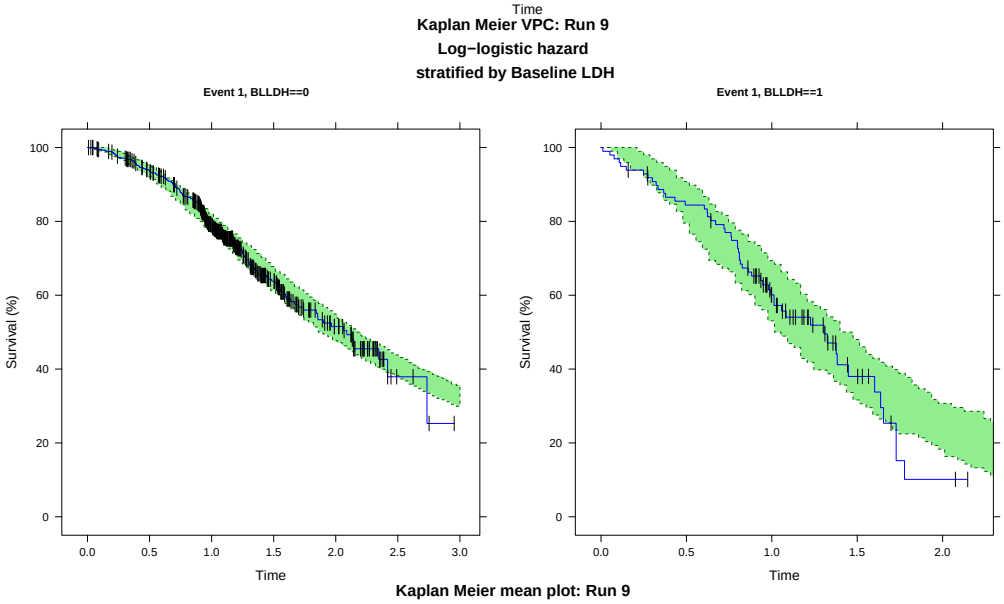
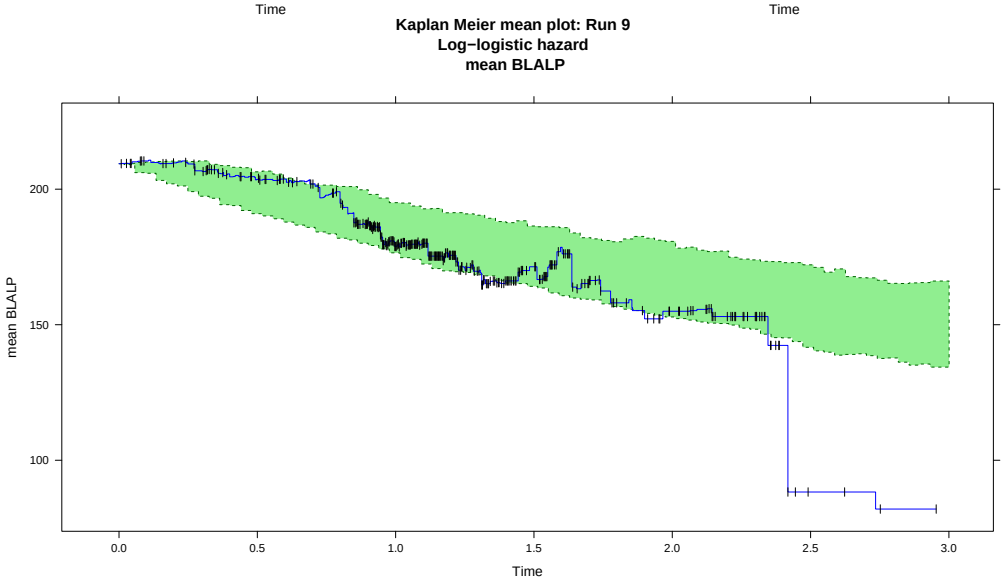


Figure 41: Residual-based diagnostics - Martingale plot


Kaplan Meier VPC: Run 9
Log−logistic hazard
Survival (%)
Time


Kaplan Meier VPC: Run 9
Log−logistic hazard
stratified by Baseline LDH
Event 1, BLLDH==0
Event 1, BLLDH==1
Survival (%)
Time


Kaplan Meier mean plot: Run 9
Log−logistic hazard
mean BLALP
mean BLALP
Time

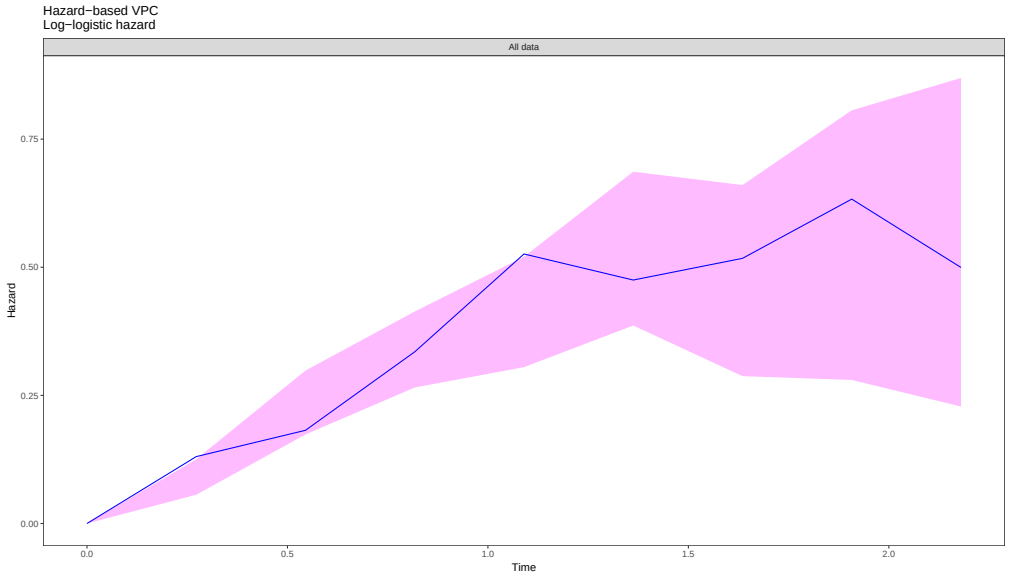
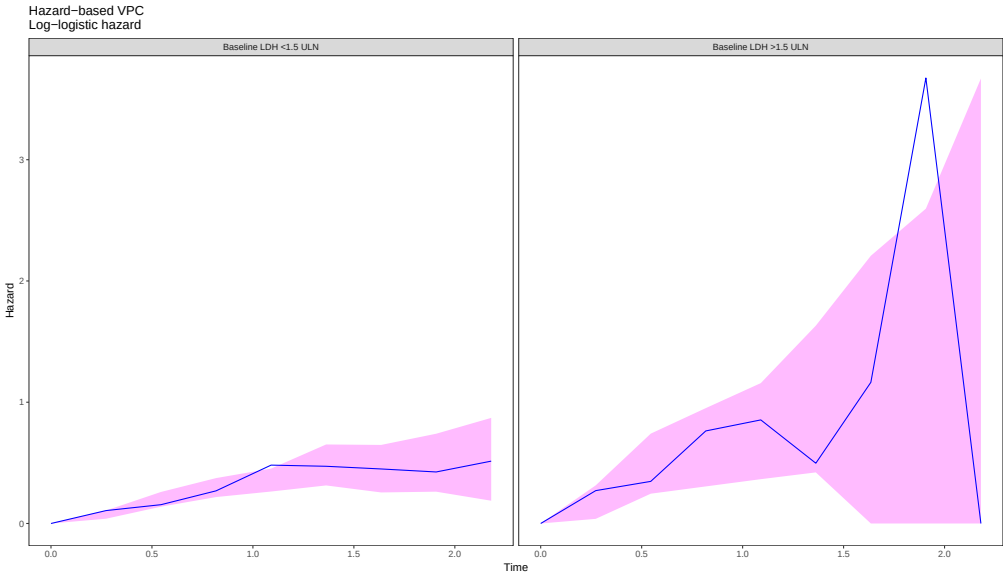


Figure 42: Simulation-based diagnostic: Hazard based VPC



7.0.12 Run 10 - Log-logistic Hazard + log baseline ALP & LDH effect (on BASE)

```
##==================================== Run notes  ====================================##
# Evidence:    Residuals plot show a trend with baseline LDH & ALP
# Question:    What effect does baseline LDH have on the baseline hazard
# Based on:    6
# Description: log linear models for BLALP and BLLDH
##-------------------------------------------------------------------------------------##
# next.mod(6,10,nm.dir)
show.mod(10, nm.dir) # print model
```

```
## ;; 1. Based on: 6
## ;; 2. Description:
## ;;   Covariate TTE model
## ;; 3. Label:
## ;;    log-logistic hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;;     log linear model (log BL ALP), linear model (BL LDH)
## ;; 6. Interindividual variability:
## ;; 7. Interoccasion variability:
## ;; 8. Residual variability:
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    TTE model - Project DataSphere # 78
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM LOGBLALP
## ;----------------------------------------------------data description
##
## ; ID, subject identifier
##
## ; TIME, in years
##
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
##
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
##
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
##
## ; CENS, censored event, 0 = no, 1 = yes
##
## ; MAXT, last recorded event per patient (either death or censor)
##
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
##
## ; GENDER, bianry covariate (0=male,1=female)
##
```

```
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
##
## ; BLAGE, categorical, age group in years
##
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
##
## ; BLALB, continuous, ALB test values at baseline
##
## ; BLALP, continuous, ALP test values at baseline
##
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
##
## ; OSTIM, observed time in days to event or censor time
## ; LOGBLALP, log (BLLDH)
## ;----------------------------------------------------
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2.csv IGNORE=@
##
## IGNORE(NOLDH.EQ.1) ; 24 patients missing LDH data
##
## ;Sim_start : remove from simulation model
##   IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
##
## ;IGNORE=(STIME.EQ.0) ;; observed time, ignore for simulation
##
## ;Sim_end
## $SUBROUTINE ADVAN=13 TOL=9
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ==========================
## $PK
##  DELTA = THETA(1)* EXP(ETA(1))
##  GAMMA = THETA(2)
##  SLP1 = THETA(3)
##  SLP2 = THETA(4)
##
## ;;================================= DIFFERENTIAL EQUATIONS ====================================
## ; Typical Value Log-logistic hazard,  h0(t) = exp(delta) kt^(k-1) / (1+ exp(delta)*t^k), where k = g
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = EXP(DELTA)*GAMMA*(T+DEL)**(GAMMA-1) / (1 + EXP(DELTA)*(T+DEL)**GAMMA)
## ALP = SLP1*LOGBLALP      ; baseline ALP effect
## LDH = SLP2*BLLDH ; effect of LDH > 1.5 ULN
##
## DADT(1) = BASE
##
## DADT(1) = BASE * EXP(ALP + LDH)
## ;;================================= MODEL FIT ================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
```

```
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;-----------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;-----------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=EXP(DELTA)*GAMMA*(TIME+DELX)**(GAMMA-1) / (1 + EXP(DELTA)*(TIME+DELX)**GAMMA)
##  ALPX = SLP1*LOGBLALP    ; baseline ALP effect
##  LDHX = SLP2*BLLDH   ; effect of LDH > 1.5 ULN
##  HAZNOW= BASEX * EXP(ALPX + LDHX)
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================= RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================= SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
```

```
## ;;================================ INITIAL ESTIMATES ================================
##
## $THETA  -1.17 ; delta
##  (0,1.85) ; gamma
##  0.009 ; slope1 ALP
##  0.5 ; slope2  LDH
## $OMEGA  0  FIX  ; place holder
## ;;============================ ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_10
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
##
## ;;================================ TABLES ================================
## $TABLE      NOPRINT ONEHEADER FILE=mytab10 ID TIME DV EVID MDV PRED CHZ
##             SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE BASE
##             BASEX DELTA GAMMA SLP1 SLP2 BLWHOSTAT BLALB BLALP
##             BLWHOLEVEL OSTIM
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab10 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab10 ID DELTA GAMMA
##             ETAS(1:LAST)

## NULL
```

7.0.12.1 Run summary

```
##  [1] "------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run10/run
##  [4] ""
##  [5] "Successful minimization                                        [    OK   ]   "
##  [6] "No rounding errors                                             [    OK   ]   "
##  [7] "No zero gradients                                              [    OK   ]   "
##  [8] "No final zero gradients                                        [    OK   ]   "
##  [9] "Hessian not reset                                              [    OK   ]   "
## [10] "No parameter near boundary                                     [    OK   ]   "
## [11] "Covariance step                                                [    OK   ]   "
## [12] ""
## [13] "Condition number                                               [    OK   ]   "
## [14] "Large correlations between parameter estimates found           [ WARNING ]   "
## [15] "\tslope1 ALP - delta    -0.98414"
## [16] ""
## [17] "Total run time for model (hours:min:sec):                  0:01:26"
## [18] "Estimation time for subproblem, sum over $EST (seconds):   54.48"
## [19] "Covariance time for subproblem, sum over $EST (seconds):   4.68"
## [20] ""
## [21] "Objective function value: 892.2317"
## [22] ""
## [23] "Condition number: 223"
## [24] ""
## [25] "Number of observation records: 666"
```

```
## [26] "Number of individuals: 666"
## [27] ""
## [28] "              THETA               OMEGA      SIGMA    "
## [29] "      delta  -3.858   (0.1201)                         "
## [30] "      gamma   1.699  (0.06038)                         "
## [31] " slope1 ALP  0.4771   (0.1809)                         "
## [32] "slope2  LDH  0.4569   (0.3481)                         "
## [33] ""
## [34] "The relative standard errors for omega and sigma are reported on the approximate"
## [35] "standard deviation scale (SE/variance estimate)/2."
## [36] "-------------------------------------------------------------------------------"
```

7.0.12.2 Diagnostic plots

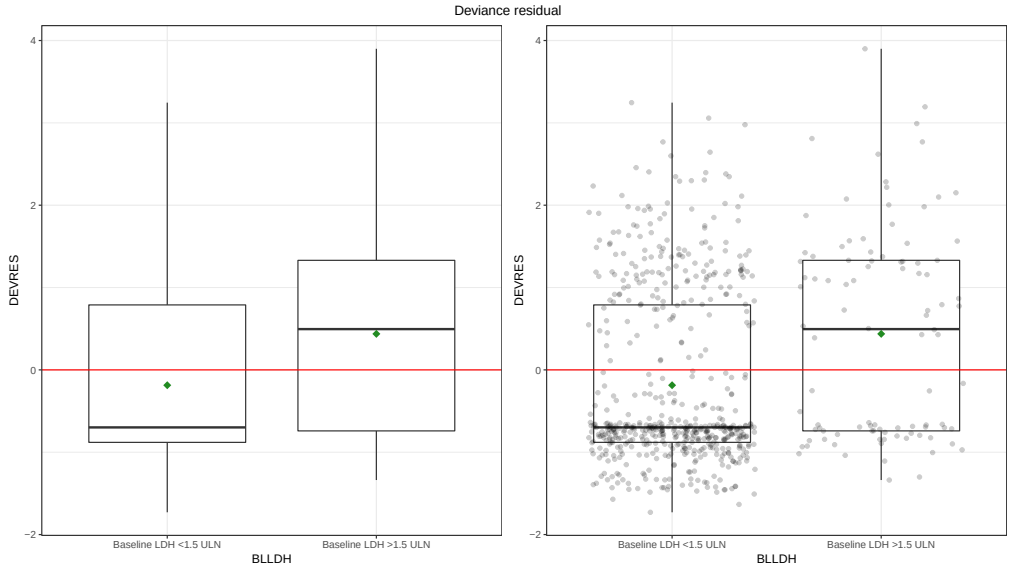


Figure 43: Residual-based diagnostics - Deviance plot

- zero reference line (red) ; mean residuals (green diamond)

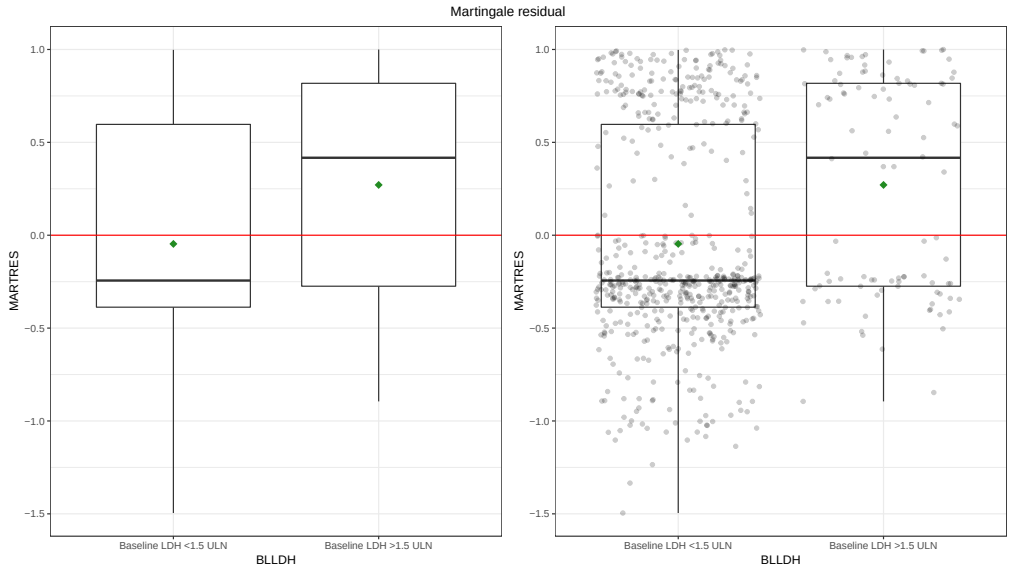
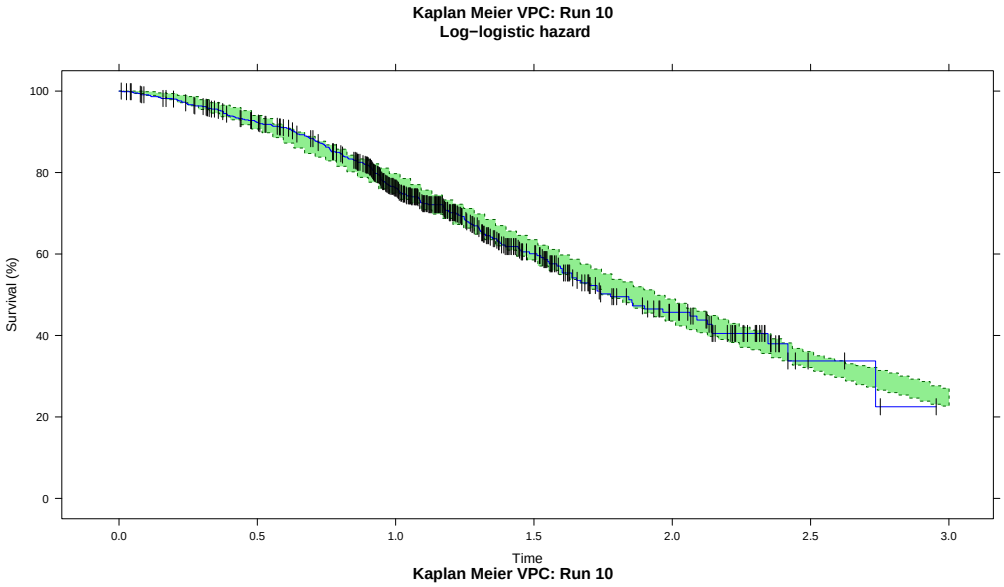
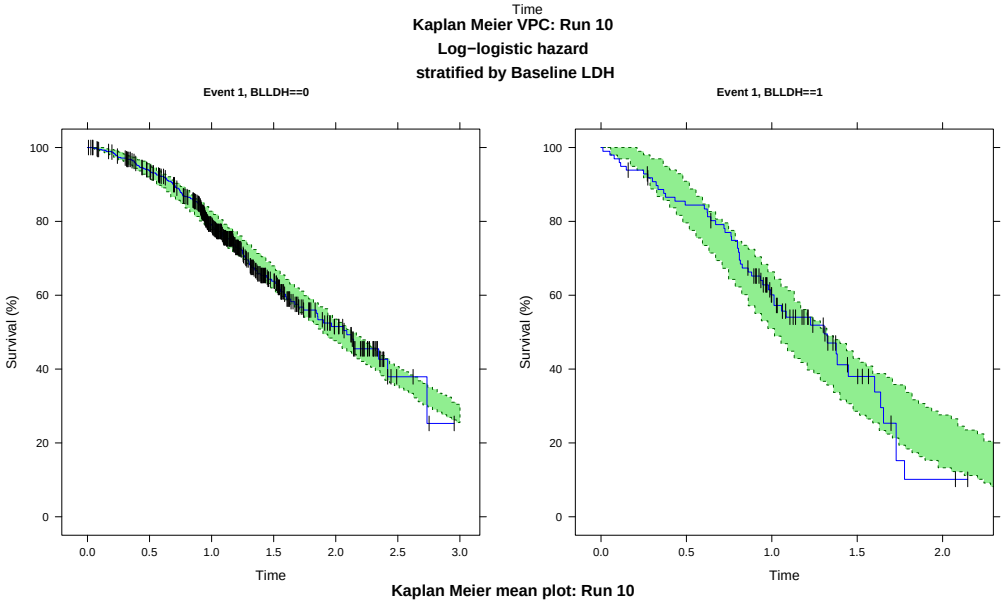
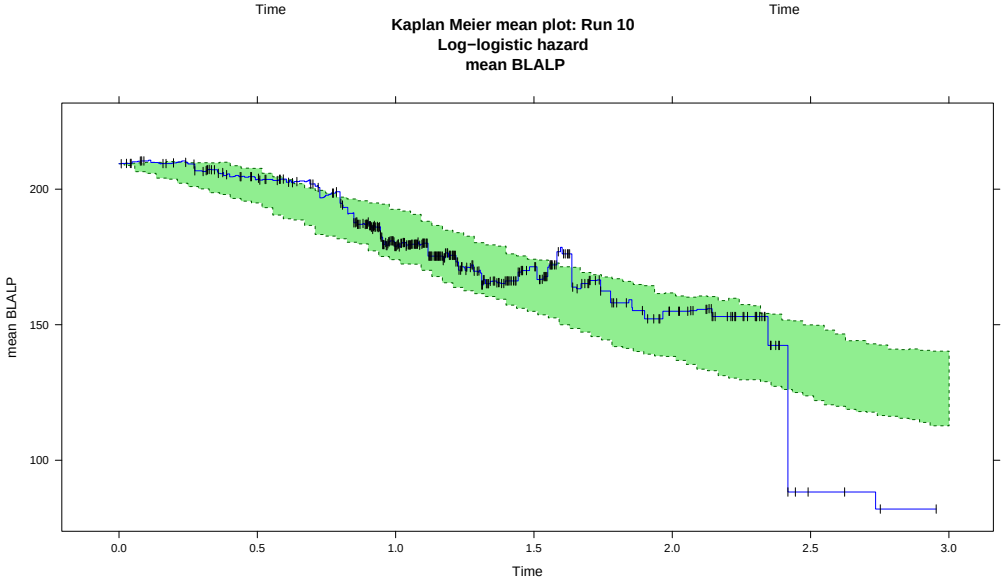


Figure 44: Residual-based diagnostics - Martingale plot


Kaplan Meier VPC: Run 10
Log−logistic hazard
Survival (%)
Time


Kaplan Meier VPC: Run 10
Log−logistic hazard
stratified by Baseline LDH
Event 1, BLLDH==0
Event 1, BLLDH==1
Survival (%)
Time


Kaplan Meier mean plot: Run 10
Log−logistic hazard
mean BLALP
mean BLALP
Time

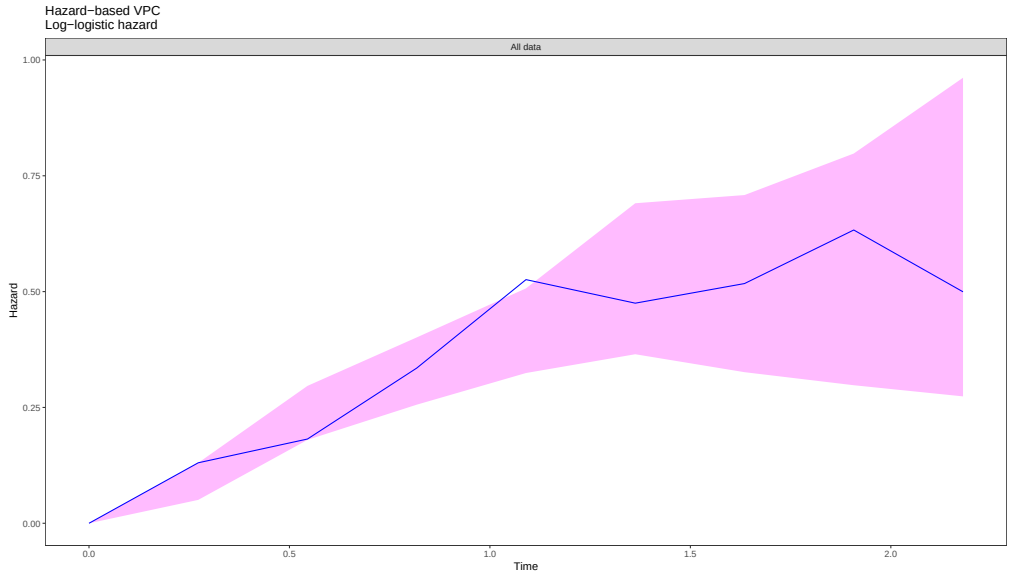


Figure 45: Simulation-based diagnostic: Hazard based VPC

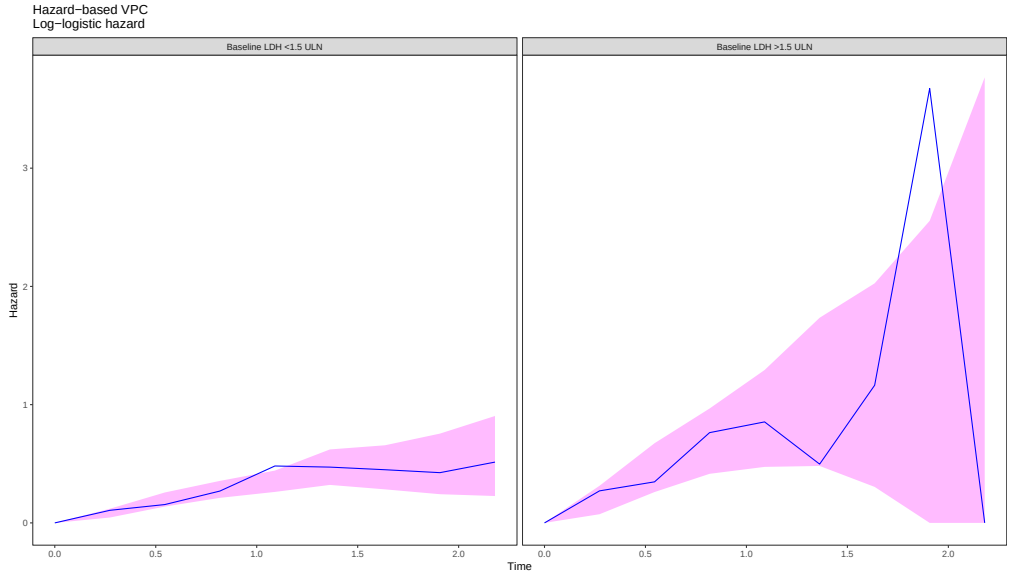
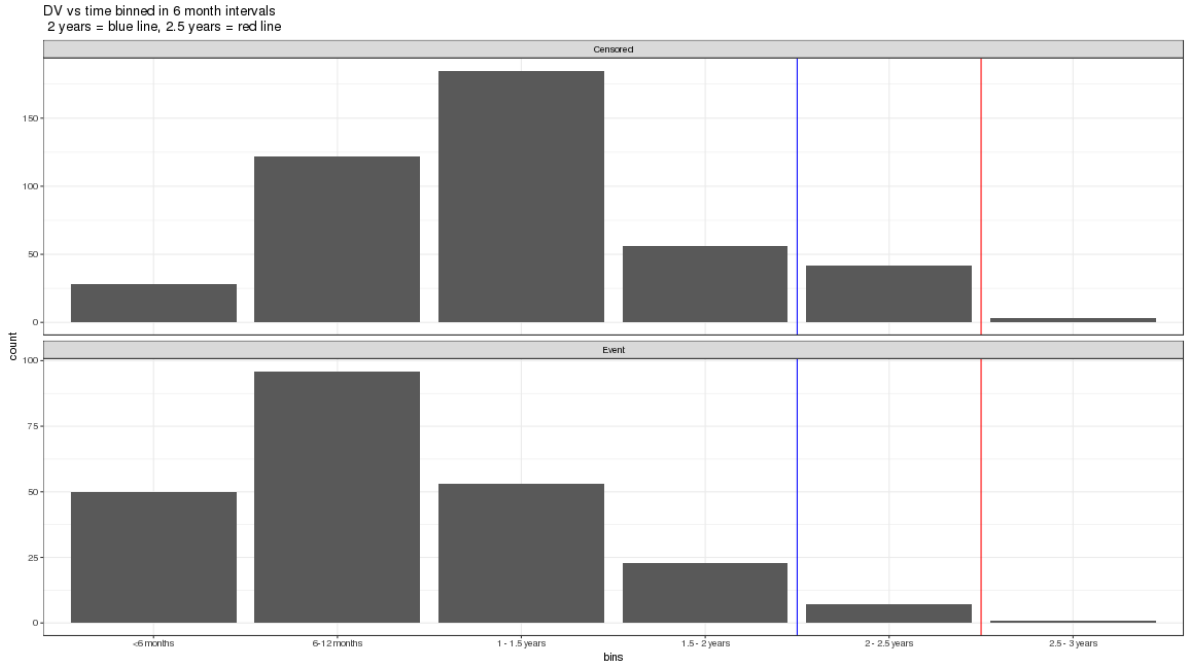


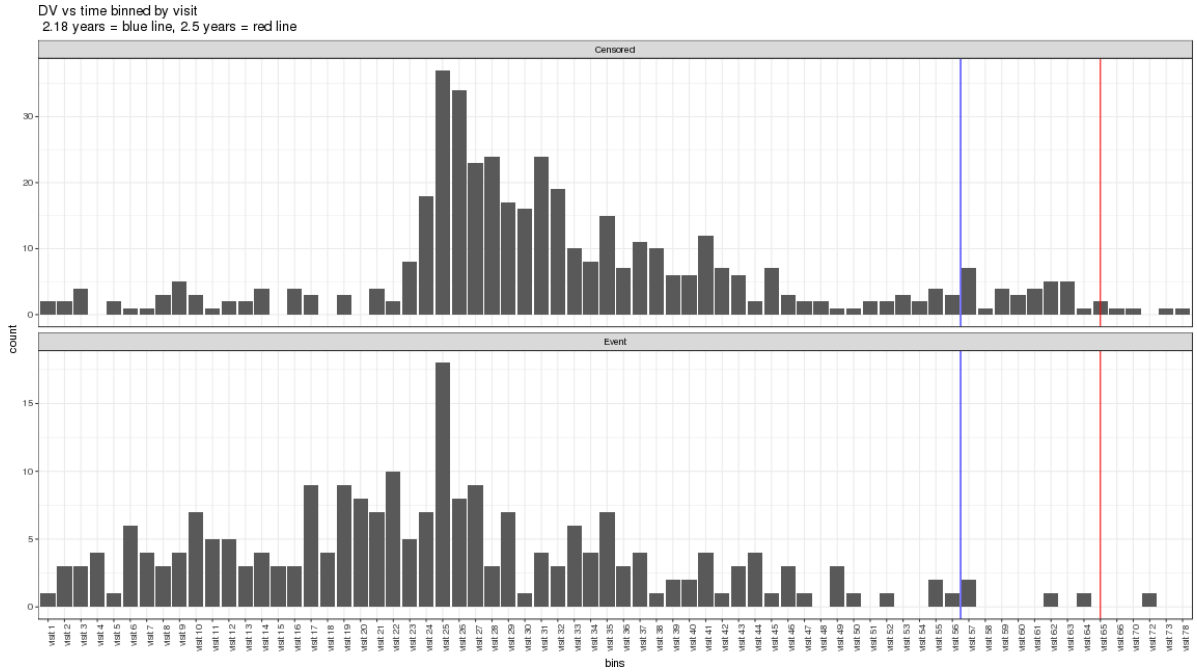
Figure 46: Simulation-based diagnostic: Hazard based VPC

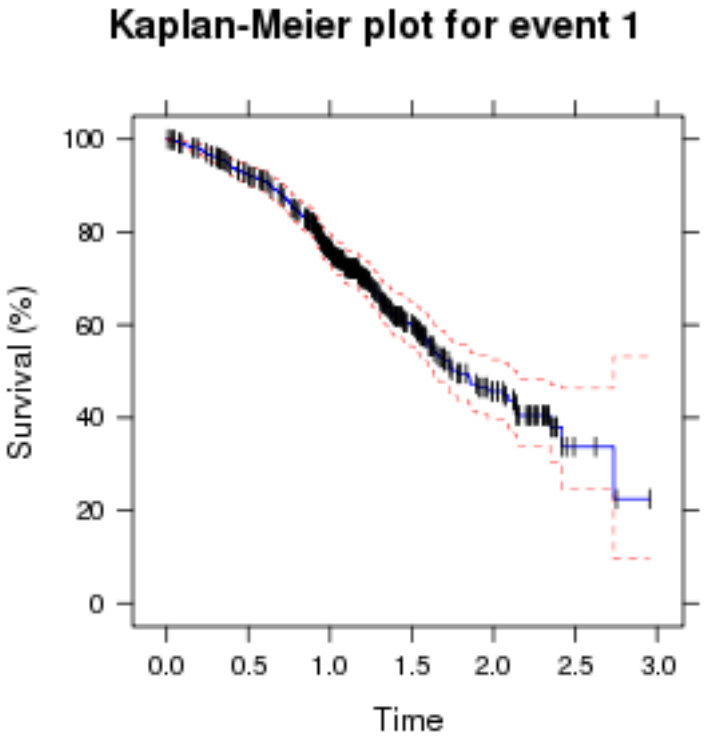
8 Data mining

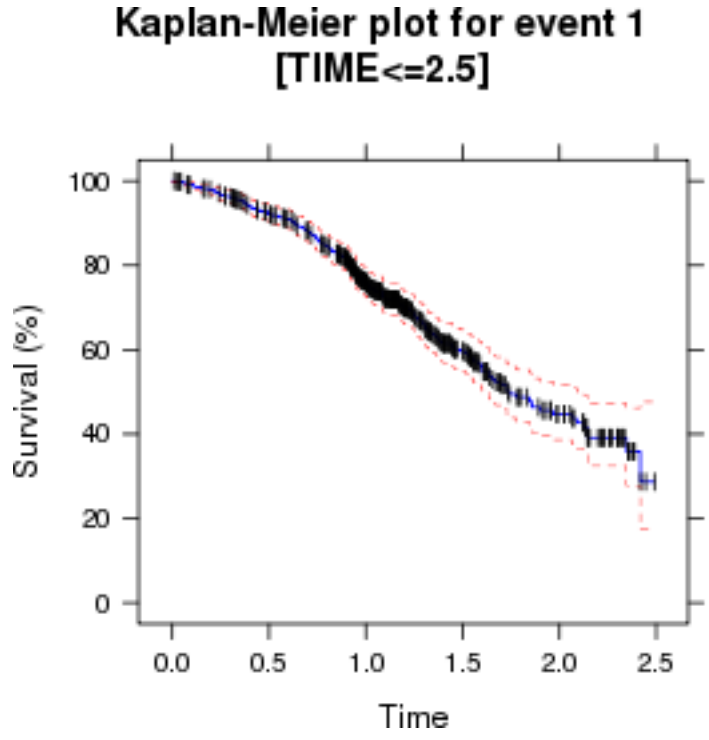
8.0.13 How informative are the data within the last year of the study?

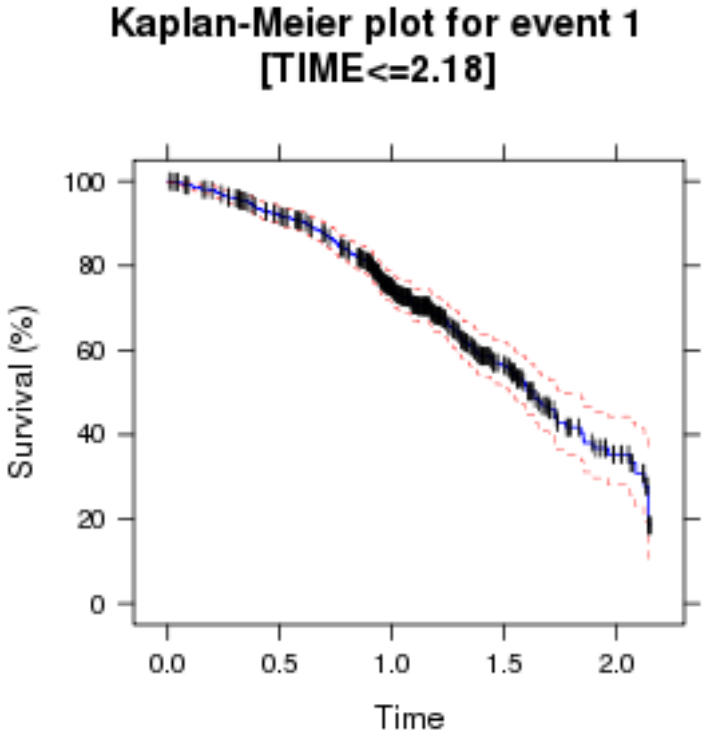
- Data within the last year of this study is mostly censored (%censored = 84.91)
- Past visit 57 (2.18 years), 3/16 records are events.
- Over 2.5 years 1/4 records is an event.
- Suggestion: ignore data over 2.5 years






Kaplan-Meier plot for event 1
Survival (%)
100
80
60
40
20
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Time


Kaplan-Meier plot for event 1
[TIME<=2.5]
Survival (%)
100
80
60
40
20
0
0.0
0.5
1.0
1.5
2.0
2.5
Time


Kaplan-Meier plot for event 1
[TIME<=2.18]
Survival (%)
100
80
60
40
20
0
0.0
0.5
1.0
1.5
2.0
Time

9 Data Assembly - Censor events over 2.18 years

```
head(ttedat) # current nonmem data set - loaded from ProjectDataSphere78_tte_V2.Rdata

# DV: censored vs events
hash(with(ttedat[ttedat$STIME==0 & ttedat$NO_LDH==0,], table(DV)))
# DV
#   0   1
# 436 230

# DV: censored vs events for LDH categories
hash(with(ttedat[ttedat$STIME==0 & ttedat$NO_LDH==0,], table(BL_LDH, DV)))
#       DV
# BL_LDH   0   1
#      0 391 177
#      1  45  53

# seperate simulation and estimation data sets
est <- ttedat %>% filter(STIME==0) %>% mutate(order=1)
head(est,20)

sim <-  ttedat %>% filter(STIME!=0) %>% mutate(order= ifelse(STIME==2, 2, 1))
head(sim,20)

# select observation data set, censor events (n=3) with times greater than 2.180 years
est1 <- est %>% mutate(time=TIME, dv=DV) %>%
            mutate(TIME = ifelse(STIME==0 & time <=2.180, time, 2.180 )) %>%
            mutate(DV = ifelse(STIME==0 & time<=2.180, dv,0 )) %>%
            mutate(time=NULL, dv=NULL)
head(est1)

# bind rows
ttedat1 <- rbind(est1, sim)

# order rows
ttedat1 <- ttedat1[order(ttedat1$ID,ttedat1$TIME, ttedat1$order),]

# add log ALB
ttedat1$LOG_BLALB <- log(ttedat1$BL_ALB)

#update maxtime
ttedat1$MAXT <- 2.180

# drop order
ttedat1$order <- NULL

# check data set
hash(summary(ttedat1))
#        ID              TIME           STIME            EVID                DV
#  Min.   :  1.0   Min.   :0.000   Min.   :0.000   Min.   :0.00000   Min.   :0.000000
#  1st Qu.:173.0   1st Qu.:0.709   1st Qu.:2.000   1st Qu.:0.00000   1st Qu.:0.000000
#  Median :345.5   Median :1.437   Median :2.000   Median :0.00000   Median :0.000000
#  Mean   :345.5   Mean   :1.453   Mean   :1.963   Mean   :0.03704   Mean   :0.004258
```

```
#  3rd Qu.:518.0   3rd Qu.:2.204   3rd Qu.:2.000   3rd Qu.:0.00000   3rd Qu.:0.000000
#  Max.   :690.0   Max.   :2.971   Max.   :2.000   Max.   :3.00000   Max.   :1.000000
#
#       CENS             MAXT          NO_LDH            GENDER           BL_LDH
#  Min.   :0.0000   Min.   :2.18   Min.   :0.00000   Min.   :0.0000   Min.   :0.0000
#  1st Qu.:0.0000   1st Qu.:2.18   1st Qu.:0.00000   1st Qu.:0.0000   1st Qu.:0.0000
#  Median :1.0000   Median :2.18   Median :0.00000   Median :0.0000   Median :0.0000
#  Mean   :0.6507   Mean   :2.18   Mean   :0.03478   Mean   :0.4203   Mean   :0.1471
#  3rd Qu.:1.0000   3rd Qu.:2.18   3rd Qu.:0.00000   3rd Qu.:1.0000   3rd Qu.:0.0000
#  Max.   :1.0000   Max.   :2.18   Max.   :1.00000   Max.   :1.0000   Max.   :1.0000
#                                                                      NA's   :1944
#      BL_AGE        BL_WHOSTAT         BL_ALB          BL_ALP         BL_WHOLEVEL
#  Min.   :2.000   Min.   :0.0000   Min.   :16.00   Min.   :  37.79   Min.   :0.0000
#  1st Qu.:2.000   1st Qu.:0.0000   1st Qu.:37.00   1st Qu.:  83.38   1st Qu.:0.0000
#  Median :2.000   Median :0.0000   Median :41.00   Median : 132.50   Median :0.0000
#  Mean   :2.407   Mean   :0.4319   Mean   :40.87   Mean   : 210.07   Mean   :0.4333
#  3rd Qu.:3.000   3rd Qu.:1.0000   3rd Qu.:44.80   3rd Qu.: 247.00   3rd Qu.:1.0000
#  Max.   :4.000   Max.   :1.0000   Max.   :55.50   Max.   :2501.00   Max.   :2.0000
#
#      OSTIM          LOG_BLALP       LOG_BLALB
#  Min.   :   3.0   Min.   :3.632   Min.   :2.773
#  1st Qu.: 314.0   1st Qu.:4.423   1st Qu.:3.611
#  Median : 377.0   Median :4.886   Median :3.714
#  Mean   : 404.2   Mean   :5.019   Mean   :3.698
#  3rd Qu.: 496.0   3rd Qu.:5.509   3rd Qu.:3.802
#  Max.   :1079.0   Max.   :7.824   Max.   :4.016
#

# DV: censored vs events (after new censoring rule)
hash(with(ttedat1[ttedat1$STIME==0 & ttedat1$NO_LDH==0,], table(DV)))
# DV
#   0   1
# 439 227

hash(names(ttedat1))
#  [1] "ID"          "TIME"        "STIME"       "EVID"        "DV"          "CENS"        "MAXT"
#  [9] "GENDER"      "BL_LDH"      "BL_AGE"      "BL_WHOSTAT"  "BL_ALB"      "BL_ALP"      "BL_WHOLEVEL
# [17] "LOG_BLALP"   "LOG_BLALB"


#..............................................................................
# write nonmem data file, specs and rdata
#..............................................................................

fileout <- 'ProjectDataSphere78_tte_V2_1'


# NM data file
datOUT <- file.path(data.dir, sprintf('%s.csv', fileout))
write.nm(ttedat1, file=datOUT, quote=FALSE, row.names=FALSE)

# Specs
specsOUT <- file.path(data.dir,sprintf('Specs_%s.csv', fileout))
```

```r
write.csv(specification(ttedat1), file=specsOUT)


meanlogALP <-  mean(ttedat1$LOG_BLALP[ttedat1$STIME==0 & ttedat1$NO_LDH==0]) ; meanlogALP
# [1] 5.012664

medianlogALP <- median(ttedat1$LOG_BLALP[ttedat1$STIME==0 & ttedat1$NO_LDH==0]) ; medianlogALP
# [1] 4.875

meanlogALB <-  mean(ttedat1$LOG_BLALB[ttedat1$STIME==0 & ttedat1$NO_LDH==0]) ; meanlogALB
# [1]  3.697778

medianlogALB <- median(ttedat1$LOG_BLALB[ttedat1$STIME==0 & ttedat1$NO_LDH==0]) ; medianlogALB
# [1] 3.713572
```

10 Proportional hazards models (censor time 2.18 years)

10.0.14 Run 11 - Weibull Hazard + log baseline ALP & LDH effect (on BASE)

```r
# next.mod(8,11,nm.dir)
show.mod(11, nm.dir) # print model
```

```
## ;; 1. Based on: 8
## ;; 2. Description:
## ;;    Covariate TTE model
## ;; 3. Label:
## ;;    Weibull hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;;     log linear model (log BL ALP), linear model (BL LDH)
## ;; 6. Interindividual variability:
## ;;    NA
## ;; 7. Interoccasion variability:
## ;;    NA
## ;; 8. Residual variability:
## ;;    NA
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    Base TTE model - Project DataSphere # 78 - no missing LDH
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM LOGBLALP ; order
## ;-----------------------------------------------------data description
##
## ; ID, subject identifier
```

```
##
## ; TIME, in years
##
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
##
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
##
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
##
## ; CENS, censored event, 0 = no, 1 = yes
##
## ; MAXT, last recorded event per patient (either death or censor)
##
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
##
## ; GENDER, bianry covariate (0=male,1=female)
##
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
##
## ; BLAGE, categorical, age group in years
##
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
##
## ; BLALB, continuous, ALB test values at baseline
##
## ; BLALP, continuous, ALP test values at baseline
##
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
##
## ; OSTIM, observed time in days to event or censor time
##
## ; LOGBLALP, log (BLLDH)
##
## ;-----------------------------------------------------
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2_1.csv IGNORE=@
##
##   IGNORE(NOLDH.EQ.1)  ; 24 patients missing BL_LDH data
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
##
## ;IGNORE=(STIME.EQ.0) ; observed time, ignore for simulation
##
## ;Sim_end
## $SUBROUTINE ADVAN=13 TOL=6
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ==========================
## $PK
##
##  LAMBDA = THETA(1) * EXP(ETA(1))
##  GAMMA = THETA(2)
##  SLP1 = THETA(3)
##  SLP2 = THETA(4)
##
```

```
## ;;================================= DIFFERENTIAL EQUATIONS ==================================
## ; Typical Value Weibull hazard h0(t) = lambda*gamma*t^(gamma-1)
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## ALP = SLP1*LOGBLALP      ; baseline ALP effect
## LDH = SLP2*BLLDH ; effect of LDH > 1.5 ULN
##
## BASE = (LAMBDA*GAMMA)*(LAMBDA*(T+DEL))**(GAMMA-1)
##
## DADT(1) = BASE * EXP(ALP + LDH)
## ;;================================= MODEL FIT ===================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=(LAMBDA*GAMMA)*(LAMBDA*(TIME+DELX))**(GAMMA-1)
##  ALPX = SLP1*LOGBLALP    ; baseline ALP effect
##  LDHX = SLP2*BLLDH   ; effect of LDH > 1.5 ULN
##  HAZNOW= BASEX * EXP(ALPX + LDHX)
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================= RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
```

```
## ENDIF
##
## IWRES = 1
##
##
## ;;================================= SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES ====================================
##
## $THETA  (0,0.101) ; lambda
##  (0,1.68) ; gamma
##  0.474 ; slope1 ALP
##  0.462 ; slope2  LDH
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_11
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
##
## ;;================================= TABLES ================================
## $TABLE      NOPRINT ONEHEADER FILE=mytab11 ID TIME DV EVID MDV PRED
##             CHZ SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE
##             BASE BASEX LAMBDA GAMMA SLP1 SLP2 BLWHOSTAT BLALB BLALP
##             BLWHOLEVEL OSTIM
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab11 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab11 ID LAMBDA SLP1
##             SLP2 GAMMA BASE BASEX ETAS(1:LAST)

## NULL
```

10.0.14.1 Run summary

```
##  [1] "-----------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run11/run
##  [4] ""
##  [5] "Successful minimization                                        [    OK   ]   "
##  [6] "No rounding errors                                             [    OK   ]   "
```

```
##  [7] "No zero gradients                                                  [    OK   ]   "
##  [8] "No final zero gradients                                            [    OK   ]   "
##  [9] "Hessian not reset                                                  [    OK   ]   "
## [10] "No parameter near boundary                                         [    OK   ]   "
## [11] "Covariance step                                                    [    OK   ]   "
## [12] ""
## [13] "Condition number                                                   [    OK   ]   "
## [14] "Correlations                                                       [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:27"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   55.27"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   2.69"
## [19] ""
## [20] "Objective function value: 882.9426"
## [21] ""
## [22] "Condition number: 260.4"
## [23] ""
## [24] "Number of observation records: 666"
## [25] "Number of individuals: 666"
## [26] ""
## [27] "              THETA              OMEGA      SIGMA    "
## [28] "     lambda  0.1056  (0.2877)                        "
## [29] "      gamma   1.684  (0.0622)                        "
## [30] " slope1 ALP  0.4608  (0.1997)                        "
## [31] "slope2  LDH   0.468  (0.3474)                        "
## [32] ""
## [33] "The relative standard errors for omega and sigma are reported on the approximate"
## [34] "standard deviation scale (SE/variance estimate)/2."
## [35] "-------------------------------------------------------------------------------"
```

10.0.14.2 Diagnostic plots

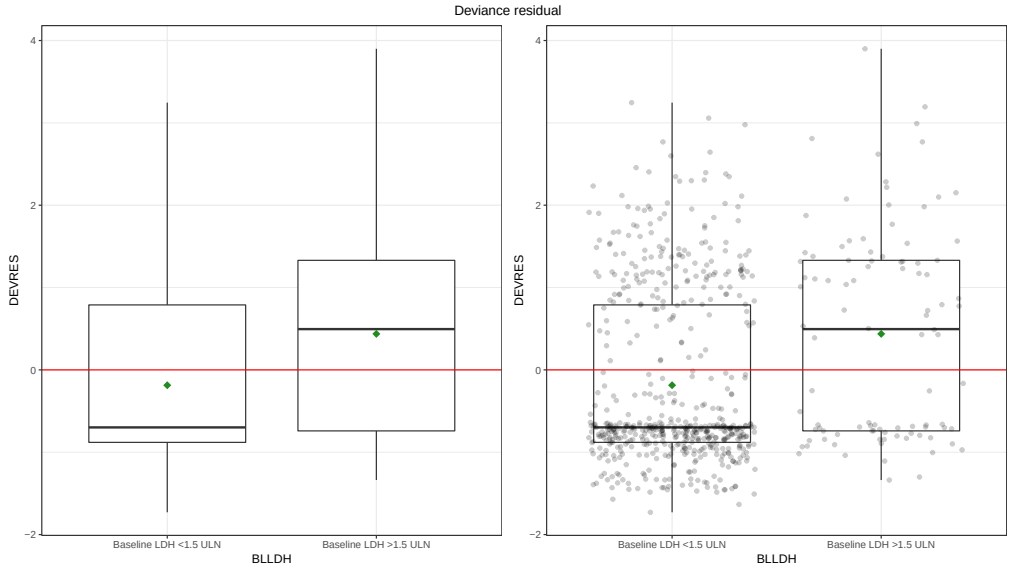


Figure 47: Residual-based diagnostics - Deviance plot

- zero reference line (red) ; mean residuals (green diamond)

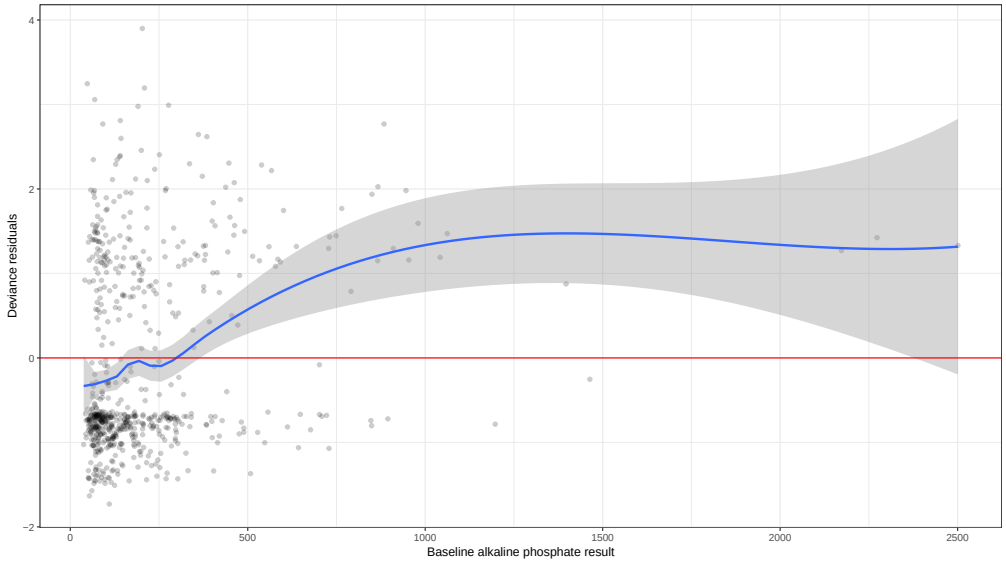


Figure 48: Residual-based diagnostics - Deviance plot

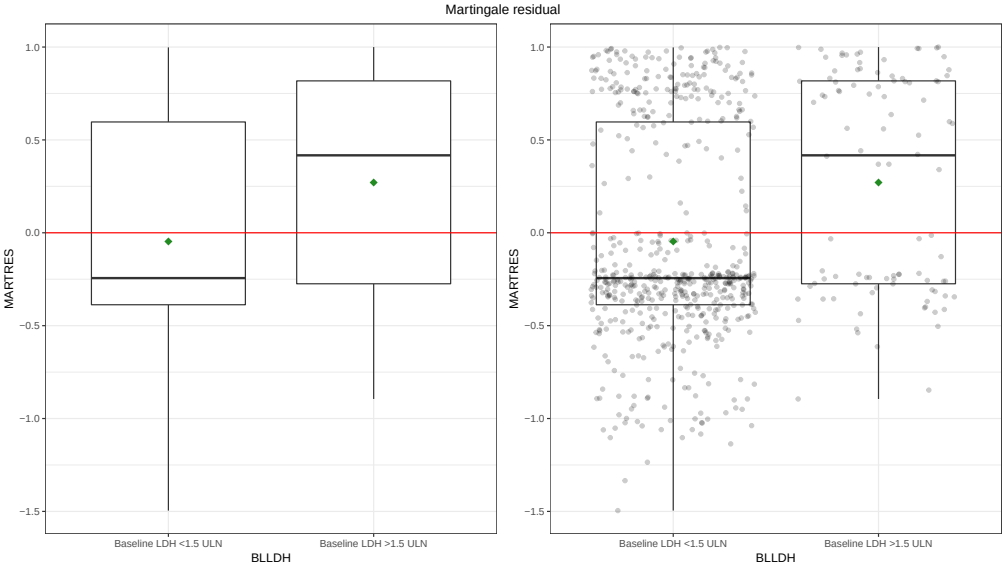


Figure 49: Residual-based diagnostics - Martingale plot

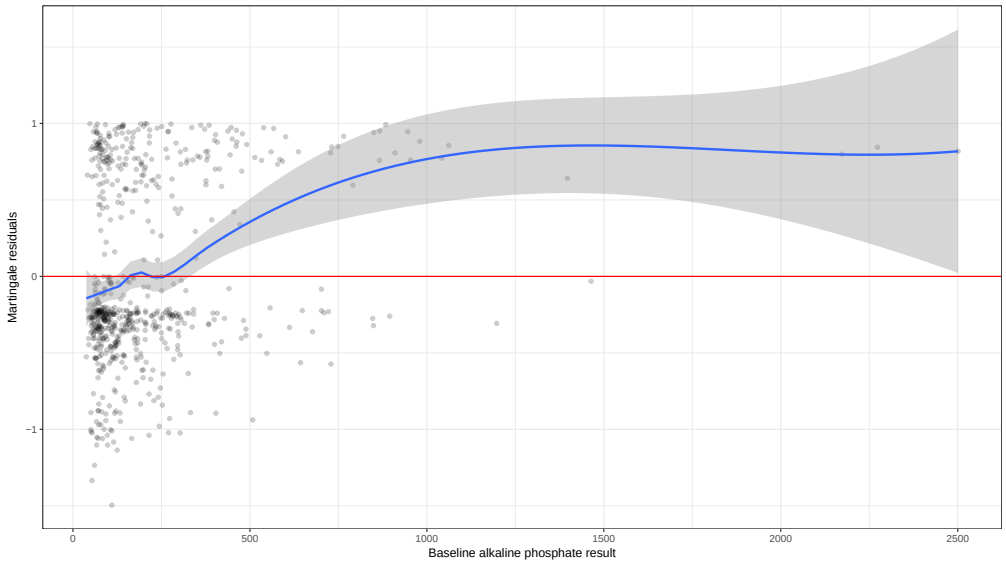
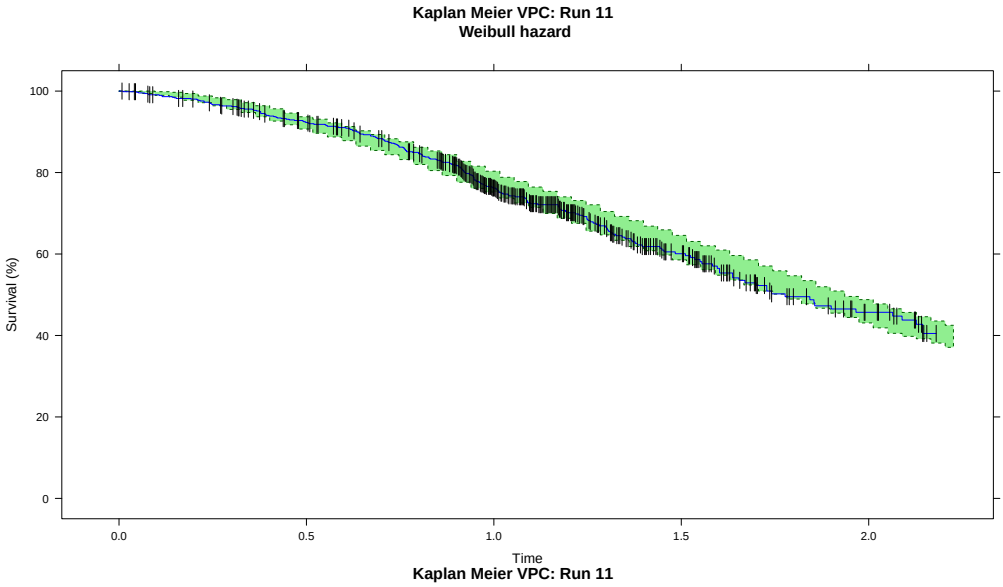
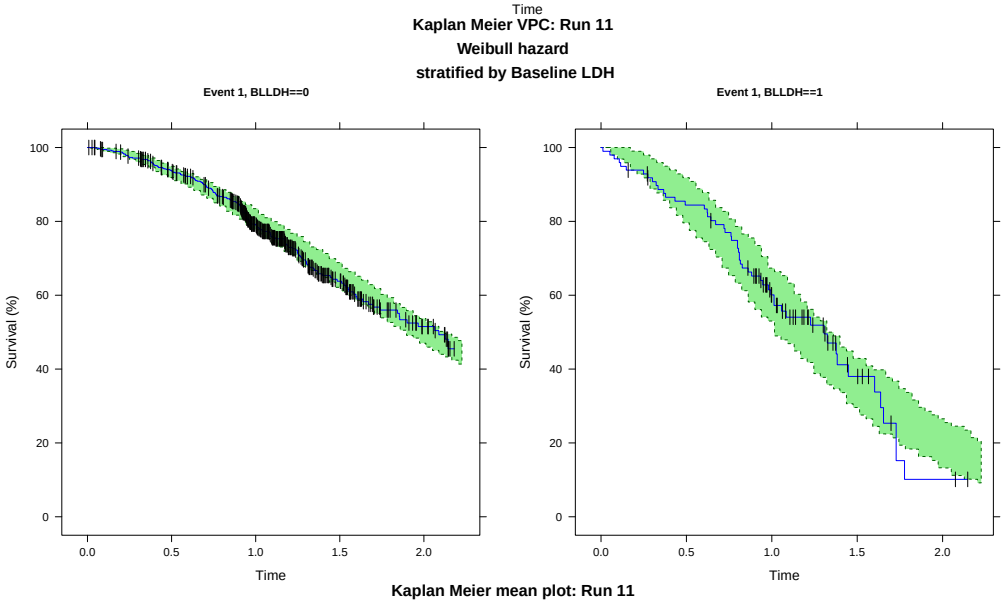
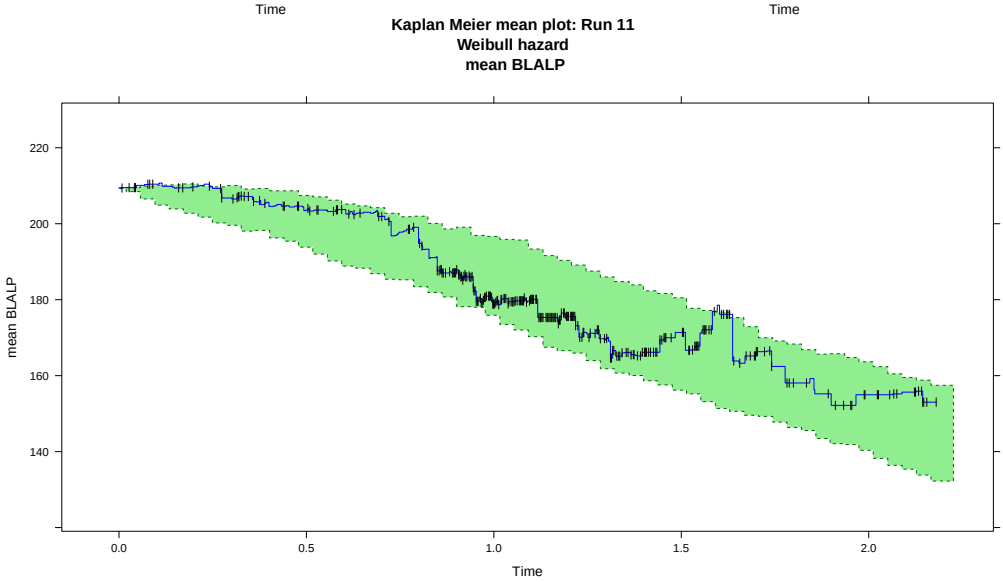


Figure 50: Residual-based diagnostics - Martingale plot


Kaplan Meier VPC: Run 11
Weibull hazard
Survival (%)
Time


Kaplan Meier VPC: Run 11
Weibull hazard
stratified by Baseline LDH
Event 1, BLLDH==0
Event 1, BLLDH==1
Survival (%)
Time


Kaplan Meier mean plot: Run 11
Weibull hazard
mean BLALP
mean BLALP
Time

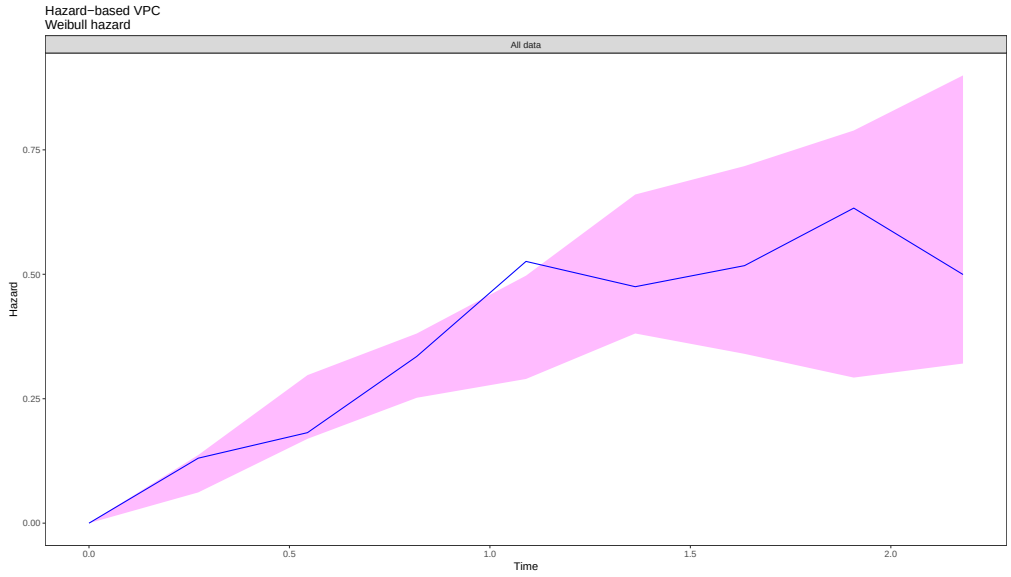


Figure 51: Simulation-based diagnostic: Hazard based VPC

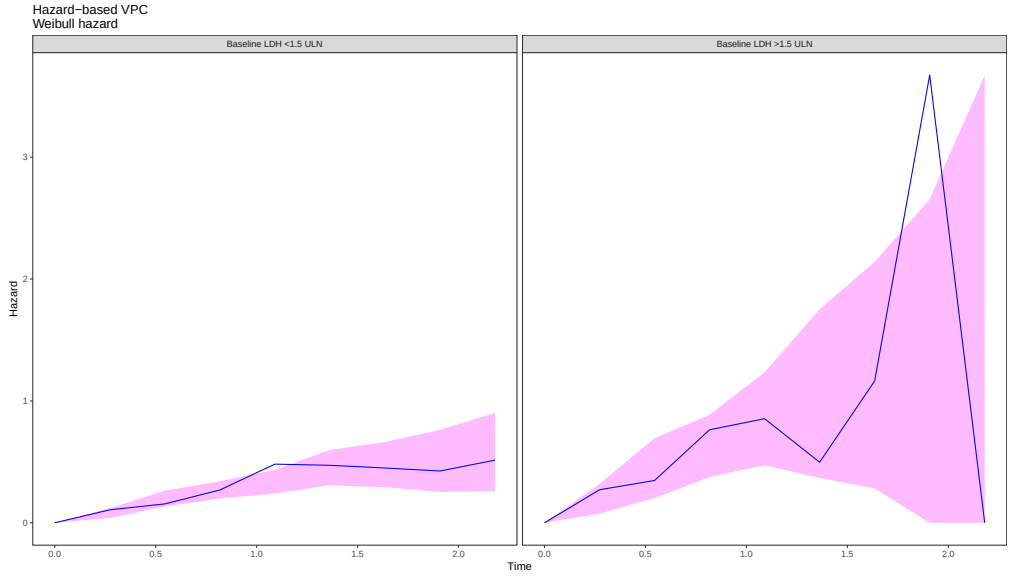


Figure 52: Simulation-based diagnostic: Hazard based VPC

10.0.15 Run 12 - Weibull Hazard + log baseline ALP & LDH effect (on BASE)

```
# next.mod(10,12,nm.dir)
show.mod(12, nm.dir) # print model
```

```
## ;; 1. Based on: 10
## ;; 2. Description:
## ;;   Covariate TTE model
## ;; 3. Label:
## ;;    log-logistic hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;;     log linear model (log BL ALP), linear model (BL LDH)
## ;; 6. Interindividual variability:
## ;; 7. Interoccasion variability:
## ;; 8. Residual variability:
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    TTE model - Project DataSphere # 78
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM LOGBLALP ; order
## ;-----------------------------------------------------data description
##
## ; ID, subject identifier
##
## ; TIME, in years
##
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
##
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
##
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
##
## ; CENS, censored event, 0 = no, 1 = yes
##
## ; MAXT, last recorded event per patient (either death or censor)
##
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
##
## ; GENDER, bianry covariate (0=male,1=female)
##
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
##
## ; BLAGE, categorical, age group in years
##
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
##
```

```
## ; BLALB, continuous, ALB test values at baseline
##
## ; BLALP, continuous, ALP test values at baseline
##
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
##
## ; OSTIM, observed time in days to event or censor time
##
## ; LOGBLALP, log (BLLDH)
##
## ;-----------------------------------------------------
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2_1.csv IGNORE=@
##    IGNORE(NOLDH.EQ.1)  ; 24 patients missing BL_LDH data
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
##
## ;IGNORE=(STIME.EQ.0) ; observed time, ignore for simulation
##
## ;Sim_end
##
## $SUBROUTINE ADVAN=13 TOL=9
##
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##  DELTA = THETA(1)* EXP(ETA(1))
##  GAMMA = THETA(2)
##  SLP1 = THETA(3)
##  SLP2 = THETA(4)
##
## ;;================================ DIFFERENTIAL EQUATIONS ================================
## ; Typical Value Log-logistic hazard,  h0(t) = exp(delta) kt^(k-1) / (1+ exp(delta)*t^k), where k = g
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = EXP(DELTA)*GAMMA*(T+DEL)**(GAMMA-1) / (1 + EXP(DELTA)*(T+DEL)**GAMMA)
## ALP = SLP1*LOGBLALP      ; baseline ALP effect
## LDH = SLP2*BLLDH ; effect of LDH > 1.5 ULN
##
## DADT(1) = BASE
##
## DADT(1) = BASE * EXP(ALP + LDH)
## ;;================================ MODEL FIT ================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
```

```
## ;------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=EXP(DELTA)*GAMMA*(TIME+DELX)**(GAMMA-1) / (1 + EXP(DELTA)*(TIME+DELX)**GAMMA)
##  ALPX = SLP1*LOGBLALP    ; baseline ALP effect
##  LDHX = SLP2*BLLDH   ; effect of LDH > 1.5 ULN
##  HAZNOW= BASEX * EXP(ALPX + LDHX)
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================ RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================ SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================ INITIAL ESTIMATES ====================================
##
## $THETA  -3.86 ; delta
```

```
##  (0,1.7) ; gamma
##  0.477 ; slope1 ALP
##  0.457 ; slope2  LDH
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ==============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_12
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
##
## ;;================================ TABLES ================================
## $TABLE      NOPRINT ONEHEADER FILE=mytab12 ID TIME DV EVID MDV PRED
##             CHZ SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE
##             BASE BASEX DELTA GAMMA SLP1 SLP2 BLWHOSTAT BLALB BLALP
##             BLWHOLEVEL OSTIM
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab12 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab12 ID DELTA GAMMA
##             ETAS(1:LAST)
```

```
## NULL
```

10.0.15.1 Run summary

```
##  [1] "-------------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run12/run
##  [4] ""
##  [5] "Successful minimization                                          [    OK   ]   "
##  [6] "No rounding errors                                               [    OK   ]   "
##  [7] "No zero gradients                                                [    OK   ]   "
##  [8] "No final zero gradients                                          [    OK   ]   "
##  [9] "Hessian not reset                                                [    OK   ]   "
## [10] "No parameter near boundary                                       [    OK   ]   "
## [11] "Covariance step                                                  [    OK   ]   "
## [12] ""
## [13] "Condition number                                                 [    OK   ]   "
## [14] "Large correlations between parameter estimates found             [ WARNING ]   "
## [15] "\tslope1 ALP - delta   -0.984825"
## [16] ""
## [17] "Total run time for model (hours:min:sec):                  0:01:33"
## [18] "Estimation time for subproblem, sum over $EST (seconds):   59.26"
## [19] "Covariance time for subproblem, sum over $EST (seconds):   4.65"
## [20] ""
## [21] "Objective function value: 883.1451"
## [22] ""
## [23] "Condition number: 232.9"
## [24] ""
## [25] "Number of observation records: 666"
## [26] "Number of individuals: 666"
## [27] ""
## [28] "              THETA               OMEGA      SIGMA    "
```

```
## [29] "      delta  -3.796   (0.1252)                        "
## [30] "      gamma   1.705  (0.06215)                        "
## [31] " slope1 ALP  0.4656   (0.1912)                        "
## [32] "slope2  LDH  0.4628    (0.348)                        "
## [33] ""
## [34] "The relative standard errors for omega and sigma are reported on the approximate"
## [35] "standard deviation scale (SE/variance estimate)/2."
## [36] "-----------------------------------------------------------------------------"
```

10.0.15.2 Diagnostic plots

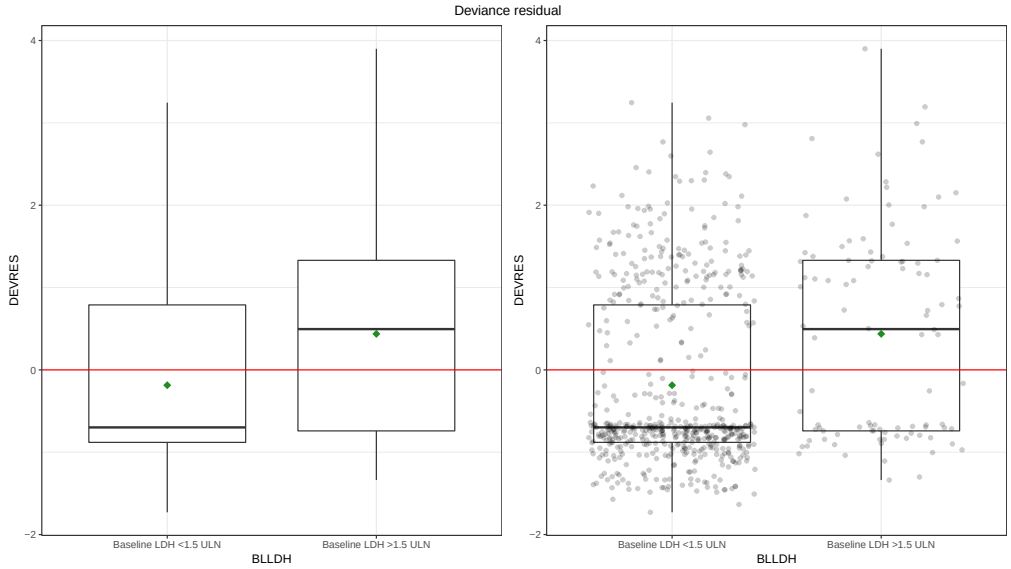


Figure 53: Residual-based diagnostics - Deviance plot

- zero reference line (red) ; mean residuals (green diamond)

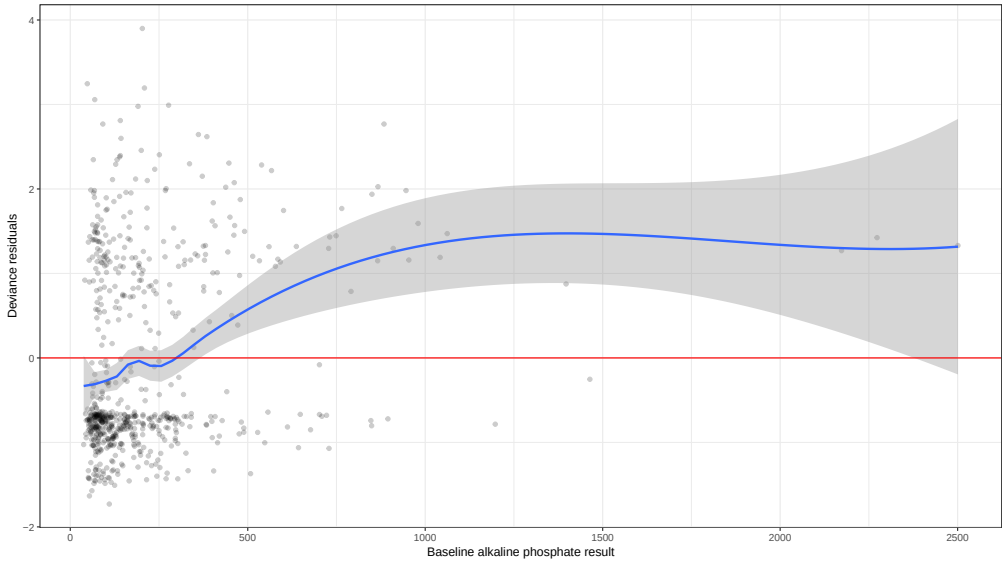


Figure 54: Residual-based diagnostics - Deviance plot

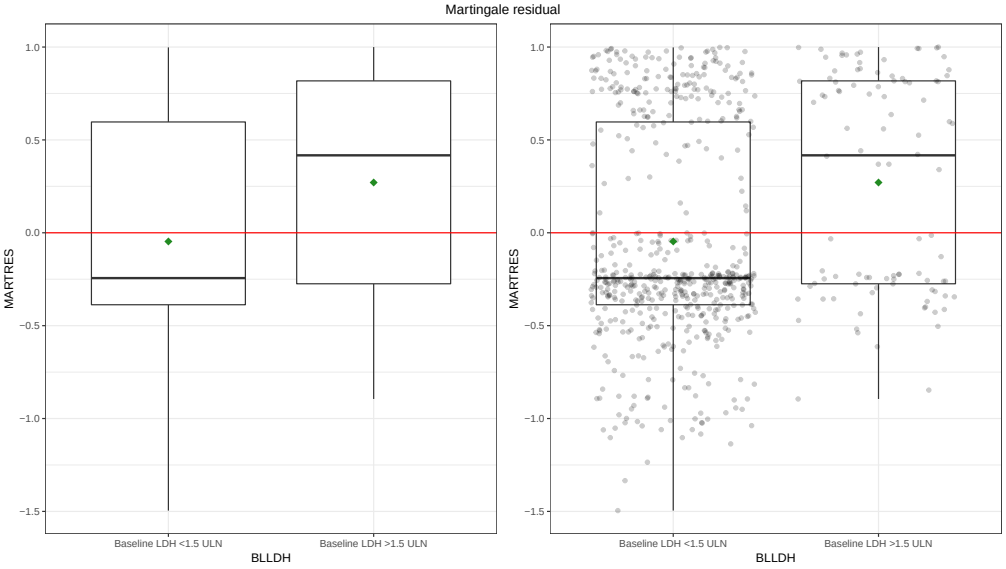


Figure 55: Residual-based diagnostics - Martingale plot

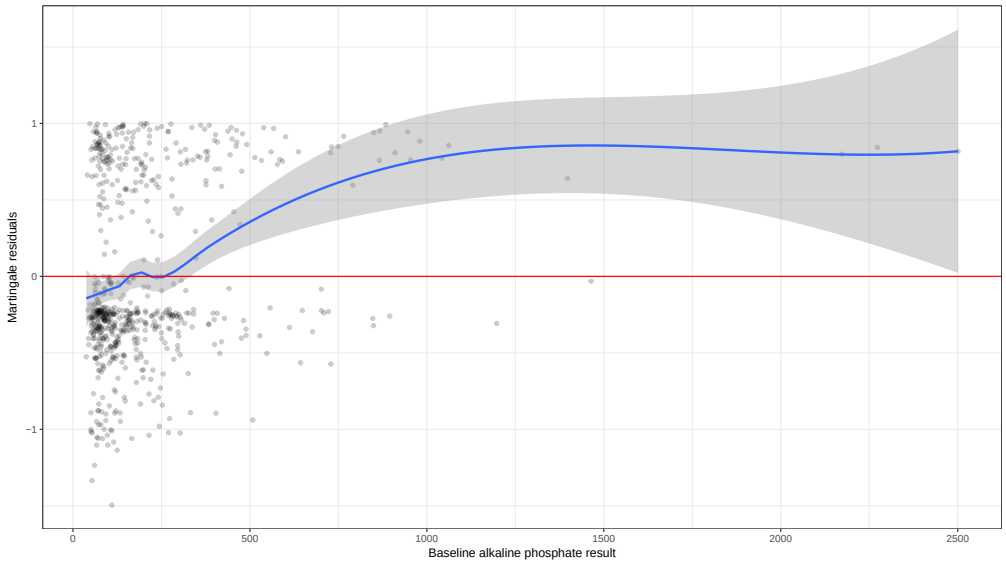
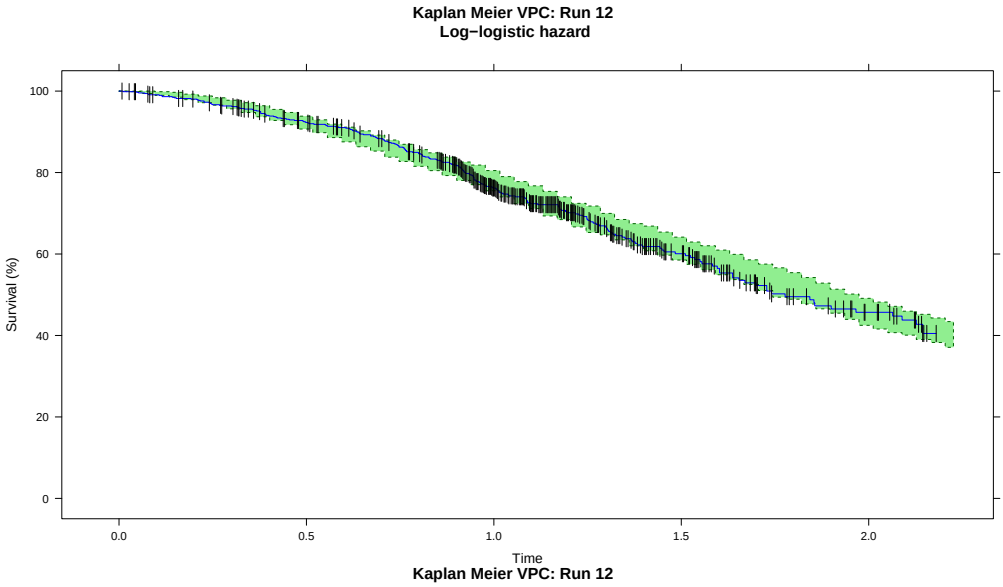
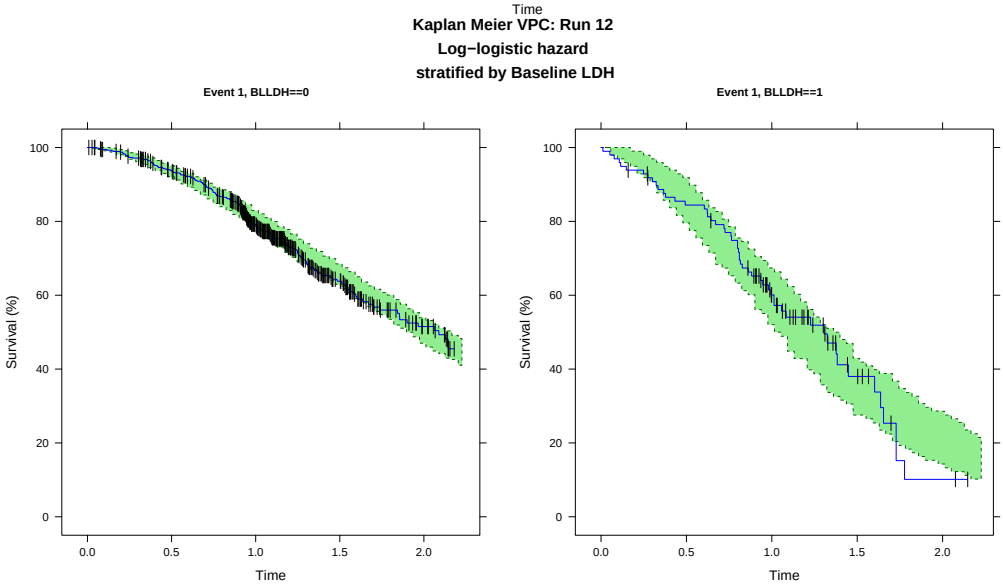


Figure 56: Residual-based diagnostics - Martingale plot


Kaplan Meier VPC: Run 12
Log−logistic hazard
Survival (%)
Time


Kaplan Meier VPC: Run 12
Log−logistic hazard
stratified by Baseline LDH
Event 1, BLLDH==0
Event 1, BLLDH==1
Survival (%)
Time

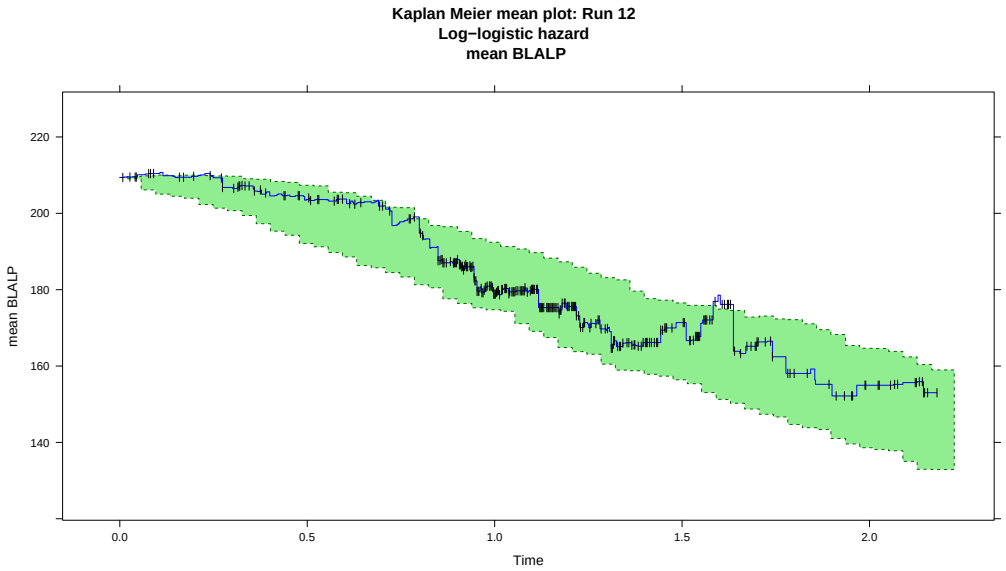


Figure 57: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

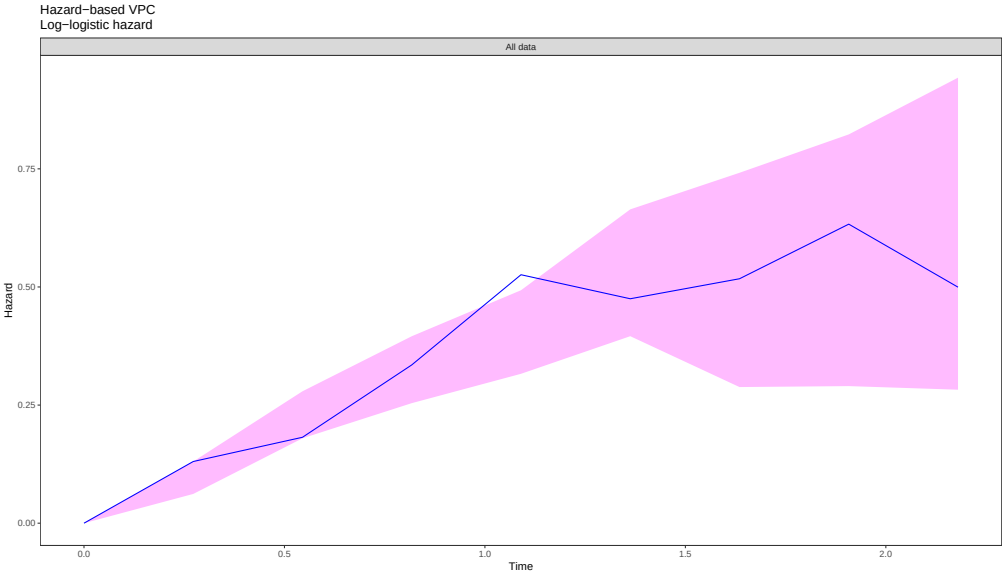


Figure 58: Simulation-based diagnostic: Hazard based VPC

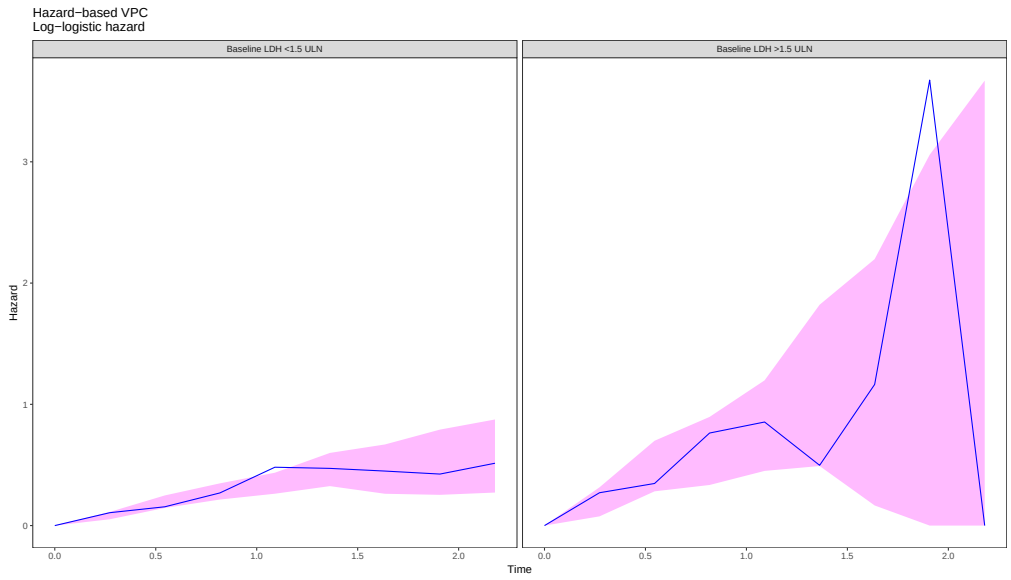


Figure 59: Simulation-based diagnostic: Hazard based VPC

10.0.16 Run 13 - Weibull Hazard + normalized log baseline ALP & LDH effect (on BASE)

```
# next.mod(12,13,nm.dir)
show.mod(13, nm.dir) # print model
```

```
## ;; 1. Based on: 12
## ;; 2. Description:
## ;;   Covariate TTE model
## ;; 3. Label:
## ;;    log-logistic hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;;     log linear model (log BL ALP), linear model (BL LDH)
## ;; 6. Interindividual variability:
## ;; 7. Interoccasion variability:
## ;; 8. Residual variability:
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
##
## $PROBLEM    TTE model - Project DataSphere # 78
##
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM LOGBLALP ; order
##
## ;-------------------------------------------------------data description
## ; ID, subject identifier
## ; TIME, in years
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
## ; CENS, censored event, 0 = no, 1 = yes
## ; MAXT, last recorded event per patient (either death or censor)
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
## ; GENDER, bianry covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
## ; OSTIM, observed time in days to event or censor time
## ; LOGBLALP, log (BLLDH)
## ;-----------------------------------------------------
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2_1.csv IGNORE=@
##    IGNORE(NOLDH.EQ.1)  ; 24 patients missing BL_LDH data
##
## ;Sim_start : remove from simulation model
```

```
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
## ;IGNORE=(STIME.EQ.0) ; observed time, ignore for simulation
## ;Sim_end
##
## $SUBROUTINE ADVAN=13 TOL=9
##
## $MODEL      COMP=(HAZARD)
## ;;========================== PARAMETER DEFINITIONS ==========================
## $PK
##  DELTA = THETA(1)* EXP(ETA(1))
##  GAMMA = THETA(2)
##  SLP1 = THETA(3)
##  SLP2 = THETA(4)
##
##  MEANLOGBLALP = 5.013
## ; MEIDANLOGBLALP =  4.875
##
## ;;================================ DIFFERENTIAL EQUATIONS ================================
## ; Typical Value Log-logistic hazard
## ; h0(t) = exp(delta) kt^(k-1) / (1+ exp(delta)*t^k)
## ; where k = gamma
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = EXP(DELTA)*GAMMA*(T+DEL)**(GAMMA-1) / (1 + EXP(DELTA)*(T+DEL)**GAMMA)
## ALP = SLP1*(LOGBLALP-MEANLOGBLALP)   ; normalized baseline ALP effect  - mean
## LDH = SLP2*BLLDH ; effect of LDH > 1.5 ULN
##
## DADT(1) = BASE
##
## DADT(1) = BASE * EXP(ALP + LDH)
## ;;================================ MODEL FIT ================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=EXP(DELTA)*GAMMA*(TIME+DELX)**(GAMMA-1) / (1 + EXP(DELTA)*(TIME+DELX)**GAMMA)
##  ALPX = SLP1*(LOGBLALP-MEANLOGBLALP) ; normalized baseline ALP effect  - mean
##  LDHX = SLP2*BLLDH   ; effect of LDH > 1.5 ULN
```

```
##  HAZNOW= BASEX * EXP(ALPX + LDHX)
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================= RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================= SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES =====================================
##
## $THETA  -3.8 ; delta
##  (0,1.71) ; gamma
##  0.466 ; slope1 ALP
##  0.463 ; slope2  LDH
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_13
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
```

```
##
## ;;================================ TABLES ================================
## $TABLE      NOPRINT ONEHEADER FILE=mytab13 ID TIME DV EVID MDV PRED
##             CHZ SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE
##             BASE BASEX DELTA GAMMA SLP1 SLP2 BLWHOSTAT BLALB BLALP
##             BLWHOLEVEL OSTIM
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab13 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab13 ID DELTA GAMMA
##             ETAS(1:LAST)
```

```
## NULL
```

10.0.16.1 Run summary

```
##  [1] "-------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run13/run
##  [4] ""
##  [5] "Successful minimization                                          [    OK   ]   "
##  [6] "No rounding errors                                               [    OK   ]   "
##  [7] "No zero gradients                                                [    OK   ]   "
##  [8] "No final zero gradients                                          [    OK   ]   "
##  [9] "Hessian not reset                                                [    OK   ]   "
## [10] "No parameter near boundary                                       [    OK   ]   "
## [11] "Covariance step                                                  [    OK   ]   "
## [12] ""
## [13] "Condition number                                                 [    OK   ]   "
## [14] "Correlations                                                     [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:21"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   48.5"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   4.21"
## [19] ""
## [20] "Objective function value: 887.1535"
## [21] ""
## [22] "Condition number: 4.56"
## [23] ""
## [24] "Number of observation records: 666"
## [25] "Number of individuals: 666"
## [26] ""
## [27] "              THETA               OMEGA      SIGMA    "
## [28] "      delta  -1.329  (0.07016)                         "
## [29] "      gamma   1.885  (0.06791)                         "
## [30] " slope1 ALP   0.458   (0.1994)                         "
## [31] "slope2  LDH   0.468   (0.3454)                         "
## [32] ""
## [33] "The relative standard errors for omega and sigma are reported on the approximate"
## [34] "standard deviation scale (SE/variance estimate)/2."
## [35] "-------------------------------------------------------------------------"
```

10.0.16.2 Diagnostic plots

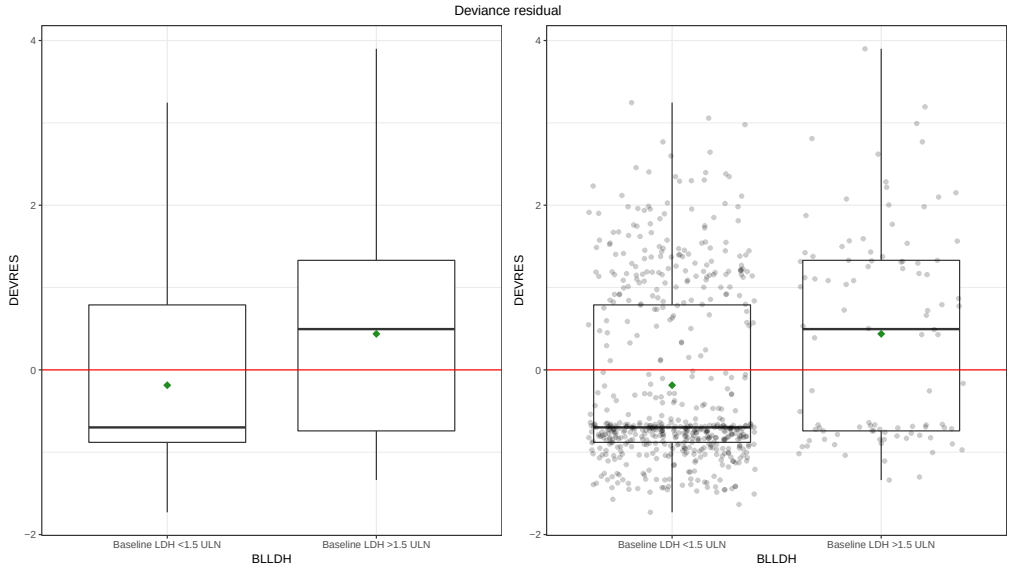


Figure 60: Residual-based diagnostics - Deviance plot

- zero reference line (red) ; mean residuals (green diamond)

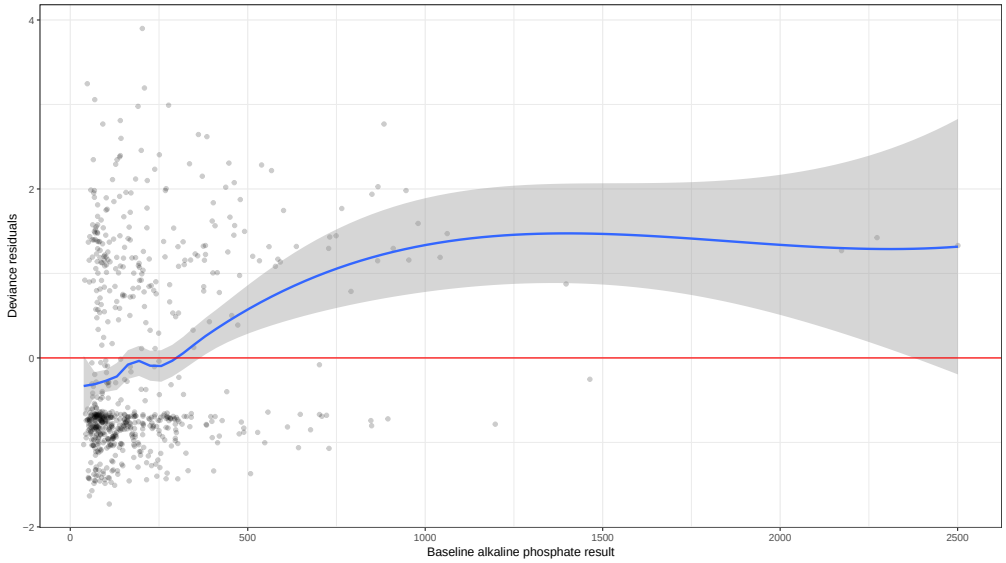


Figure 61: Residual-based diagnostics - Deviance plot

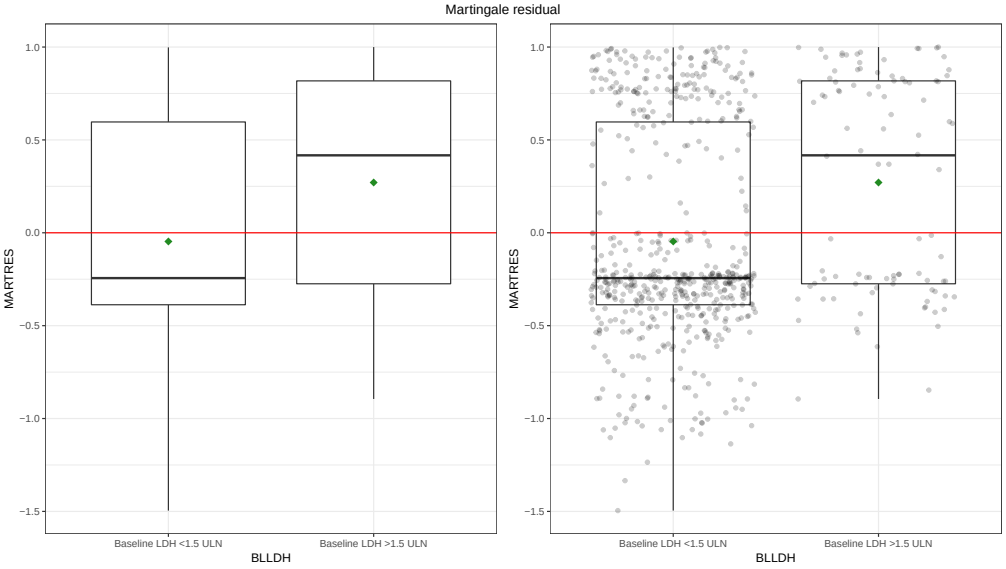


Figure 62: Residual-based diagnostics - Martingale plot

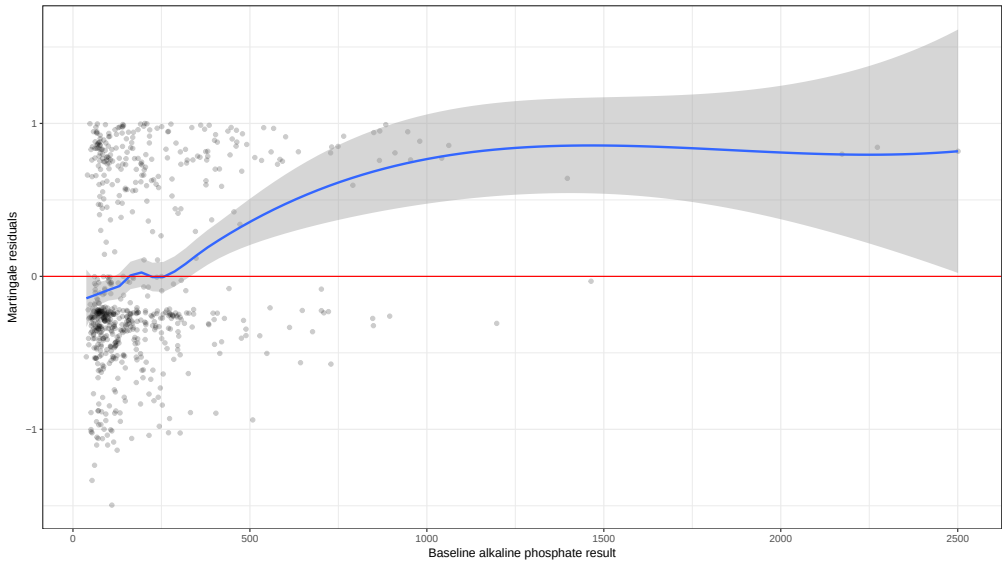
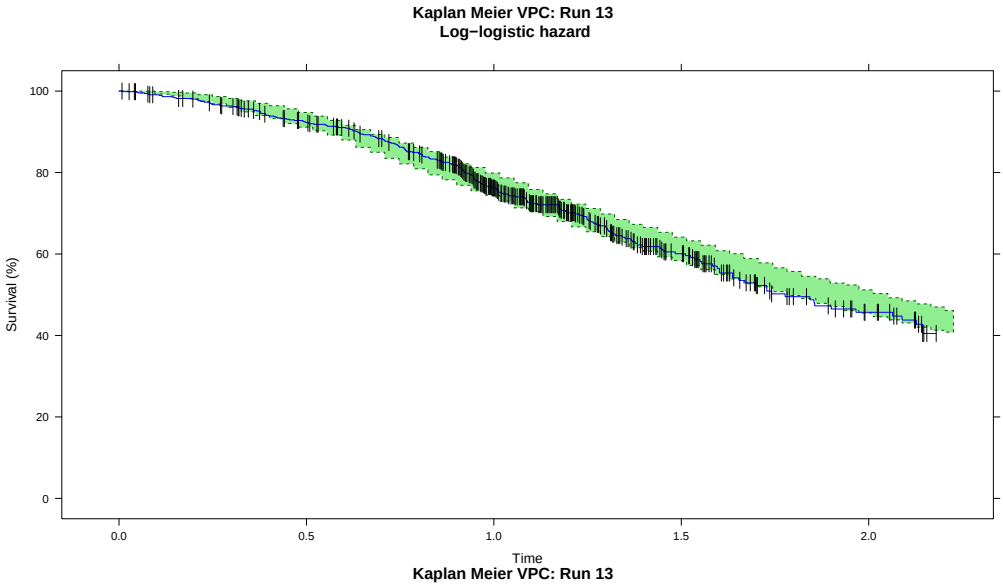
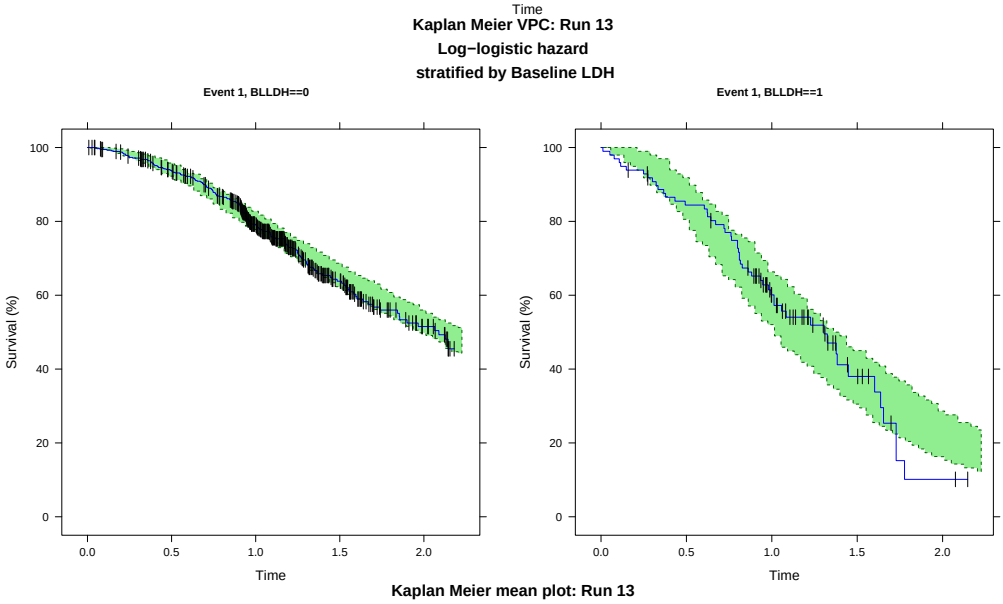
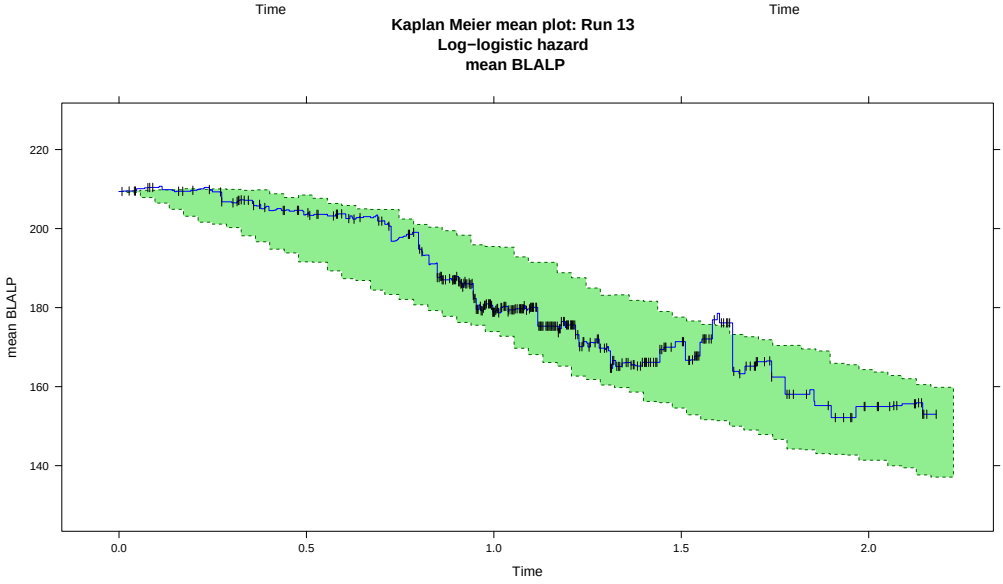


Figure 63: Residual-based diagnostics - Martingale plot


Kaplan Meier VPC: Run 13
Log−logistic hazard
Survival (%)
Time


Kaplan Meier VPC: Run 13
Log−logistic hazard
stratified by Baseline LDH
Event 1, BLLDH==0
Event 1, BLLDH==1
Survival (%)
Time


Kaplan Meier mean plot: Run 13
Log−logistic hazard
mean BLALP
mean BLALP
Time

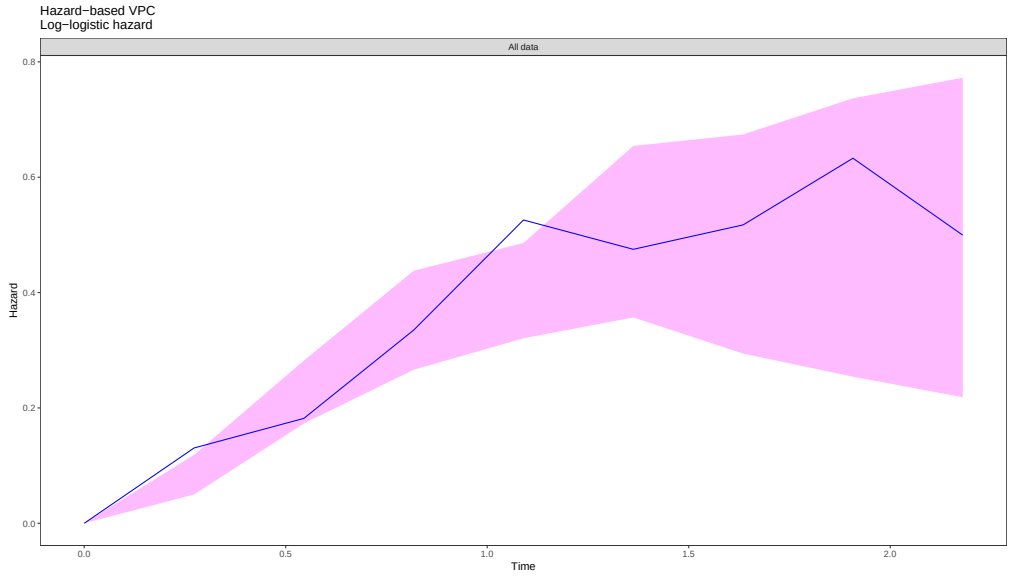


Figure 64: Simulation-based diagnostic: Hazard based VPC

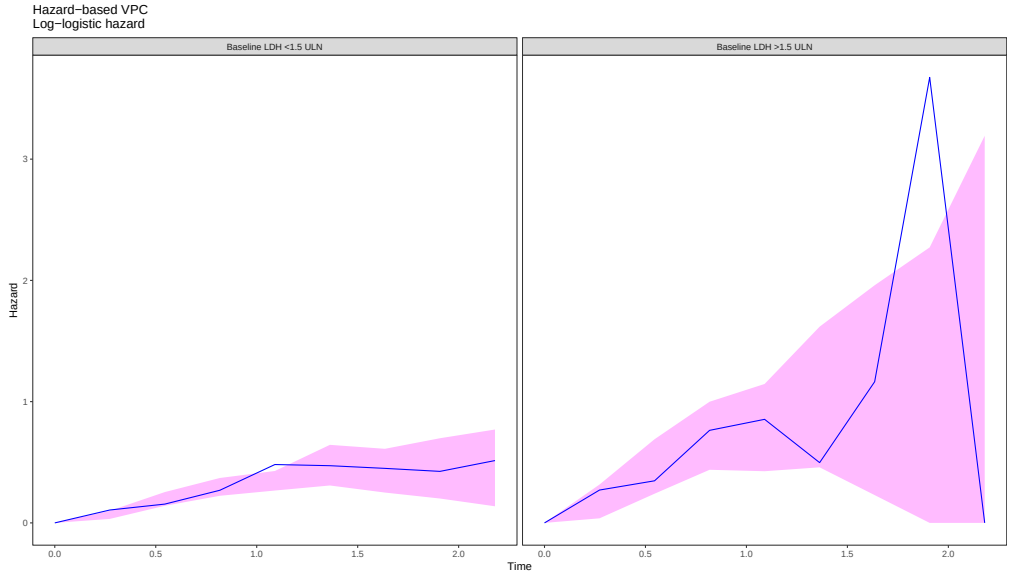


Figure 65: Simulation-based diagnostic: Hazard based VPC

11 Selected models for publication

Notes:

- subjects missing baseline covariates are excluded
- events occuring after 2.18 years are censored
- continous covariates selected for analysis: baseline ALB and baseline ALP
- categorical covariates selected for analysis: baseline LDH and Who status

11.1 Weibull hazard model (base and covariate)

11.1.1 Run 14 - base model

```
# next.mod(11,14,nm.dir)
show.mod(14, nm.dir) # print model
```

```
## ;; 1. Based on: 11
## ;; 2. Description:
## ;;    Base TTE model
## ;; 3. Label:
## ;;    Weibull hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;;     NA
## ;; 6. Interindividual variability:
## ;;    NA
## ;; 7. Interoccasion variability:
## ;;    NA
## ;; 8. Residual variability:
## ;;    NA
## ;; 9. Estimation:
## ;;    LAPLACE
##
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
##
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
##
## $PROBLEM    Base TTE model - Project DataSphere # 78 - no missing LDH
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM LOGBLALP ; order
##
## ;----------------------------------------------------data description
## ; ID, subject identifier
## ; TIME, in years
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
## ; CENS, censored event, 0 = no, 1 = yes
```

```
## ; MAXT, last recorded event per patient (either death or censor)
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
## ; GENDER, bianry covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
## ; OSTIM, observed time in days to event or censor time
## ; LOGBLALP, log (BLLDH)
## ;-----------------------------------------------------
##
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2_1.csv IGNORE=@
##             IGNORE(NOLDH.EQ.1); 24 patients missing BL_LDH data
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
## ;IGNORE=(STIME.EQ.0) ; observed time, ignore for simulation
## ;Sim_end
##
## $SUBROUTINE ADVAN=13 TOL=9
##
##
## $MODEL      COMP=(HAZARD)
##
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##
##  LAMBDA = THETA(1) * EXP(ETA(1))
##  GAMMA = THETA(2)
##
## ;;======================== DIFFERENTIAL EQUATIONS ====================================
## ; Typical Value Weibull hazard
## ; h0(t) = lambda*gamma*t^(gamma-1)
##
## $DES
##
##
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = (LAMBDA*GAMMA)*(LAMBDA*(T+DEL))**(GAMMA-1)
##
## DADT(1) = BASE
##
##
## ;;================================= MODEL FIT ==================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
```

```
## ;Sim_end
##
## ;------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=(LAMBDA*GAMMA)*(LAMBDA*(TIME+DELX))**(GAMMA-1)
##  HAZNOW= BASEX
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================= RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
## ;;================================= SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES =====================================
##
## $THETA  (0,0.438) ; lambda
##  (0,1.59) ; gamma
```

```
##
## $OMEGA  0  FIX  ; place holder
## ;;============================ ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_14
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
##
## ;;============================== TABLES ==============================
## $TABLE      NOPRINT ONEHEADER FILE=mytab14 ID TIME DV EVID MDV PRED
##             CHZ SUR HAZNOW MARTRES DEVRES NOLDH GENDER  BLAGE
##             BASE BASEX LAMBDA GAMMA BLLDH BLWHOSTAT BLALB BLALP
##             BLWHOLEVEL GENDER OSTIM
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab14 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab14 ID LAMBDA GAMMA BASE BASEX ETAS(1:LAST)
## NULL
```

11.1.1.1 Run summary

```
##  [1] "-------------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run14/run
##  [4] ""
##  [5] "Successful minimization                                          [    OK   ]   "
##  [6] "No rounding errors                                               [    OK   ]   "
##  [7] "No zero gradients                                                [    OK   ]   "
##  [8] "No final zero gradients                                          [    OK   ]   "
##  [9] "Hessian not reset                                                [    OK   ]   "
## [10] "No parameter near boundary                                       [    OK   ]   "
## [11] "Covariance step                                                  [    OK   ]   "
## [12] ""
## [13] "Condition number                                                 [    OK   ]   "
## [14] "Correlations                                                     [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:09"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   38.13"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   1.17"
## [19] ""
## [20] "Objective function value: 929.8144"
## [21] ""
## [22] "Condition number: 4.263"
## [23] ""
## [24] "Number of observation records: 666"
## [25] "Number of individuals: 666"
## [26] ""
## [27] "         THETA               OMEGA      SIGMA    "
## [28] "lambda  0.4387    (0.052)                        "
## [29] " gamma   1.625  (0.06141)                        "
## [30] ""
## [31] "The relative standard errors for omega and sigma are reported on the approximate"
```

```
## [32] "standard deviation scale (SE/variance estimate)/2."
## [33] "------------------------------------------------------------------------"
```

11.1.1.2 Diagnostic plots

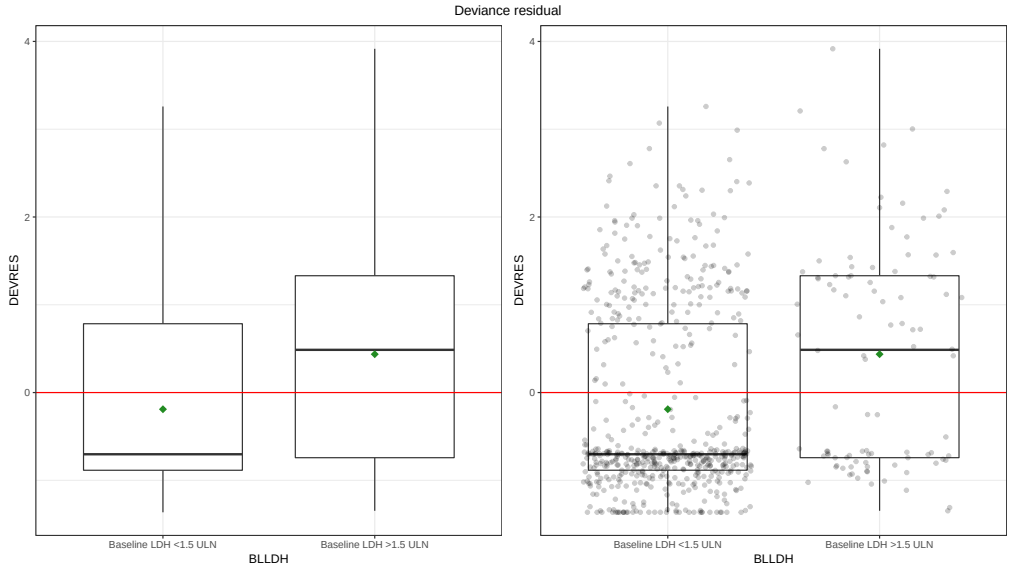


Figure 66: Residual-based diagnostics - Deviance plot

- zero reference line (red) ; mean residuals (green diamond)

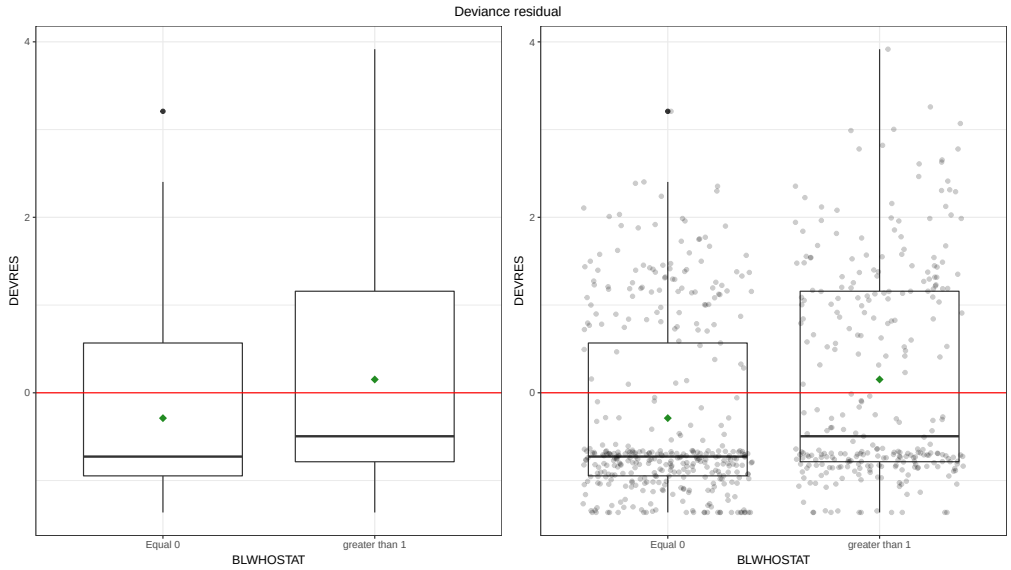


Figure 67: Residual-based diagnostics - Deviance plot

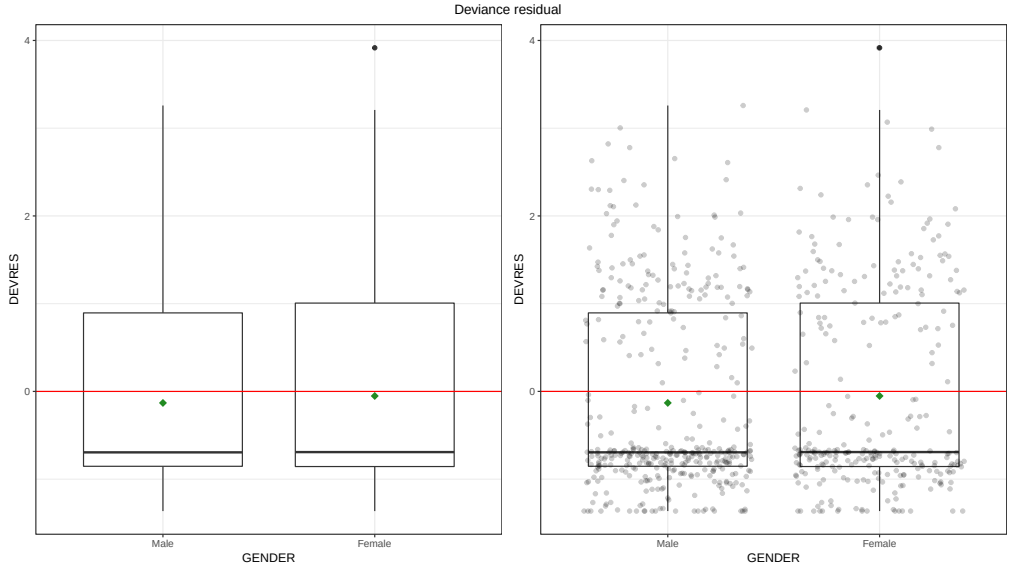


Figure 68: Residual-based diagnostics - Deviance plot

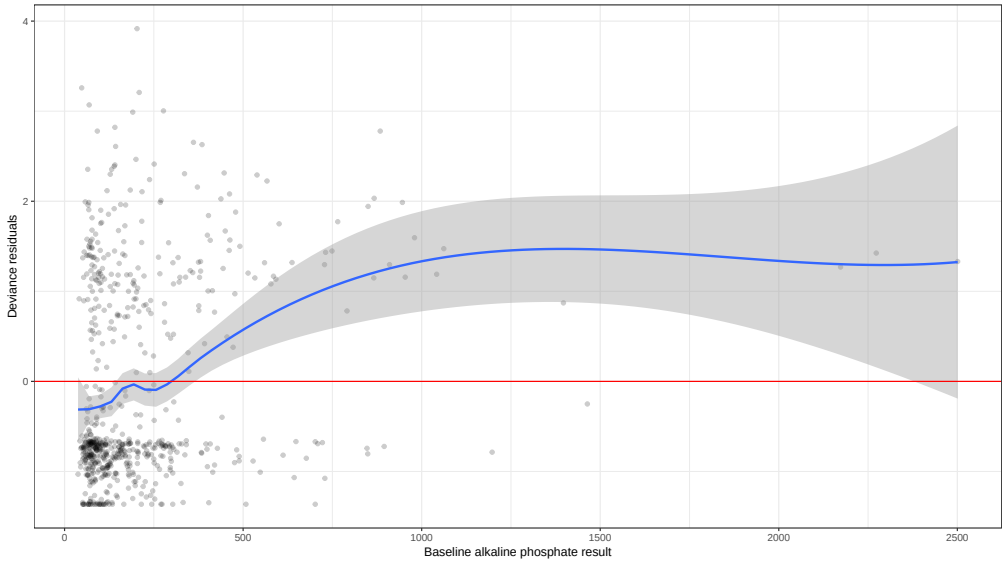


Figure 69: Residual-based diagnostics - Deviance plot

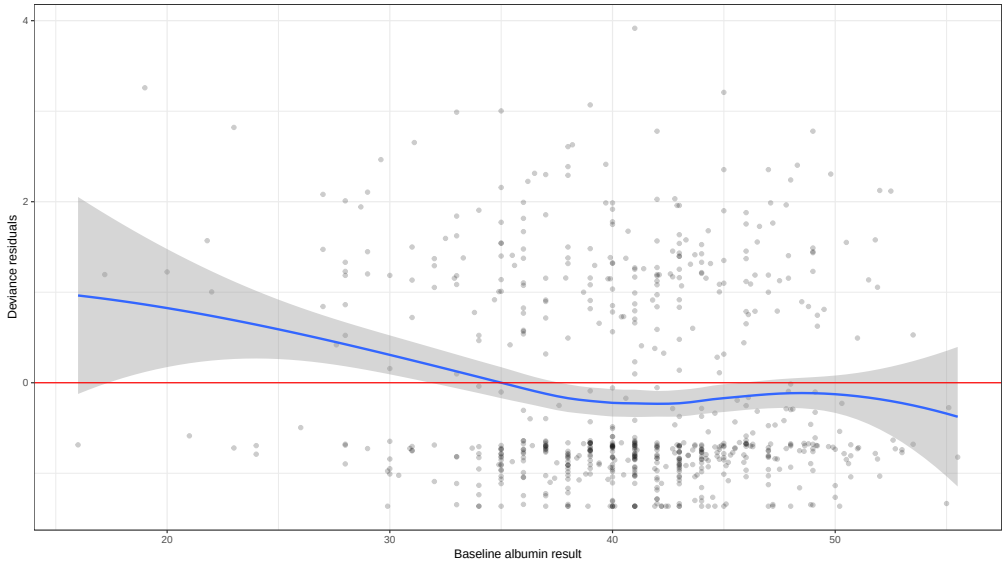


Figure 70: Residual-based diagnostics - Deviance plot

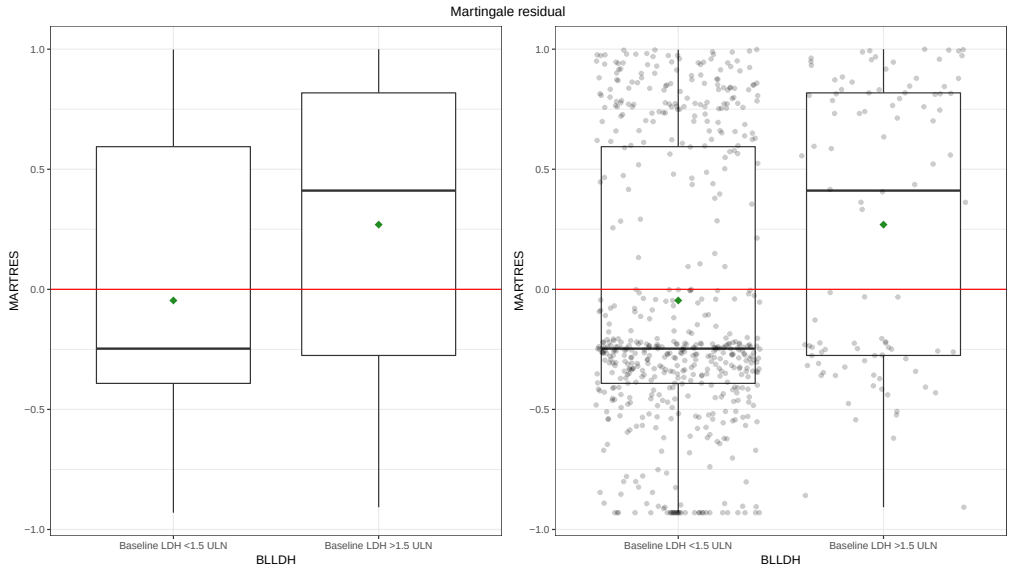


Figure 71: Residual-based diagnostics - Martingale plot

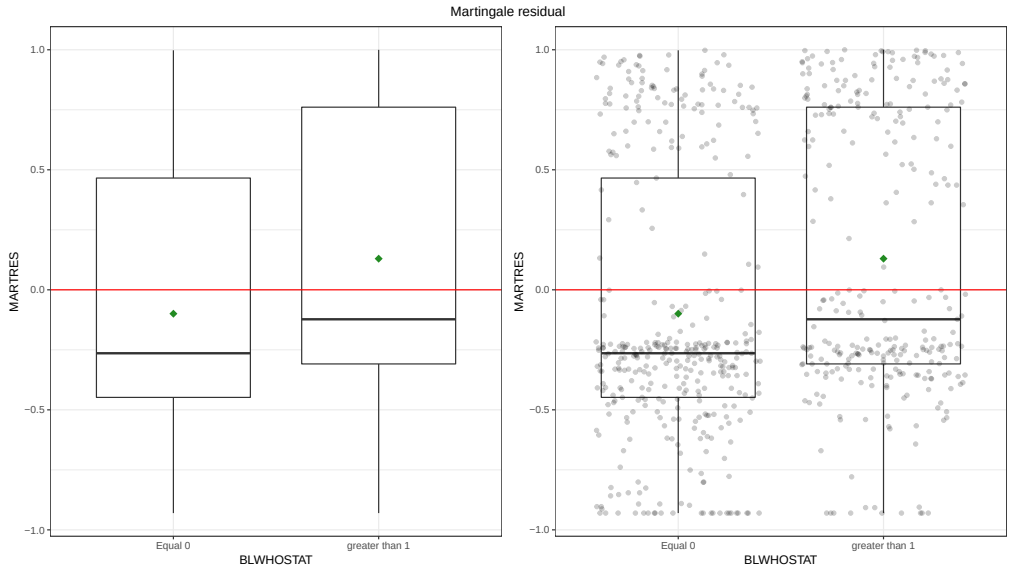


Figure 72: Residual-based diagnostics - Martingale plot

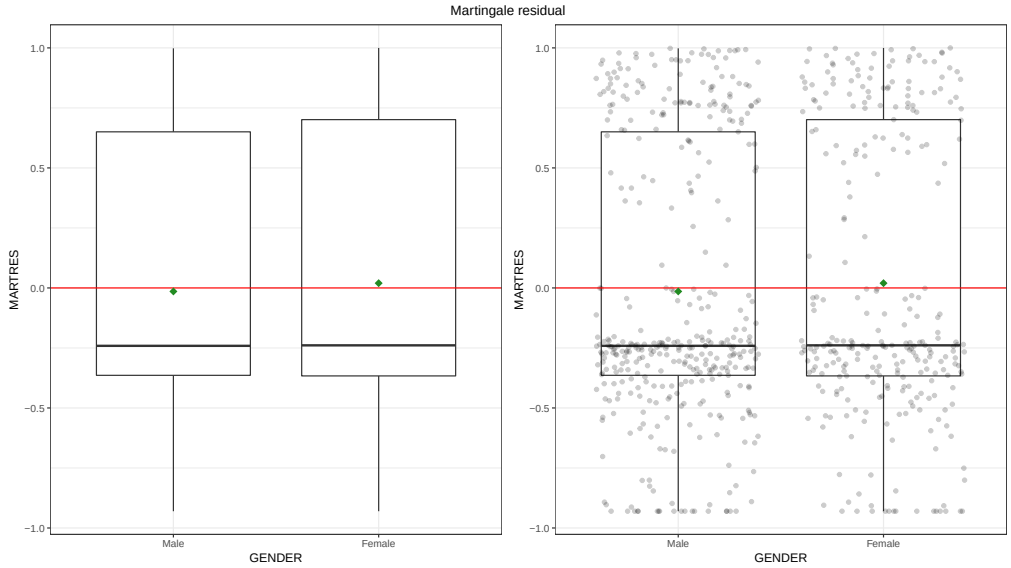


Figure 73: Residual-based diagnostics - Martingale plot

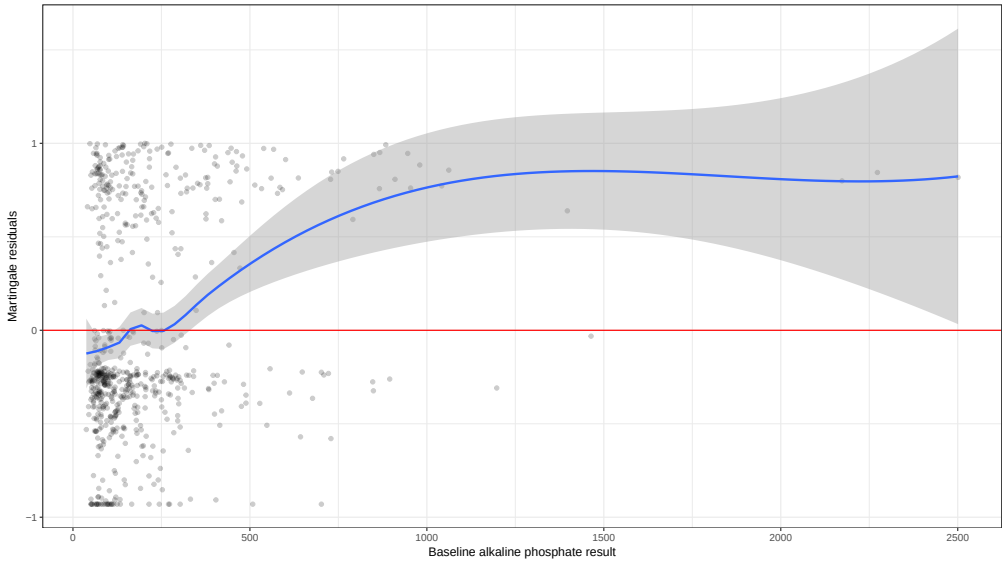


Figure 74: Residual-based diagnostics - Martingale plot

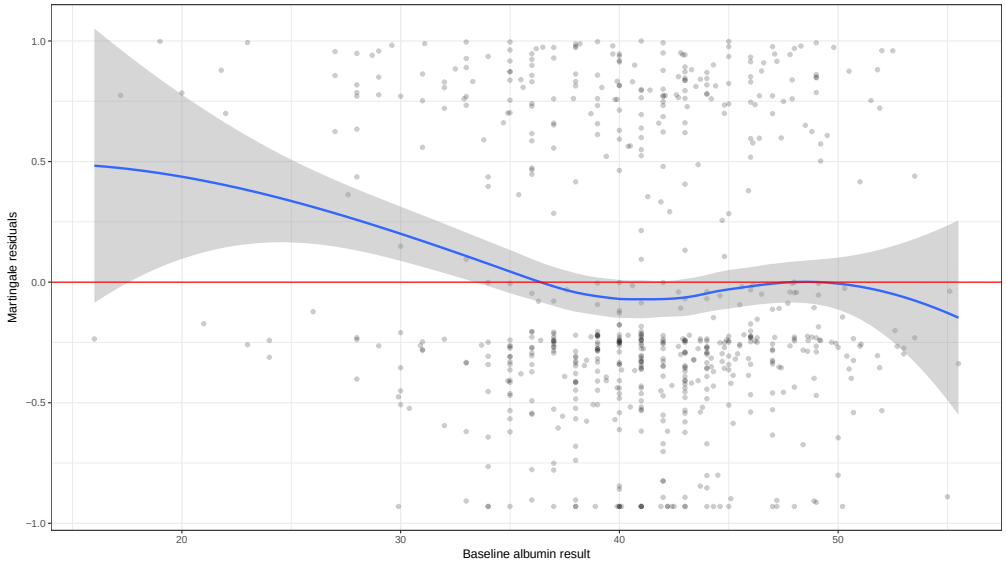


Figure 75: Residual-based diagnostics - Martingale plot

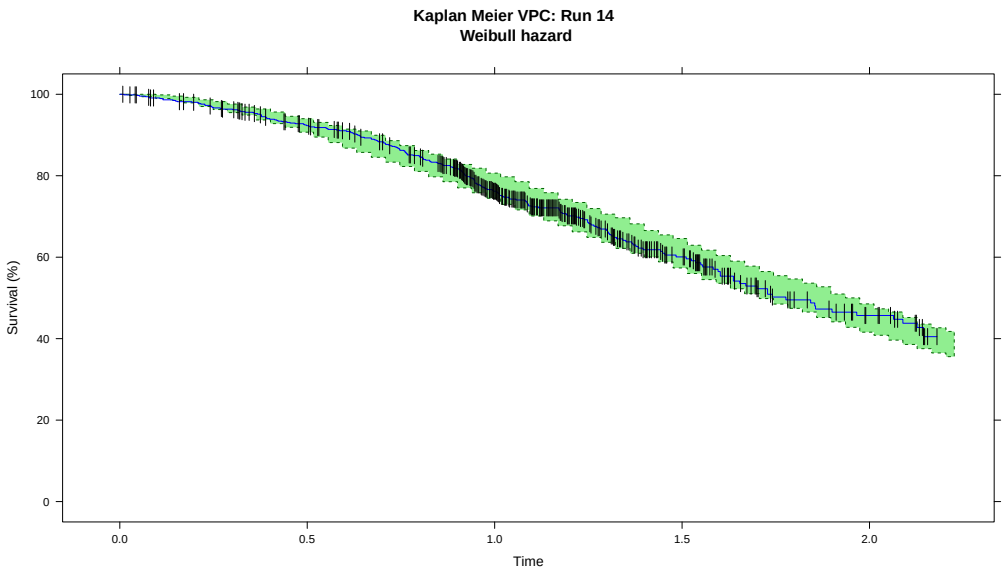


Figure 76: Simulation-based diagnostic

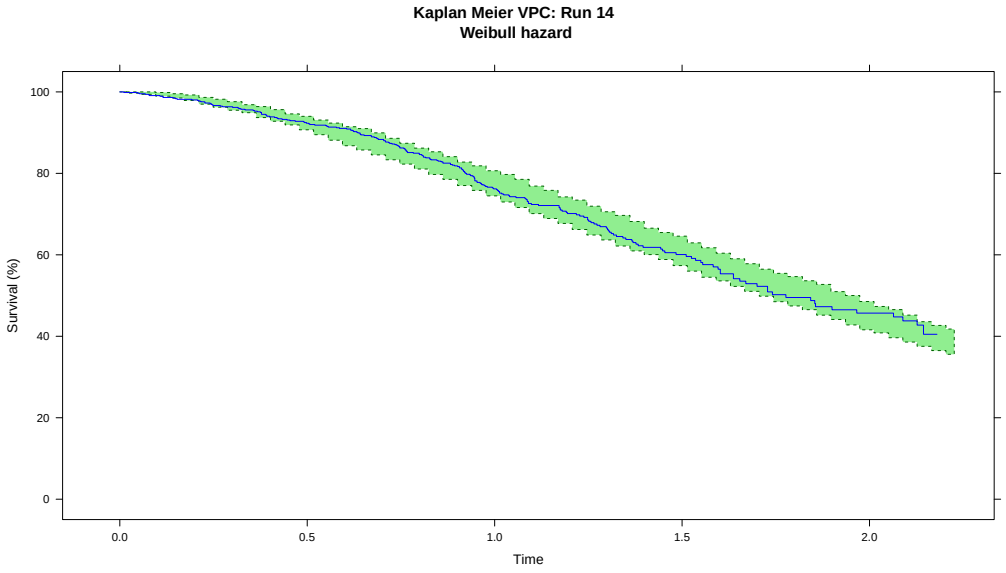


Figure 77: Simulation-based diagnostic

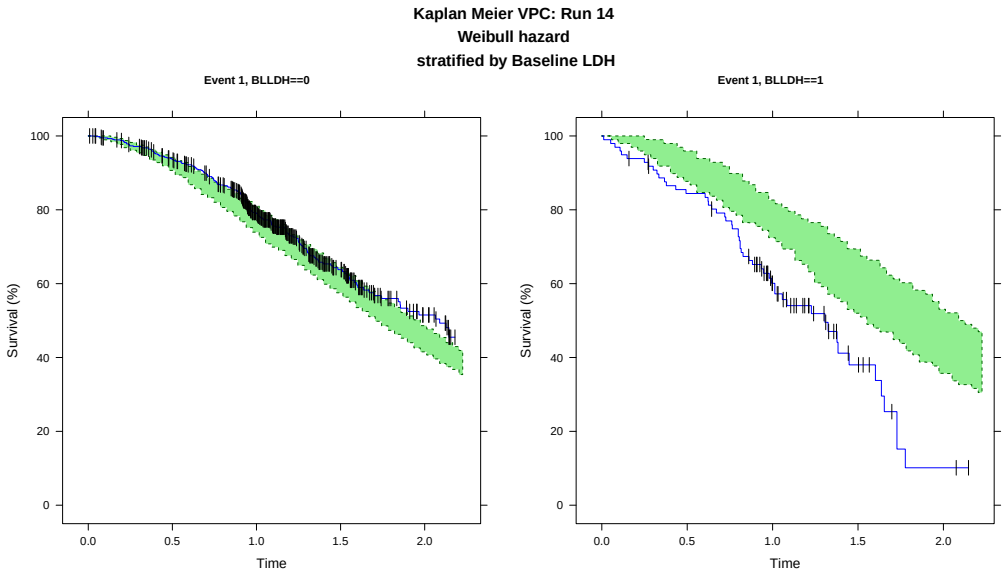


Figure 78: Simulation-based diagnostic - stratified by baseline LDH

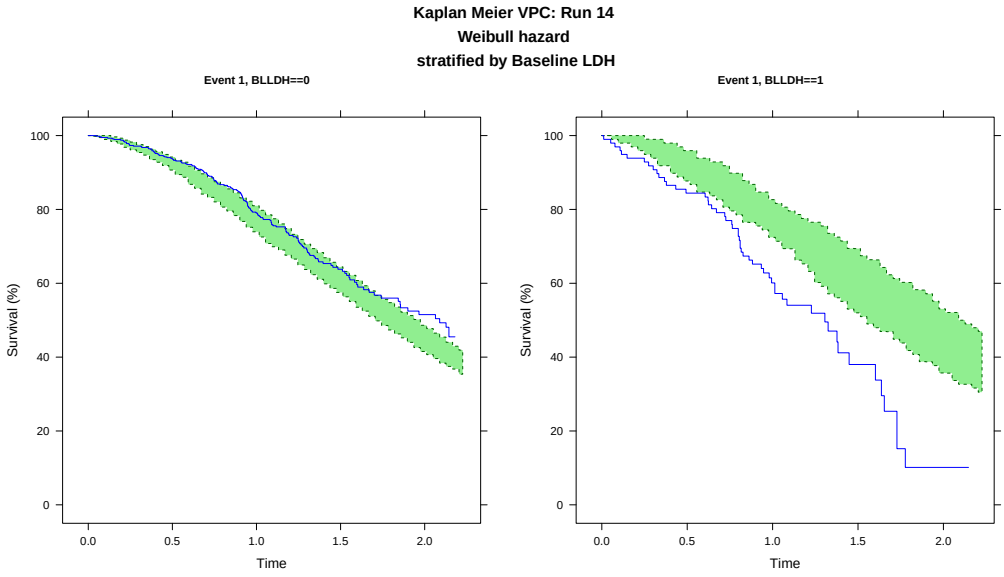


Figure 79: Simulation-based diagnostic - stratified by baseline LDH

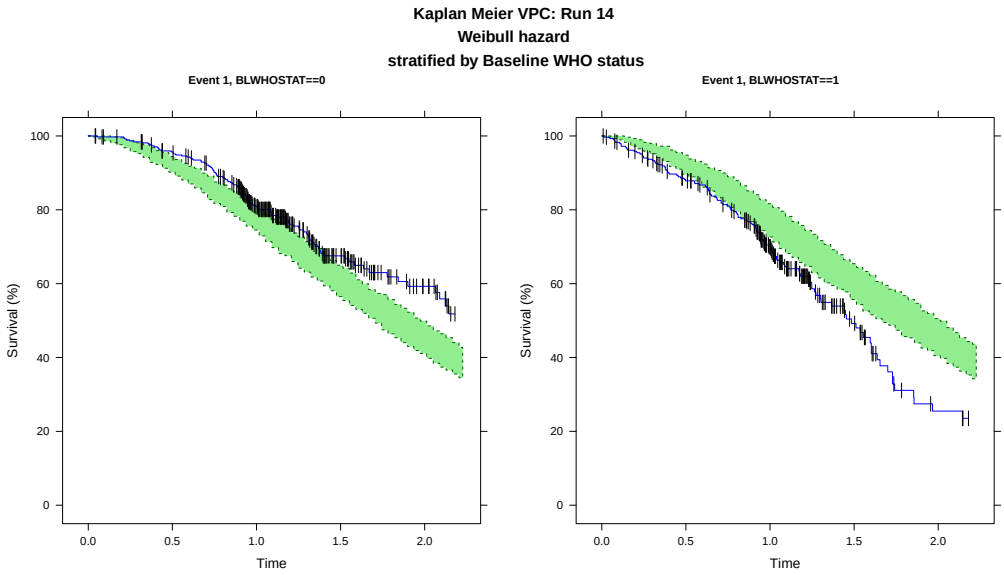


Figure 80: Simulation-based diagnostic - stratified by baseline WHO status

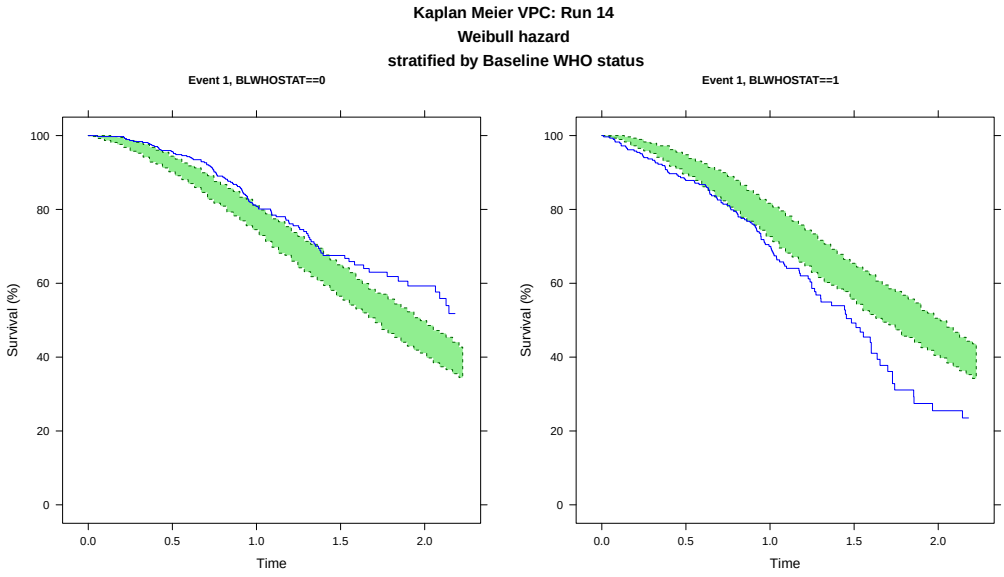


Figure 81: Simulation-based diagnostic - stratified by baseline WHO status

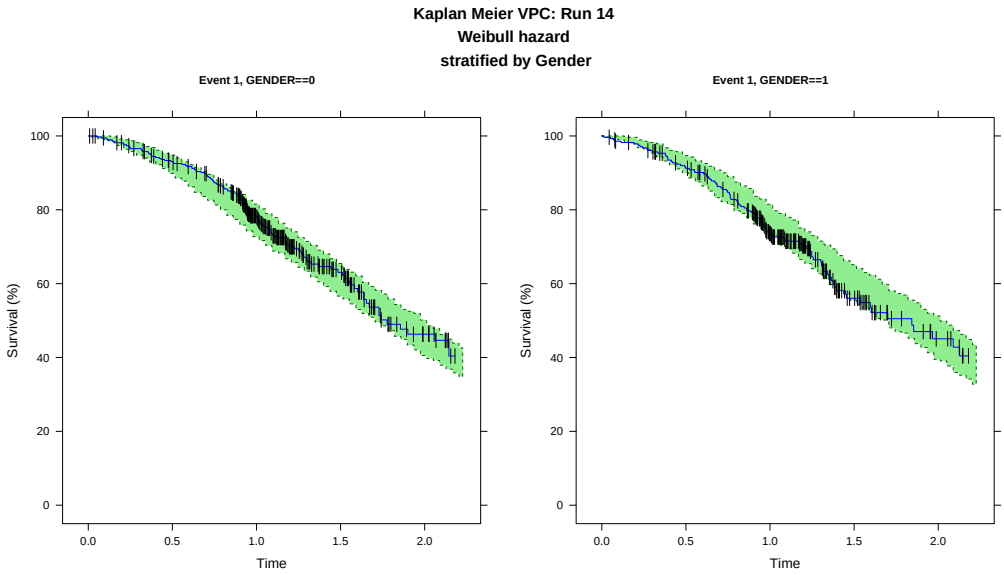


Figure 82: Simulation-based diagnostic - stratified by baseline Gender

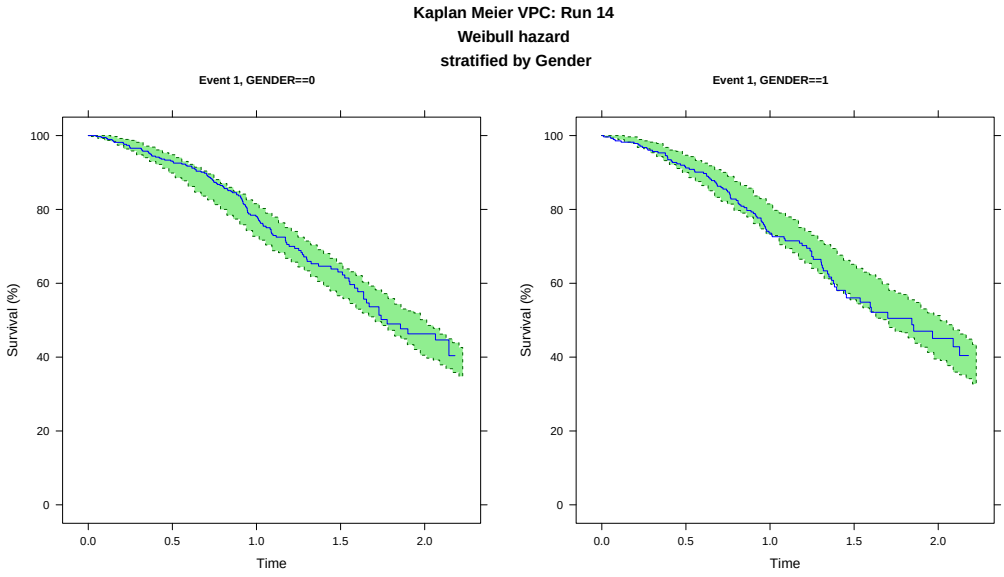


Figure 83: Simulation-based diagnostic - stratified by baseline Gender

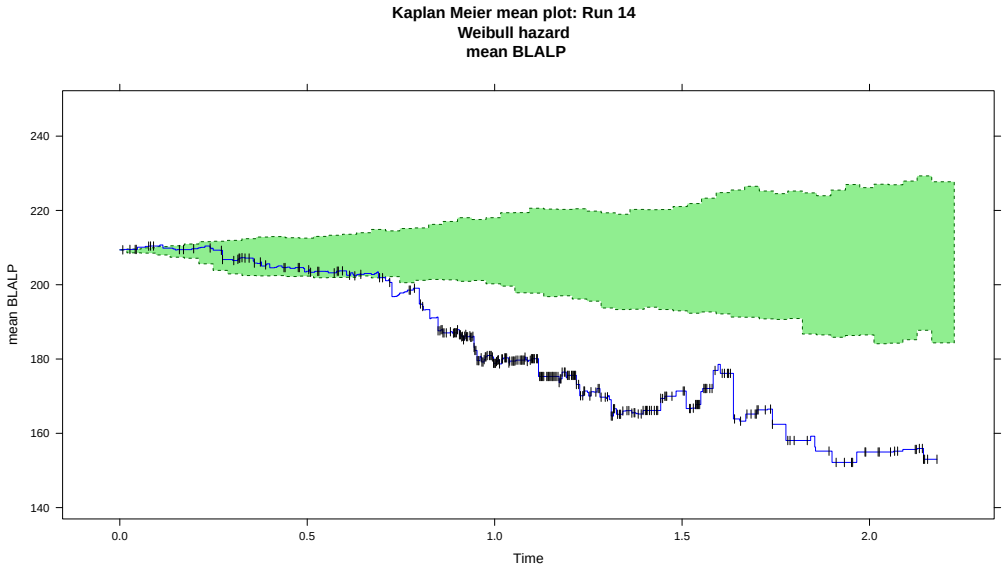


Figure 84: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

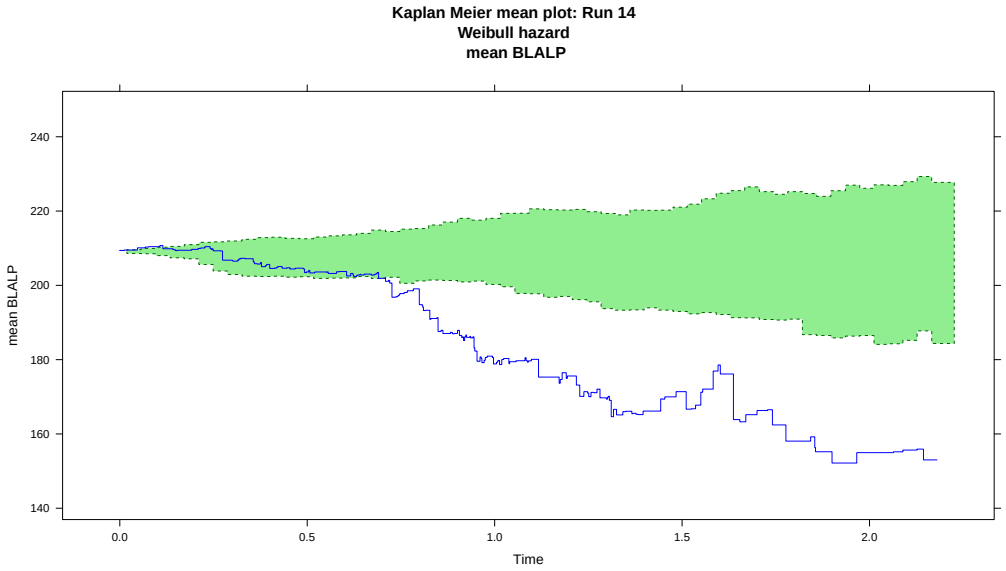


Figure 85: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

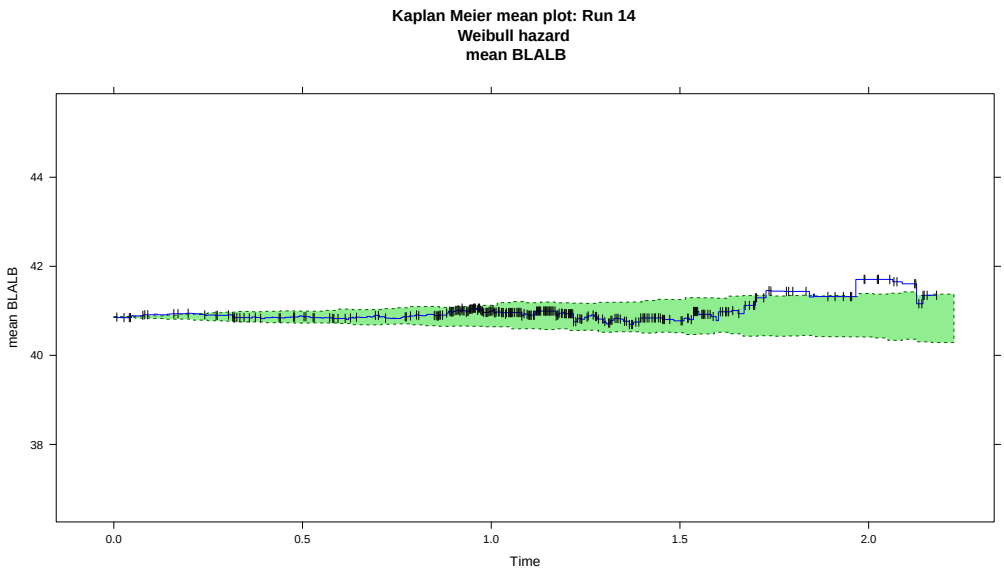


Figure 86: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

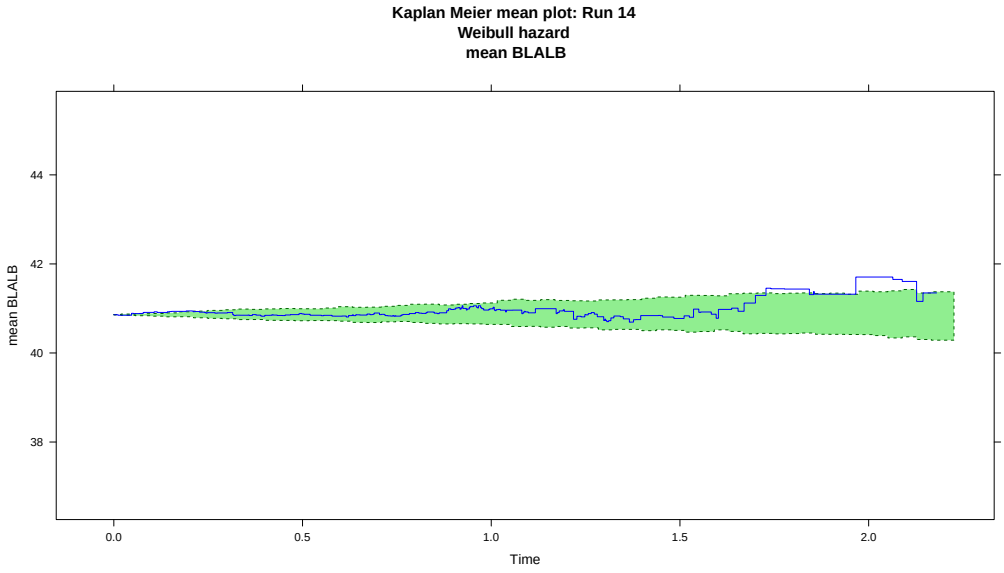


Figure 87: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

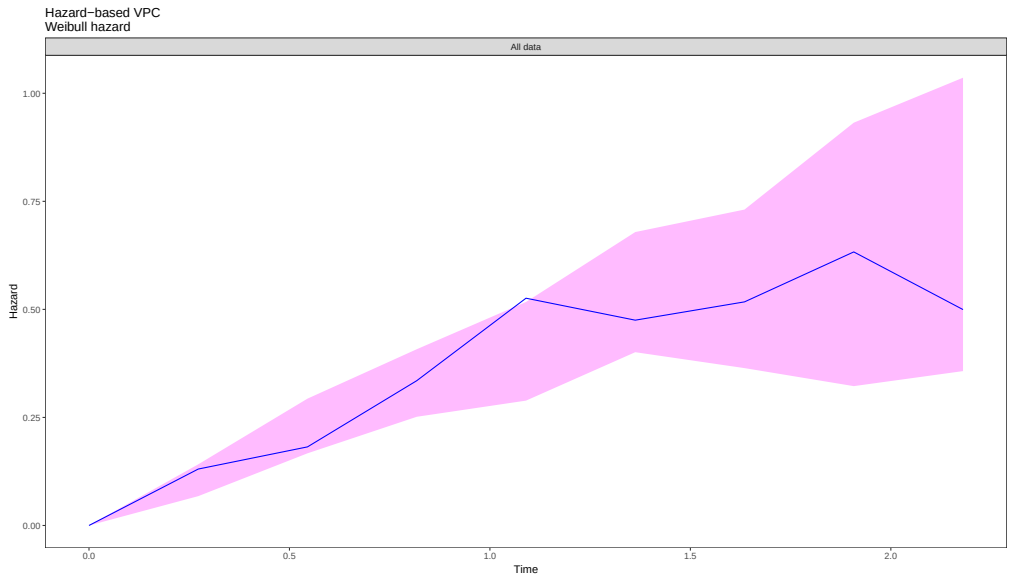


Figure 88: Simulation-based diagnostic: Hazard based VPC

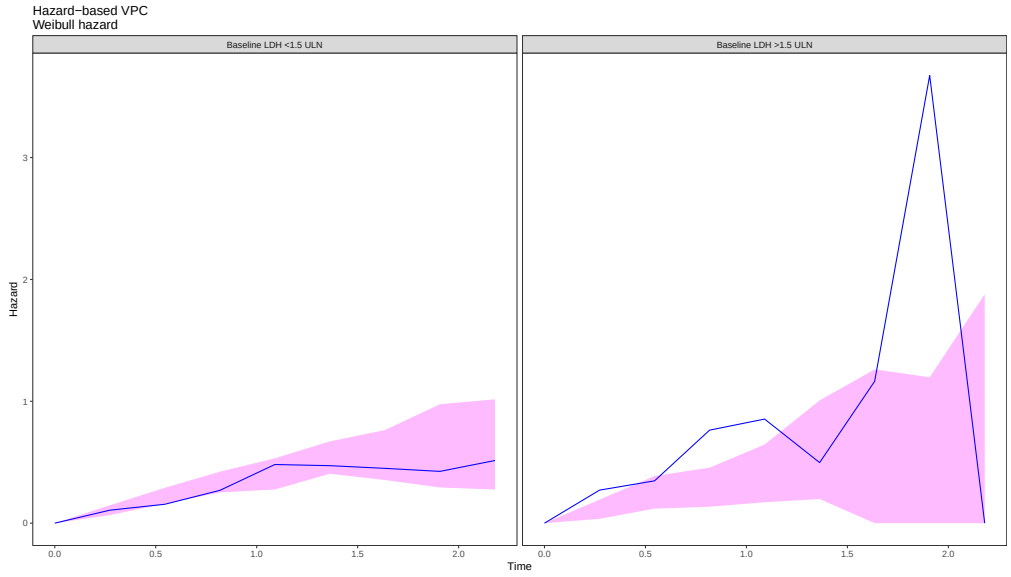


Figure 89: Simulation-based diagnostic: Hazard based VPC

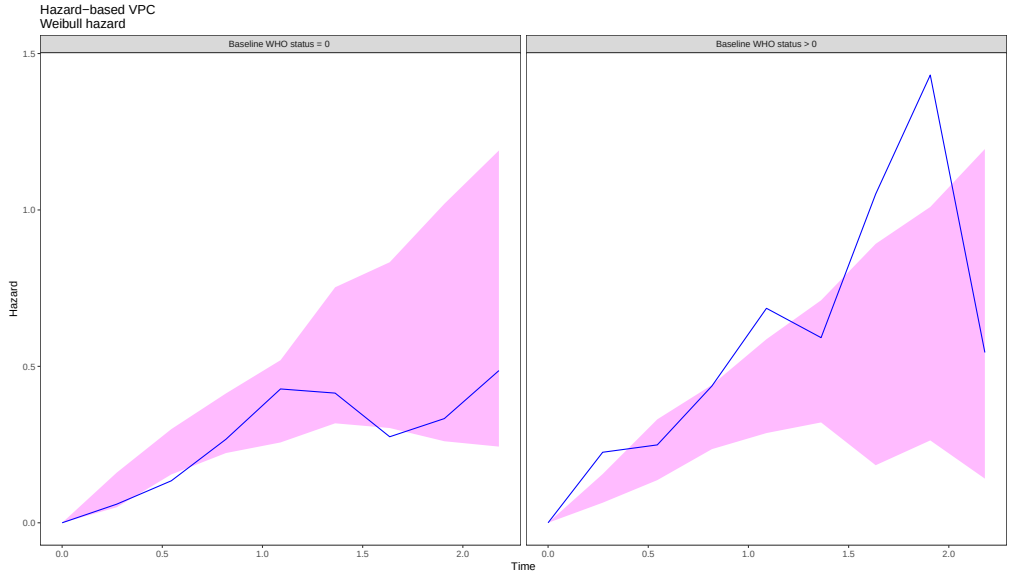


Figure 90: Simulation-based diagnostic: Hazard based VPC

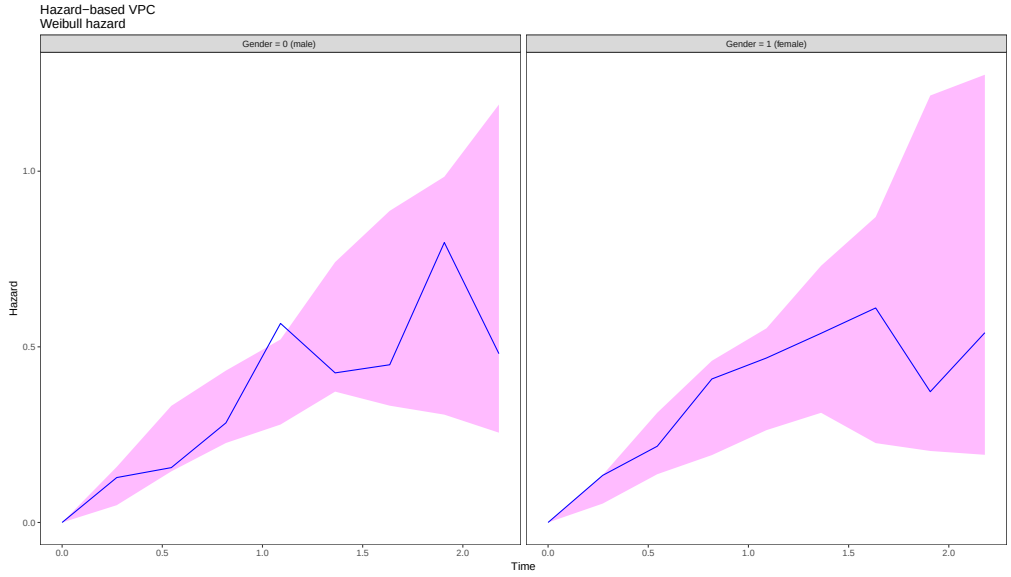


Figure 91: Simulation-based diagnostic: Hazard based VPC

11.1.2 Run 15 - covariate model

```
# next.mod(14,15,nm.dir)
show.mod(15, nm.dir) # print model
```

```
## ;; 1. Based on: 14
## ;; 2. Description:
## ;;    Covariate TTE model
## ;; 3. Label:
## ;;    Weibull hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;;     NA
## ;; 6. Interindividual variability:
## ;;    NA
## ;; 7. Interoccasion variability:
## ;;    NA
## ;; 8. Residual variability:
## ;;    NA
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    Base TTE model - Project DataSphere # 78 - no missing LDH
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM LOGBLALP ; order
##
## ;-----------------------------------------------------data description
##
## ; ID, subject identifier
## ; TIME, in years
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
## ; CENS, censored event, 0 = no, 1 = yes
## ; MAXT, last recorded event per patient (either death or censor)
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
## ; GENDER, bianry covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
## ; OSTIM, observed time in days to event or censor time
## ; LOGBLALP, log (BLLDH)
##
## ;-----------------------------------------------------
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2_1.csv IGNORE=@
```

```
##
##  IGNORE(NOLDH.EQ.1) ; 24 patients missing BL_LDH data
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
## ;IGNORE=(STIME.EQ.0) ; observed time, ignore for simulation
## ;Sim_end
##
## $SUBROUTINE ADVAN=13 TOL=9
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##
##  LAMBDA = THETA(1)* EXP(ETA(1))
##  GAMMA = THETA(2)
##  SLP1 = THETA(3)
##  SLP2 = THETA(4)
##
## ;;======================== DIFFERENTIAL EQUATIONS ==================================
## ; Typical Value Weibull hazard
## ; h0(t) = lambda*gamma*t^(gamma-1)
##
## $DES
##
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = (LAMBDA*GAMMA)*(LAMBDA*(T+DEL))**(GAMMA-1)
## ALP = SLP1*LOGBLALP      ; baseline ALP effect
## LDH = SLP2*BLLDH ; effect of LDH > 1.5 ULN
##
## DADT(1) = BASE * EXP(ALP + LDH)
##
##
## ;;================================= MODEL FIT ==================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
##
## ;------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=(LAMBDA*GAMMA)*(LAMBDA*(TIME+DELX))**(GAMMA-1)
##  ALPX = SLP1*LOGBLALP    ; baseline ALP effect
```

```
##  LDHX = SLP2*BLLDH   ; effect of LDH > 1.5 ULN
##  HAZNOW= BASEX * EXP(ALPX + LDHX)
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================= RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
## ;;================================= SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES =====================================
##
## $THETA  (0,0.439) ; lambda
##  (0,1.63) ; gamma
##   0.477 ; slope1 ALP
##  0.457 ; slope2  LDH
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_15
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
```

```
##
## ;;================================ TABLES ================================
## $TABLE      NOPRINT ONEHEADER FILE=mytab15 ID TIME DV EVID MDV PRED
##             CHZ SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLAGE BASE
##             BASEX LAMBDA GAMMA BLLDH BLWHOSTAT BLALB BLALP BLWHOLEVEL
##             GENDER OSTIM
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab15 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab15 ID LAMBDA GAMMA
##             BASE BASEX ETAS(1:LAST)
```

```
## NULL
```

11.1.2.1 Run summary

```
##  [1] "-------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run15/run
##  [4] ""
##  [5] "Successful minimization                                          [    OK   ]   "
##  [6] "No rounding errors                                               [    OK   ]   "
##  [7] "No zero gradients                                                [    OK   ]   "
##  [8] "No final zero gradients                                          [    OK   ]   "
##  [9] "Hessian not reset                                                [    OK   ]   "
## [10] "No parameter near boundary                                       [    OK   ]   "
## [11] "Covariance step                                                  [    OK   ]   "
## [12] ""
## [13] "Condition number                                                 [    OK   ]   "
## [14] "Correlations                                                     [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:02:06"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   94.53"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   3.34"
## [19] ""
## [20] "Objective function value: 882.9424"
## [21] ""
## [22] "Condition number: 260.2"
## [23] ""
## [24] "Number of observation records: 666"
## [25] "Number of individuals: 666"
## [26] ""
## [27] "              THETA               OMEGA      SIGMA    "
## [28] "     lambda  0.1055   (0.2876)                         "
## [29] "      gamma   1.684  (0.06227)                         "
## [30] " slope1 ALP  0.4609   (0.1997)                         "
## [31] "slope2  LDH   0.468   (0.3474)                         "
## [32] ""
## [33] "The relative standard errors for omega and sigma are reported on the approximate"
## [34] "standard deviation scale (SE/variance estimate)/2."
## [35] "-------------------------------------------------------------------------"
```

11.1.2.2 Diagnostic plots

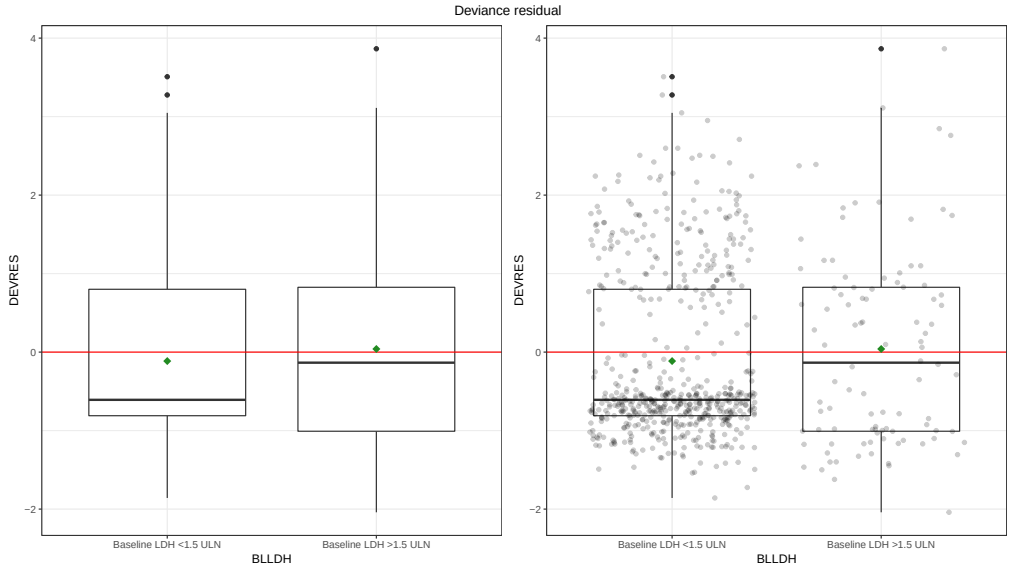


Figure 92: Residual-based diagnostics - Deviance plot

- zero reference line (red) ; mean residuals (green diamond)

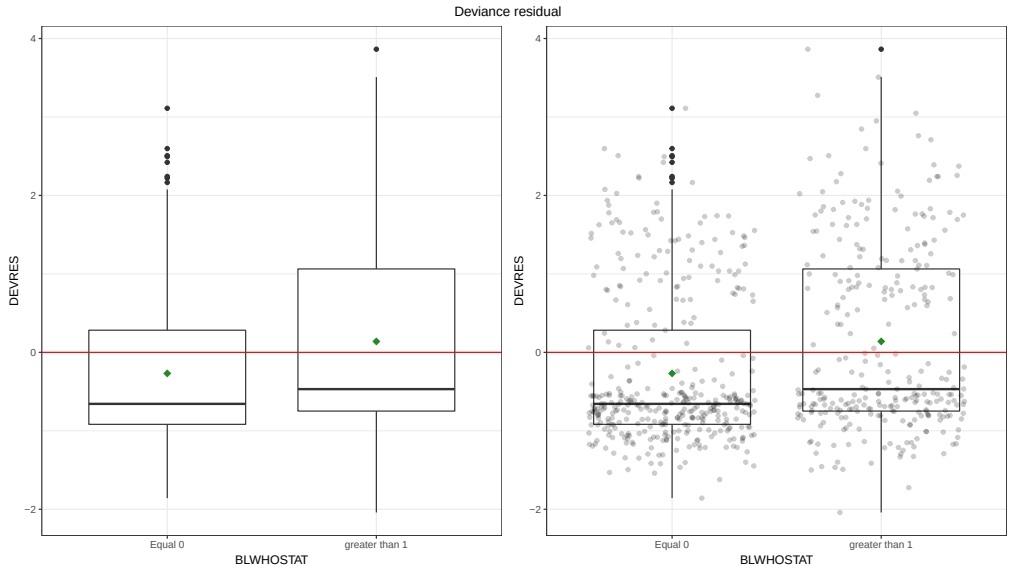


Figure 93: Residual-based diagnostics - Deviance plot

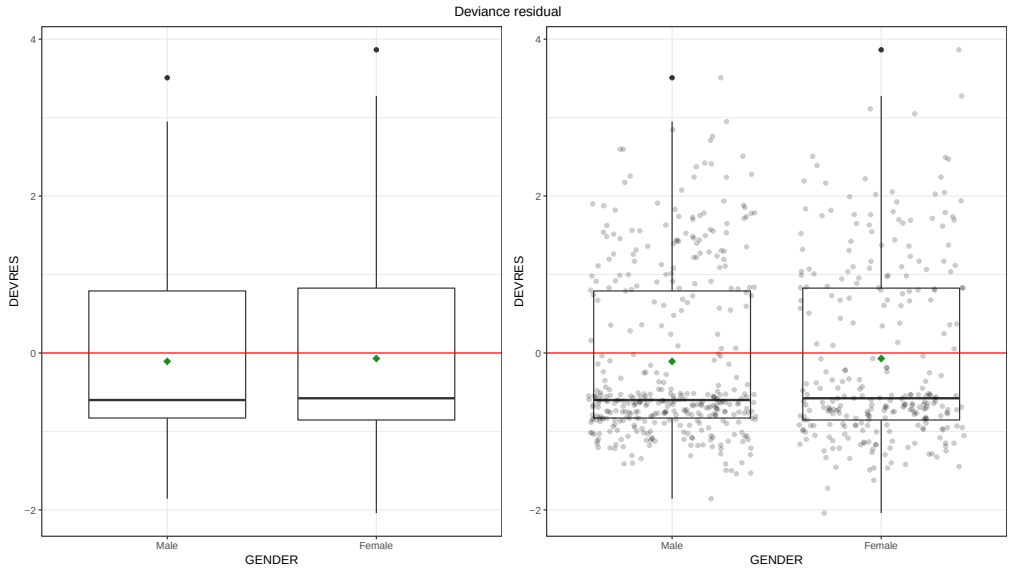


Figure 94: Residual-based diagnostics - Deviance plot

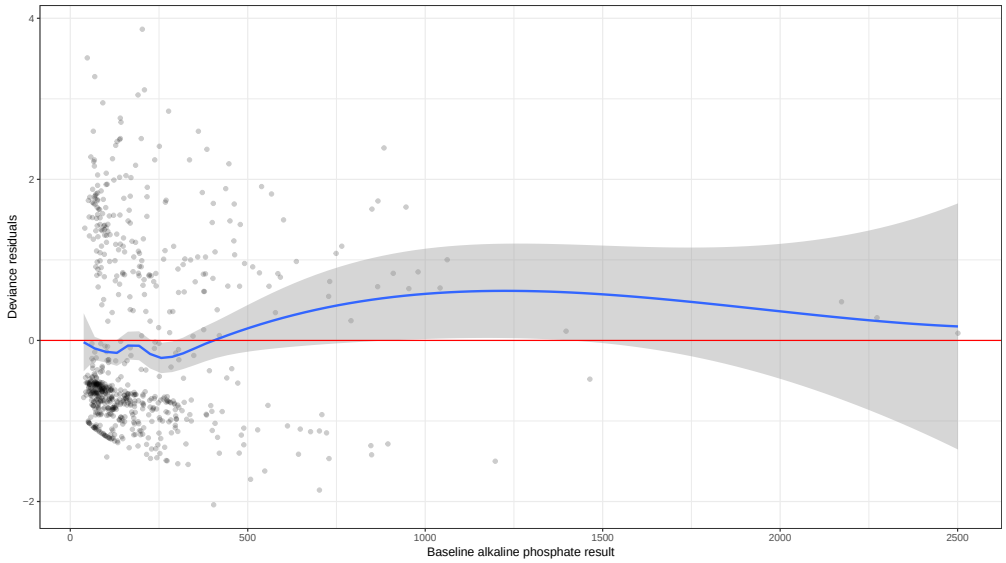


Figure 95: Residual-based diagnostics - Deviance plot

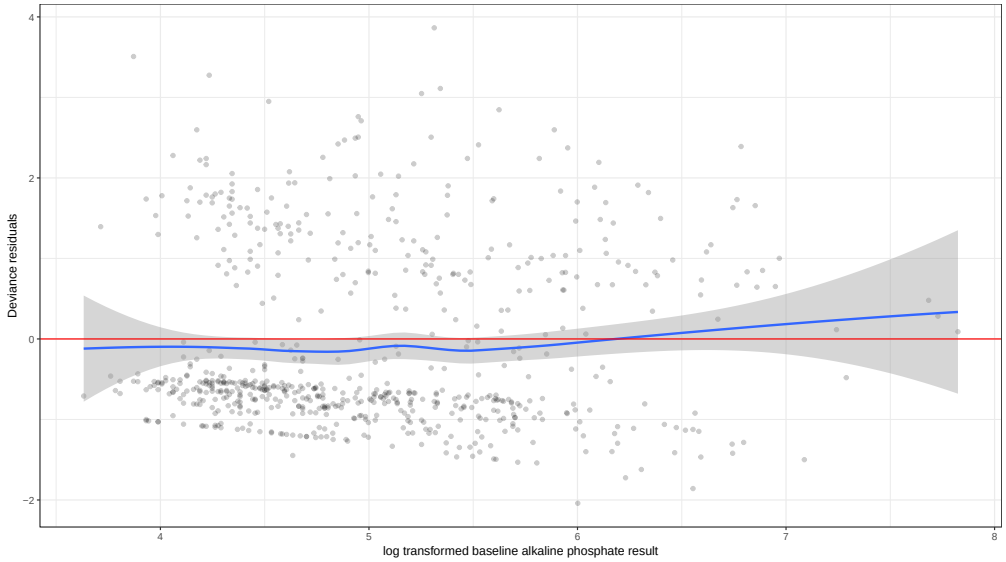


Figure 96: Residual-based diagnostics - Deviance plot

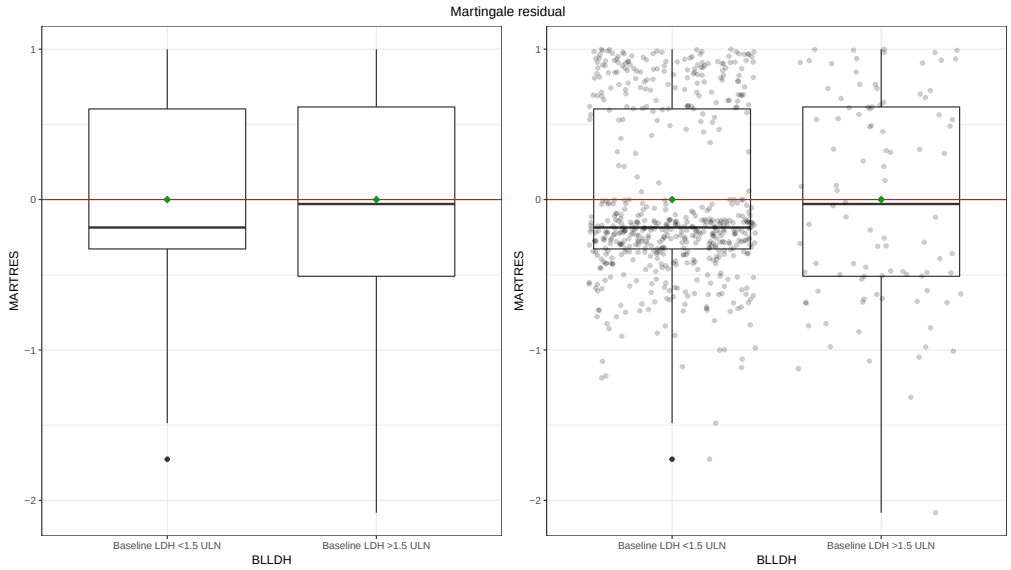


Figure 97: Residual-based diagnostics - Martingale plot

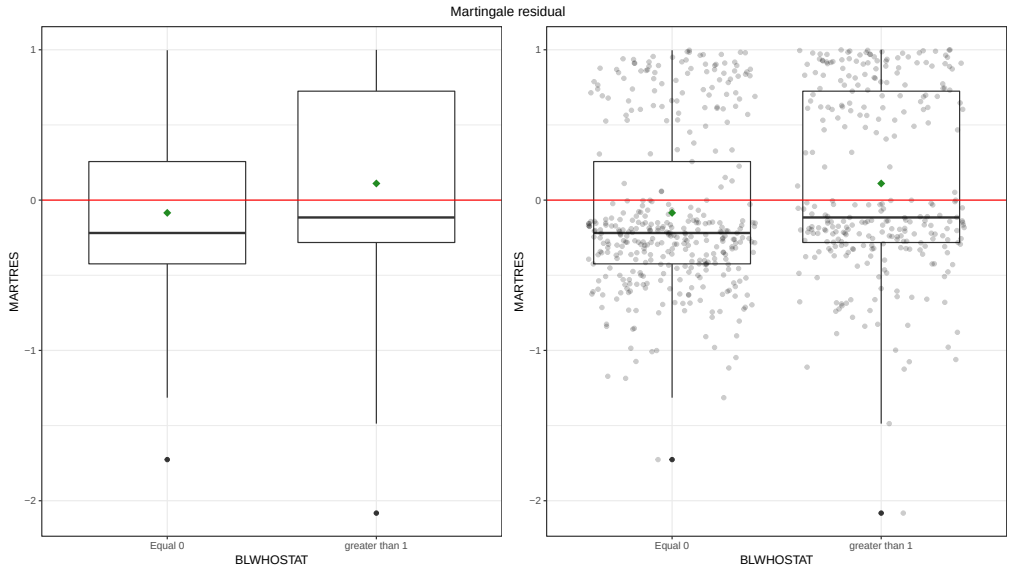


Figure 98: Residual-based diagnostics - Martingale plot

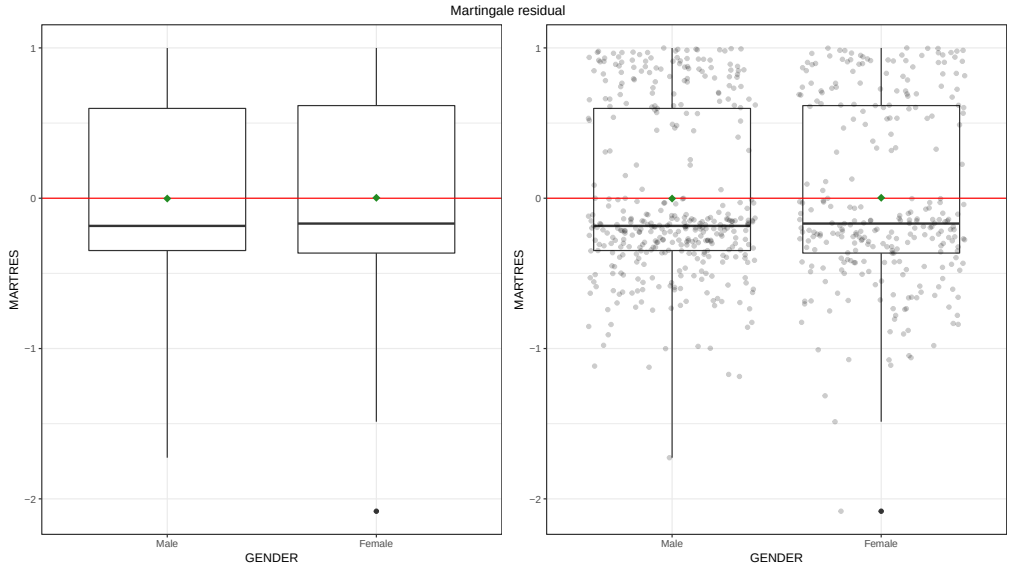


Figure 99: Residual-based diagnostics - Martingale plot

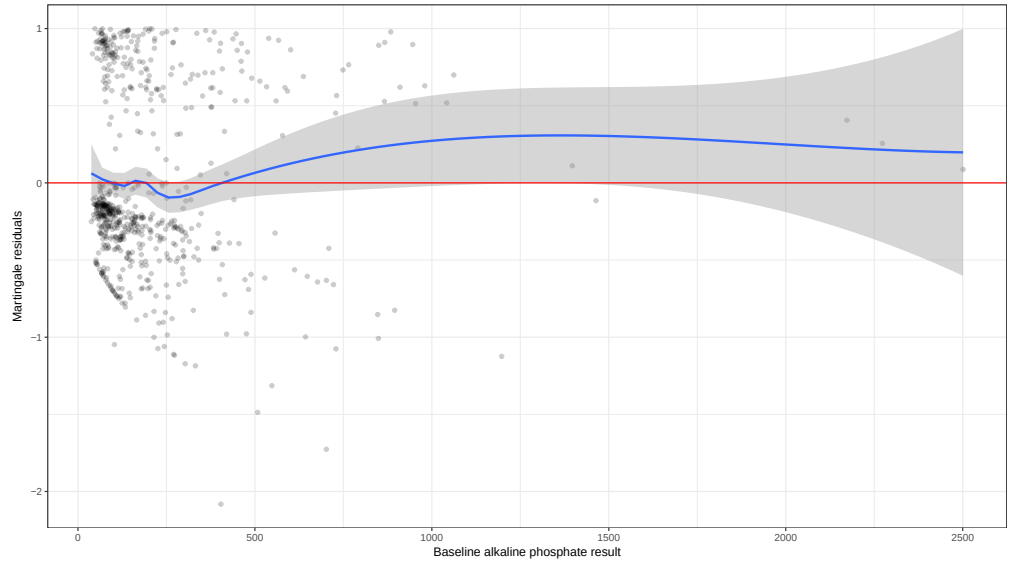


Figure 100: Residual-based diagnostics - Martingale plot

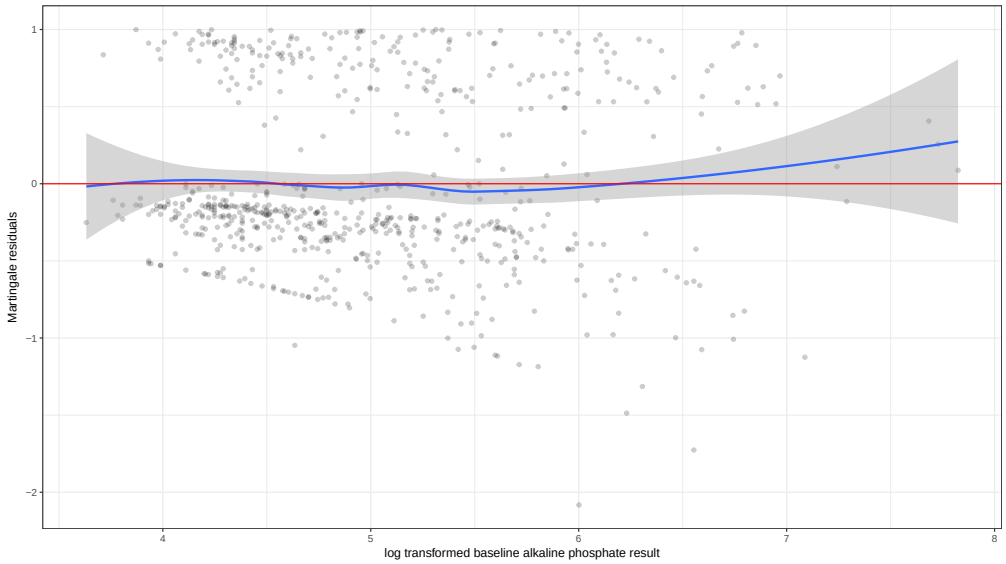


Figure 101: Residual-based diagnostics - Martingale plot

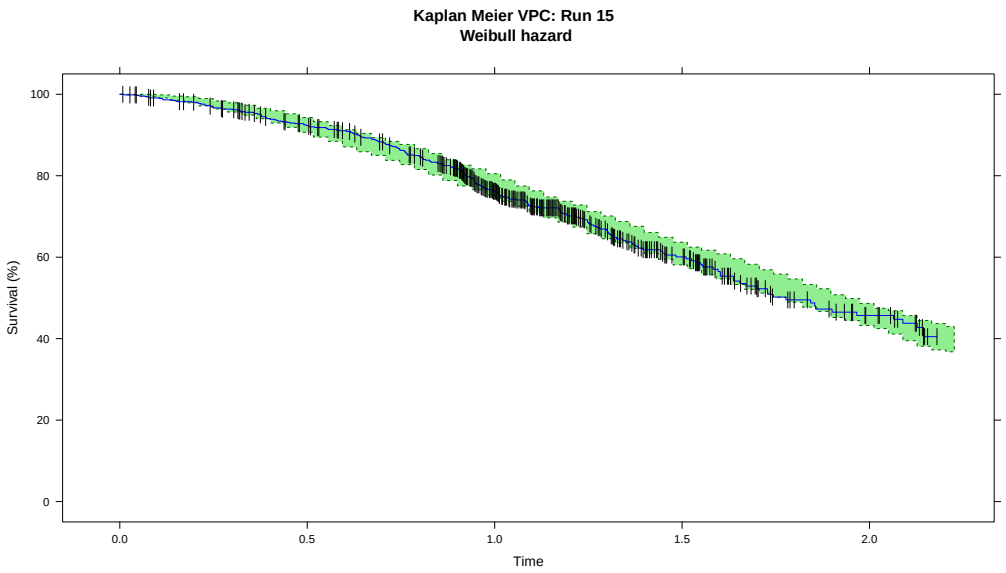


Figure 102: Simulation-based diagnostic

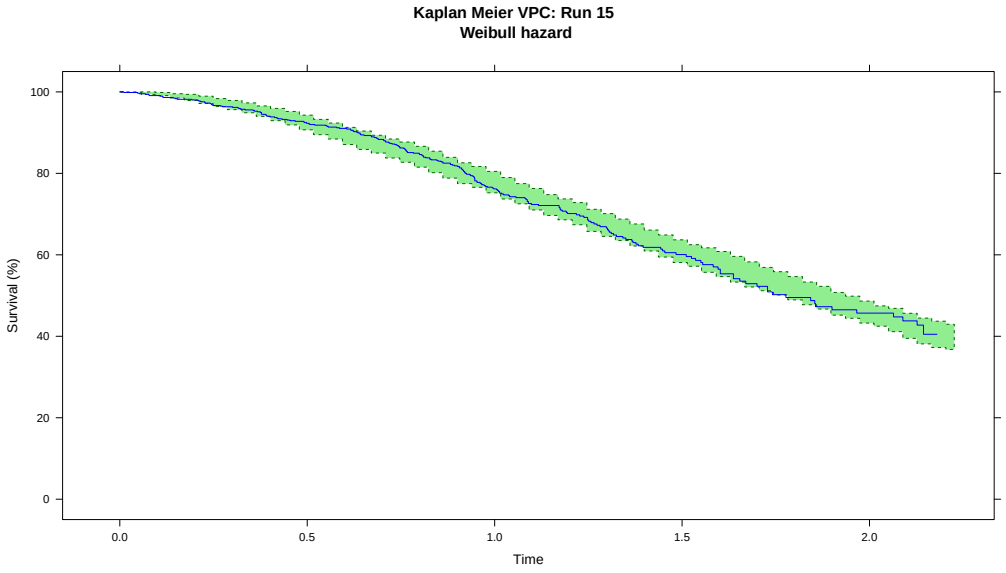


Figure 103: Simulation-based diagnostic

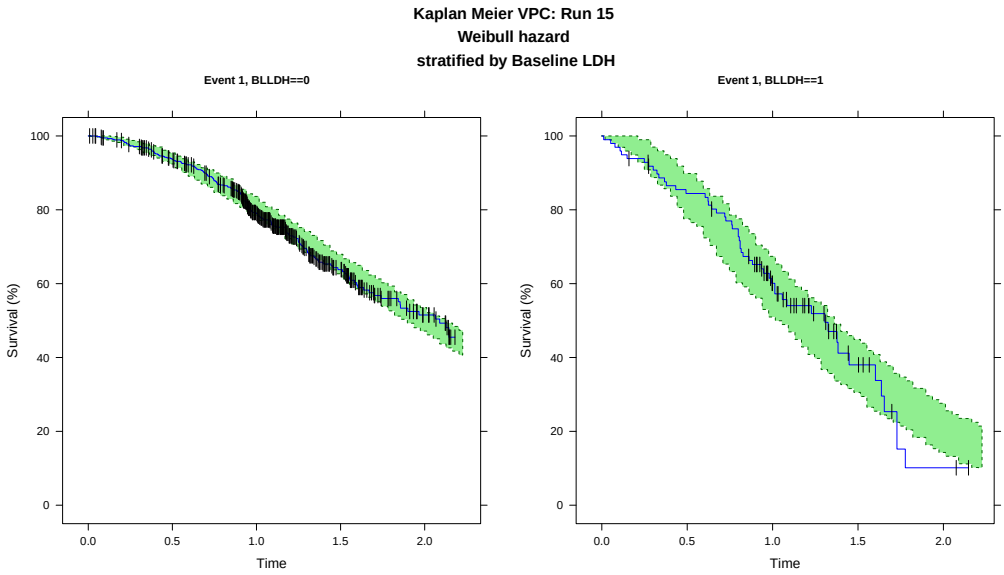


Figure 104: Simulation-based diagnostic - stratified by baseline LDH

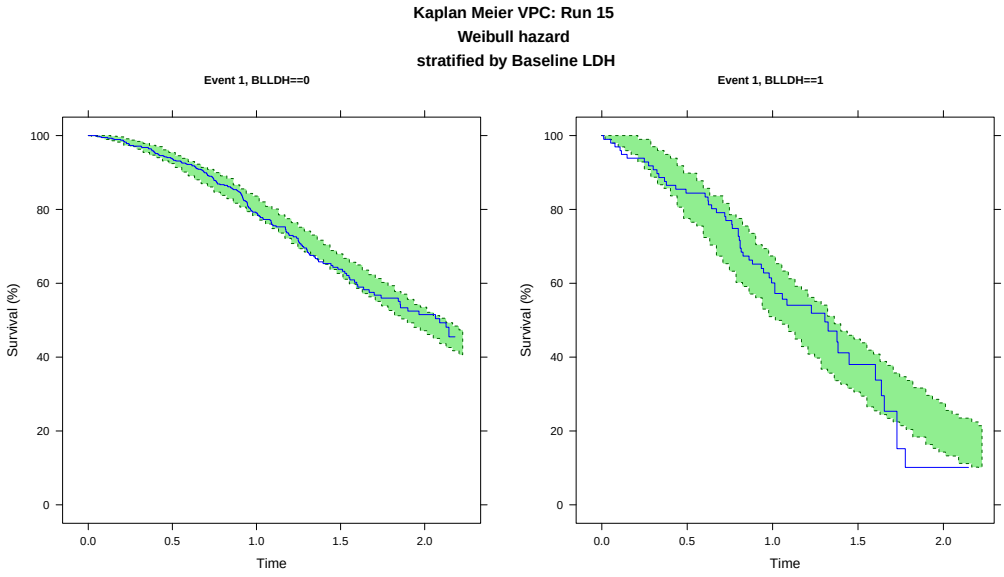


Figure 105: Simulation-based diagnostic - stratified by baseline LDH

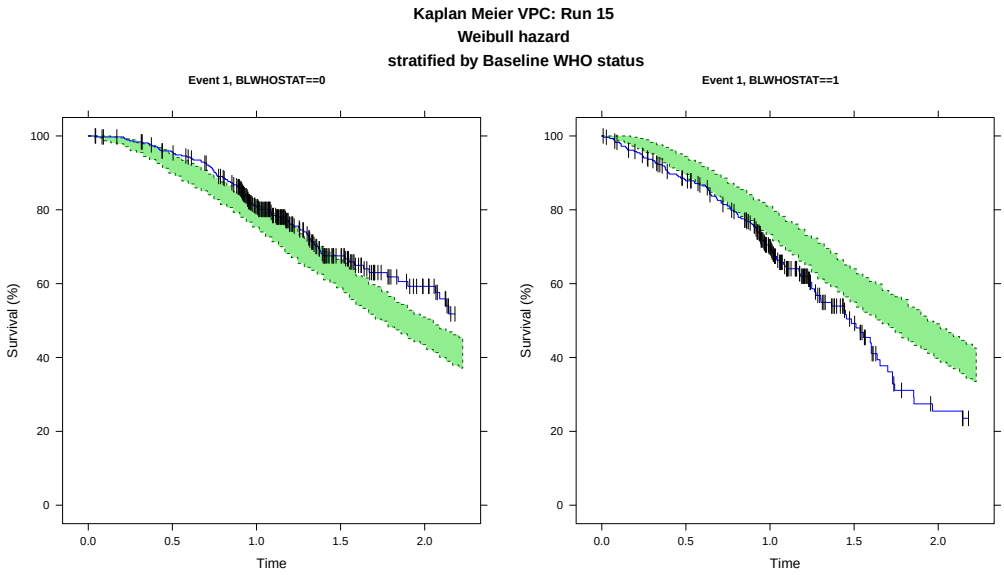


Figure 106: Simulation-based diagnostic - stratified by baseline WHO status

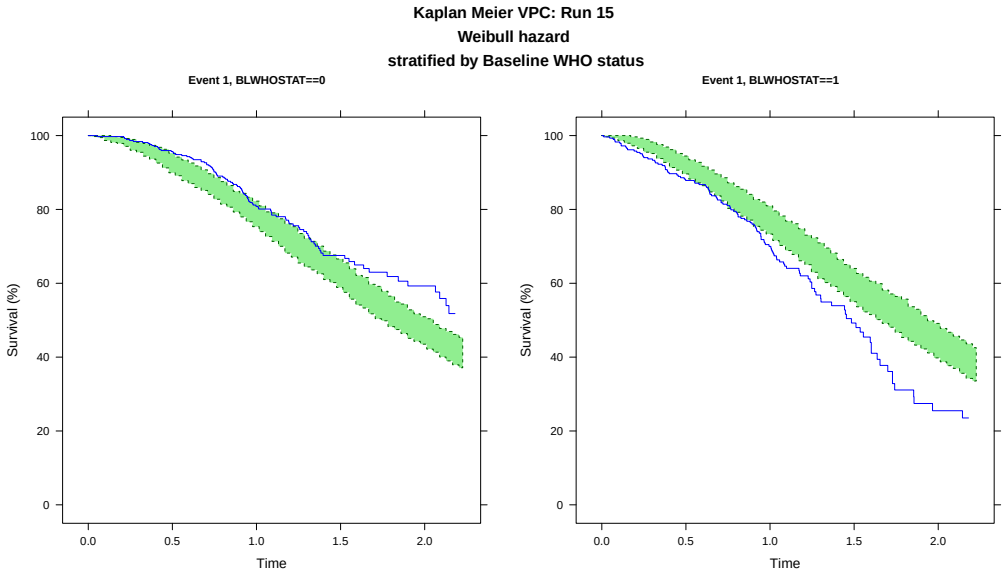


Figure 107: Simulation-based diagnostic - stratified by baseline WHO status

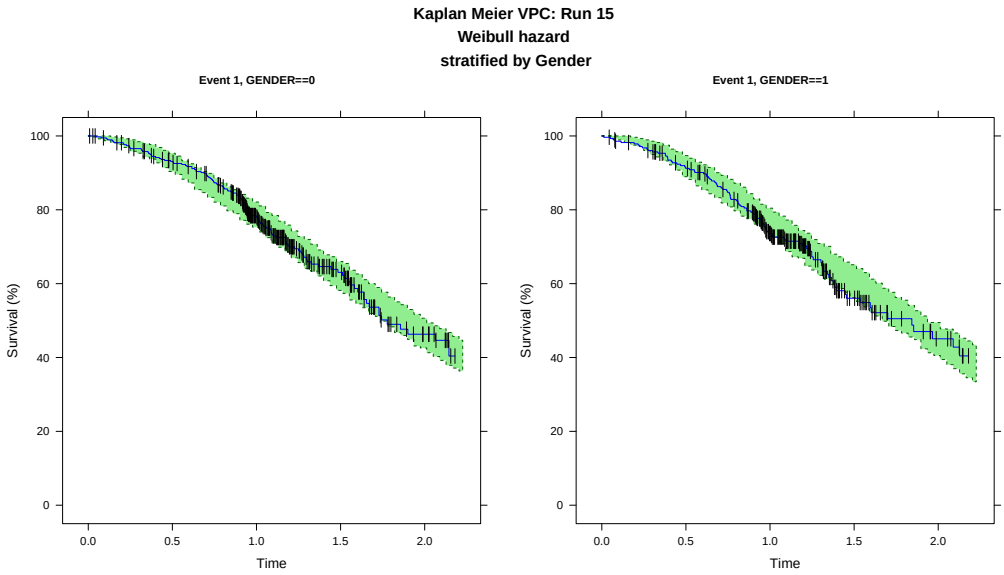


Figure 108: Simulation-based diagnostic - stratified by baseline Gender

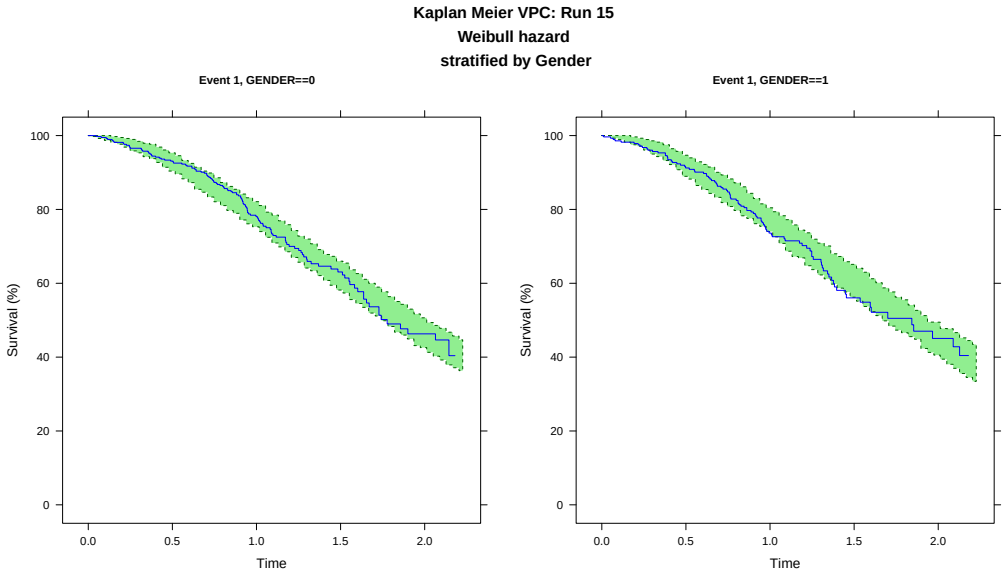


Figure 109: Simulation-based diagnostic - stratified by baseline Gender

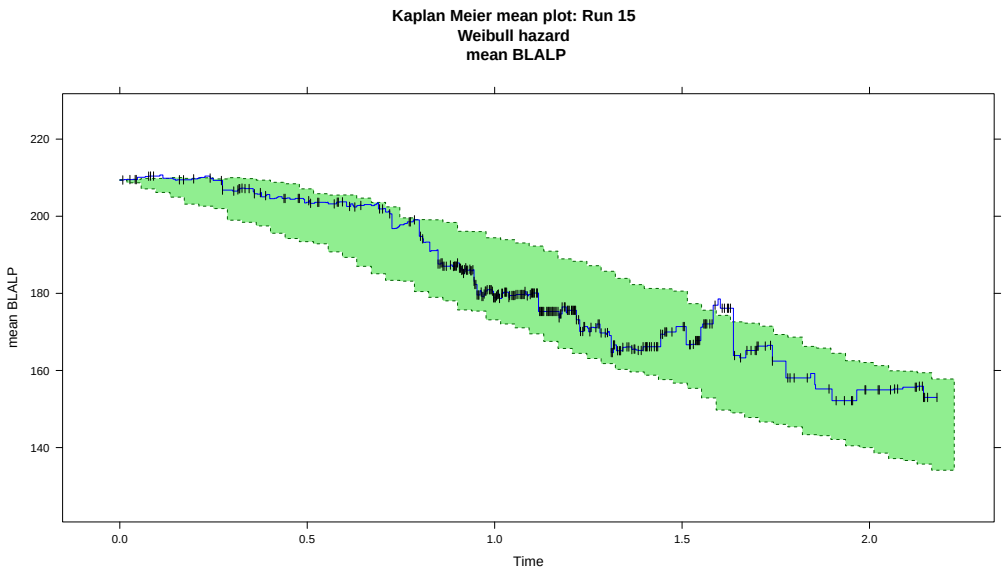


Figure 110: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

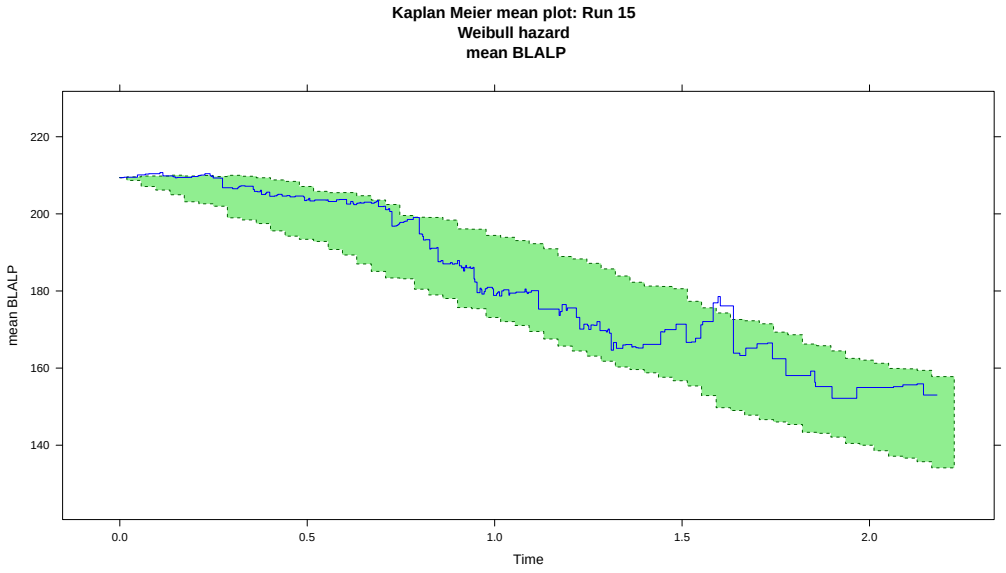


Figure 111: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

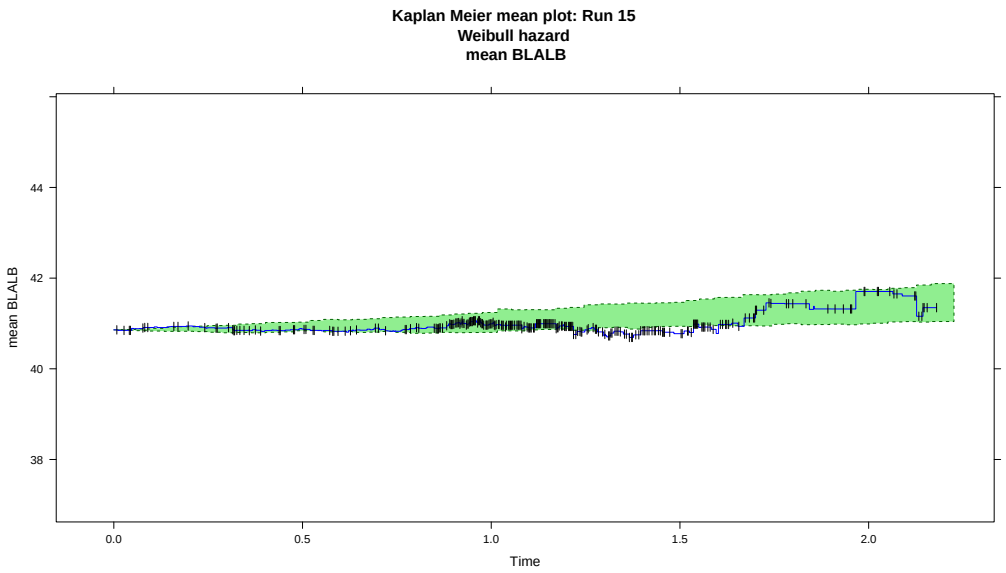


Figure 112: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

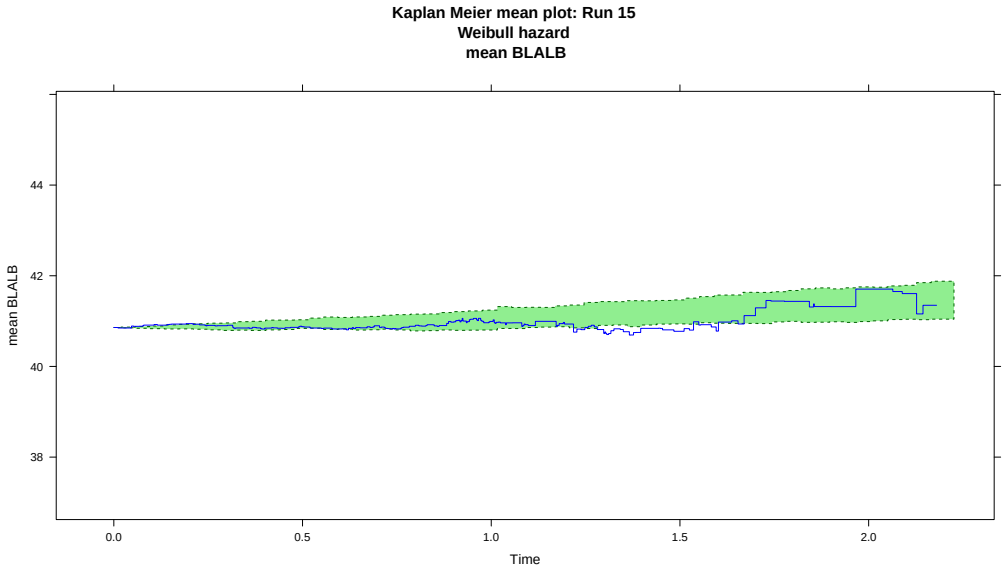


Figure 113: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

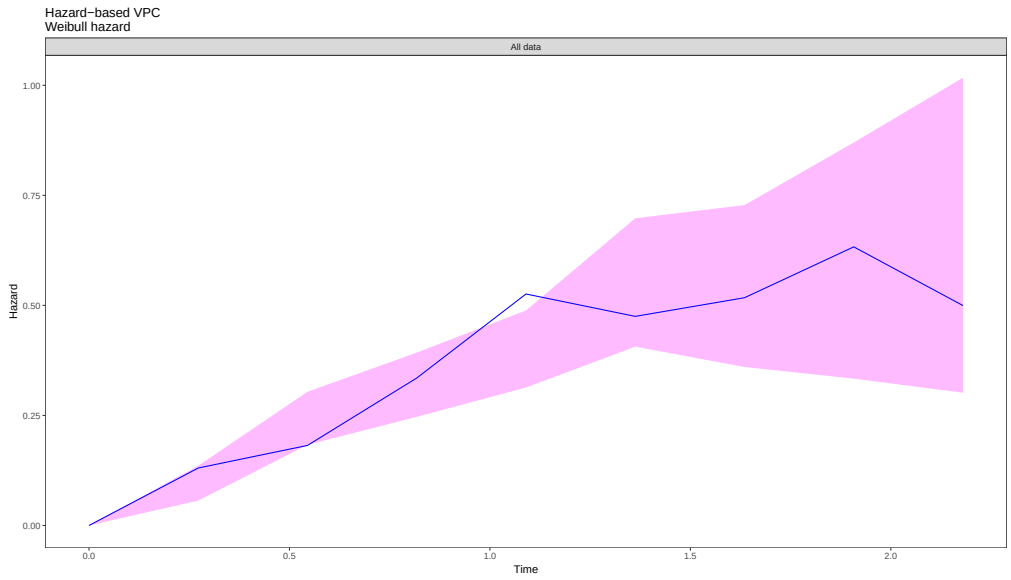


Figure 114: Simulation-based diagnostic: Hazard based VPC

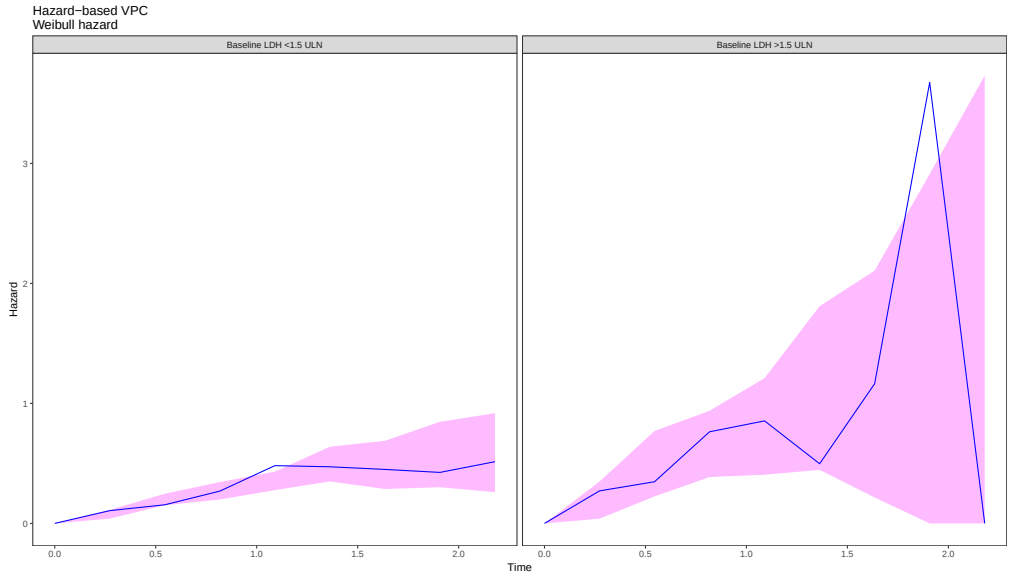


Figure 115: Simulation-based diagnostic: Hazard based VPC

11.1.3 Run 16 - covariate model 2 - evaluate baseline WHO status

```
# next.mod(15,16,nm.dir)
show.mod(16, nm.dir) # print model
```

```
## ;; 1. Based on: 15
## ;; 2. Description:
## ;;    Covariate TTE model  2
## ;; 3. Label:
## ;;    Weibull hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;;     NA
## ;; 6. Interindividual variability:
## ;;    NA
## ;; 7. Interoccasion variability:
## ;;    NA
## ;; 8. Residual variability:
## ;;    NA
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    Base TTE model - Project DataSphere # 78 - no missing LDH
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM LOGBLALP LOGBLALB
##
```

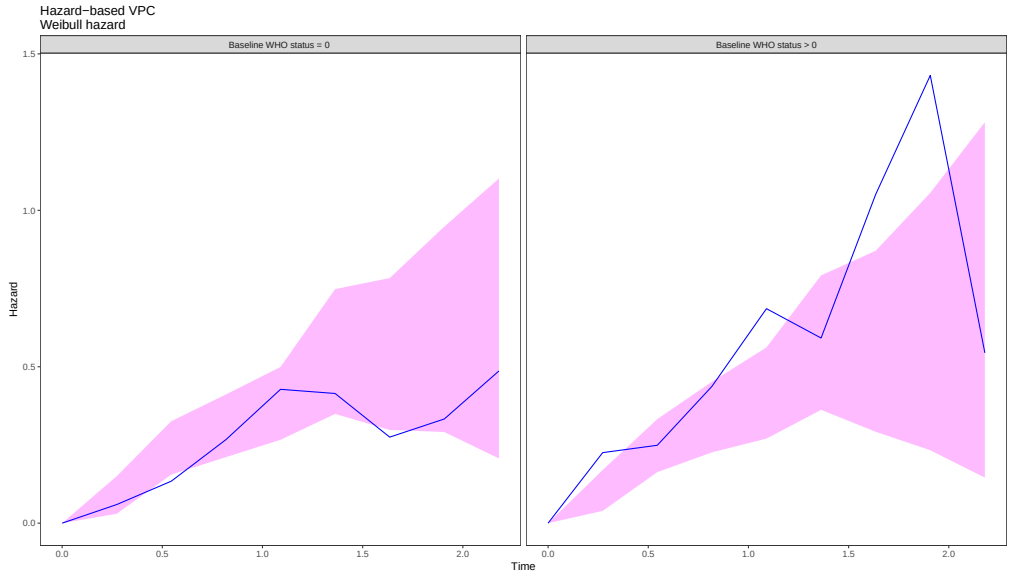


Figure 116: Simulation-based diagnostic: Hazard based VPC

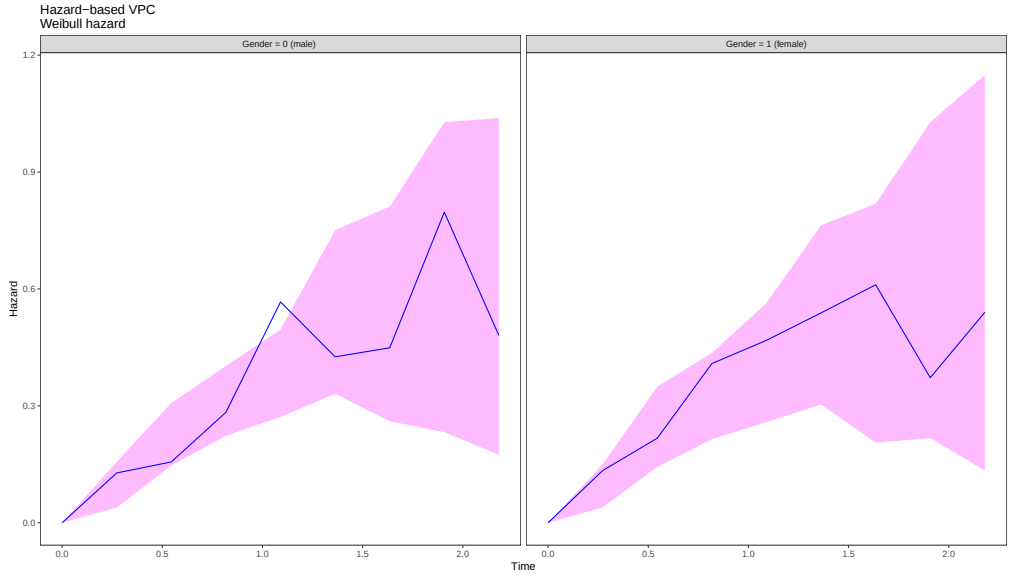


Figure 117: Simulation-based diagnostic: Hazard based VPC

```
## ;-----------------------------------------------------data description
## ; ID, subject identifier
## ; TIME, in years
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
## ; CENS, censored event, 0 = no, 1 = yes
## ; MAXT, last recorded event per patient (either death or censor)
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
## ; GENDER, bianry covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
## ; OSTIM, observed time in days to event or censor time
## ; LOGBLALP, log (BLALP)
## ; LOGBLALB, log (BLALB)
## ;-------------------------------------------------------
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2_1.csv IGNORE=@
## IGNORE(NOLDH.EQ.1)  ; 24 patients missing BL_LDH data
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
## ;IGNORE=(STIME.EQ.0) ; observed time, ignore for simulation
## ;Sim_end
##
## $SUBROUTINE ADVAN=13 TOL=9
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##
##  LAMBDA = THETA(1)* EXP(ETA(1))
##  GAMMA = THETA(2)
##  SLP1 = THETA(3)
##  SLP2 = THETA(4)
##  SLP3 = THETA(5)
##
## ; MEANLOGBLALP = 5.013
## ; MEIDANLOGBLALP =  4.875
##
## ;;======================== DIFFERENTIAL EQUATIONS ==================================
## ; Typical Value Weibull hazard
## ; h0(t) = lambda*gamma*t^(gamma-1)
##
## $DES
##
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = (LAMBDA*GAMMA)*(LAMBDA*(T+DEL))**(GAMMA-1)
## ALP = SLP1*LOGBLALP      ; baseline ALP effect
## LDH = SLP2*BLLDH ; effect of LDH > 1.5 ULN
## WHO = SLP3*BLWHOSTAT ; effect of baseline who status > 0
```

```
##
## DADT(1) = BASE * EXP(ALP + LDH + WHO)
##
##
## ;;================================= MODEL FIT ==================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
##
## ;------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=(LAMBDA*GAMMA)*(LAMBDA*(TIME+DELX))**(GAMMA-1)
##  ALPX = SLP1*LOGBLALP    ; baseline ALP effect
##  LDHX = SLP2*BLLDH   ; effect of LDH > 1.5 ULN
##  WHOX = SLP3*BLWHOSTAT ; effect of baseline who status > 0
##  HAZNOW= BASEX * EXP(ALPX + LDHX + WHOX)
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================= RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
## ;;================================= SIMULATION ============================================
## ;Simulation for model evaluation
##
```

```
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================ INITIAL ESTIMATES ================================
##
## $THETA  (0,0.106) ; lambda
##  (0,1.68) ; gamma
##  0.461 ; slope1 ALP
##  0.468 ; slope2  LDH
##  0.001; slope3  WHO
## $OMEGA  0  FIX  ; place holder
## ;;============================ ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_16
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
##
## ;;================================ TABLES ================================
## $TABLE      NOPRINT ONEHEADER FILE=mytab16 ID TIME DV EVID MDV PRED
##             CHZ SUR HAZNOW MARTRES DEVRES NOLDH BLAGE BASE
##             BASEX LAMBDA GAMMA BLLDH BLWHOSTAT BLALB BLALP BLWHOLEVEL
##             GENDER OSTIM
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab16 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab16 ID LAMBDA GAMMA
##             BASE BASEX ETAS(1:LAST)

## NULL
```

11.1.3.1 Run summary

```
##  [1] "-------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run16/run
##  [4] ""
##  [5] "Successful minimization                                        [    OK   ]   "
##  [6] "No rounding errors                                             [    OK   ]   "
##  [7] "No zero gradients                                              [    OK   ]   "
##  [8] "No final zero gradients                                        [    OK   ]   "
##  [9] "Hessian not reset                                              [    OK   ]   "
## [10] "No parameter near boundary                                     [    OK   ]   "
## [11] "Covariance step                                                [    OK   ]   "
## [12] ""
## [13] "Condition number                                               [    OK   ]   "
```

```
## [14] "Correlations                                                        [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:02:02"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   87.21"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   5.11"
## [19] ""
## [20] "Objective function value: 864.3343"
## [21] ""
## [22] "Condition number: 276.5"
## [23] ""
## [24] "Number of observation records: 666"
## [25] "Number of individuals: 666"
## [26] ""
## [27] "              THETA              OMEGA      SIGMA    "
## [28] "     lambda  0.1012  (0.2975)                        "
## [29] "      gamma   1.706  (0.0621)                        "
## [30] " slope1 ALP  0.4327  (0.2229)                        "
## [31] "slope2  LDH  0.4332  (0.3833)                        "
## [32] "slope3  WHO  0.5787  (0.2275)                        "
## [33] ""
## [34] "The relative standard errors for omega and sigma are reported on the approximate"
## [35] "standard deviation scale (SE/variance estimate)/2."
## [36] "-------------------------------------------------------------------------------"
```

11.1.3.2 Diagnostic plots

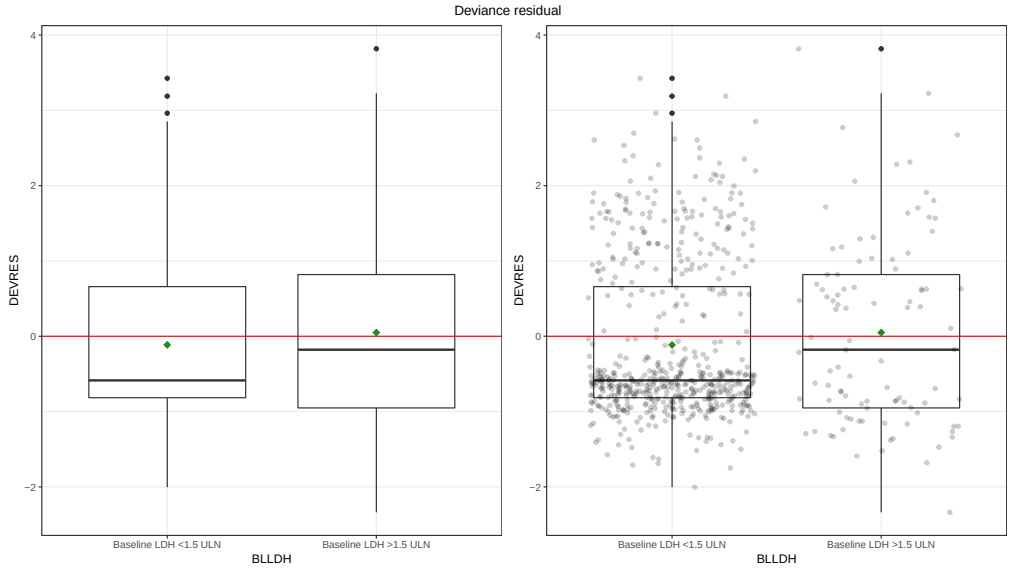


Figure 118: Residual-based diagnostics - Deviance plot

- zero reference line (red) ; mean residuals (green diamond)

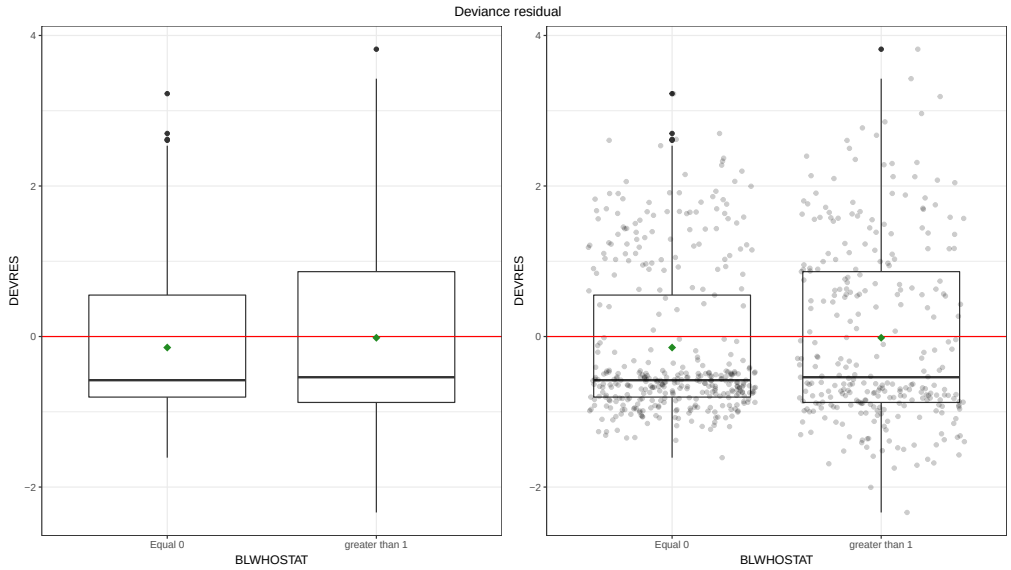


Figure 119: Residual-based diagnostics - Deviance plot

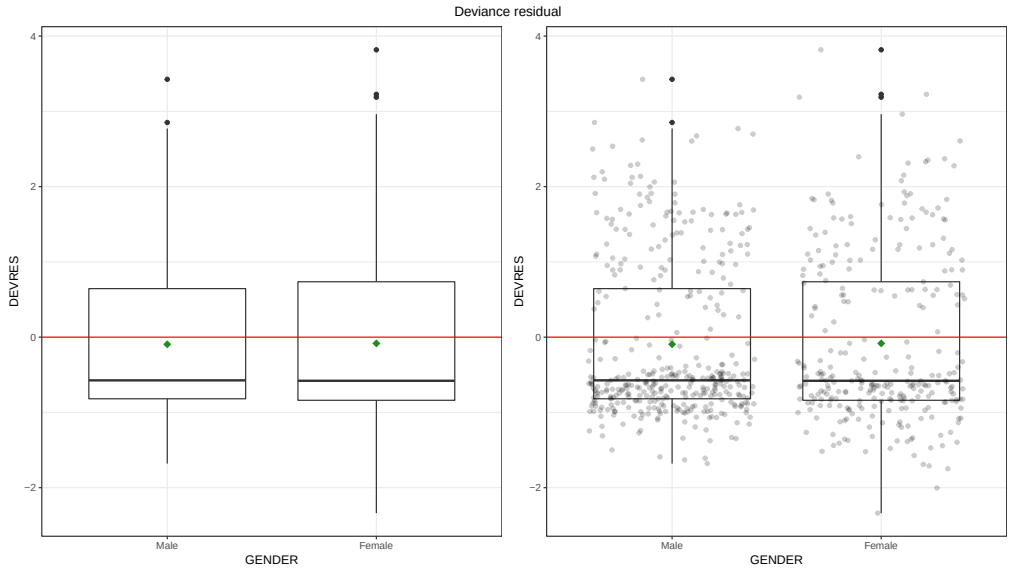


Figure 120: Residual-based diagnostics - Deviance plot

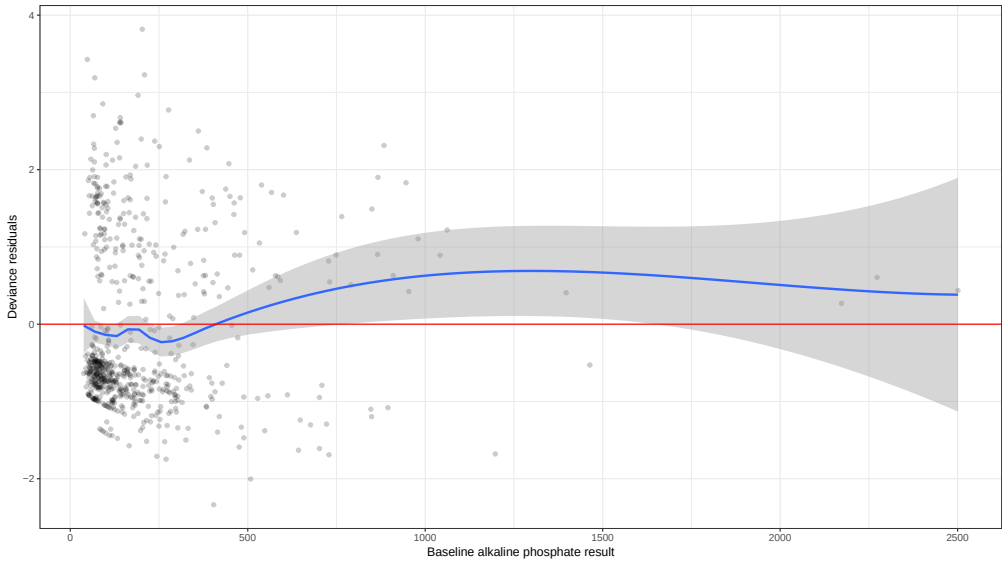


Figure 121: Residual-based diagnostics - Deviance plot

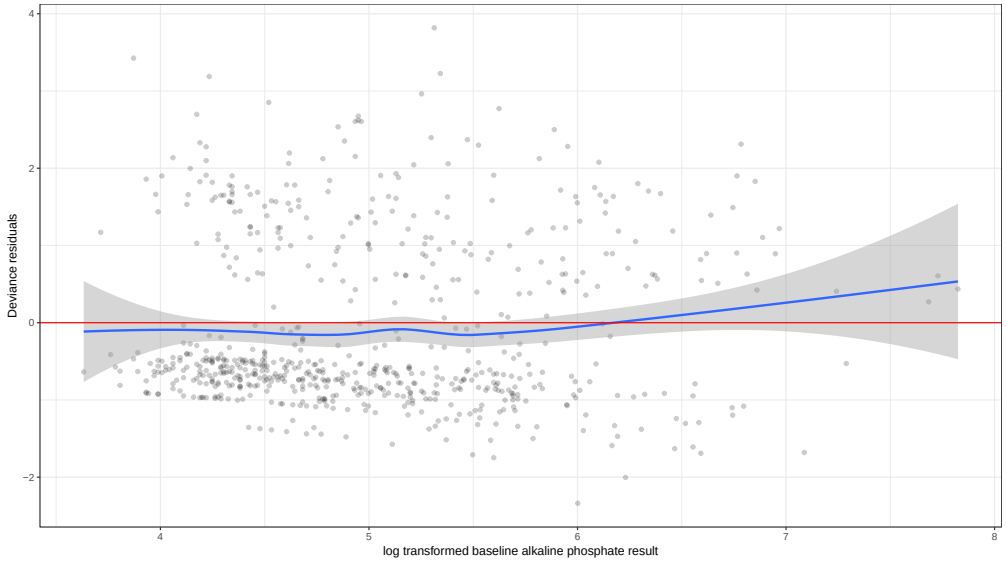


Figure 122: Residual-based diagnostics - Deviance plot

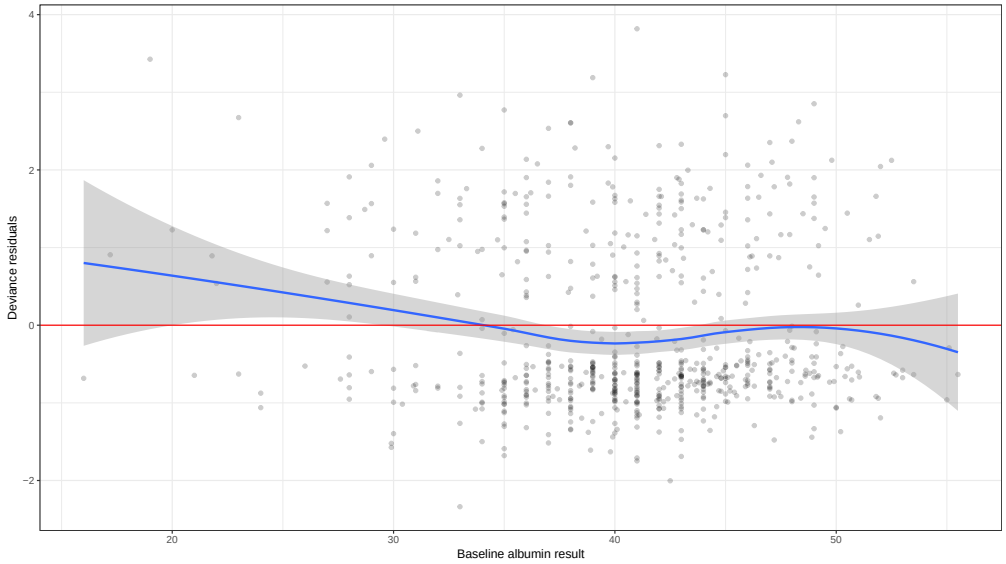


Figure 123: Residual-based diagnostics - Deviance plot

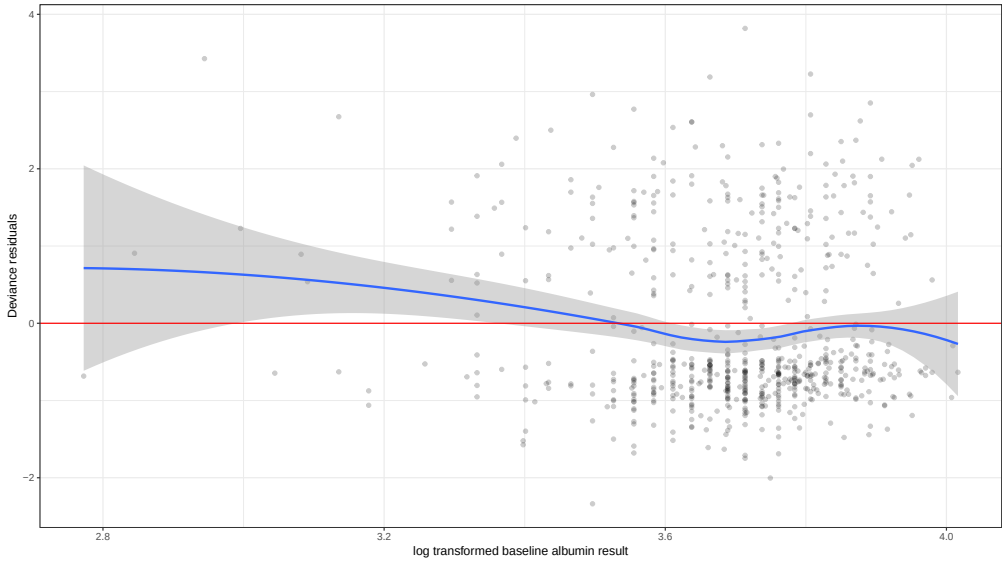


Figure 124: Residual-based diagnostics - Deviance plot

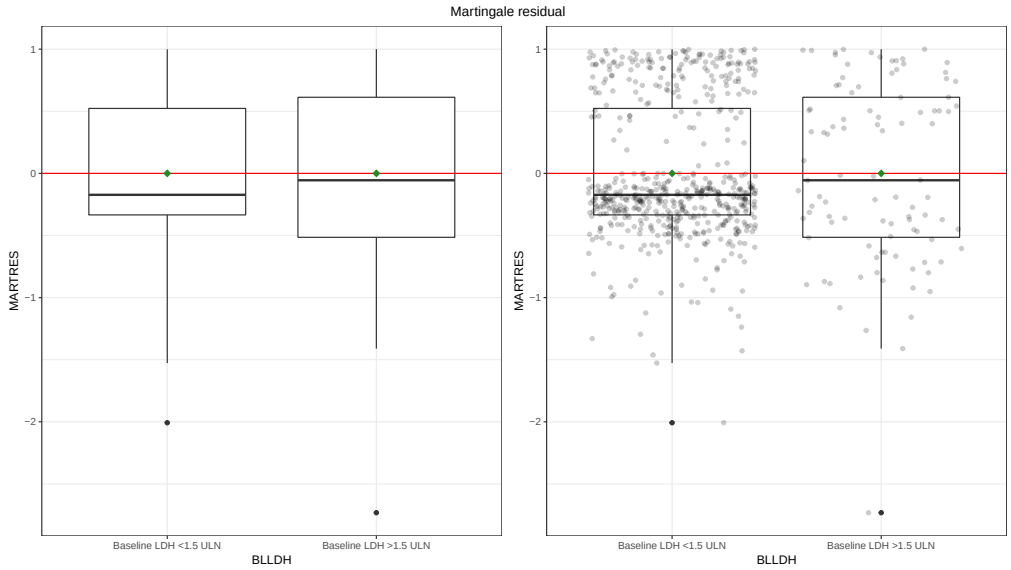


Figure 125: Residual-based diagnostics - Martingale plot

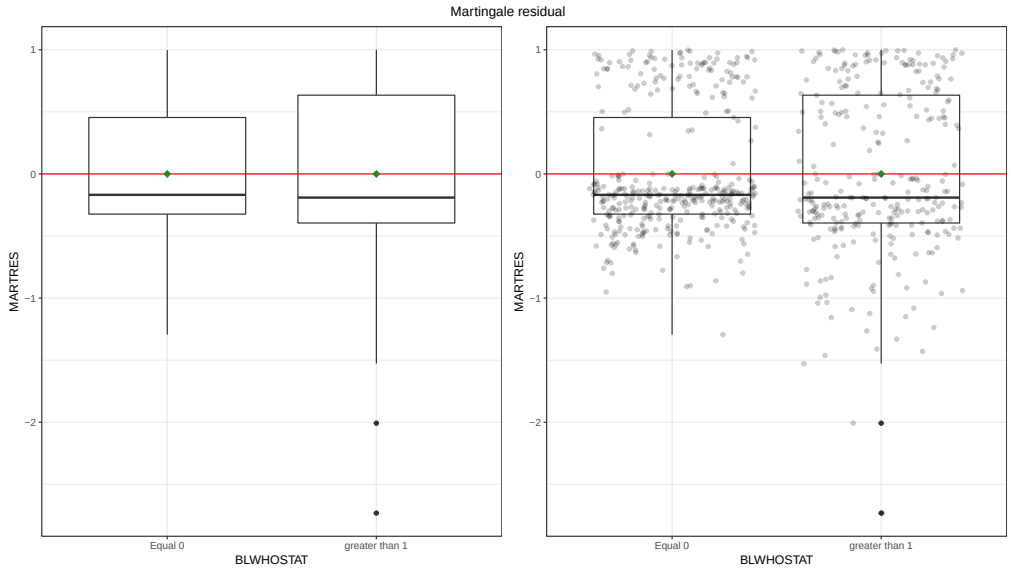


Figure 126: Residual-based diagnostics - Martingale plot

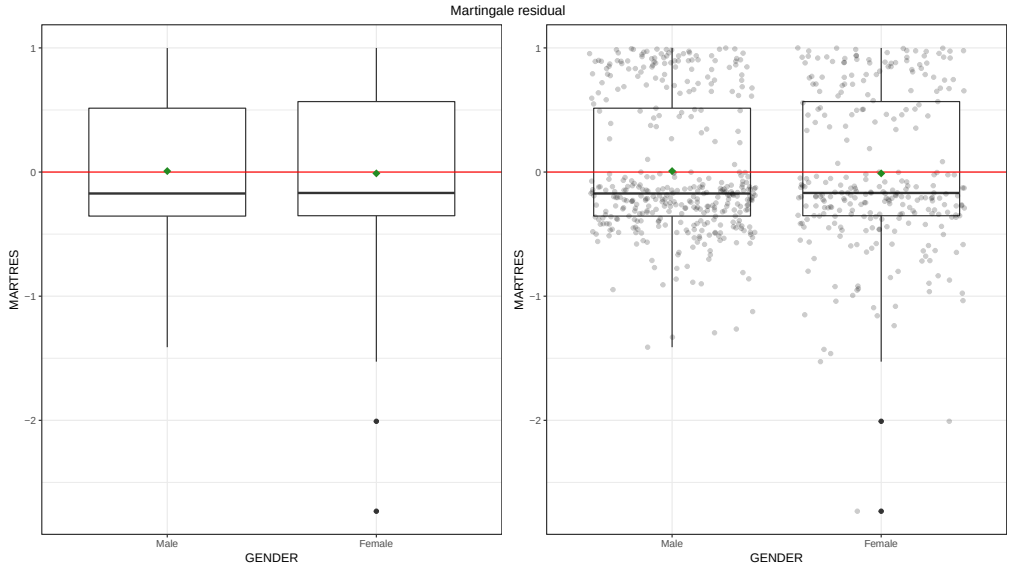


Figure 127: Residual-based diagnostics - Martingale plot

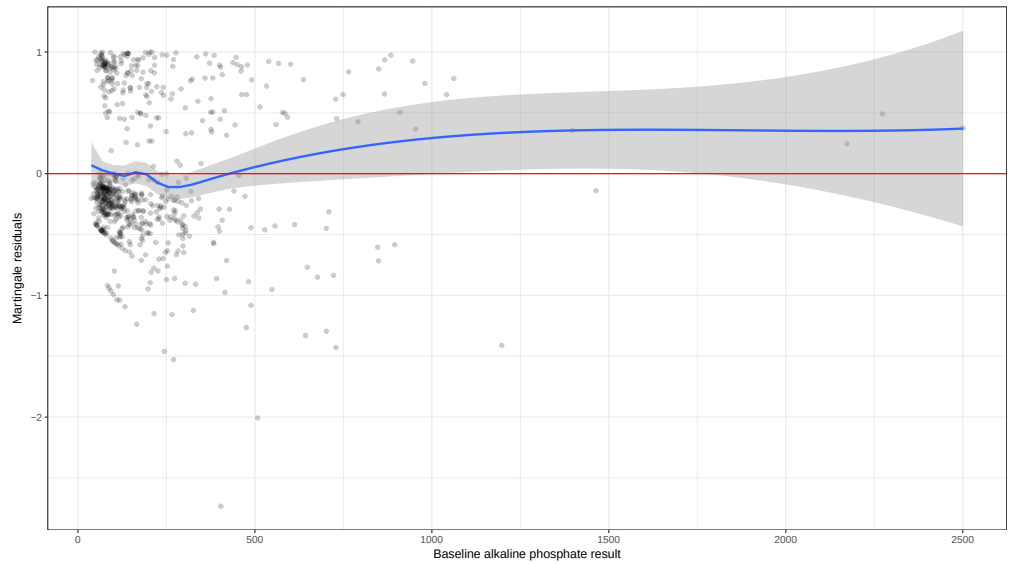
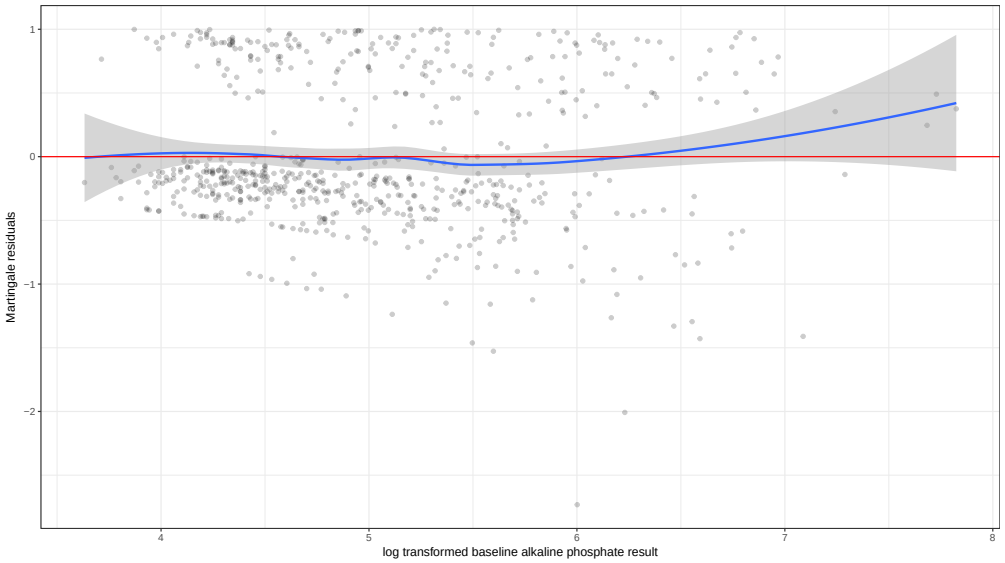
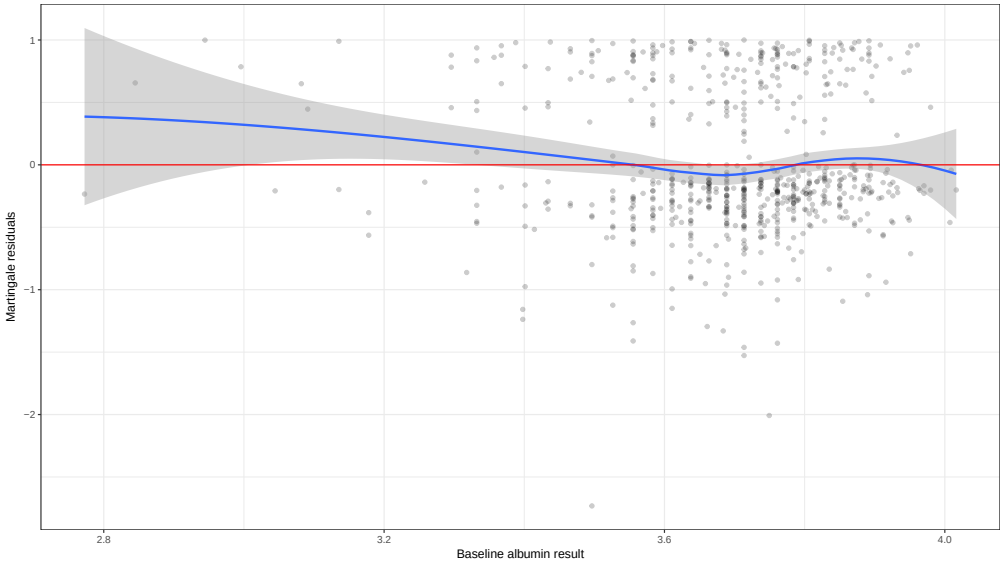


Figure 128: Residual-based diagnostics - Martingale plot


Martingale residuals
1
0
−1
−2
4
5
6
7
8
log transformed baseline alkaline phosphate result


Martingale residuals
1
0
−1
−2
2.8
3.2
3.6
4.0
Baseline albumin result

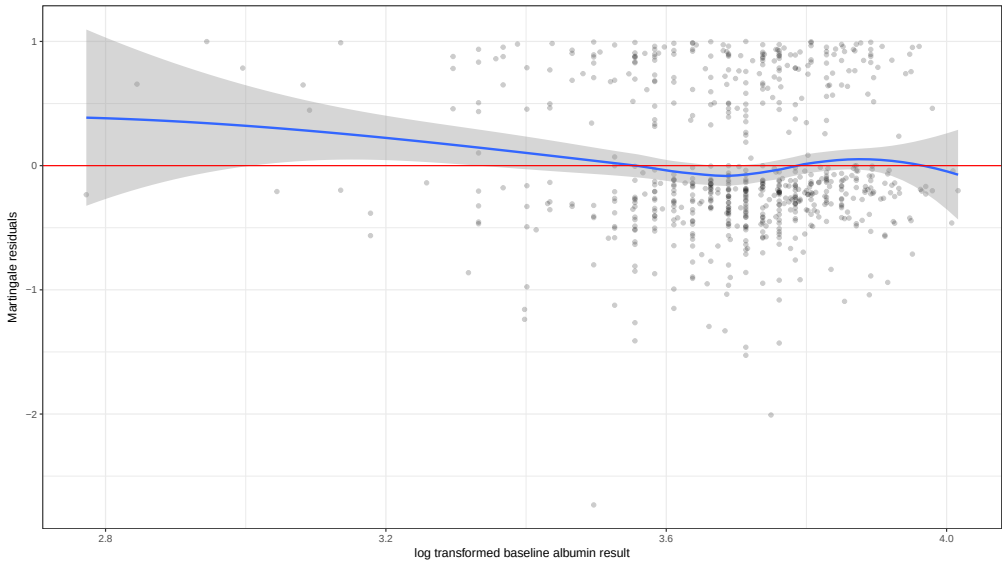


Figure 129: Residual-based diagnostics - Martingale plot

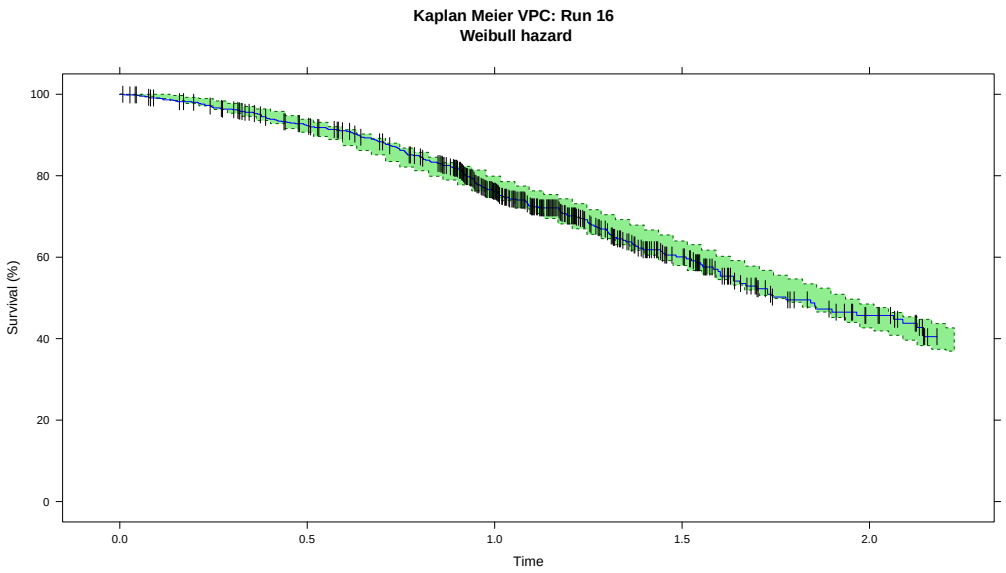


Figure 130: Simulation-based diagnostic

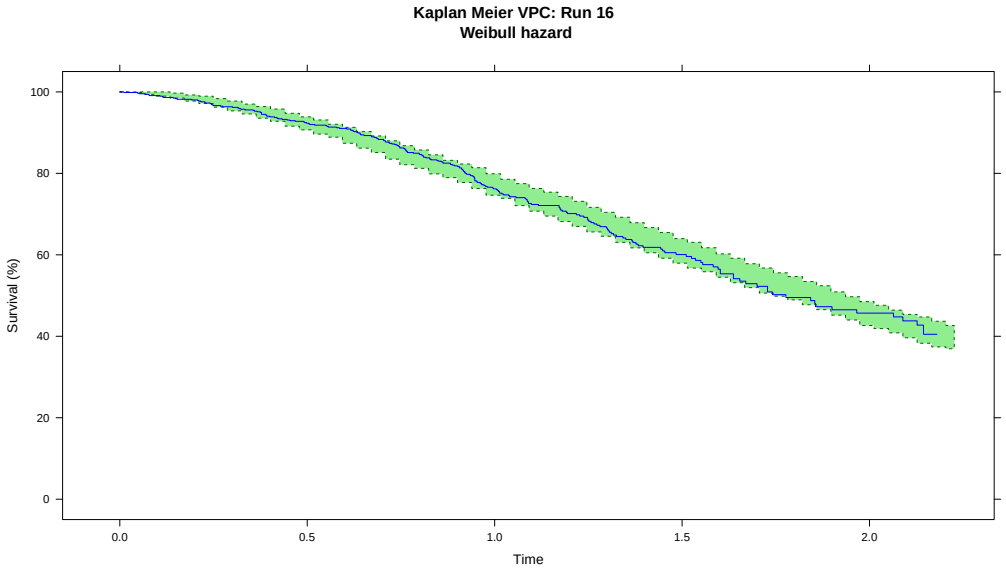


Figure 131: Simulation-based diagnostic

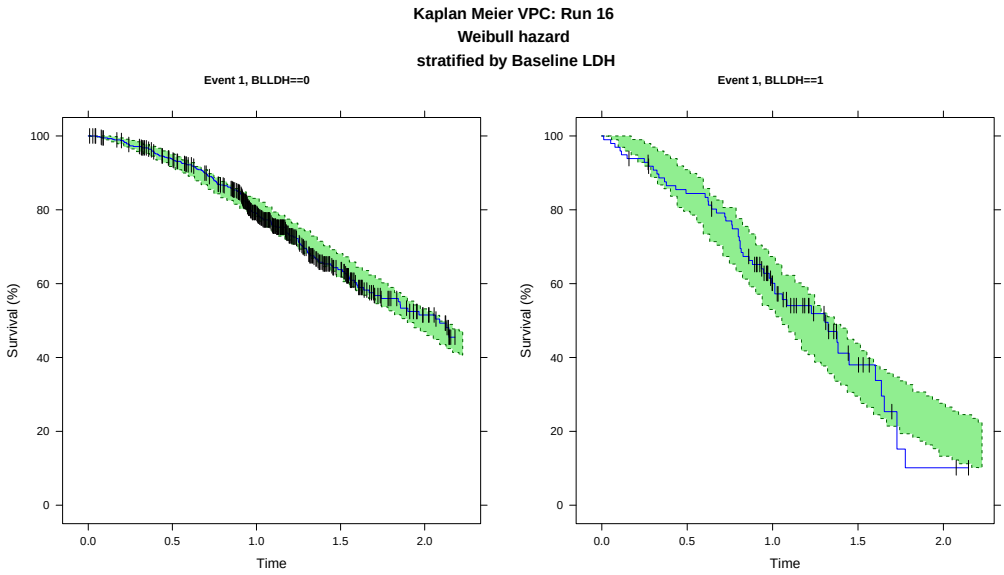


Figure 132: Simulation-based diagnostic - stratified by baseline LDH

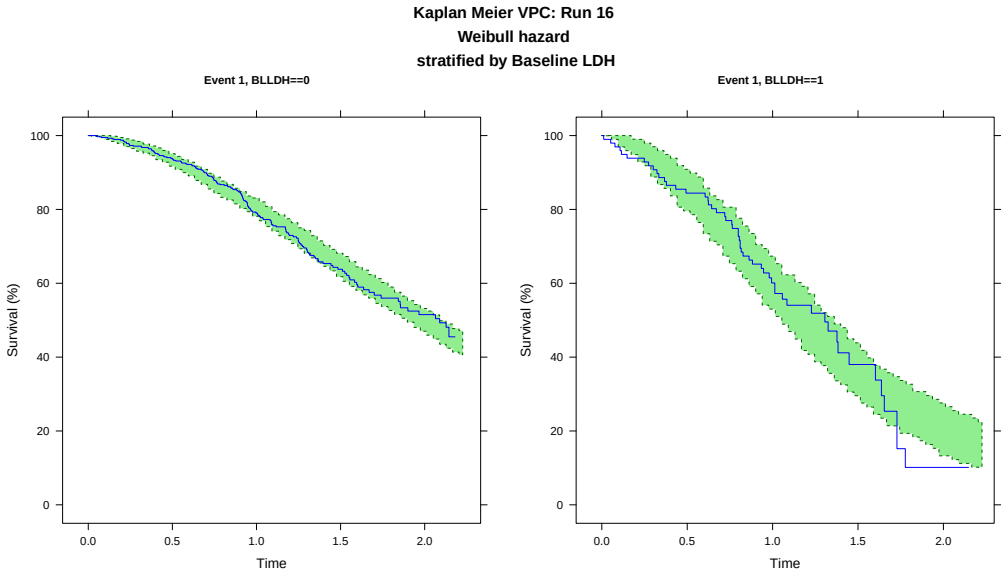


Figure 133: Simulation-based diagnostic - stratified by baseline LDH

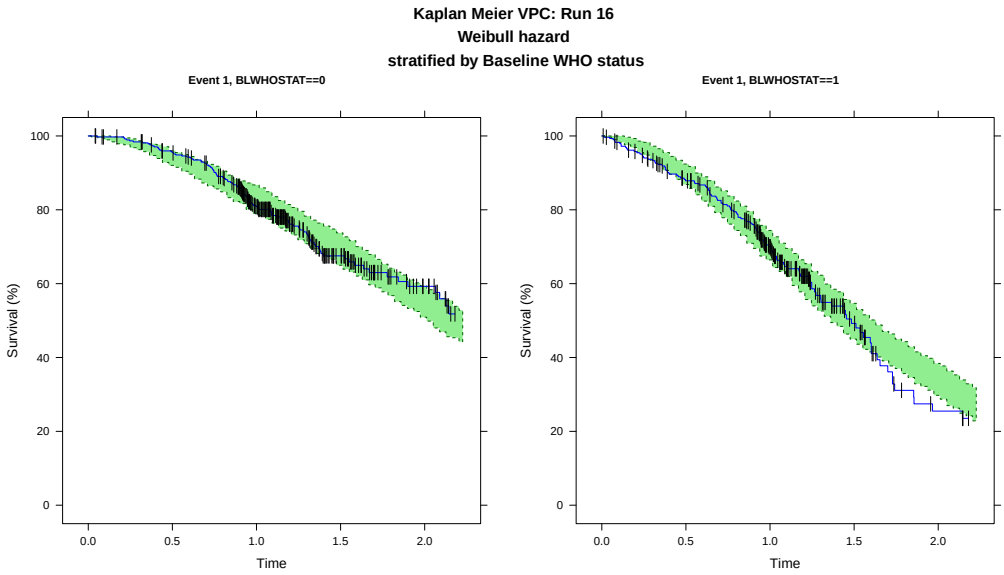


Figure 134: Simulation-based diagnostic - stratified by baseline WHO status

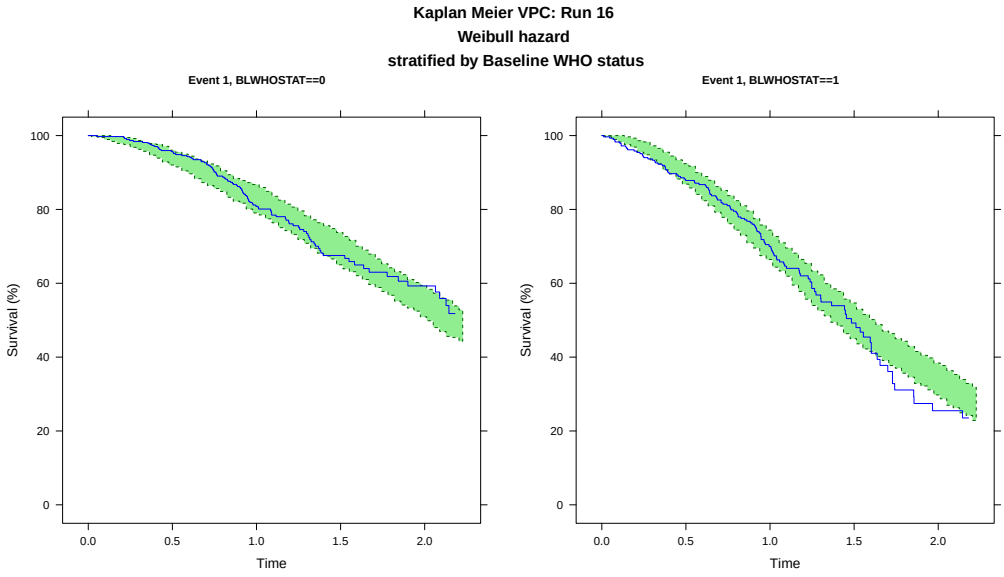


Figure 135: Simulation-based diagnostic - stratified by baseline WHO status

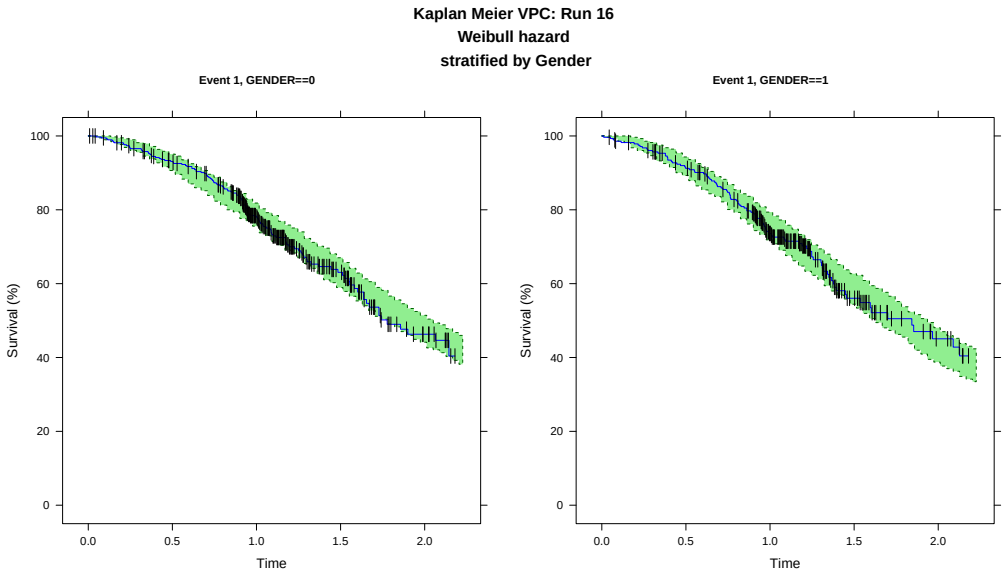


Figure 136: Simulation-based diagnostic - stratified by baseline Gender

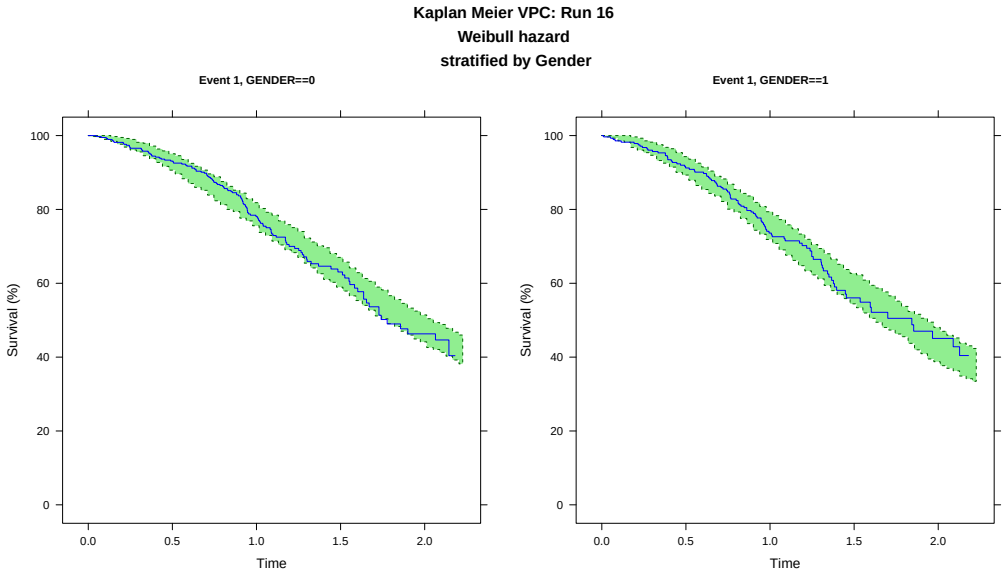


Figure 137: Simulation-based diagnostic - stratified by baseline Gender

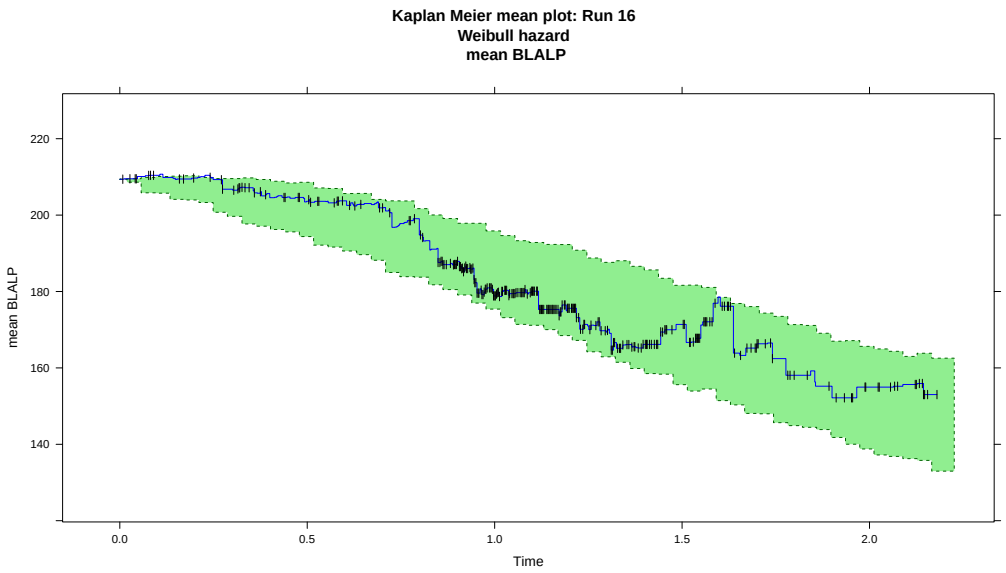


Figure 138: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

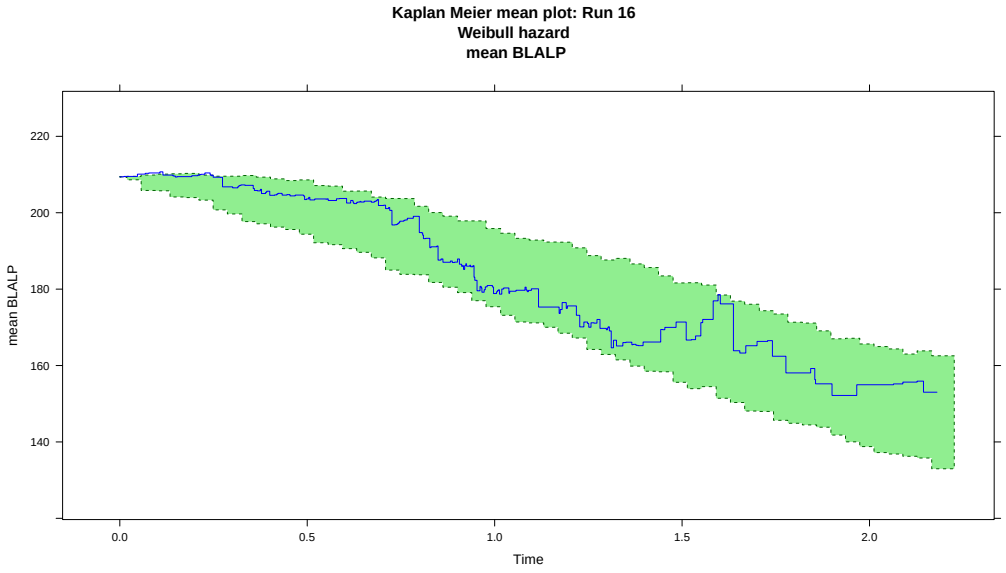


Figure 139: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

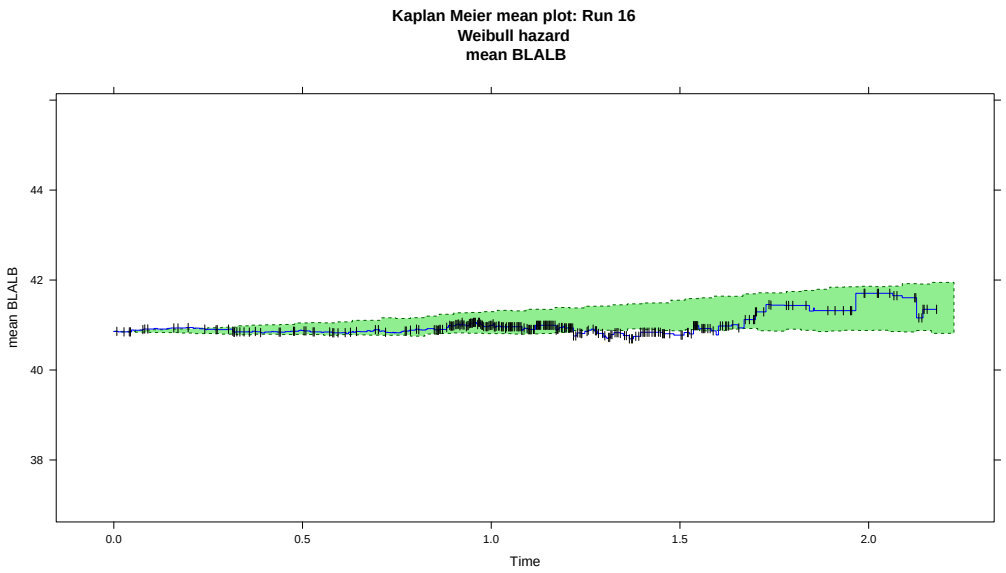


Figure 140: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

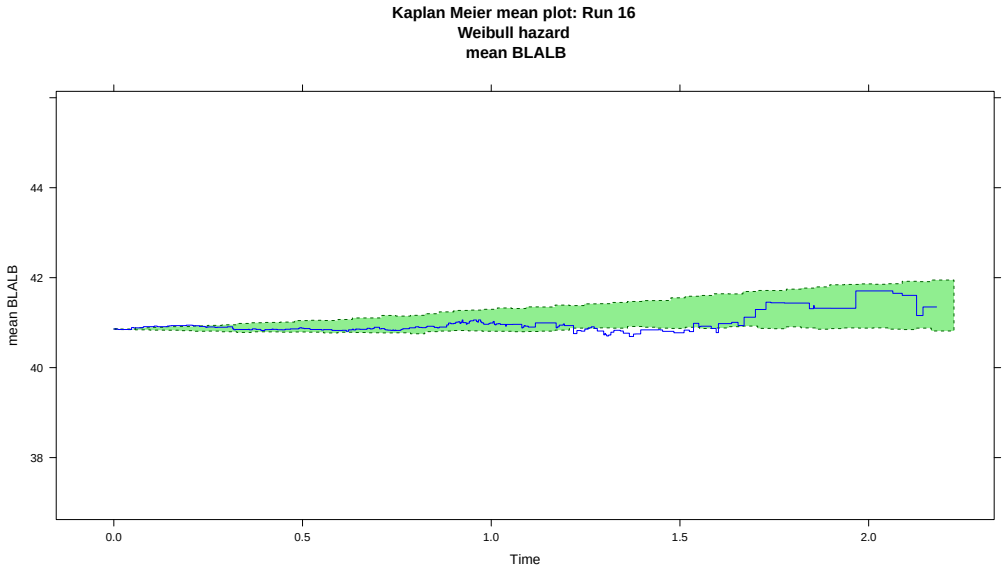


Figure 141: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

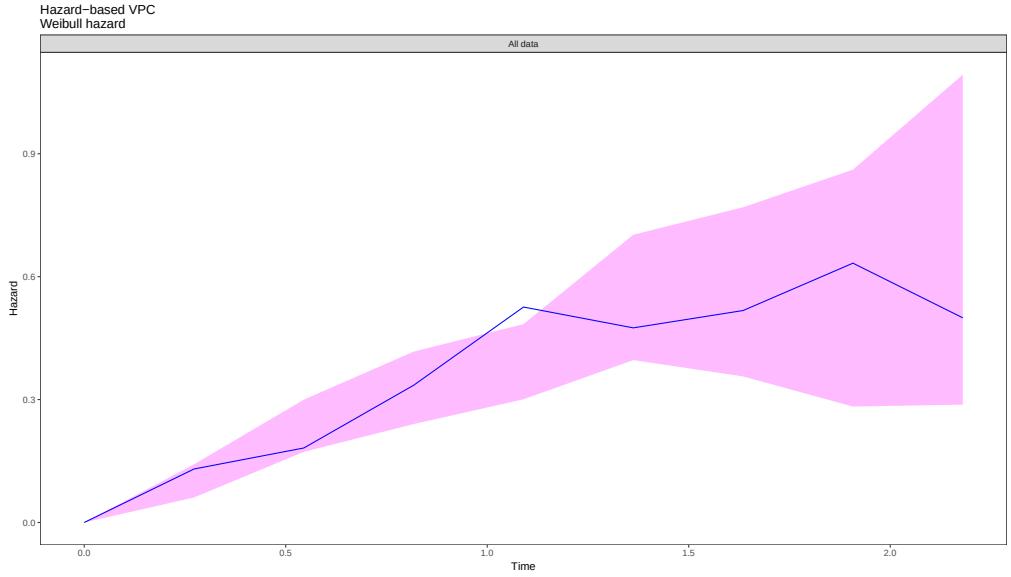


Figure 142: Simulation-based diagnostic: Hazard based VPC

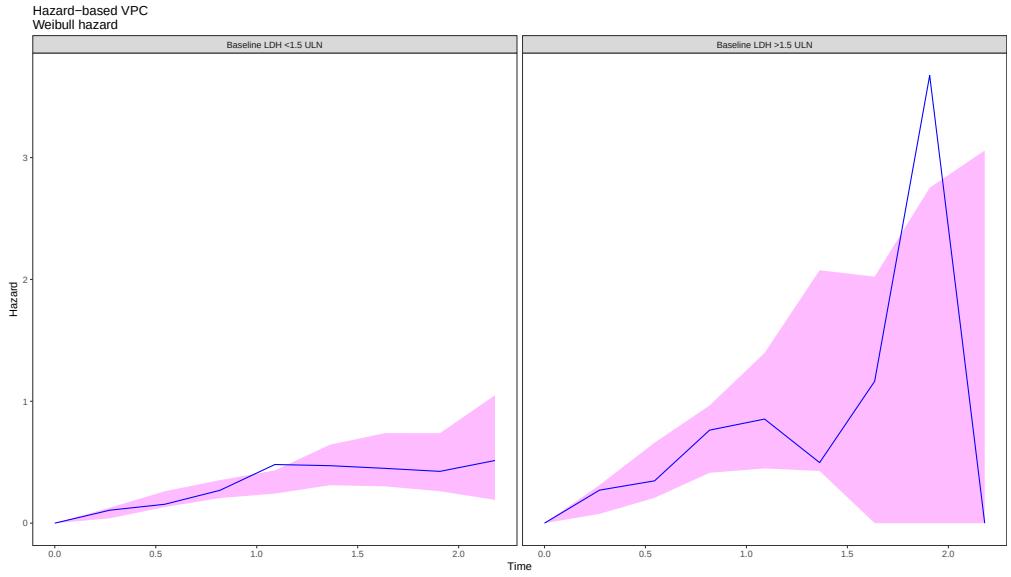


Figure 143: Simulation-based diagnostic: Hazard based VPC

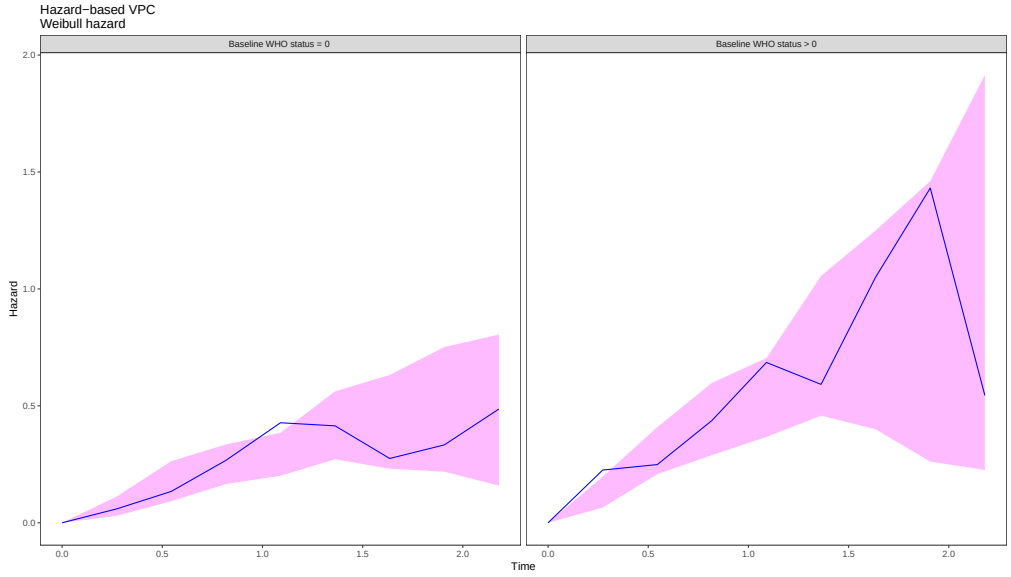


Figure 144: Simulation-based diagnostic: Hazard based VPC

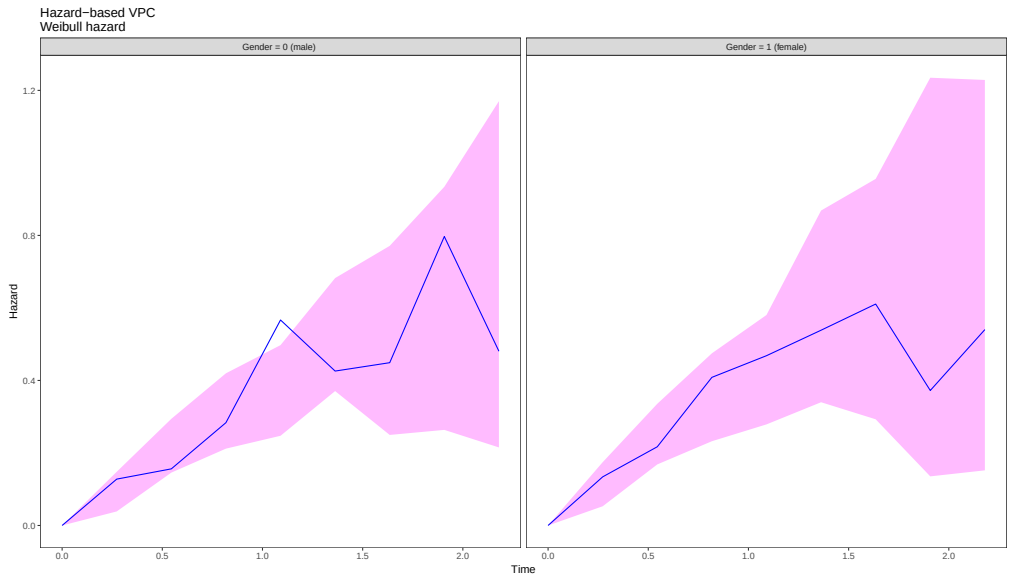


Figure 145: Simulation-based diagnostic: Hazard based VPC

11.2 Log-logistic hazard model (base and final)

11.2.1 Run 17 - base model

```
# next.mod(16,17,nm.dir)
show.mod(17, nm.dir) # print model
```

```
## ;; 1. Based on: 13
## ;; 2. Description:
## ;;    Base model
## ;; 3. Label:
## ;;    Log logistic hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;;     NA
## ;; 6. Interindividual variability:
## ;;    NA
## ;; 7. Interoccasion variability:
## ;;    NA
## ;; 8. Residual variability:
## ;;    NA
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    Base TTE model - Project DataSphere # 78 - no missing LDH
##
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM LOGBLALP LOGBLALB
##
## ;----------------------------------------------------data description
## ; ID, subject identifier
## ; TIME, in years
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
## ; CENS, censored event, 0 = no, 1 = yes
## ; MAXT, last recorded event per patient (either death or censor)
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
## ; GENDER, bianry covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
## ; OSTIM, observed time in days to event or censor time
## ; LOGBLALP, log (BLALP)
## ; LOGBLALB, log (BLALB)
```

```
## ;----------------------------------------------------
##
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2_1.csv IGNORE=@
##
## IGNORE(NOLDH.EQ.1) ; 24 patients missing BL_LDH data
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
## ;IGNORE=(STIME.EQ.0) ; observed time, ignore for simulation
## ;Sim_end
##
## $SUBROUTINE ADVAN=13 TOL=9
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##
##  DELTA = THETA(1)* EXP(ETA(1))
##  GAMMA = THETA(2)
##
## ; MEANLOGBLALP = 5.013
## ; MEIDANLOGBLALP =  4.875
##
## ;;========================= DIFFERENTIAL EQUATIONS ==================================
## ; Typical Value Log-logistic hazard
## ; h0(t) = exp(delta) kt^(k-1) / (1+ exp(delta)*t^k)
## ; where k = gamma
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = EXP(DELTA)*GAMMA*(T+DEL)**(GAMMA-1) / (1 + EXP(DELTA)*(T+DEL)**GAMMA)
##
## DADT(1) = BASE
##
## ;;================================ MODEL FIT ==================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
##
## ;------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=EXP(DELTA)*GAMMA*(TIME+DELX)**(GAMMA-1) / (1 + EXP(DELTA)*(TIME+DELX)**GAMMA)
##  HAZNOW= BASEX
```

```
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
##
## ;;================================= RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
## ;;================================= SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES =====================================
##
## $THETA   -3.8 ; delta
##  (0,1.71) ; gamma
##
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_17
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
##
## ;;================================= TABLES ================================
```

```
## $TABLE      NOPRINT ONEHEADER FILE=mytab17 ID TIME DV EVID MDV PRED
##             CHZ SUR HAZNOW MARTRES DEVRES NOLDH BLAGE BASE
##             BASEX DELTA GAMMA BLLDH BLWHOSTAT BLALB BLALP BLWHOLEVEL
##             GENDER OSTIM
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab17 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab17 ID DELTA GAMMA
##             ETAS(1:LAST)
```

```
## NULL
```

11.2.1.1 Run summary

```
##  [1] "-------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run17/run
##  [4] ""
##  [5] "Successful minimization                                          [    OK   ]   "
##  [6] "No rounding errors                                               [    OK   ]   "
##  [7] "No zero gradients                                                [    OK   ]   "
##  [8] "No final zero gradients                                          [    OK   ]   "
##  [9] "Hessian not reset                                                [    OK   ]   "
## [10] "No parameter near boundary                                       [    OK   ]   "
## [11] "Covariance step                                                  [    OK   ]   "
## [12] ""
## [13] "Condition number                                                 [    OK   ]   "
## [14] "Correlations                                                     [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:15"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   45.82"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   1.34"
## [19] ""
## [20] "Objective function value: 933.3475"
## [21] ""
## [22] "Condition number: 1.804"
## [23] ""
## [24] "Number of observation records: 666"
## [25] "Number of individuals: 666"
## [26] ""
## [27] "        THETA               OMEGA      SIGMA    "
## [28] "delta  -1.169   (0.0711)                        "
## [29] "gamma   1.852  (0.06772)                        "
## [30] ""
## [31] "The relative standard errors for omega and sigma are reported on the approximate"
## [32] "standard deviation scale (SE/variance estimate)/2."
## [33] "-------------------------------------------------------------------------"
```

11.2.1.2 Diagnostic plots

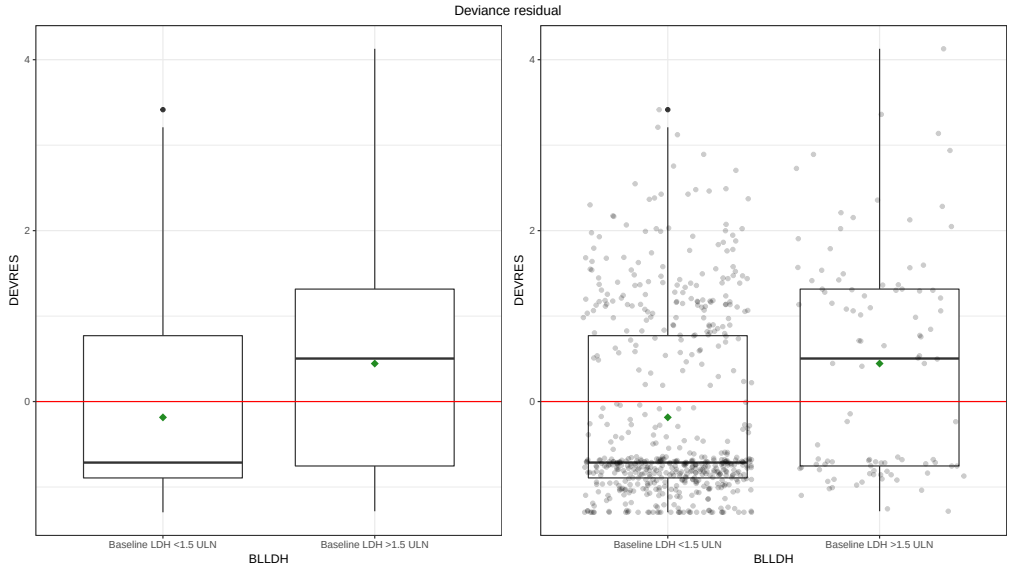


Figure 146: Residual-based diagnostics - Deviance plot

- zero reference line (red) ; mean residuals (green diamond)

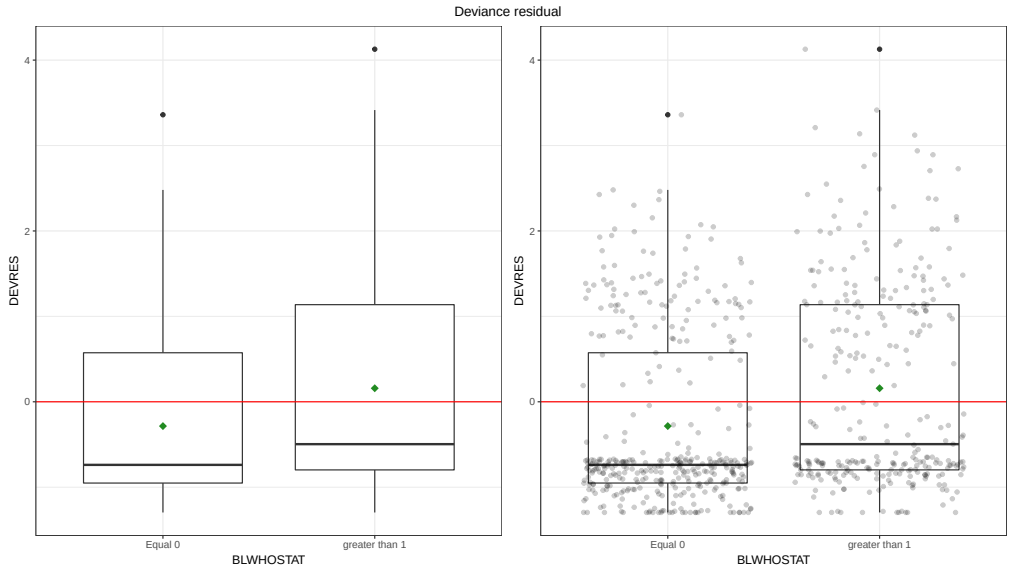


Figure 147: Residual-based diagnostics - Deviance plot

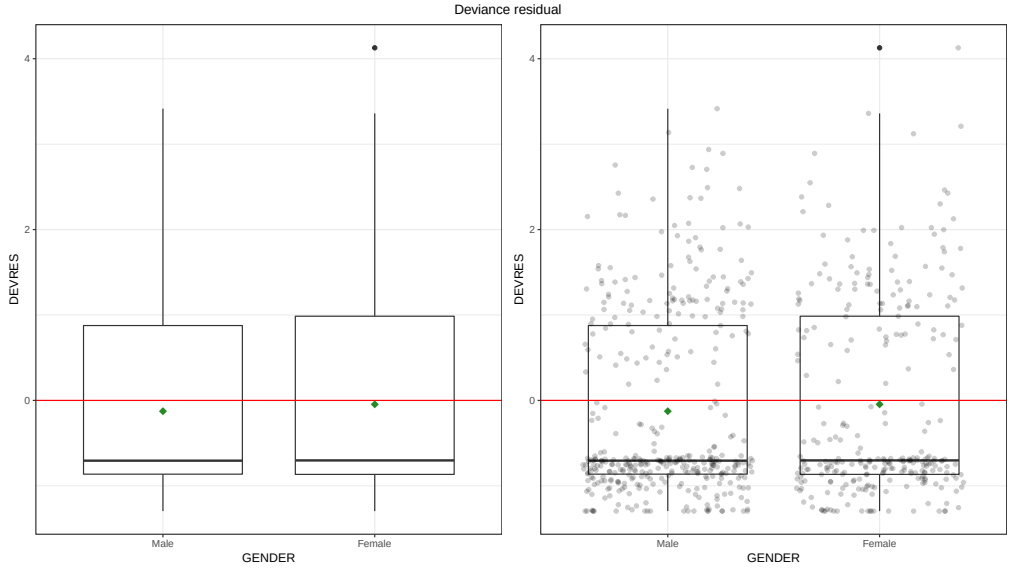


Figure 148: Residual-based diagnostics - Deviance plot

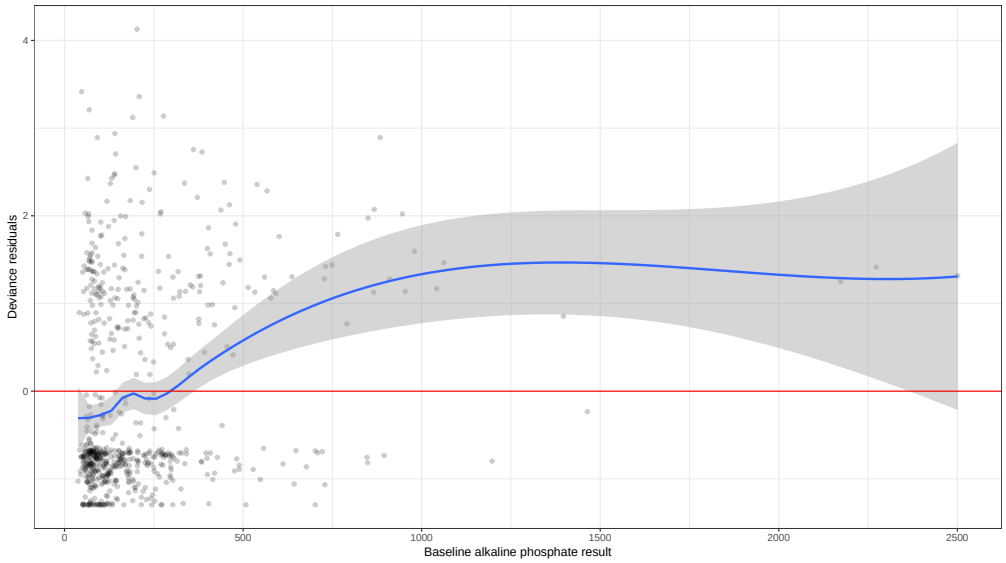


Figure 149: Residual-based diagnostics - Deviance plot

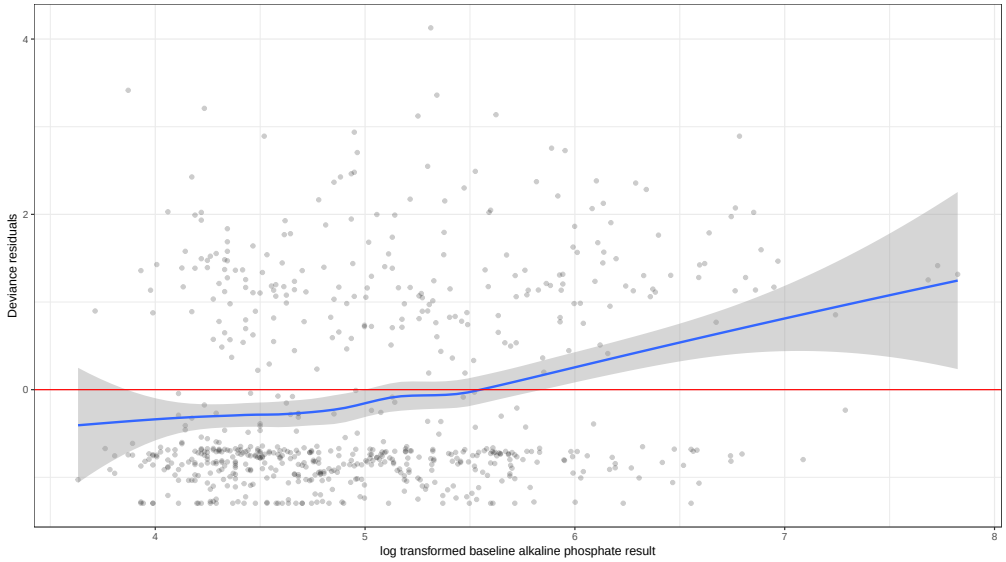


Figure 150: Residual-based diagnostics - Deviance plot

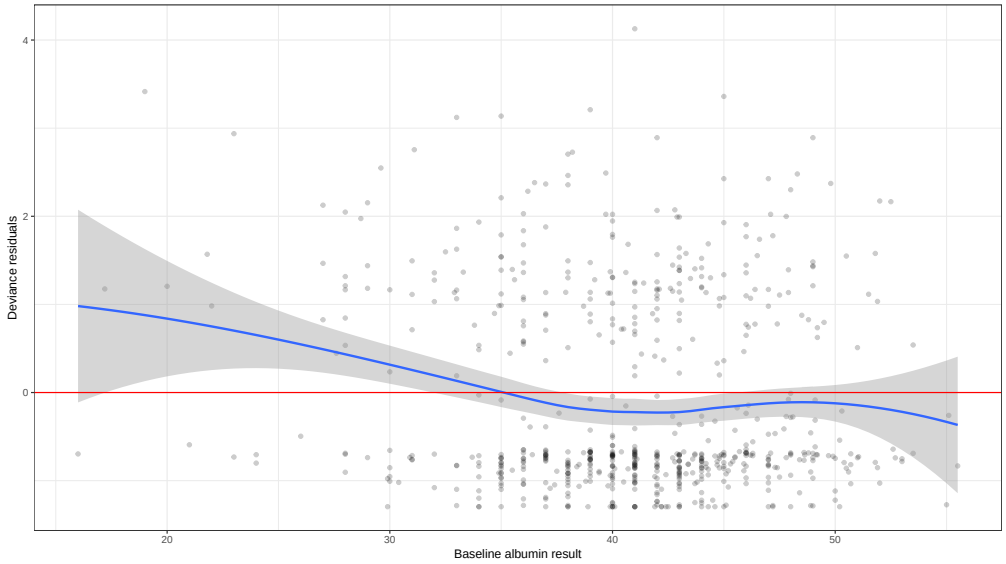


Figure 151: Residual-based diagnostics - Deviance plot

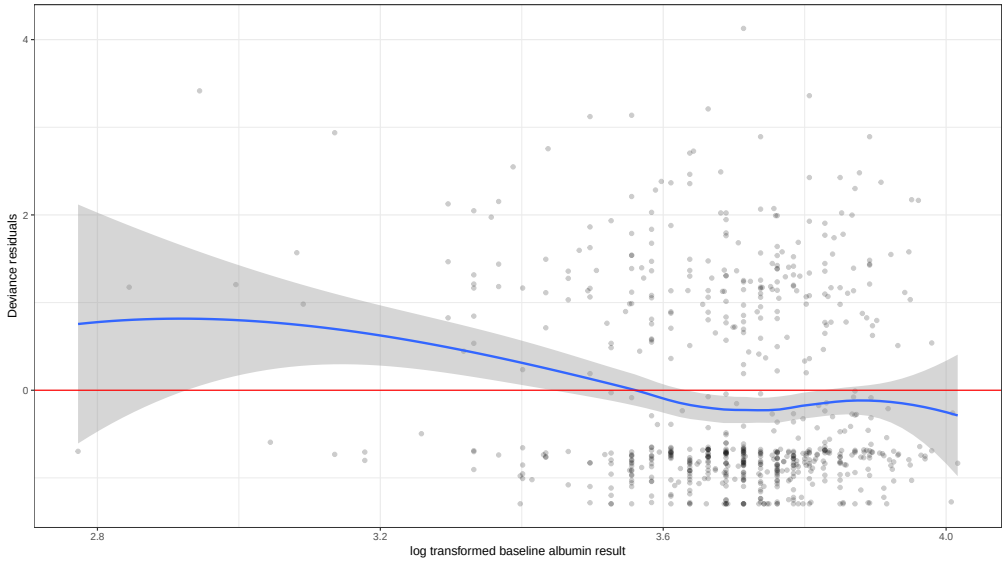


Figure 152: Residual-based diagnostics - Deviance plot

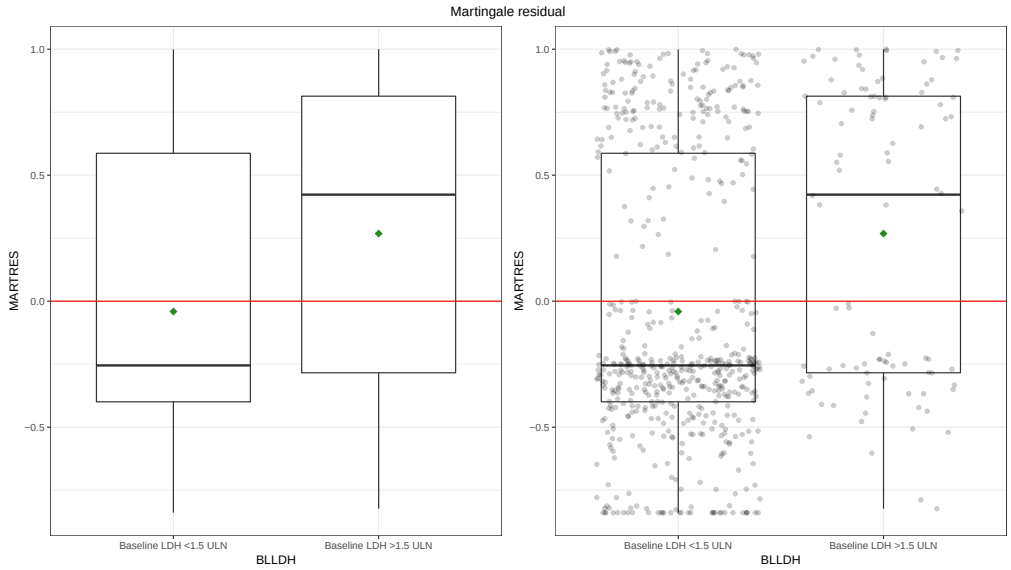


Figure 153: Residual-based diagnostics - Martingale plot

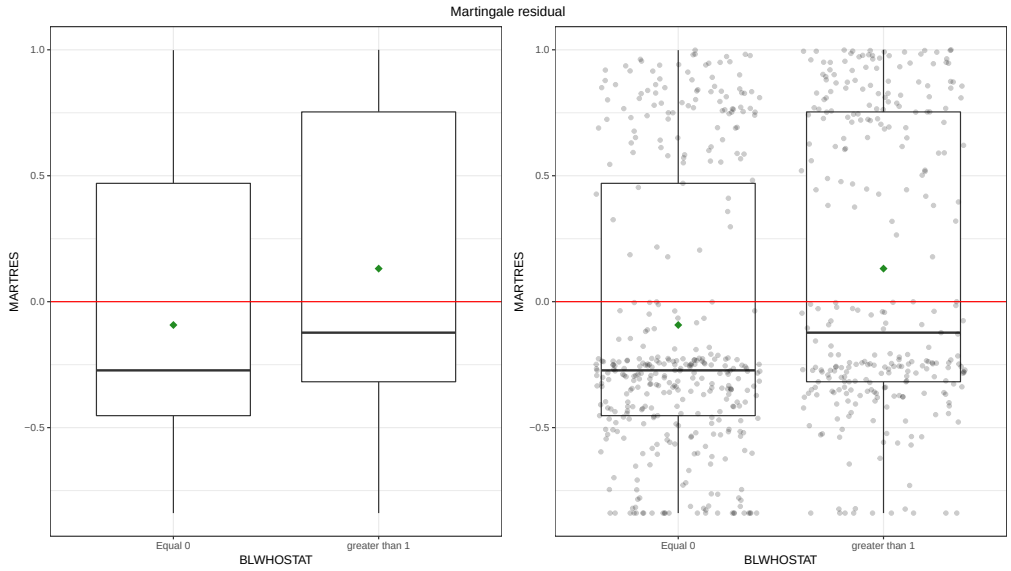


Figure 154: Residual-based diagnostics - Martingale plot

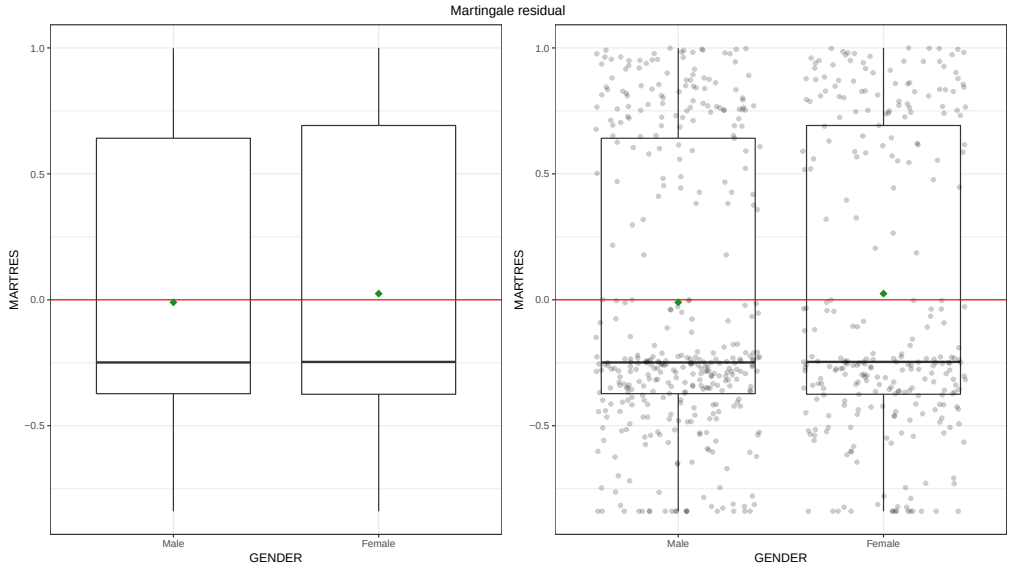


Figure 155: Residual-based diagnostics - Martingale plot

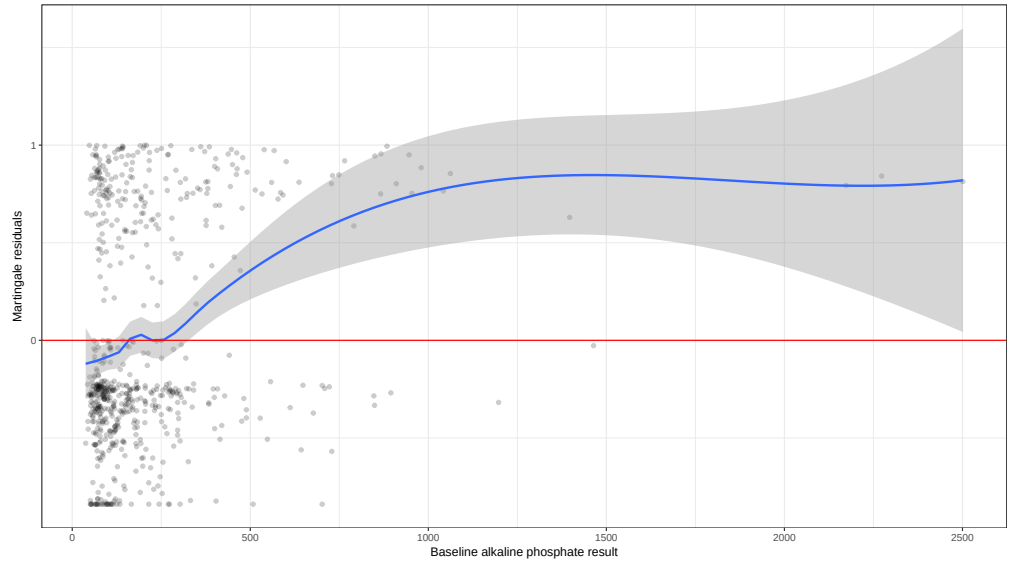
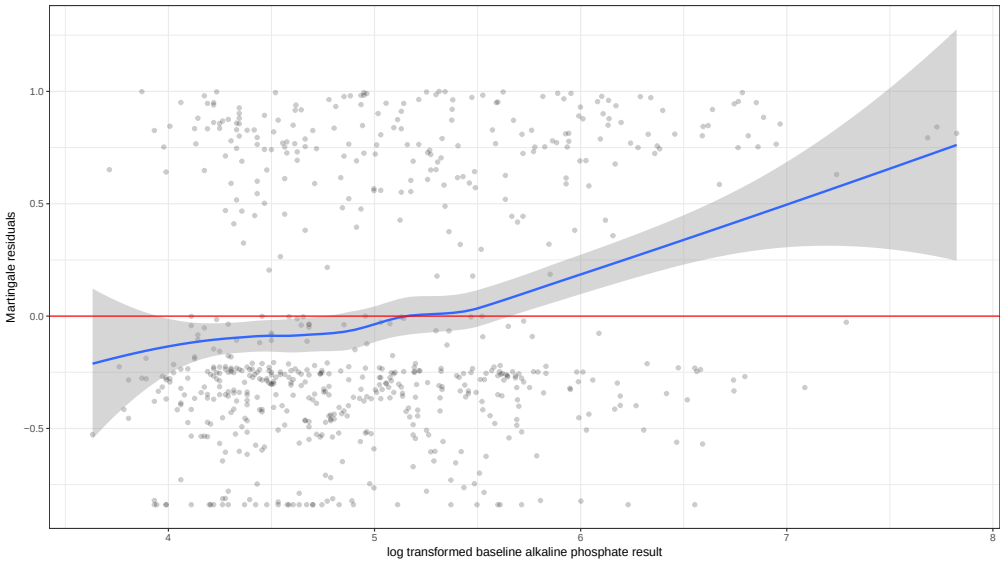
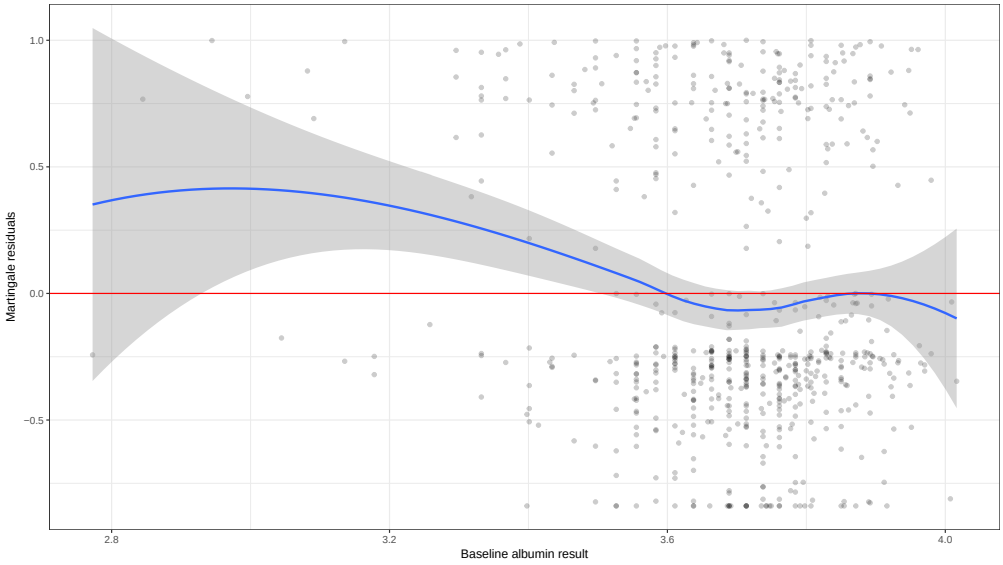


Figure 156: Residual-based diagnostics - Martingale plot


Martingale residuals
1.0
0.5
0.0
−0.5
4
5
6
7
8
log transformed baseline alkaline phosphate result


Martingale residuals
1.0
0.5
0.0
−0.5
2.8
3.2
3.6
4.0
Baseline albumin result

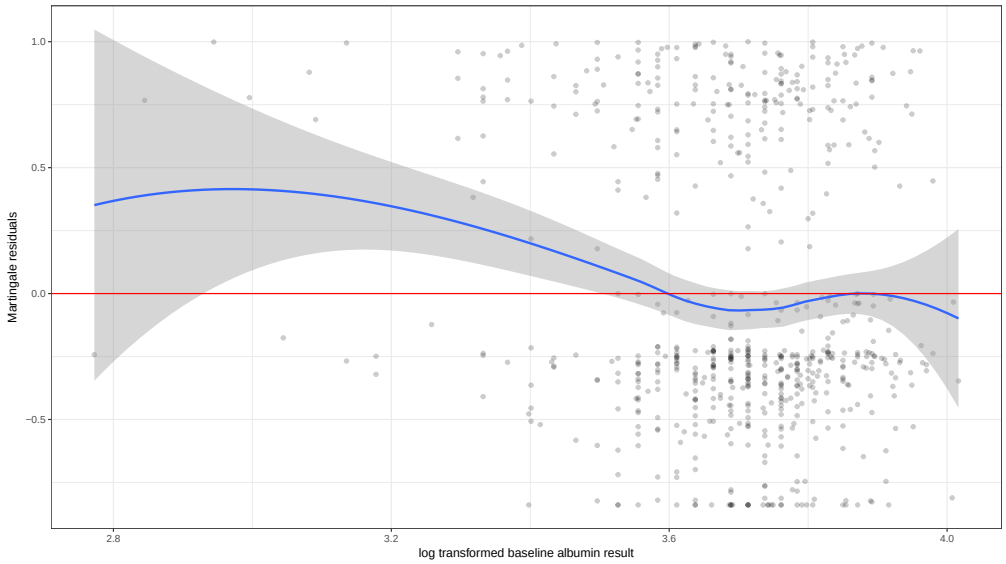


Figure 157: Residual-based diagnostics - Martingale plot

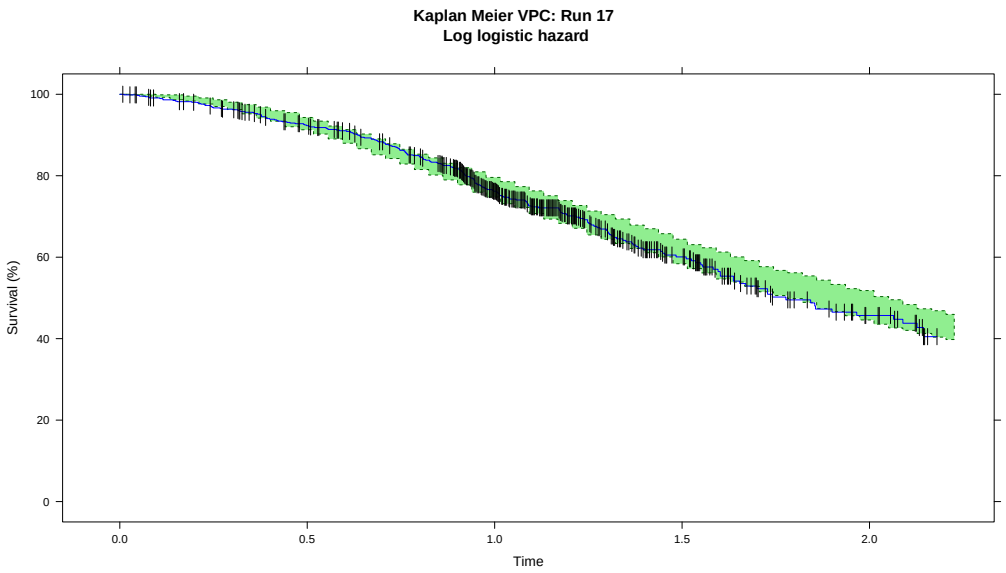


Figure 158: Simulation-based diagnostic

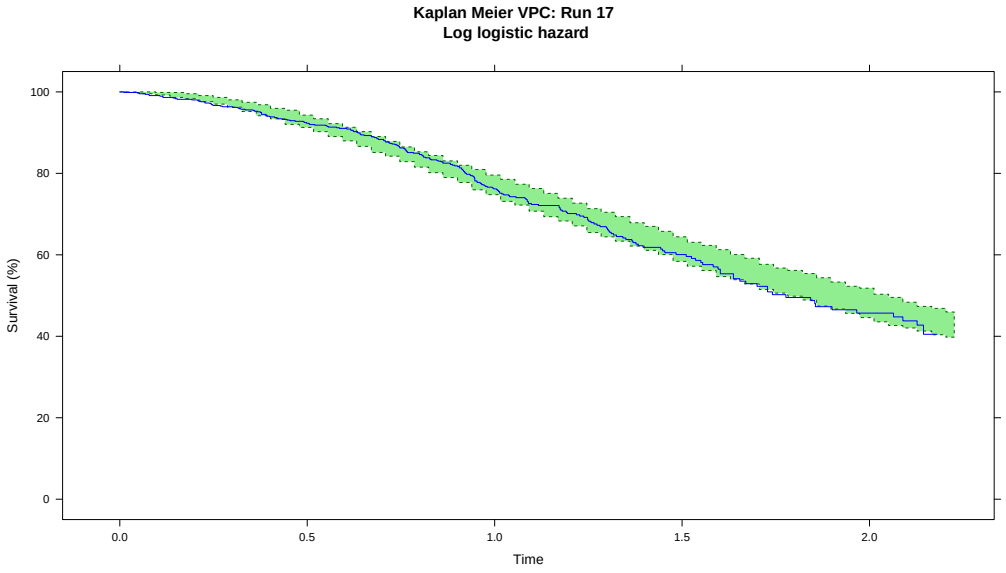


Figure 159: Simulation-based diagnostic

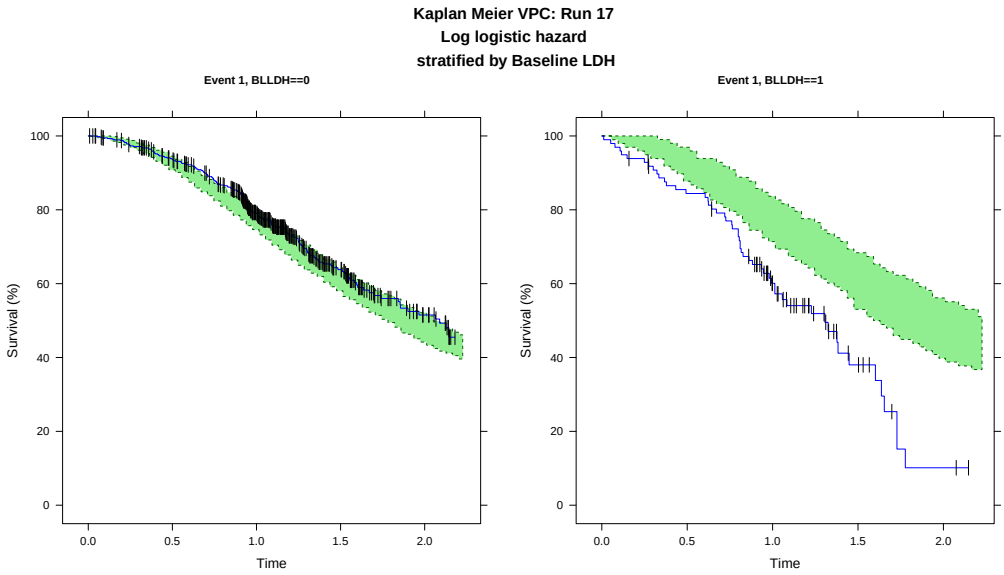


Figure 160: Simulation-based diagnostic - stratified by baseline LDH

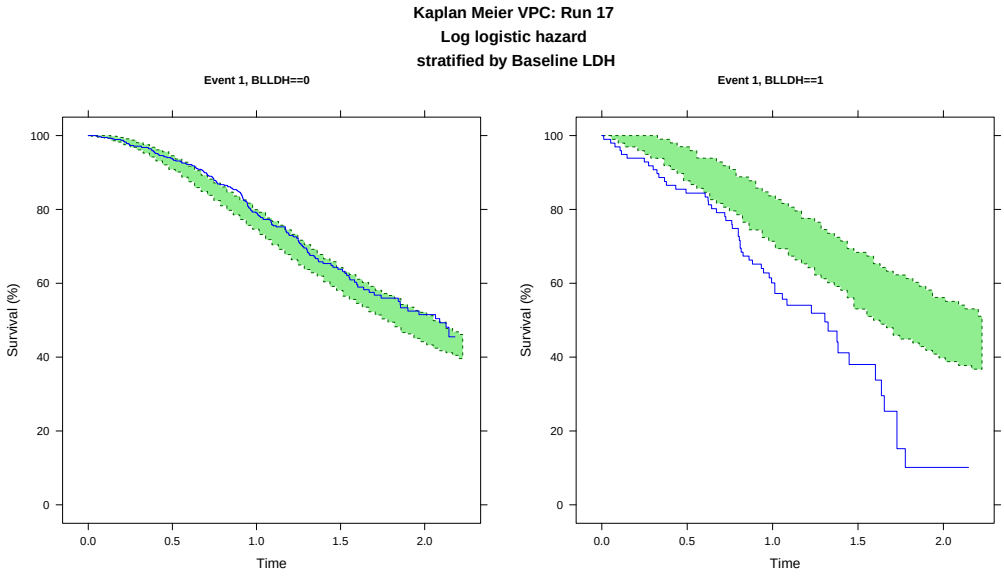


Figure 161: Simulation-based diagnostic - stratified by baseline LDH

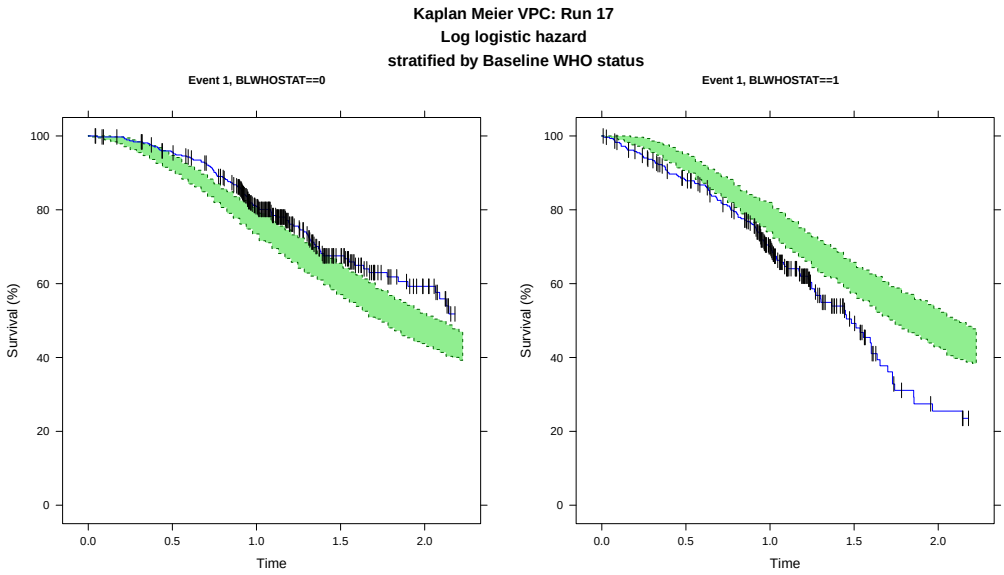


Figure 162: Simulation-based diagnostic - stratified by baseline WHO status

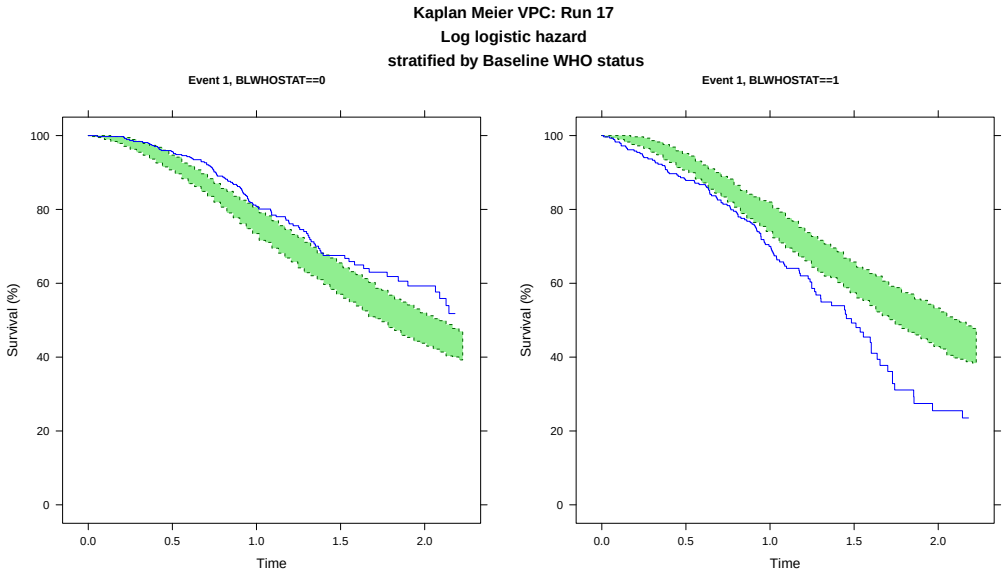


Figure 163: Simulation-based diagnostic - stratified by baseline WHO status

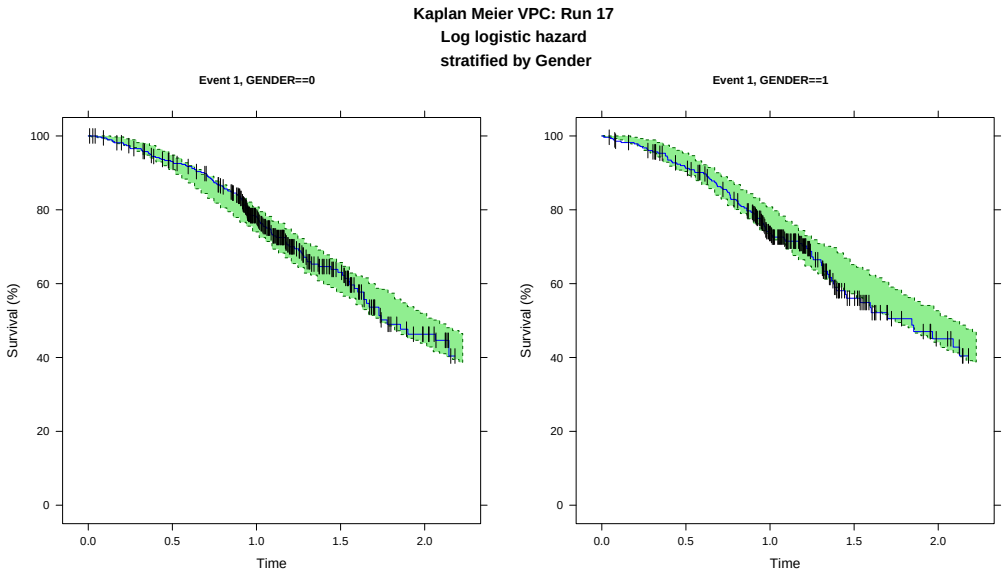


Figure 164: Simulation-based diagnostic - stratified by baseline Gender

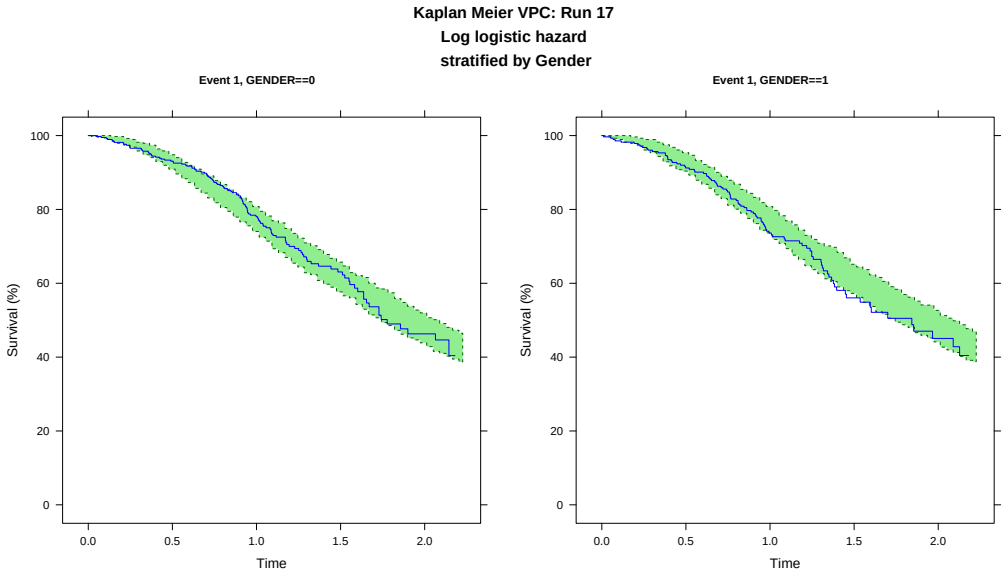


Figure 165: Simulation-based diagnostic - stratified by baseline Gender

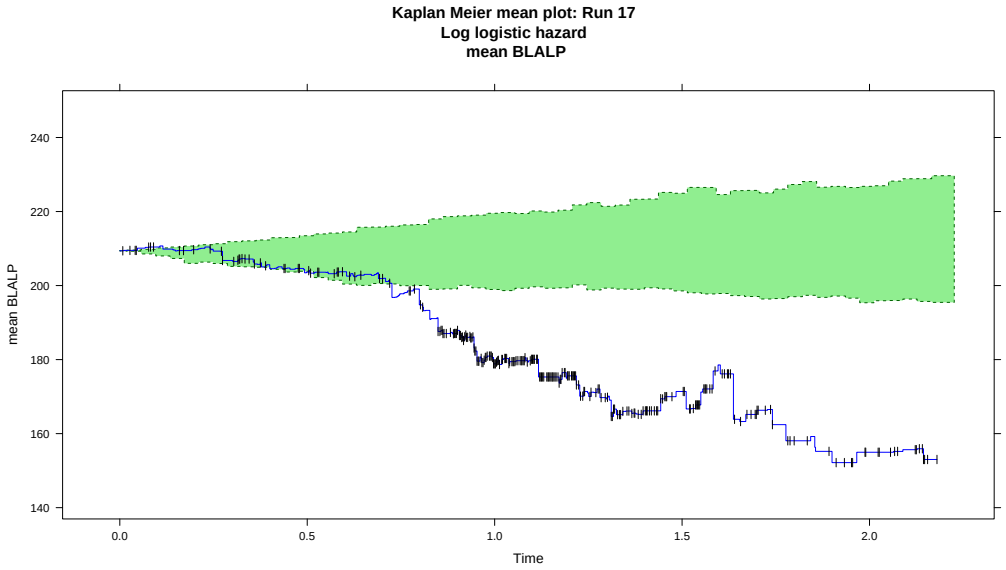


Figure 166: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

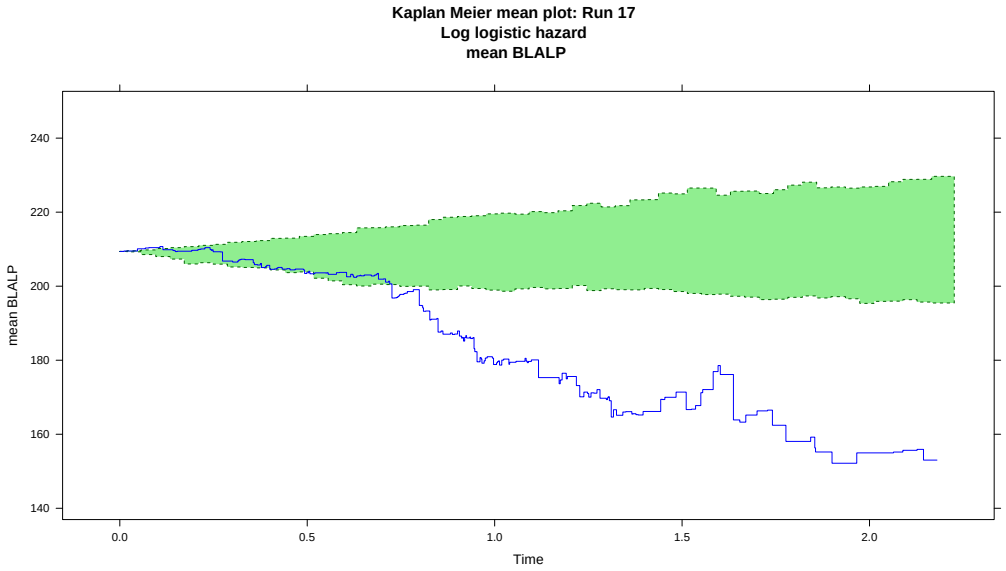


Figure 167: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

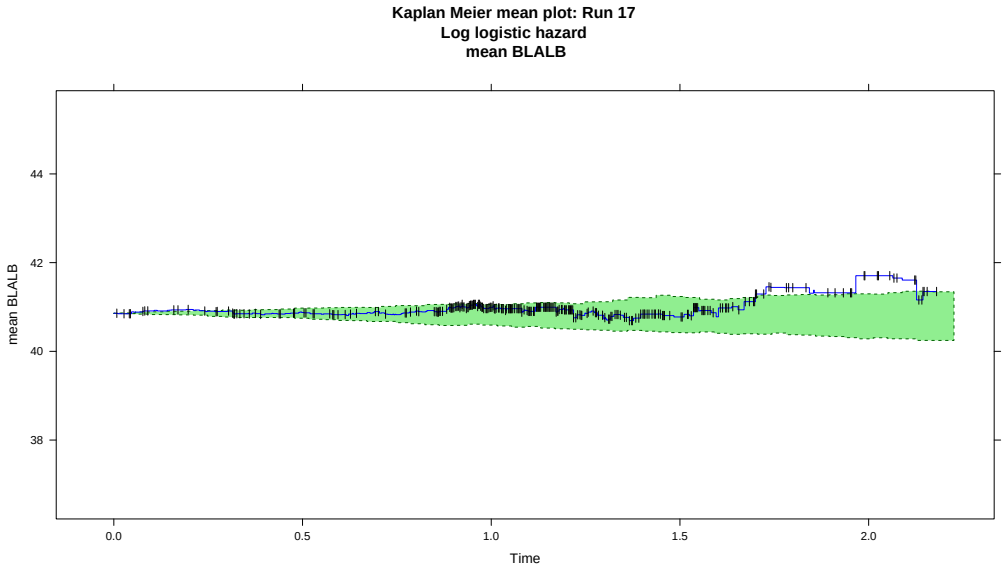


Figure 168: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

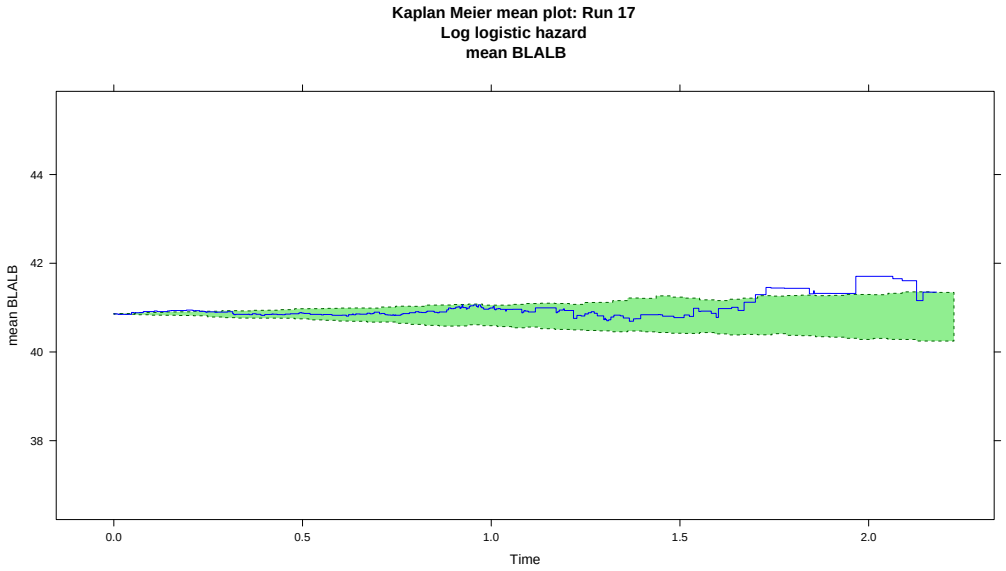


Figure 169: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

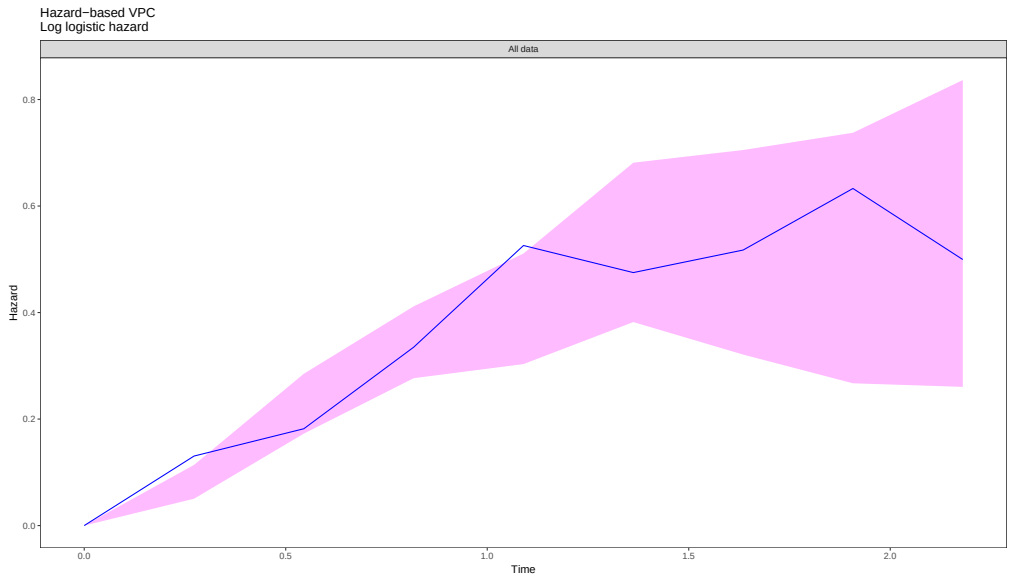


Figure 170: Simulation-based diagnostic: Hazard based VPC

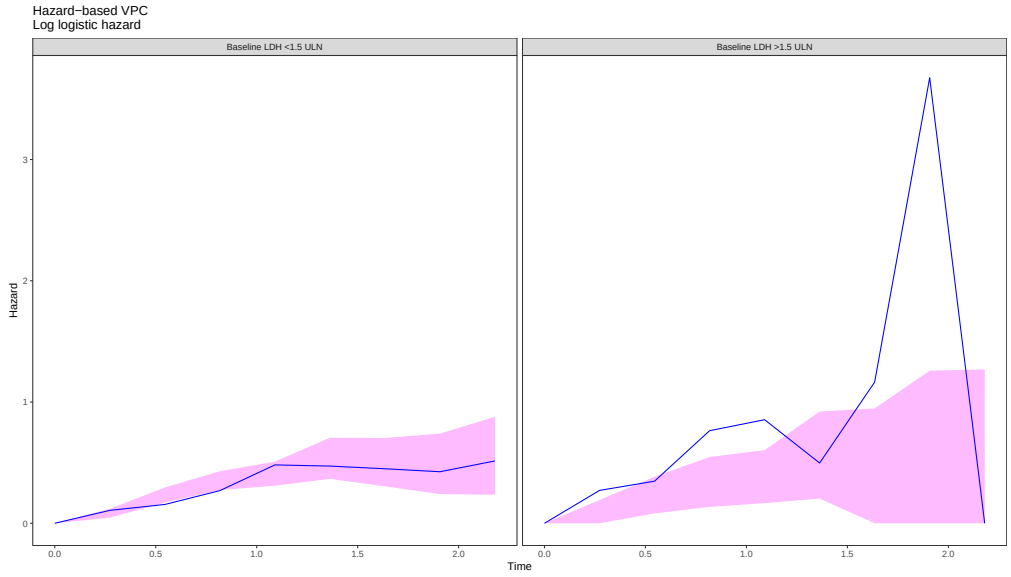


Figure 171: Simulation-based diagnostic: Hazard based VPC

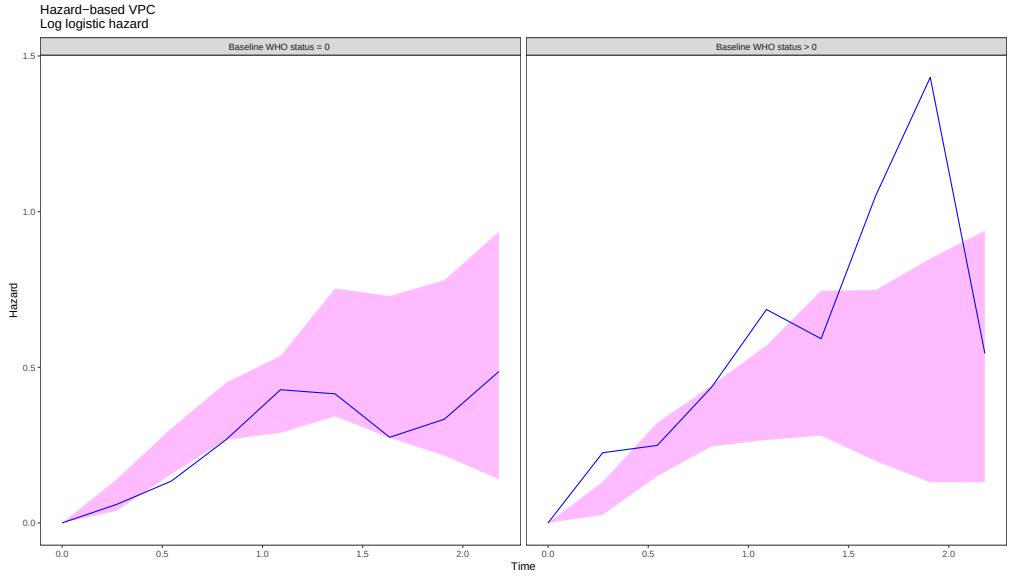


Figure 172: Simulation-based diagnostic: Hazard based VPC

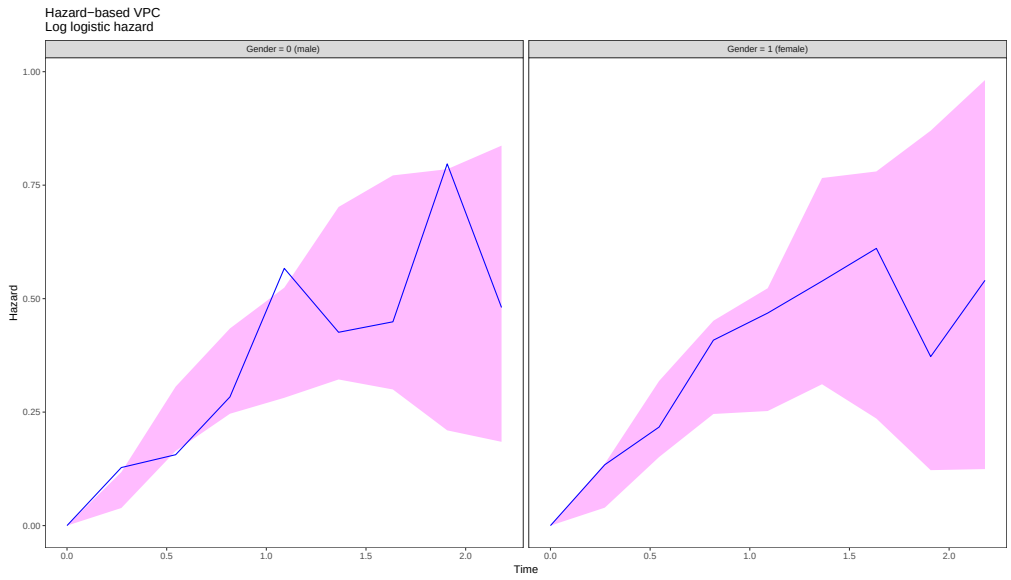


Figure 173: Simulation-based diagnostic: Hazard based VPC

11.2.2 Run 18 - covariate model

```
# next.mod(17,18,nm.dir)
show.mod(18, nm.dir) # print model
```

```
## ;; 1. Based on: 17
## ;; 2. Description:
## ;;    Covariate model
## ;; 3. Label:
## ;;    Log logistic hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;;     NA
## ;; 6. Interindividual variability:
## ;;    NA
## ;; 7. Interoccasion variability:
## ;;    NA
## ;; 8. Residual variability:
## ;;    NA
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
##
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
##
## $PROBLEM    Base TTE model - Project DataSphere # 78 - no missing LDH
##
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM LOGBLALP LOGBLALB
##
## ;-----------------------------------------------------data description
## ; ID, subject identifier
## ; TIME, in years
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
## ; CENS, censored event, 0 = no, 1 = yes
## ; MAXT, last recorded event per patient (either death or censor)
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
## ; GENDER, bianry covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
## ; OSTIM, observed time in days to event or censor time
## ; LOGBLALP, log (BLALP)
## ; LOGBLALB, log (BLALB)
```

```
## ;----------------------------------------------------
##
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2_1.csv IGNORE=@
##
## IGNORE(NOLDH.EQ.1) ; 24 patients missing BL_LDH data
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
## ;IGNORE=(STIME.EQ.0) ; observed time, ignore for simulation
## ;Sim_end
##
## $SUBROUTINE ADVAN=13 TOL=9
## $MODEL      COMP=(HAZARD)
##
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##
##  DELTA = THETA(1)* EXP(ETA(1))
##  GAMMA = THETA(2)
##  SLP1 = THETA(3)
##  SLP2 = THETA(4)
##
## MEANLOGBLALP = 5.013
## ; MEIDANLOGBLALP =  4.875
##
## ;;======================== DIFFERENTIAL EQUATIONS ==================================
## ; Typical Value Log-logistic hazard
## ; h0(t) = exp(delta) kt^(k-1) / (1+ exp(delta)*t^k)
## ; where k = gamma
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = EXP(DELTA)*GAMMA*(T+DEL)**(GAMMA-1) / (1 + EXP(DELTA)*(T+DEL)**GAMMA)
##
## ALP = SLP1*(LOGBLALP-MEANLOGBLALP)   ; normalized baseline ALP effect  - mean
##
## LDH = SLP2*BLLDH ; effect of LDH > 1.5 ULN
##
## DADT(1) = BASE * EXP(ALP + LDH)
##
## ;;================================ MODEL FIT ==================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
##
## ;------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
```

```
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=EXP(DELTA)*GAMMA*(TIME+DELX)**(GAMMA-1) / (1 + EXP(DELTA)*(TIME+DELX)**GAMMA)
##  ALPX = SLP1*(LOGBLALP-MEANLOGBLALP) ; normalized baseline ALP effect  - mean
##  LDHX = SLP2*BLLDH   ; effect of LDH > 1.5 ULN
##  HAZNOW= BASEX * EXP(ALPX + LDHX)
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
##
## ;;================================= RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
## ;;================================= SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES =====================================
##
## $THETA  -1.17 ; delta
##  (0,1.85) ; gamma
##  0.466 ; slope1 ALP
##  0.463 ; slope2  LDH
##
```

```
## $OMEGA  0  FIX  ; place holder
## ;;============================ ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_18
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
##
## ;;============================== TABLES ==============================
## $TABLE      NOPRINT ONEHEADER FILE=mytab18 ID TIME DV EVID MDV PRED
##             CHZ SUR HAZNOW MARTRES DEVRES NOLDH BLAGE BASE BASEX DELTA
##             GAMMA BLLDH BLWHOSTAT BLALB BLALP BLWHOLEVEL GENDER OSTIM
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab18 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab18 ID DELTA GAMMA
##             ETAS(1:LAST)
## NULL
```

11.2.2.1 Run summary

```
##  [1] "-------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run18/run
##  [4] ""
##  [5] "Successful minimization                                          [    OK   ]   "
##  [6] "No rounding errors                                               [    OK   ]   "
##  [7] "No zero gradients                                                [    OK   ]   "
##  [8] "No final zero gradients                                          [    OK   ]   "
##  [9] "Hessian not reset                                                [    OK   ]   "
## [10] "No parameter near boundary                                       [    OK   ]   "
## [11] "Covariance step                                                  [    OK   ]   "
## [12] ""
## [13] "Condition number                                                 [    OK   ]   "
## [14] "Correlations                                                     [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:11:44"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   465.02"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   4.74"
## [19] ""
## [20] "Objective function value: 887.1535"
## [21] ""
## [22] "Condition number: 4.559"
## [23] ""
## [24] "Number of observation records: 666"
## [25] "Number of individuals: 666"
## [26] ""
## [27] "              THETA               OMEGA      SIGMA    "
## [28] "      delta  -1.329  (0.07016)                        "
## [29] "      gamma   1.885  (0.06791)                        "
## [30] " slope1 ALP  0.4579   (0.1994)                        "
## [31] "slope2  LDH   0.468   (0.3454)                        "
## [32] ""
```

```
## [33] "The relative standard errors for omega and sigma are reported on the approximate"
## [34] "standard deviation scale (SE/variance estimate)/2."
## [35] "-------------------------------------------------------------------------"
```

11.2.2.2 Diagnostic plots

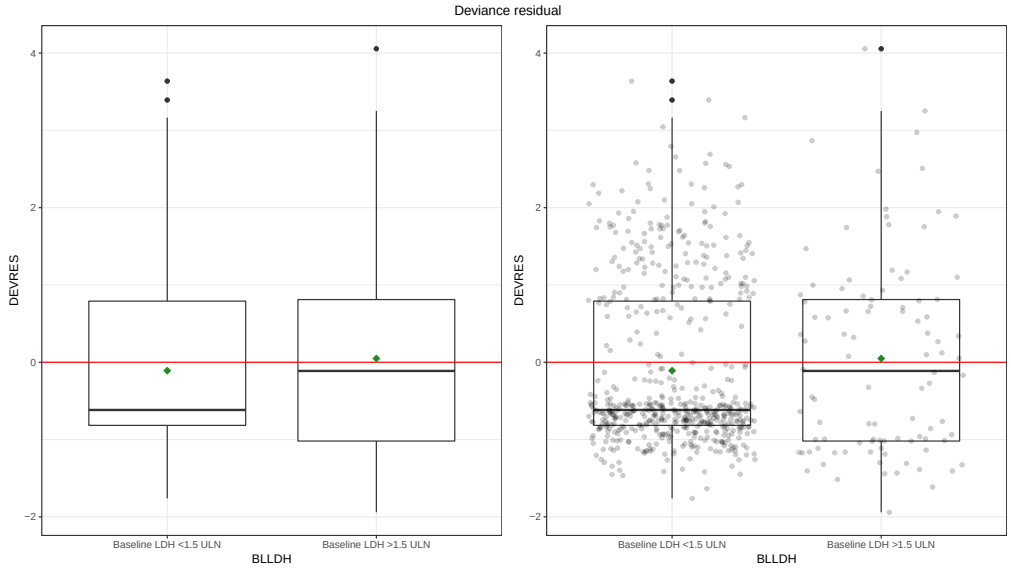


Figure 174: Residual-based diagnostics - Deviance plot

- zero reference line (red) ; mean residuals (green diamond)

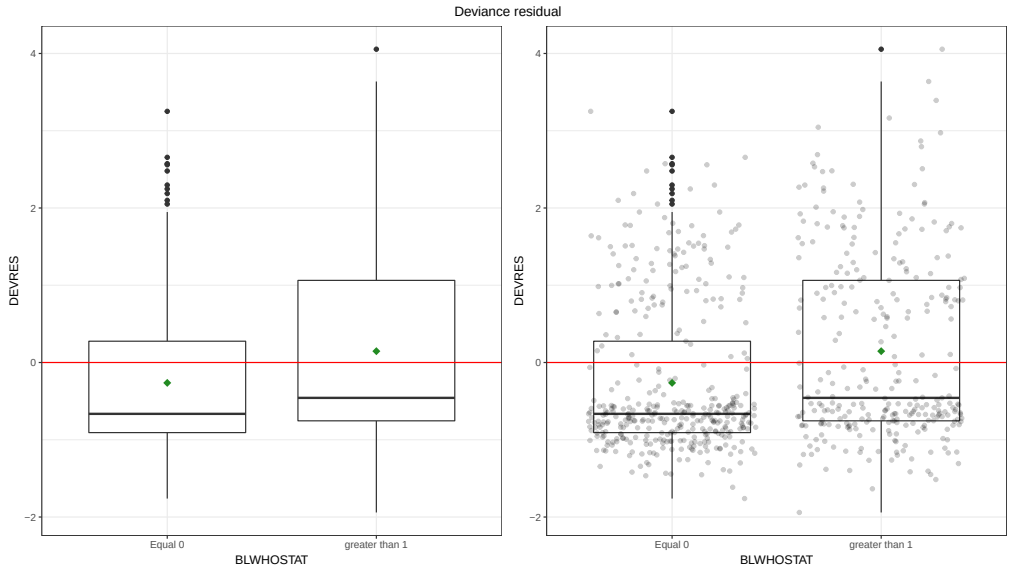


Figure 175: Residual-based diagnostics - Deviance plot

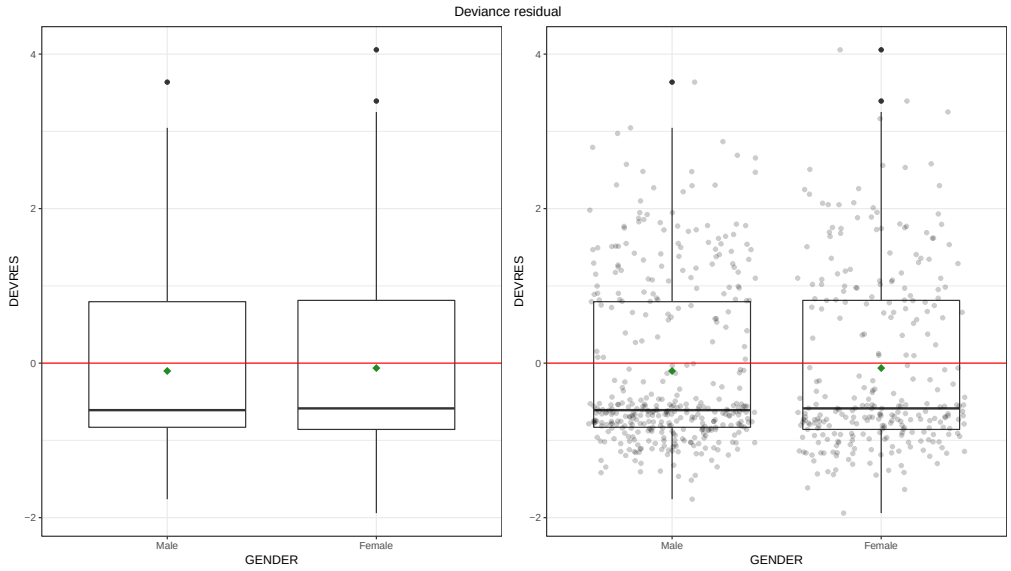


Figure 176: Residual-based diagnostics - Deviance plot

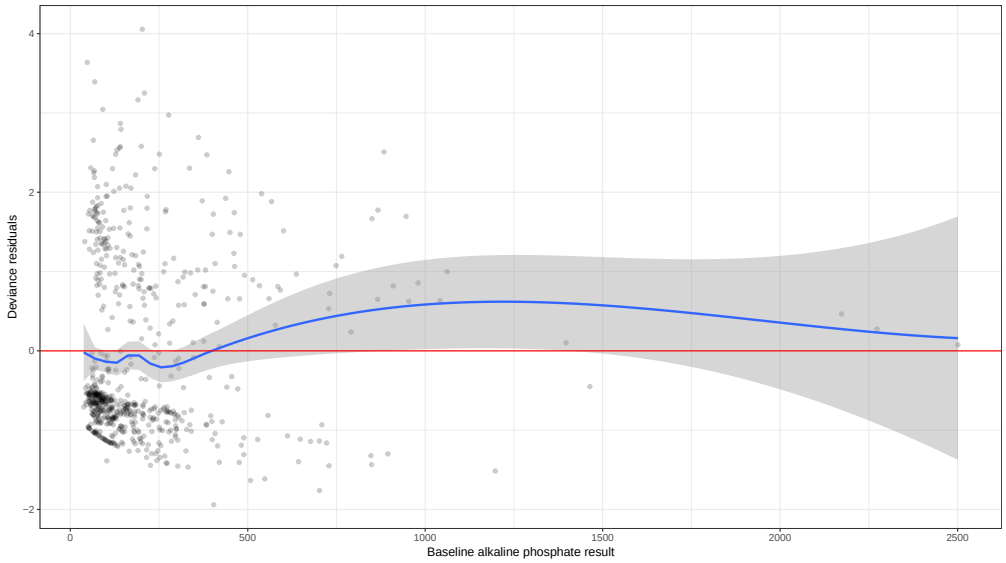


Figure 177: Residual-based diagnostics - Deviance plot

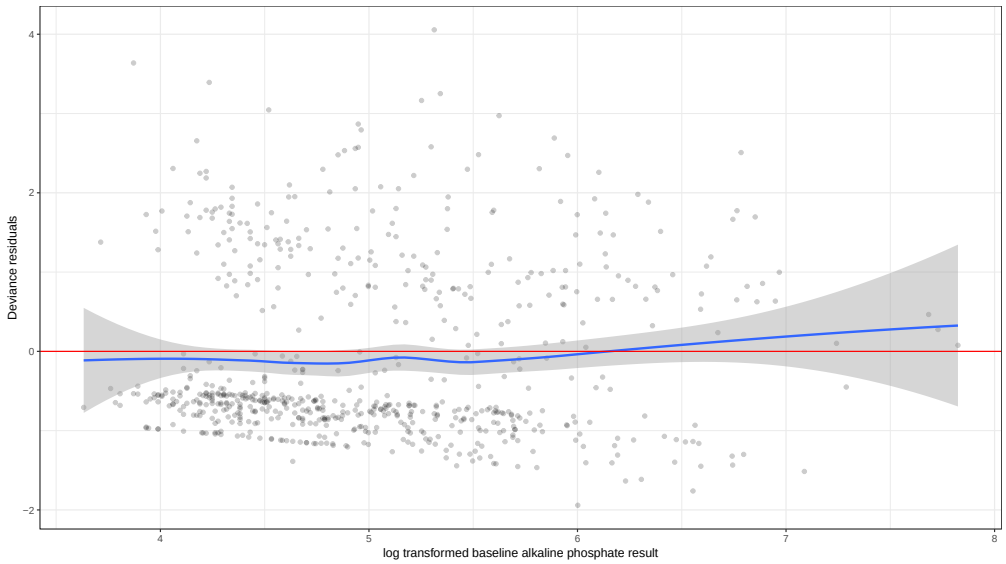


Figure 178: Residual-based diagnostics - Deviance plot

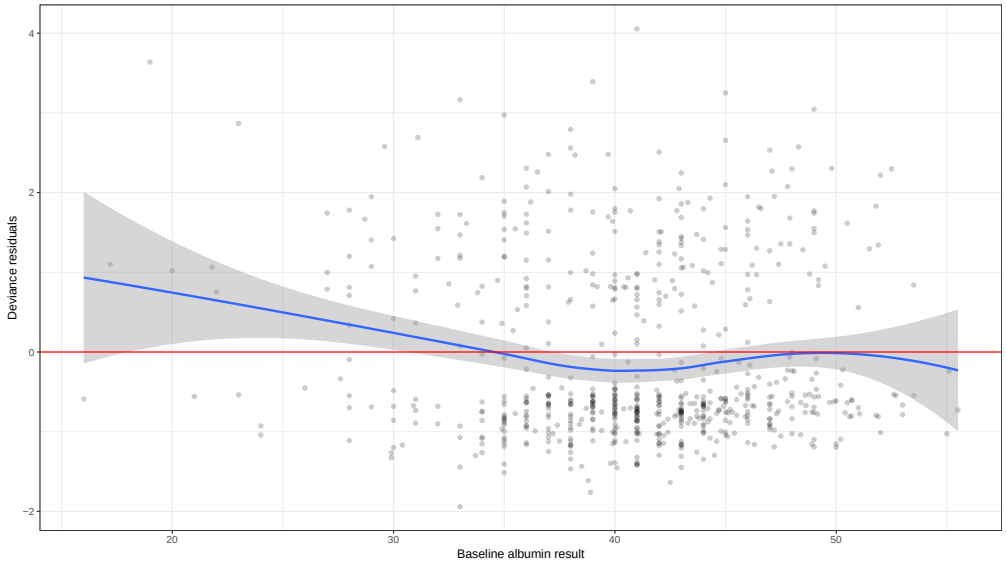


Figure 179: Residual-based diagnostics - Deviance plot

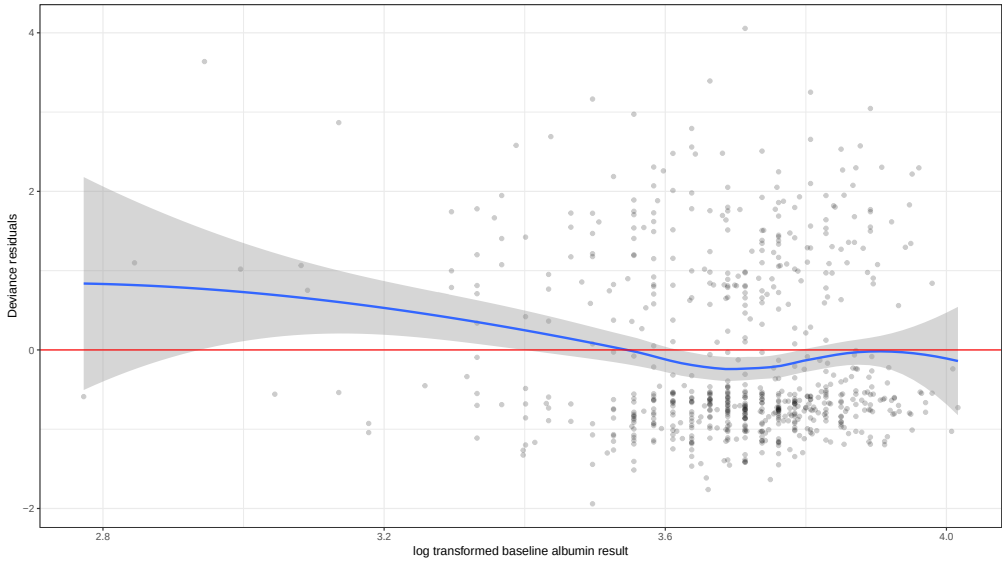


Figure 180: Residual-based diagnostics - Deviance plot

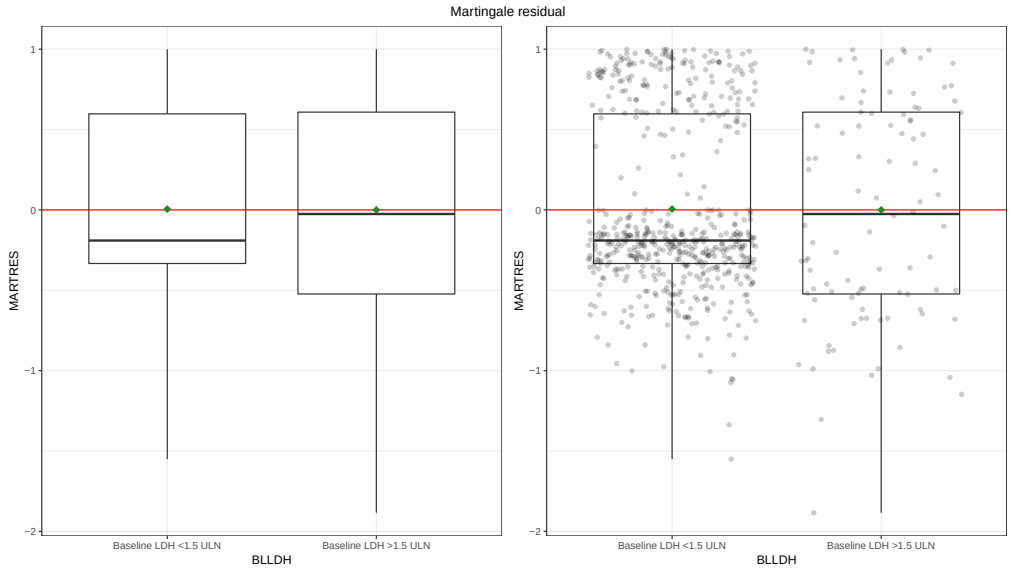


Figure 181: Residual-based diagnostics - Martingale plot

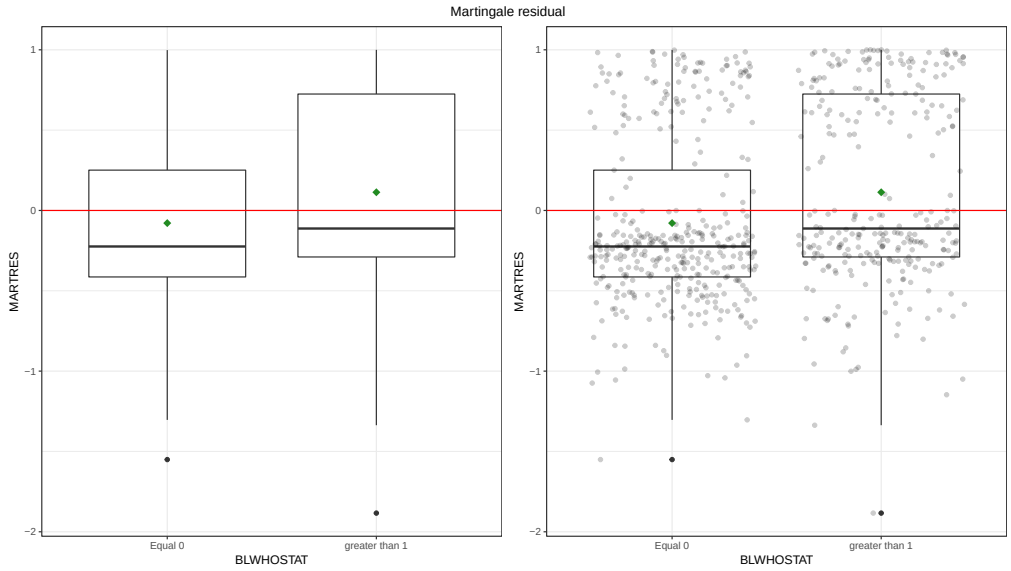


Figure 182: Residual-based diagnostics - Martingale plot

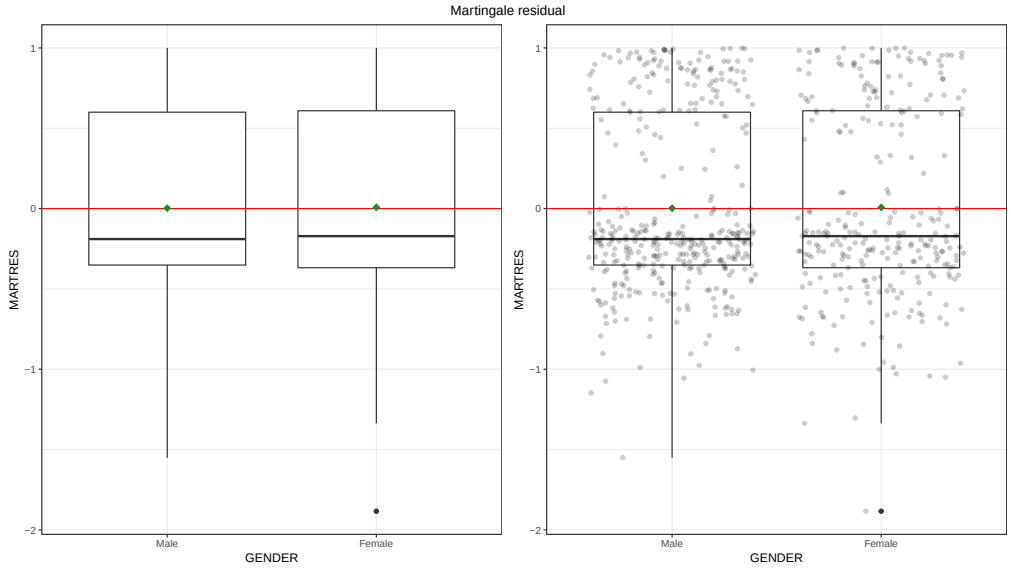


Figure 183: Residual-based diagnostics - Martingale plot

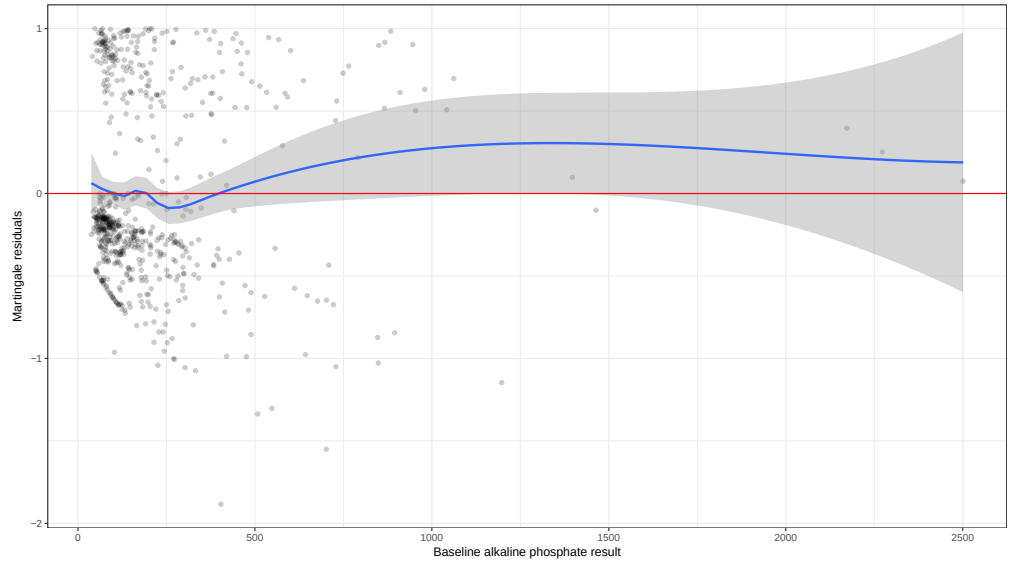
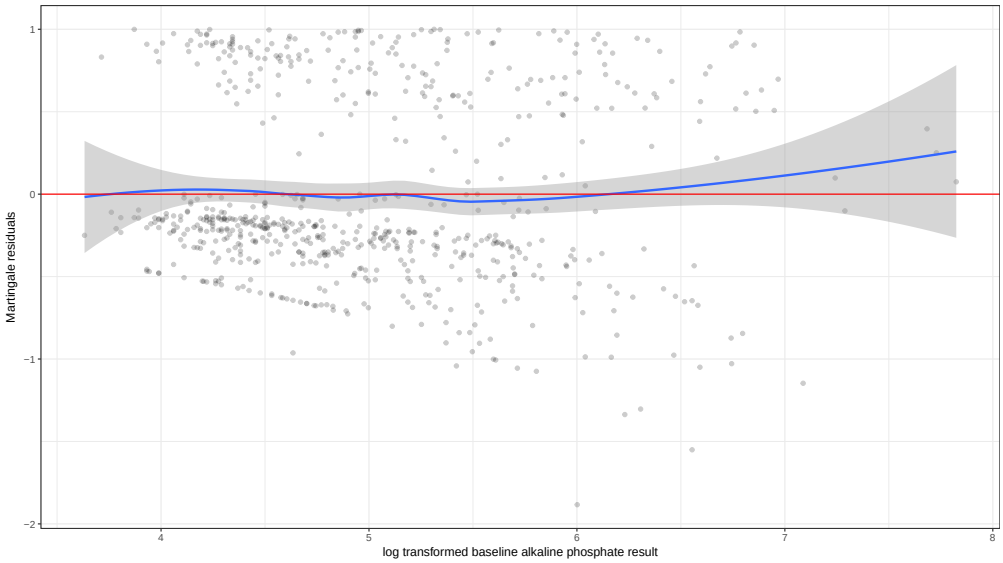
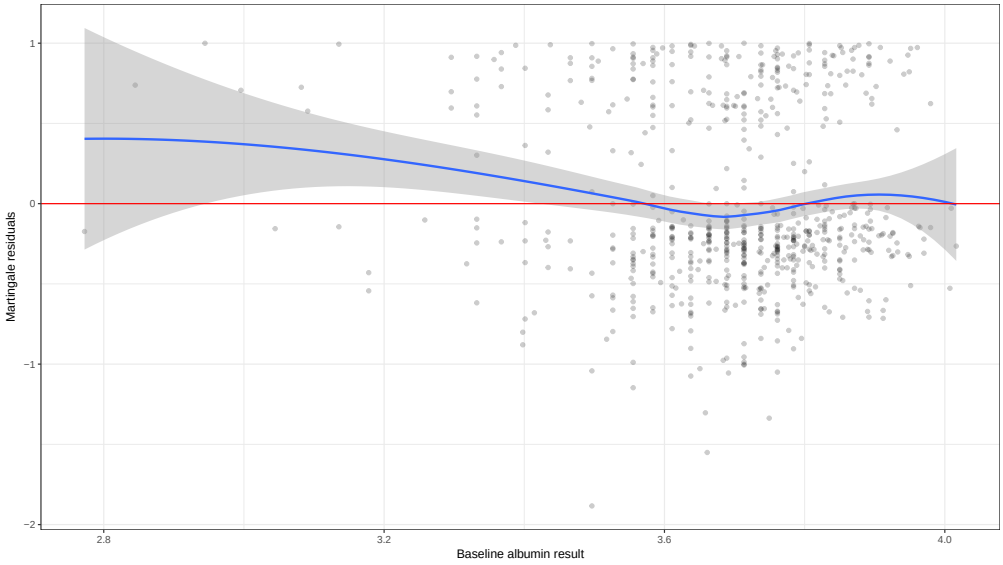


Figure 184: Residual-based diagnostics - Martingale plot


Martingale residuals
1
0
−1
−2
4
5
6
7
8
log transformed baseline alkaline phosphate result


Martingale residuals
1
0
−1
−2
2.8
3.2
3.6
4.0
Baseline albumin result

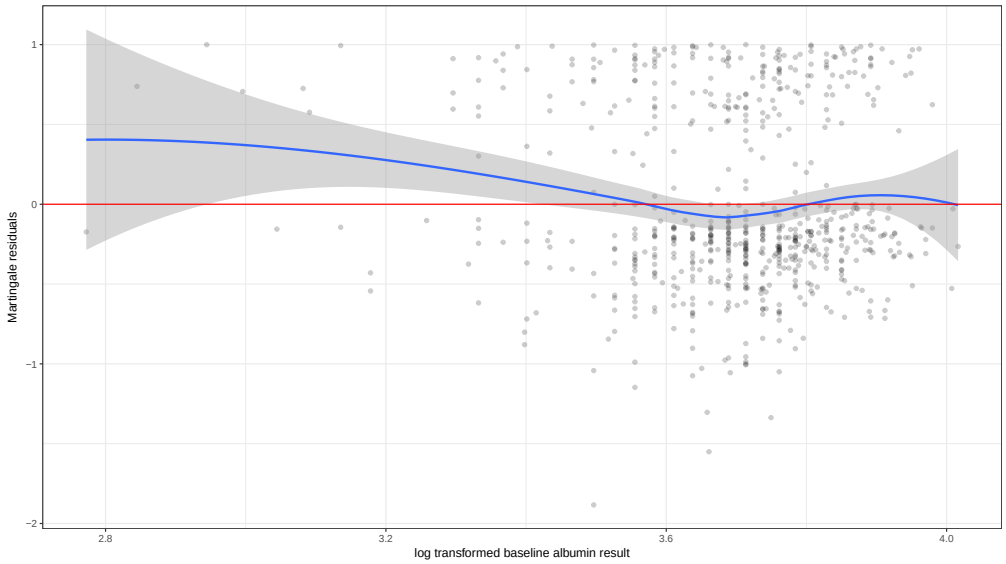


Figure 185: Residual-based diagnostics - Martingale plot

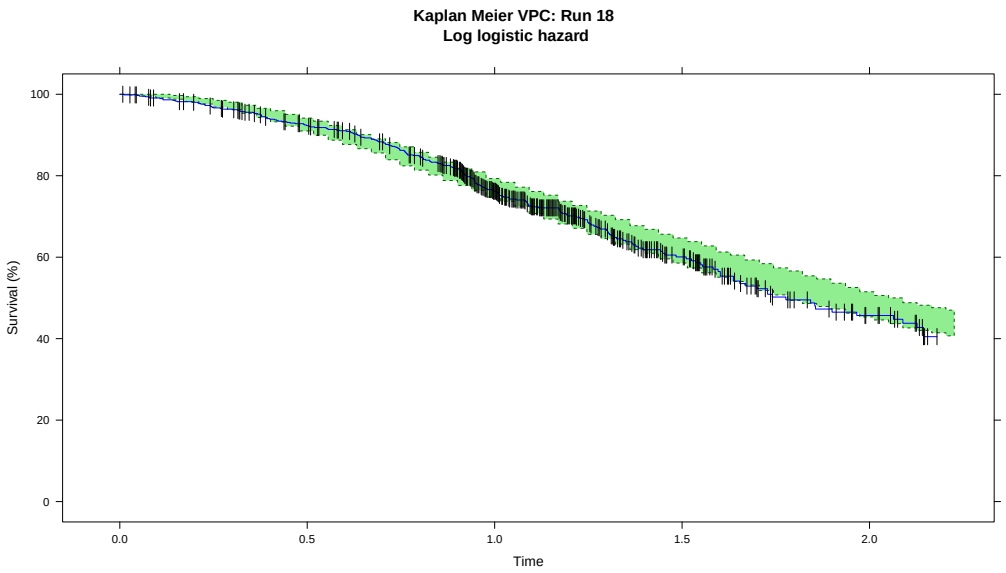


Figure 186: Simulation-based diagnostic

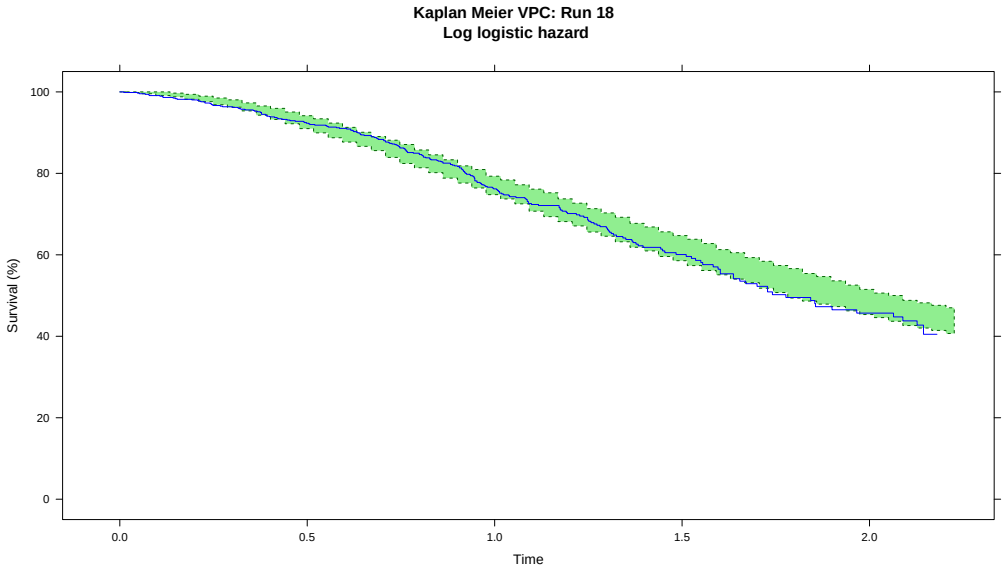


Figure 187: Simulation-based diagnostic

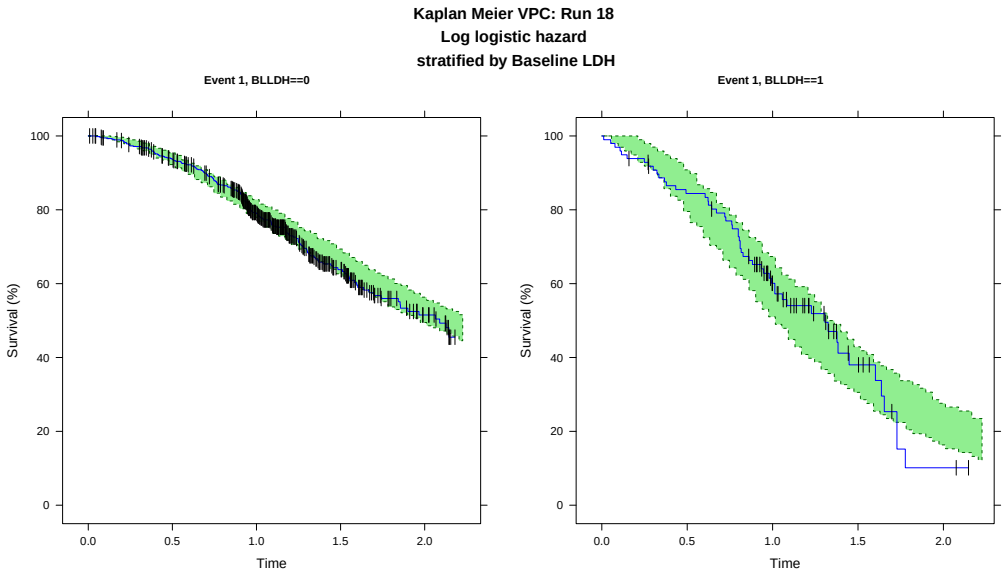


Figure 188: Simulation-based diagnostic - stratified by baseline LDH

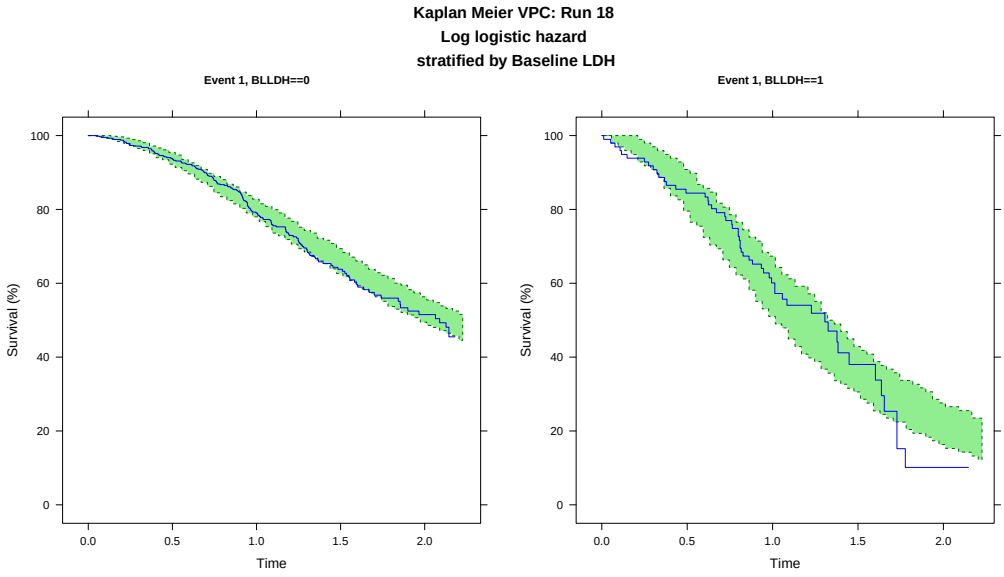


Figure 189: Simulation-based diagnostic - stratified by baseline LDH

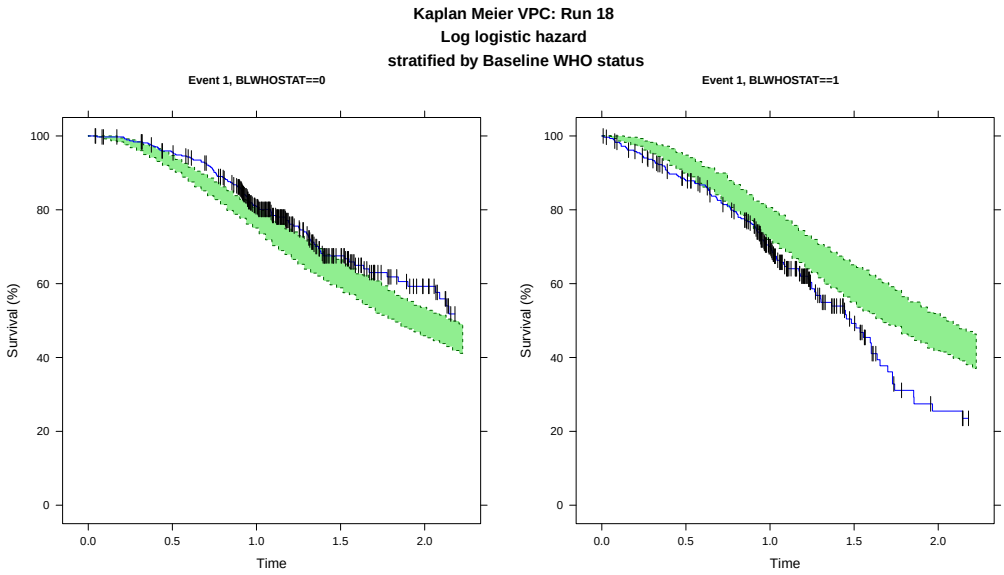


Figure 190: Simulation-based diagnostic - stratified by baseline WHO status

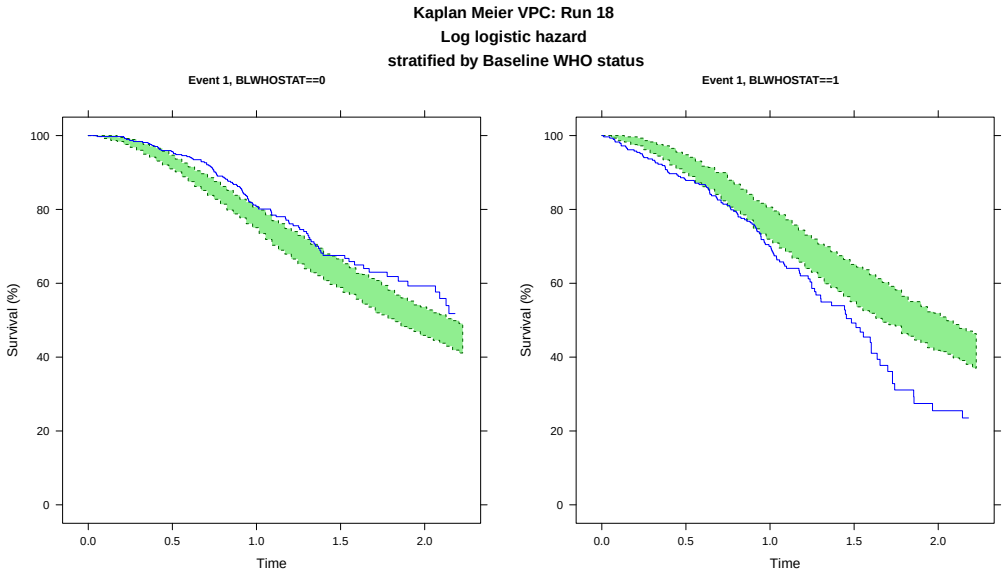


Figure 191: Simulation-based diagnostic - stratified by baseline WHO status

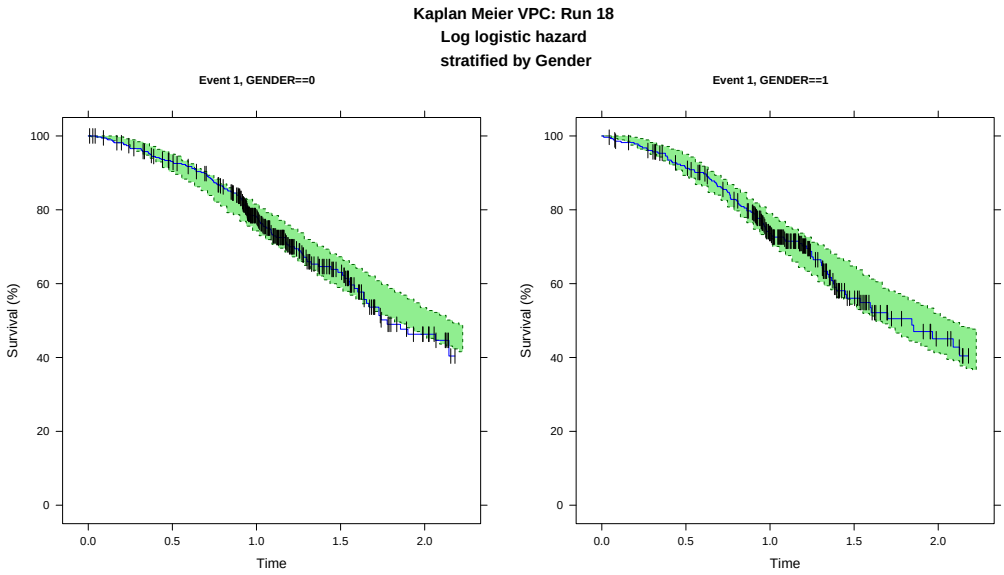


Figure 192: Simulation-based diagnostic - stratified by baseline Gender

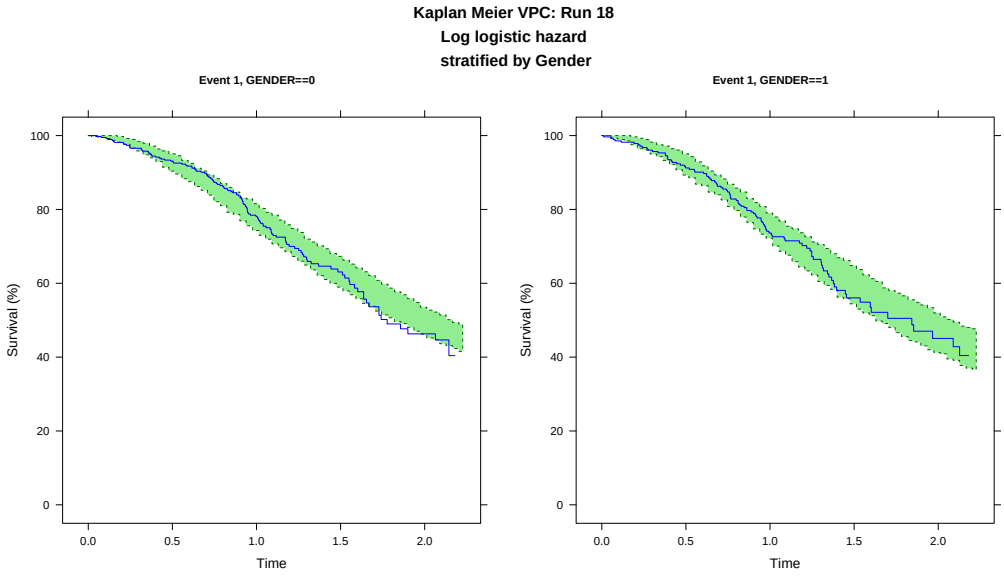


Figure 193: Simulation-based diagnostic - stratified by baseline Gender

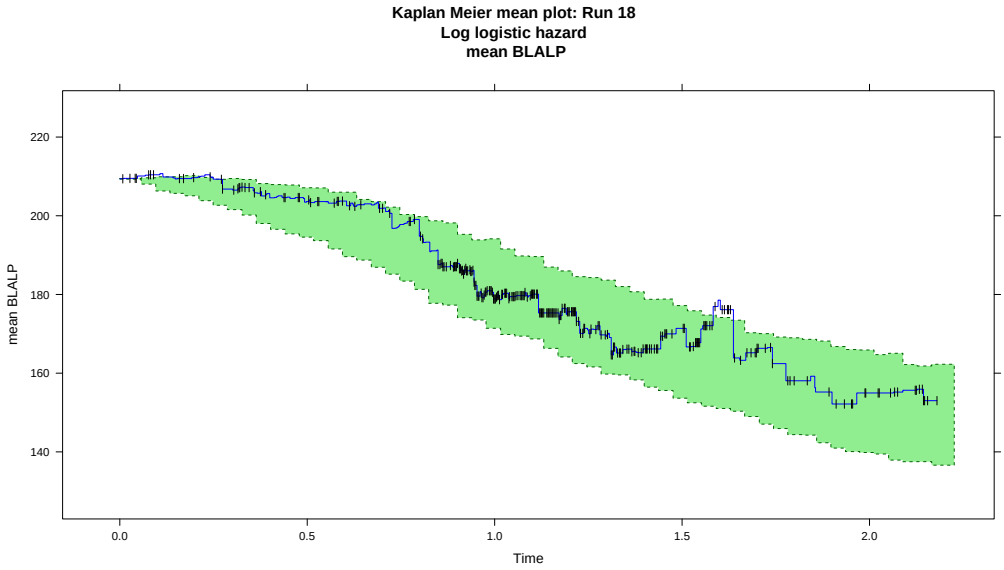


Figure 194: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

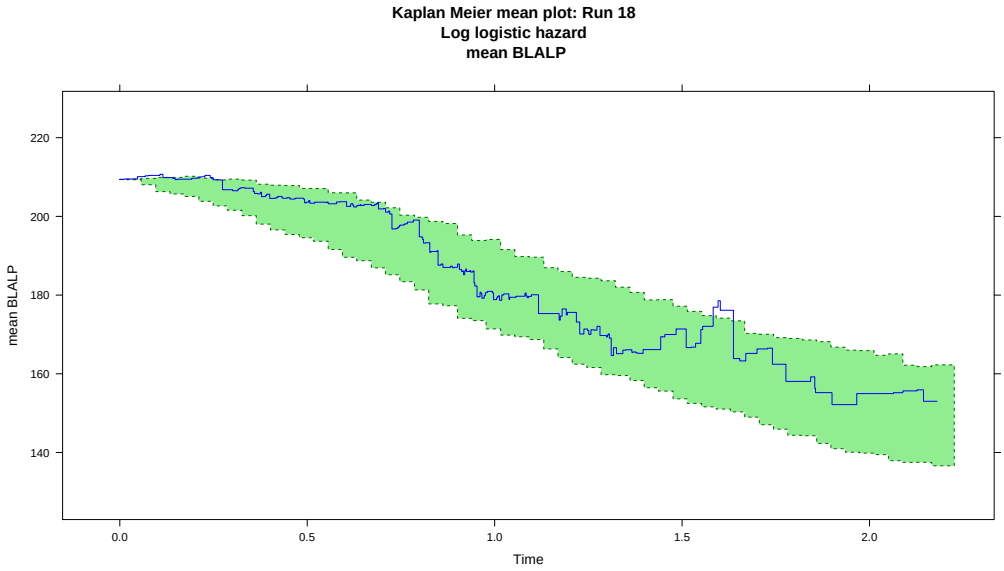


Figure 195: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

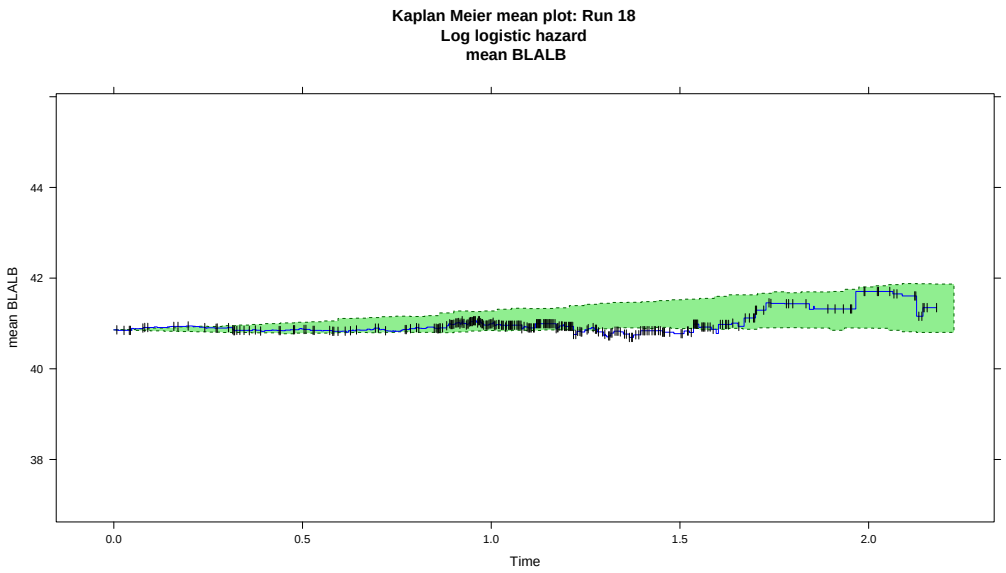


Figure 196: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

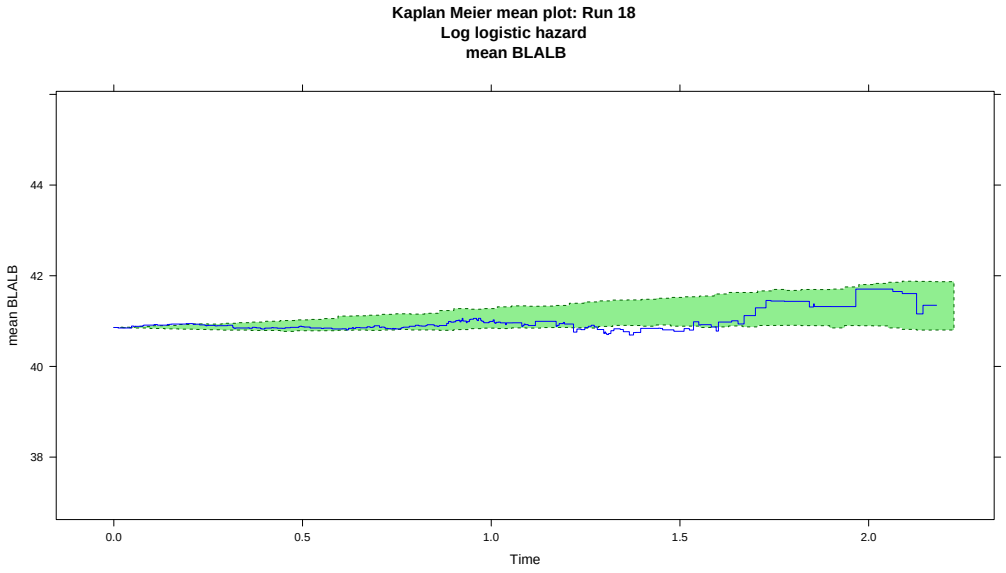


Figure 197: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

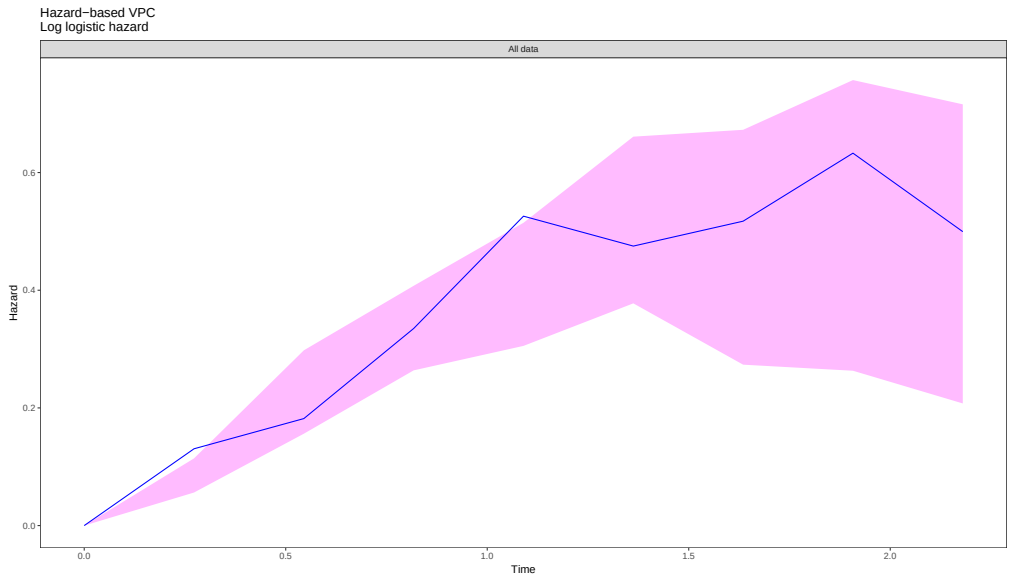


Figure 198: Simulation-based diagnostic: Hazard based VPC

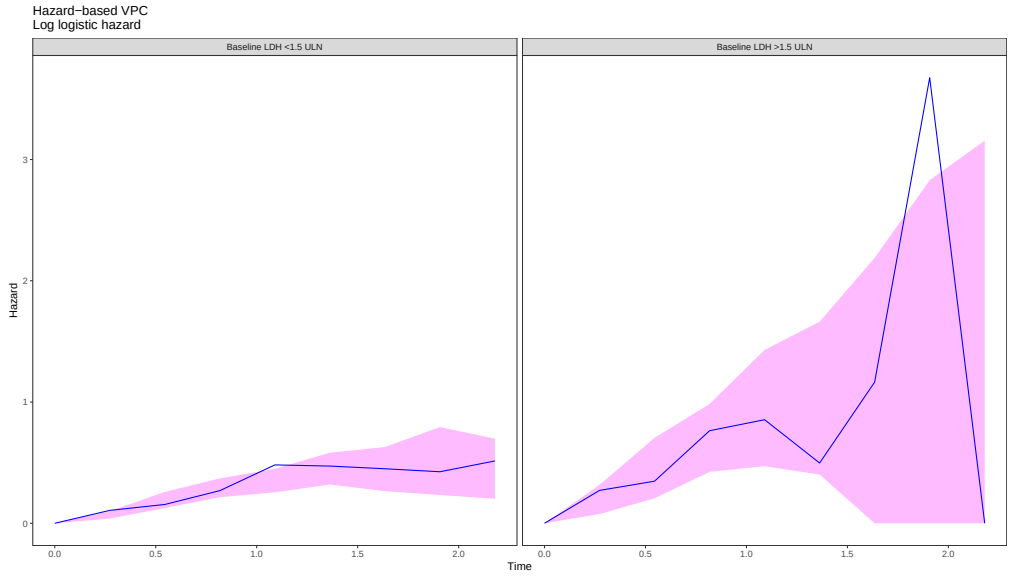


Figure 199: Simulation-based diagnostic: Hazard based VPC

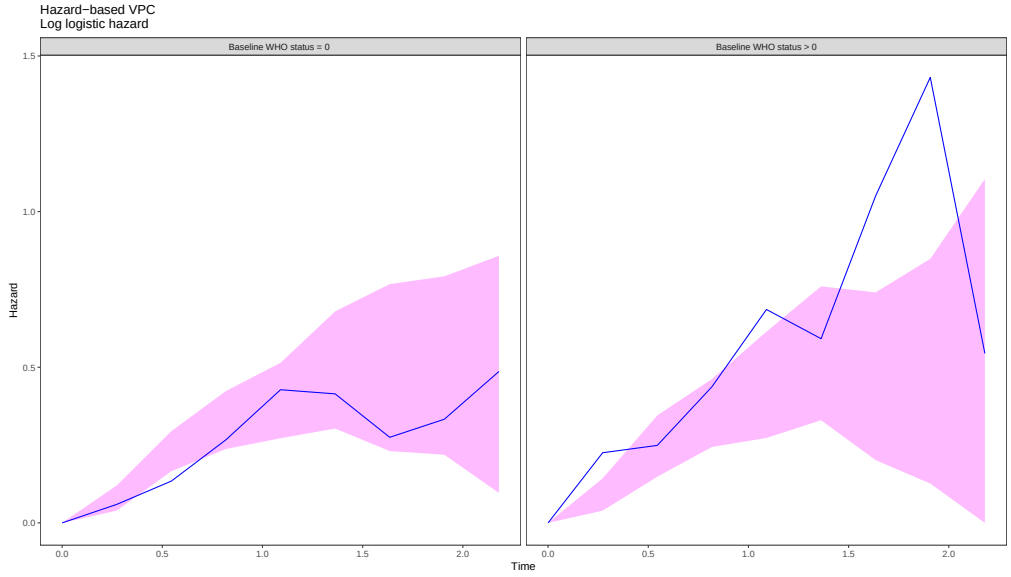


Figure 200: Simulation-based diagnostic: Hazard based VPC

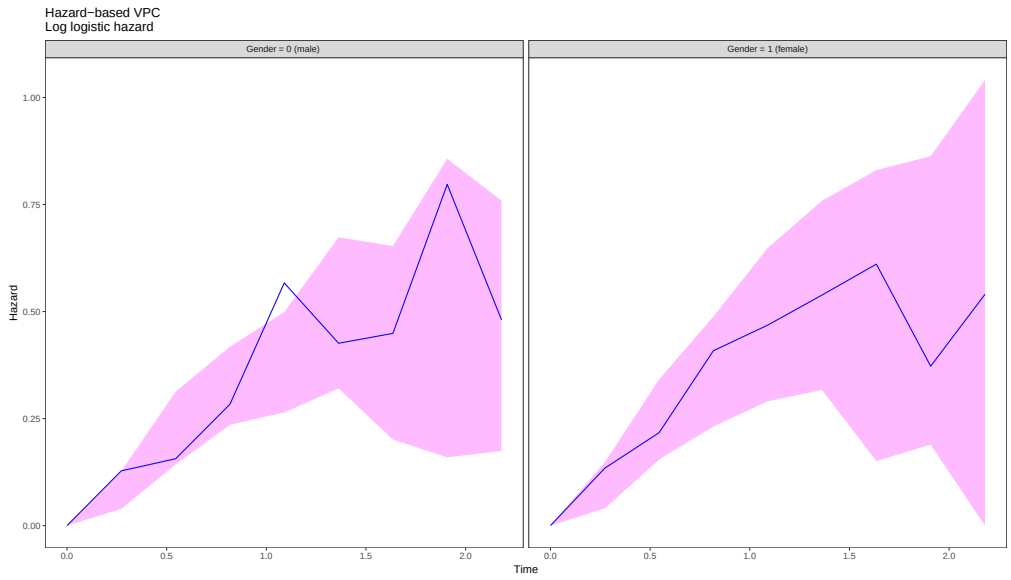


Figure 201: Simulation-based diagnostic: Hazard based VPC

11.2.3 Run 19 - covariate model

```
# next.mod(18,19,nm.dir)
show.mod(19, nm.dir) # print model
```

```
## ;; 1. Based on: 18
## ;; 2. Description:
## ;;    Covariate model 2
## ;; 3. Label:
## ;;    Log logistic hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;;     NA
## ;; 6. Interindividual variability:
## ;;    NA
## ;; 7. Interoccasion variability:
## ;;    NA
## ;; 8. Residual variability:
## ;;    NA
## ;; 9. Estimation:
## ;;    LAPLACE
##
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
##
## $PROBLEM    Covariate TTE model - Project DataSphere # 78 - no missing LDH
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM LOGBLALP LOGBLALB
##
## ;----------------------------------------------------data description
## ; ID, subject identifier
## ; TIME, in years
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
## ; CENS, censored event, 0 = no, 1 = yes
## ; MAXT, last recorded event per patient (either death or censor)
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
## ; GENDER, bianry covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
## ; OSTIM, observed time in days to event or censor time
## ; LOGBLALP, log (BLALP)
## ; LOGBLALB, log (BLALB)
## ;-----------------------------------------------------
```

```
##
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2_1.csv IGNORE=@
##
## IGNORE(NOLDH.EQ.1) ; 24 patients missing BL_LDH data
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
## ;IGNORE=(STIME.EQ.0) ; observed time, ignore for simulation
## ;Sim_end
##
## $SUBROUTINE ADVAN=13 TOL=9
## $MODEL      COMP=(HAZARD)
##
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##
##  DELTA = THETA(1)* EXP(ETA(1))
##  GAMMA = THETA(2)
##  SLP1 = THETA(3)
##  SLP2 = THETA(4)
##  SLP3 = THETA(5)
##
## MEANLOGBLALP = 5.013
## ; MEIDANLOGBLALP =  4.875
##
## ;;======================== DIFFERENTIAL EQUATIONS ==================================
## ; Typical Value Log-logistic hazard
## ; h0(t) = exp(delta) kt^(k-1) / (1+ exp(delta)*t^k)
## ; where k = gamma
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = EXP(DELTA)*GAMMA*(T+DEL)**(GAMMA-1) / (1 + EXP(DELTA)*(T+DEL)**GAMMA)
##
## ALP = SLP1*(LOGBLALP-MEANLOGBLALP)   ; normalized baseline ALP effect  - mean
##
## LDH = SLP2*BLLDH ; effect of LDH > 1.5 ULN
##
## WHO = SLP3*BLWHOSTAT ; effect of who status !=normal
##
## DADT(1) = BASE * EXP(ALP + LDH + WHO)
##
## ;;================================ MODEL FIT ==================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
##
## ;------------------------------
```

```
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=EXP(DELTA)*GAMMA*(TIME+DELX)**(GAMMA-1) / (1 + EXP(DELTA)*(TIME+DELX)**GAMMA)
##  ALPX = SLP1*(LOGBLALP-MEANLOGBLALP) ; normalized baseline ALP effect  - mean
##  LDHX = SLP2*BLLDH   ; effect of LDH > 1.5 ULN
##  WHOX = SLP3*BLWHOSTAT   ; effect of who status !=normal
##  HAZNOW= BASEX * EXP(ALPX + LDHX + WHOX)
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
##
## ;;================================ RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
## ;;================================ SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================ INITIAL ESTIMATES ====================================
##
## $THETA  -1.33 ; delta
```

```
##  (0,1.88) ; gamma
##  0.458 ; slope1 ALP
##  0.468 ; slope2  LDH
##  0.001 ; slope3 WHO
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ==============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_19
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
##
## ;;================================ TABLES ================================
## $TABLE      NOPRINT ONEHEADER FILE=mytab19 ID TIME DV EVID MDV PRED
##             CHZ SUR HAZNOW MARTRES DEVRES NOLDH BLAGE BASE BASEX DELTA
##             GAMMA BLLDH BLWHOSTAT BLALB BLALP BLWHOLEVEL GENDER OSTIM
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab19 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab19 ID DELTA GAMMA
##             ETAS(1:LAST)

## NULL
```

11.2.3.1 Run summary

```
##  [1] "------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/other_projects/PostDoc_project_ISoP/2018_TTE/NONMEM/run19/run
##  [4] ""
##  [5] "Successful minimization                                        [    OK   ]   "
##  [6] "No rounding errors                                             [    OK   ]   "
##  [7] "No zero gradients                                              [    OK   ]   "
##  [8] "No final zero gradients                                        [    OK   ]   "
##  [9] "Hessian not reset                                              [    OK   ]   "
## [10] "No parameter near boundary                                     [    OK   ]   "
## [11] "Covariance step                                                [    OK   ]   "
## [12] ""
## [13] "Condition number                                               [    OK   ]   "
## [14] "Correlations                                                   [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                 0:03:34"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   150.99"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   6.61"
## [19] ""
## [20] "Objective function value: 867.5953"
## [21] ""
## [22] "Condition number: 8.144"
## [23] ""
## [24] "Number of observation records: 666"
## [25] "Number of individuals: 666"
## [26] ""
## [27] "              THETA               OMEGA      SIGMA    "
## [28] "      delta  -1.632  (0.07021)                         "
```

```
## [29] "      gamma   1.863  (0.06711)                        "
## [30] " slope1 ALP  0.4311   (0.2228)                        "
## [31] "slope2  LDH  0.4317   (0.3826)                        "
## [32] " slope3 WHO  0.5934   (0.2212)                        "
## [33] ""
## [34] "The relative standard errors for omega and sigma are reported on the approximate"
## [35] "standard deviation scale (SE/variance estimate)/2."
## [36] "-----------------------------------------------------------------------"
```

11.2.3.2 Diagnostic plots

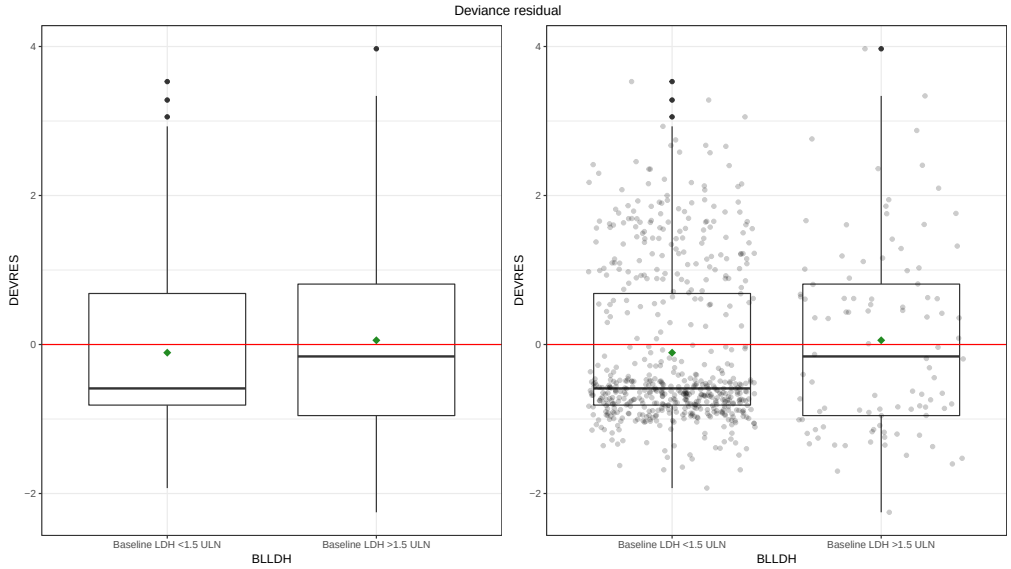


Figure 202: Residual-based diagnostics - Deviance plot

- zero reference line (red) ; mean residuals (green diamond)

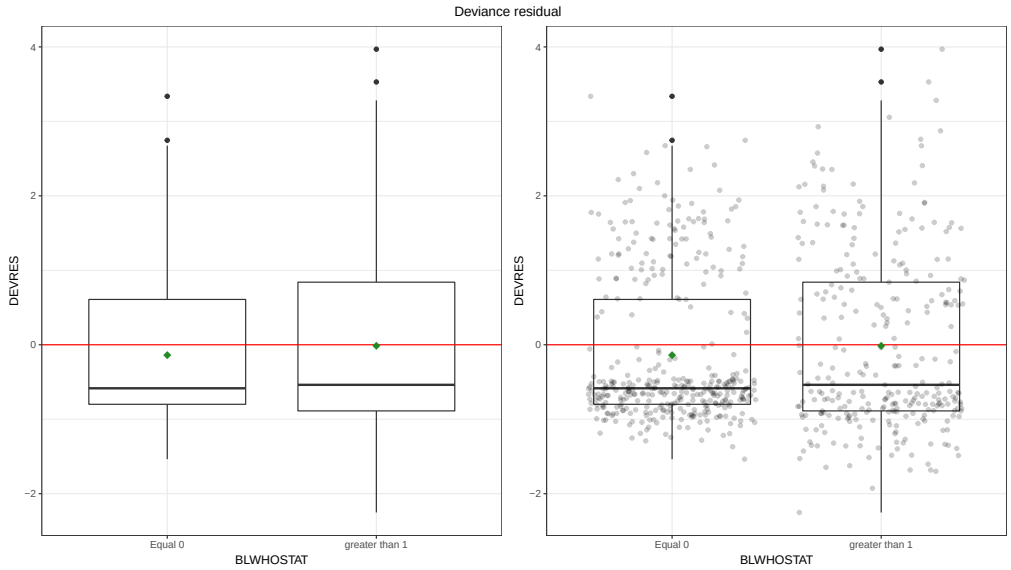


Figure 203: Residual-based diagnostics - Deviance plot

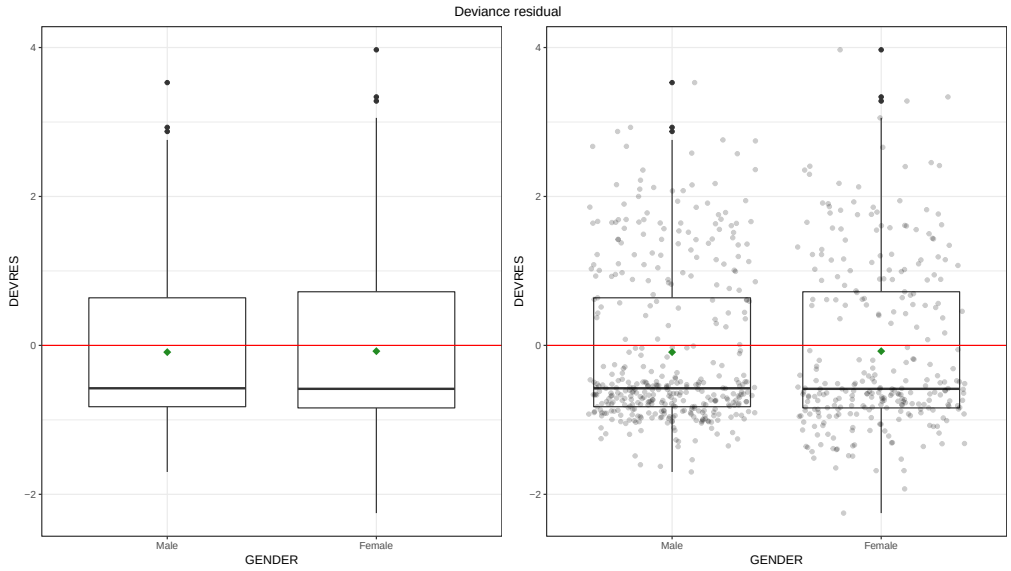


Figure 204: Residual-based diagnostics - Deviance plot

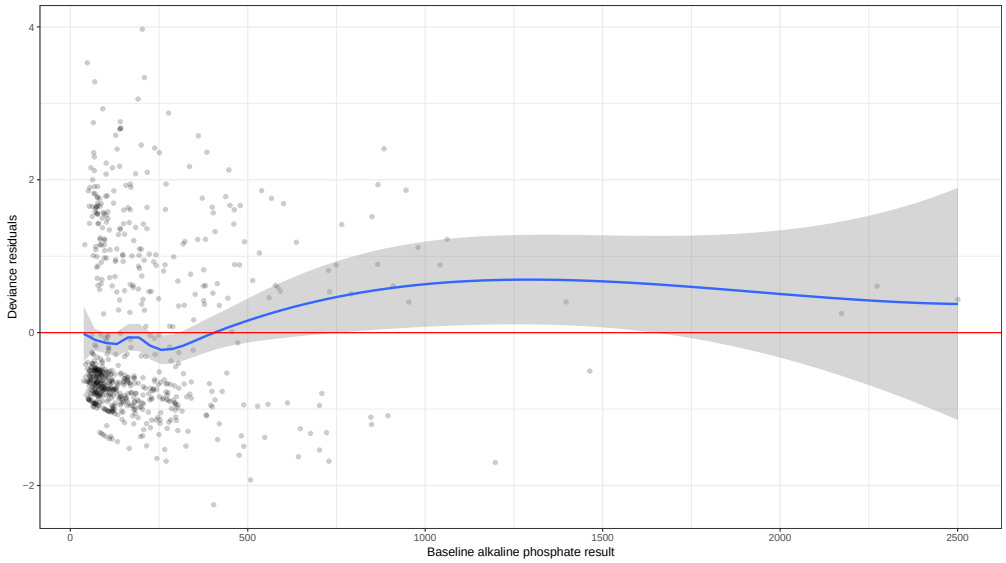


Figure 205: Residual-based diagnostics - Deviance plot

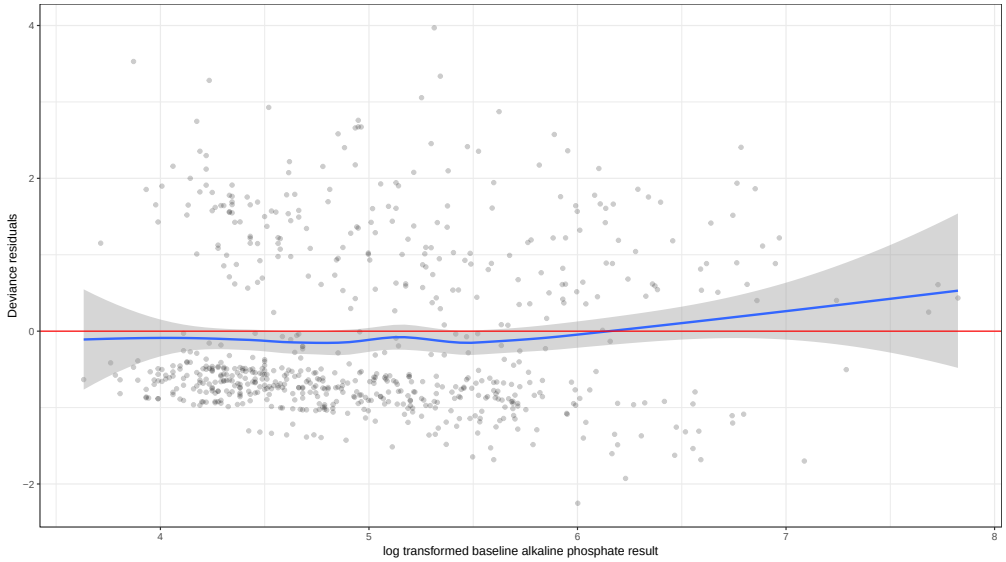


Figure 206: Residual-based diagnostics - Deviance plot

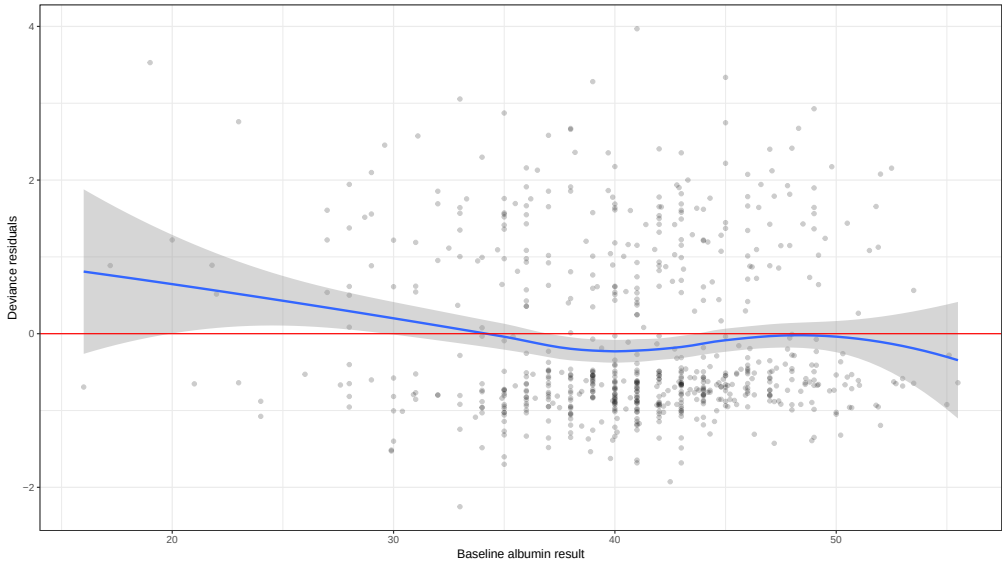


Figure 207: Residual-based diagnostics - Deviance plot

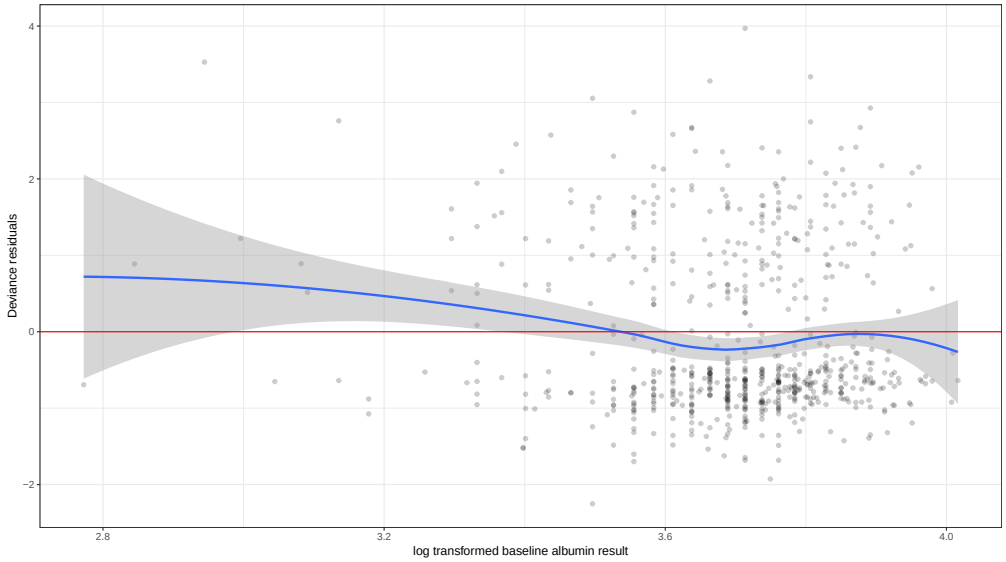


Figure 208: Residual-based diagnostics - Deviance plot

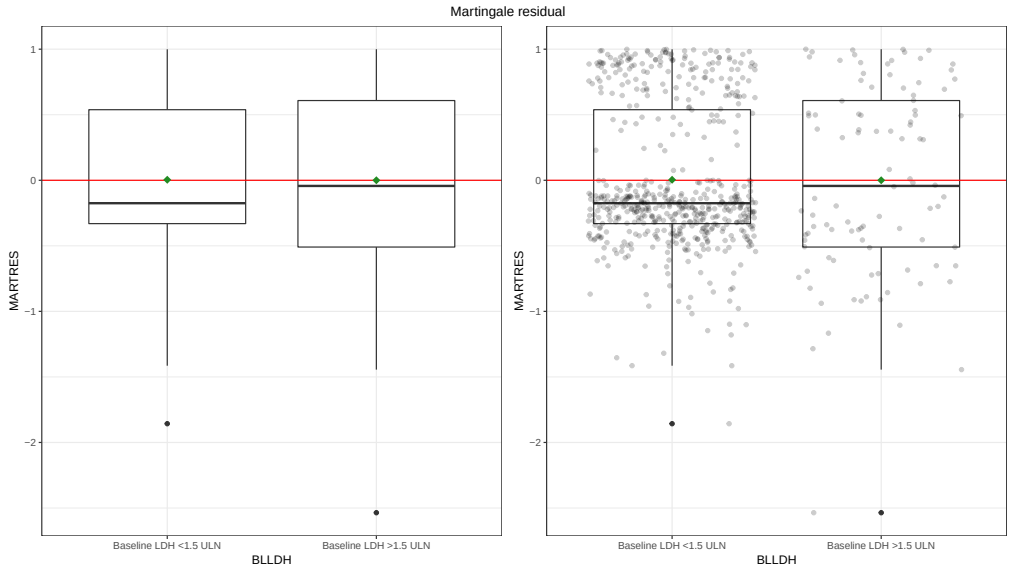


Figure 209: Residual-based diagnostics - Martingale plot

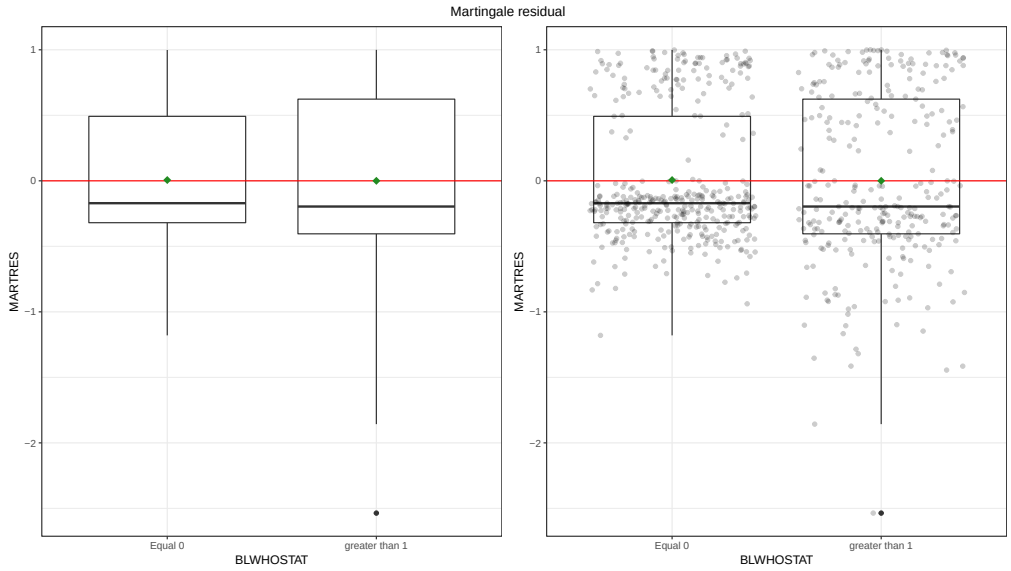


Figure 210: Residual-based diagnostics - Martingale plot

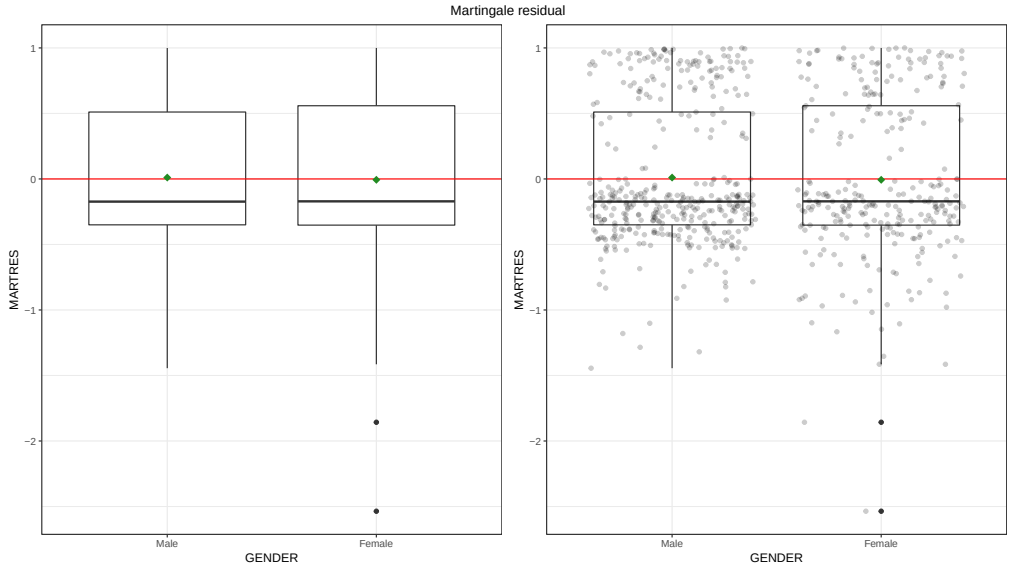


Figure 211: Residual-based diagnostics - Martingale plot

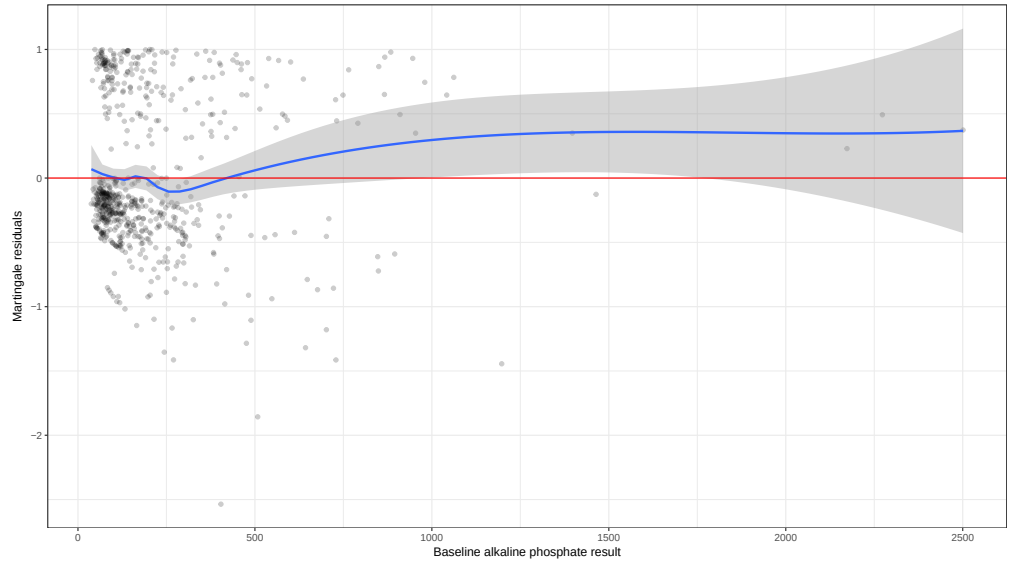
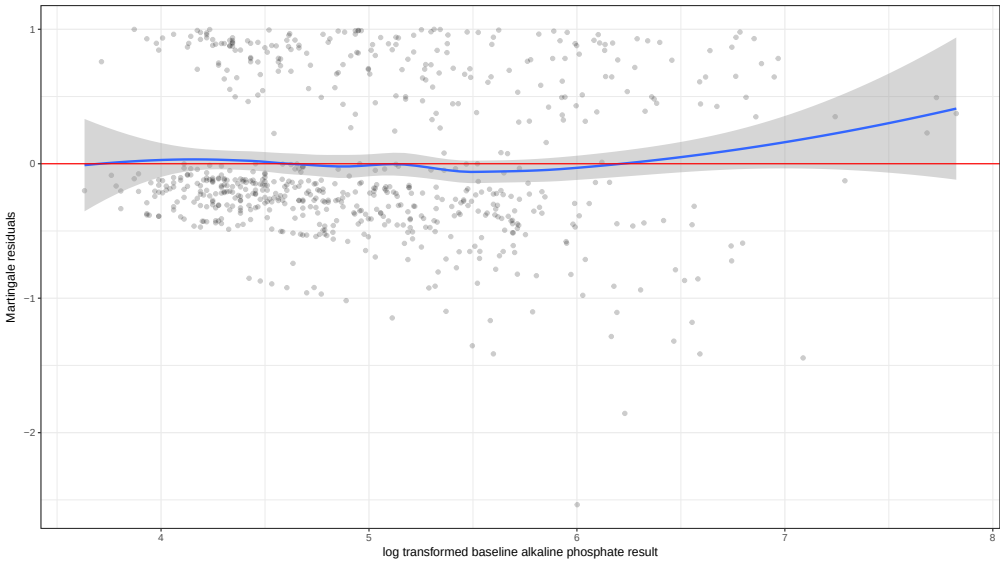
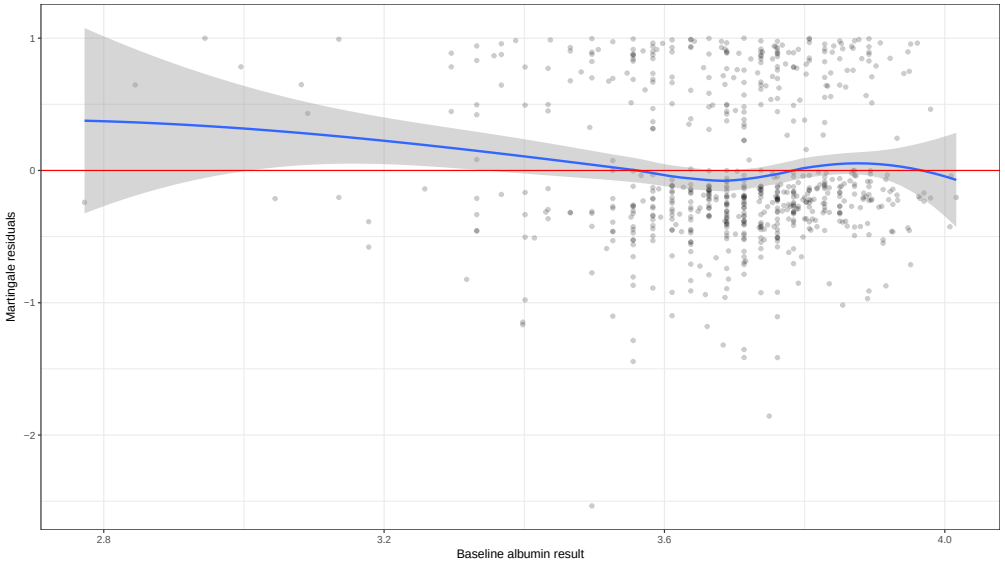


Figure 212: Residual-based diagnostics - Martingale plot


Martingale residuals
1
0
−1
−2
4
5
6
7
8
log transformed baseline alkaline phosphate result


Martingale residuals
1
0
−1
−2
2.8
3.2
3.6
4.0
Baseline albumin result

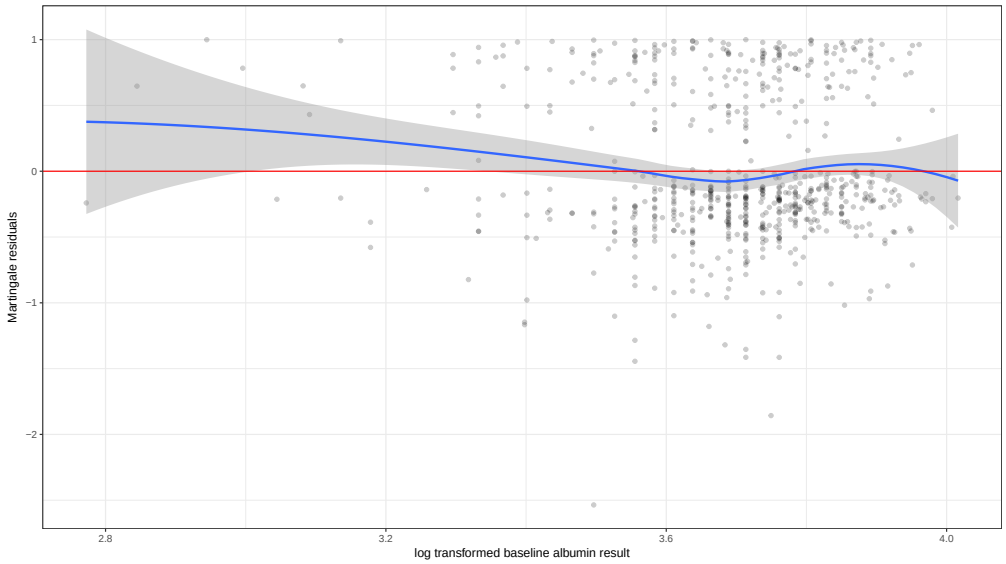


Figure 213: Residual-based diagnostics - Martingale plot

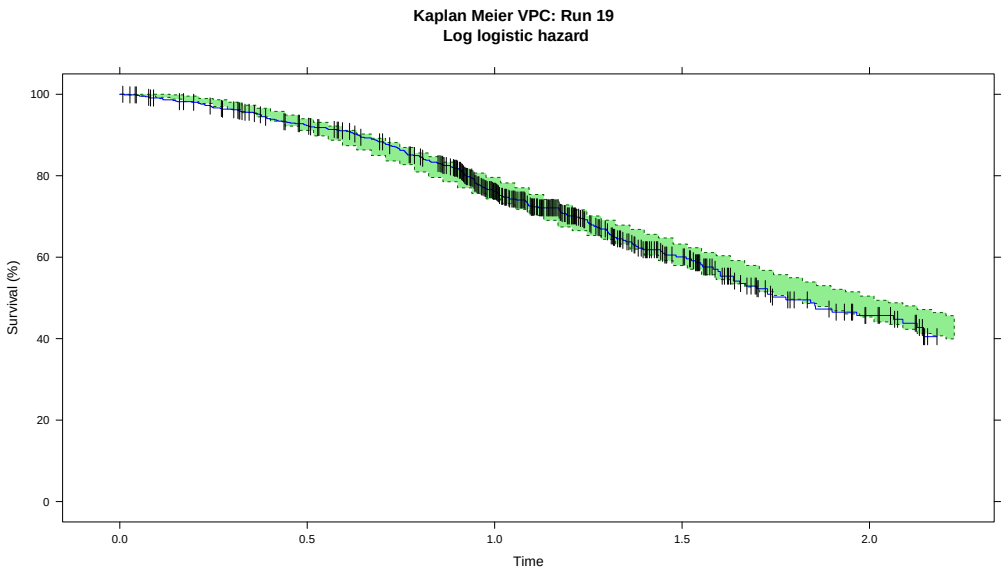


Figure 214: Simulation-based diagnostic

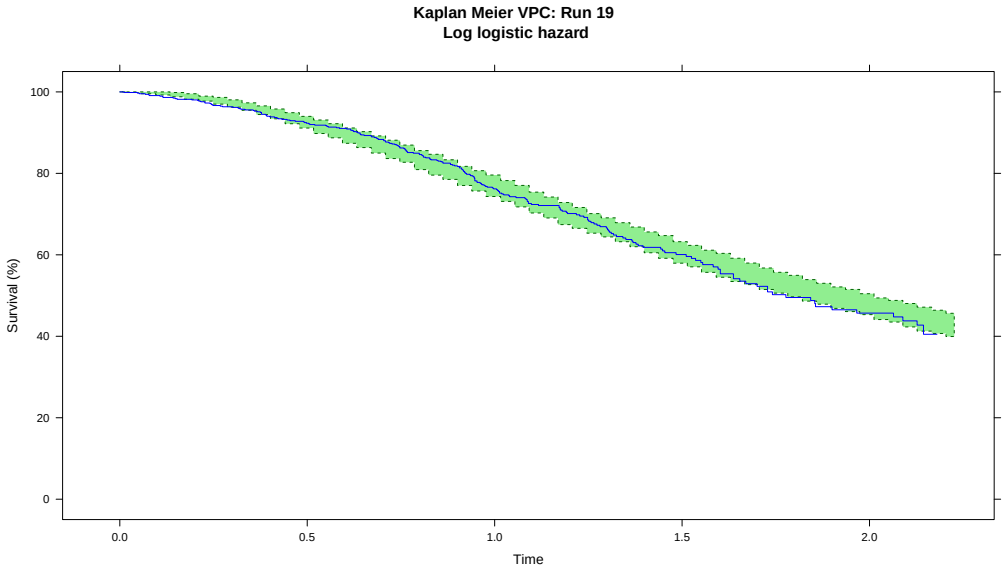


Figure 215: Simulation-based diagnostic

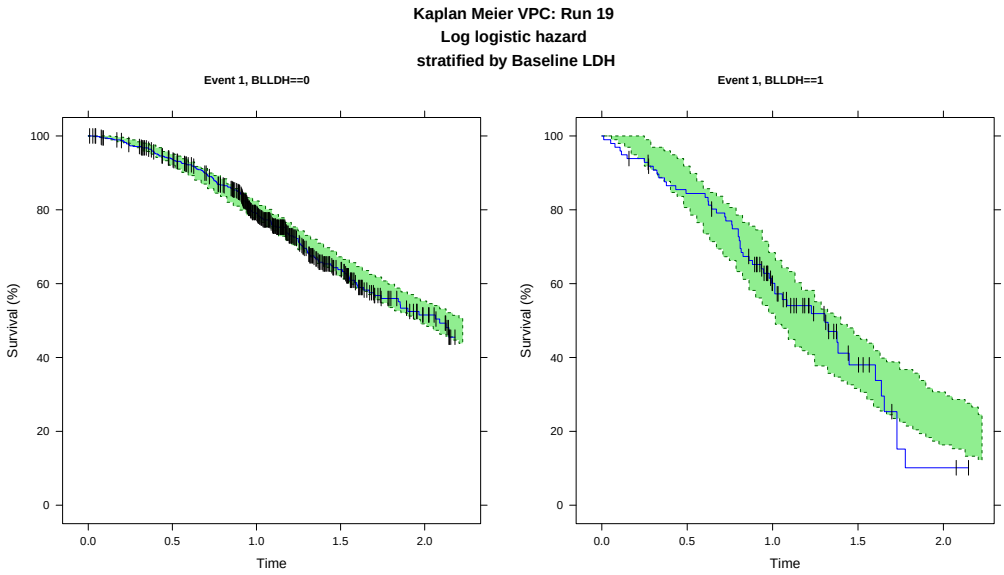


Figure 216: Simulation-based diagnostic - stratified by baseline LDH

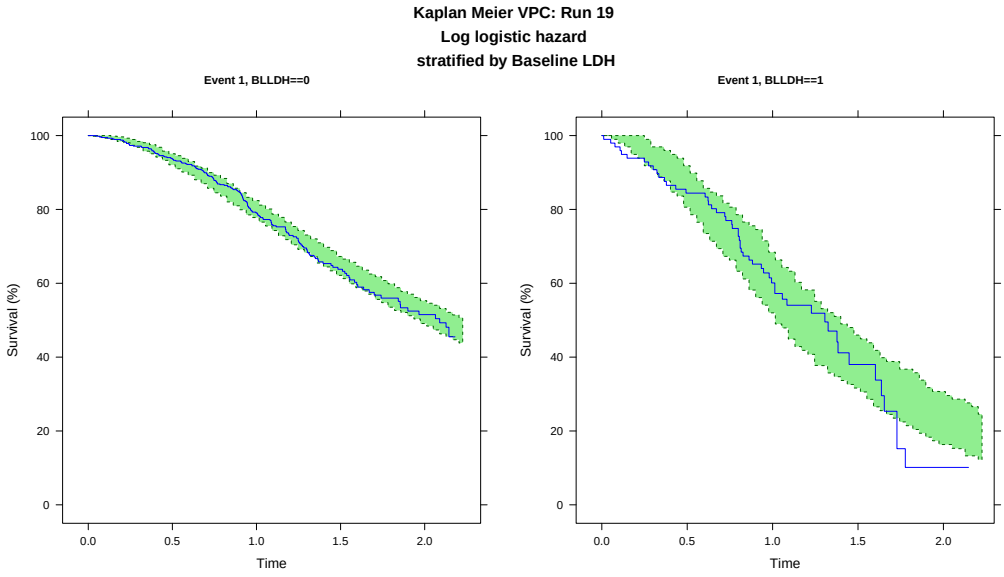


Figure 217: Simulation-based diagnostic - stratified by baseline LDH

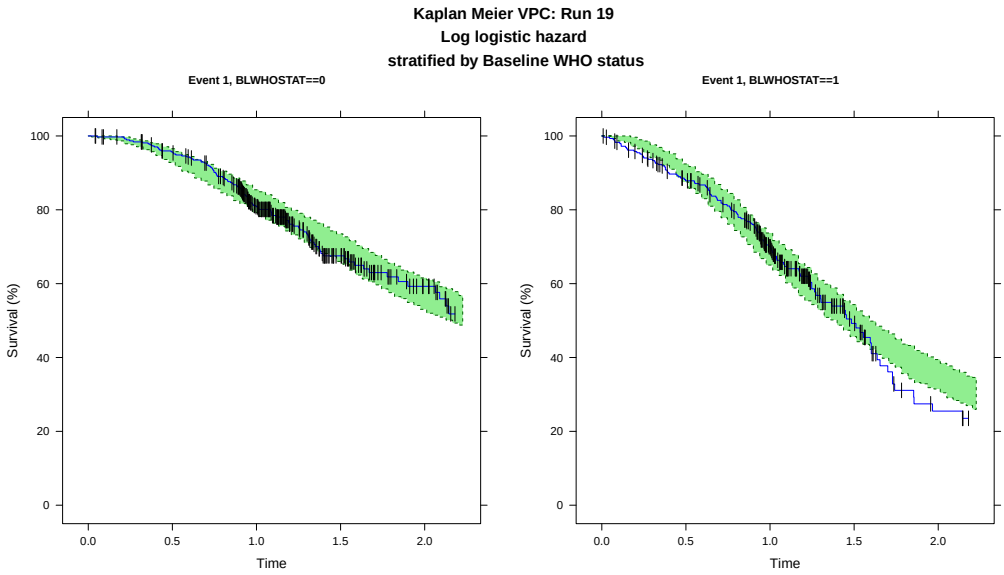


Figure 218: Simulation-based diagnostic - stratified by baseline WHO status

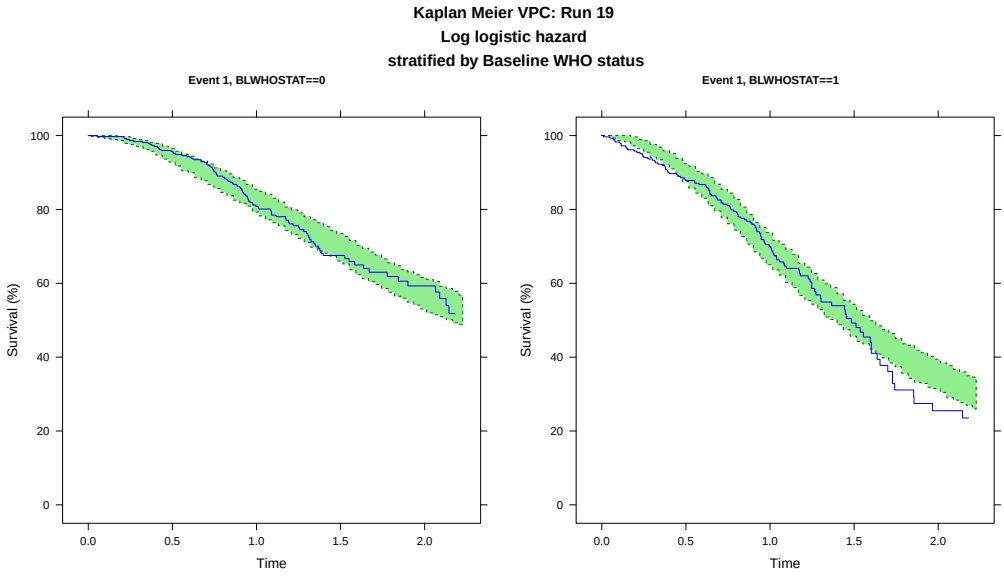


Figure 219: Simulation-based diagnostic - stratified by baseline WHO status

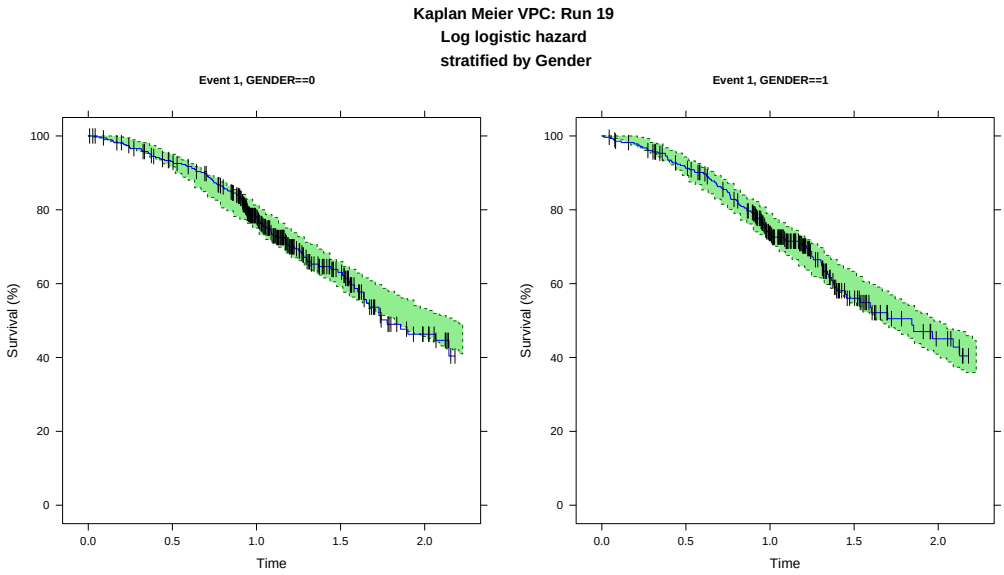


Figure 220: Simulation-based diagnostic - stratified by baseline Gender

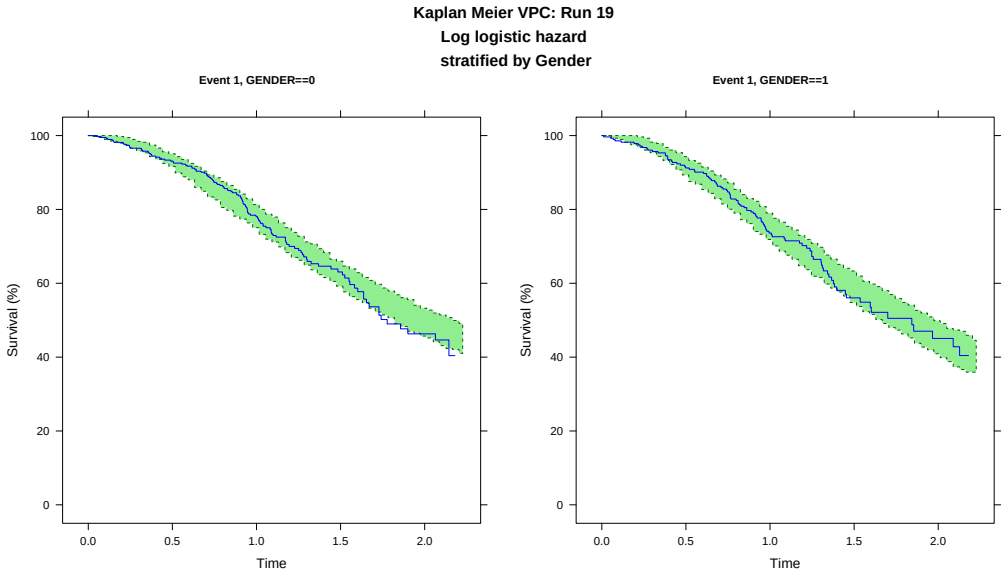


Figure 221: Simulation-based diagnostic - stratified by baseline Gender

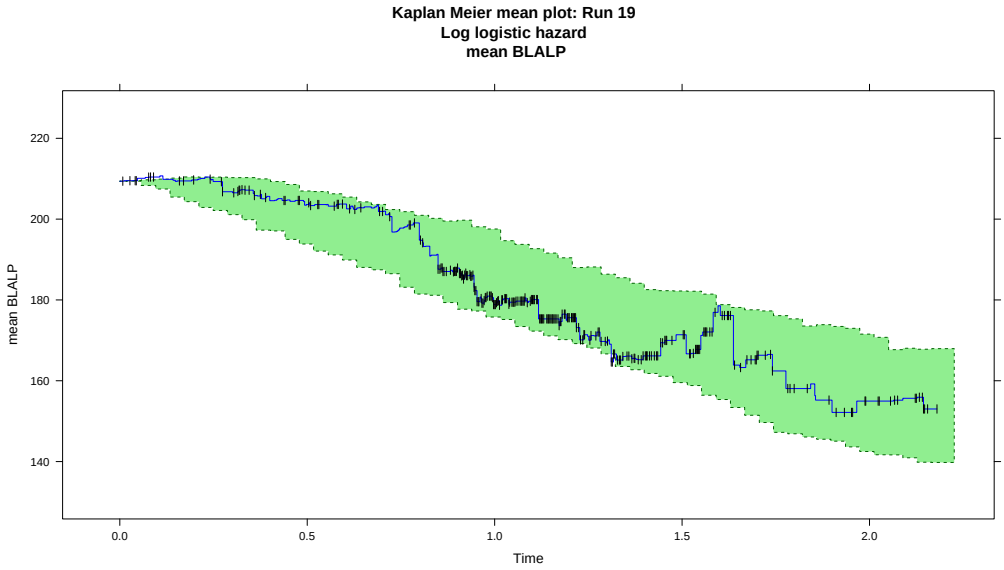


Figure 222: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

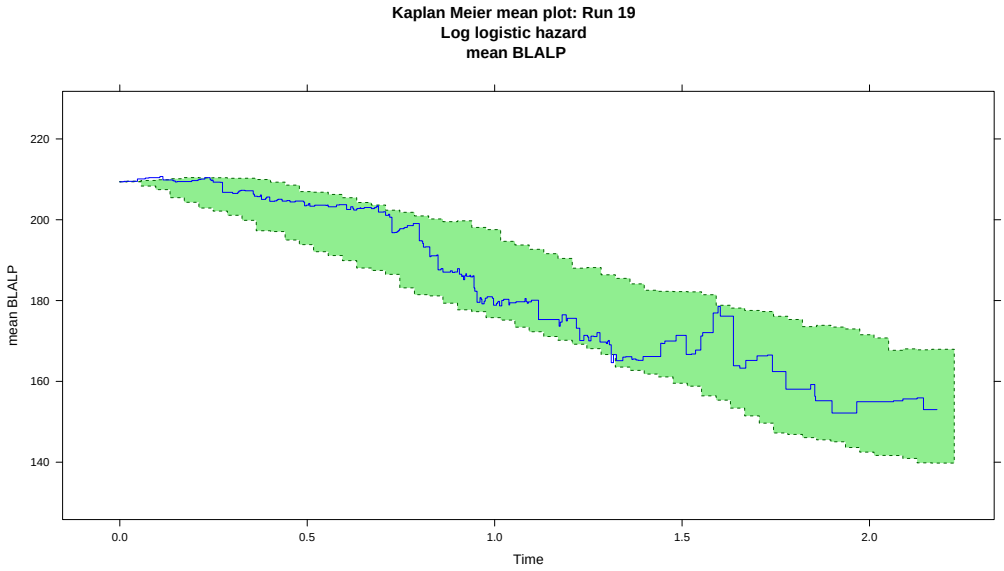


Figure 223: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

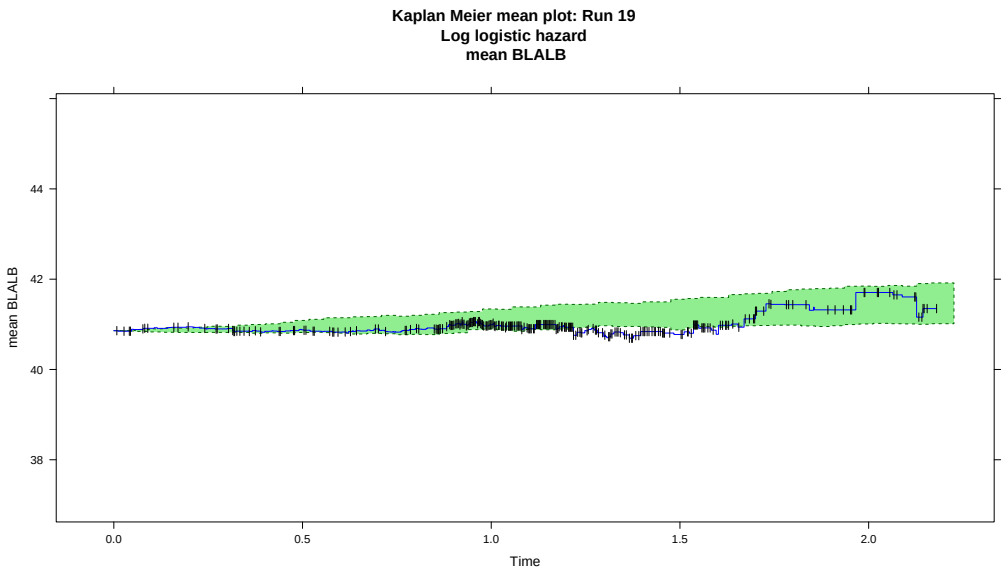


Figure 224: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

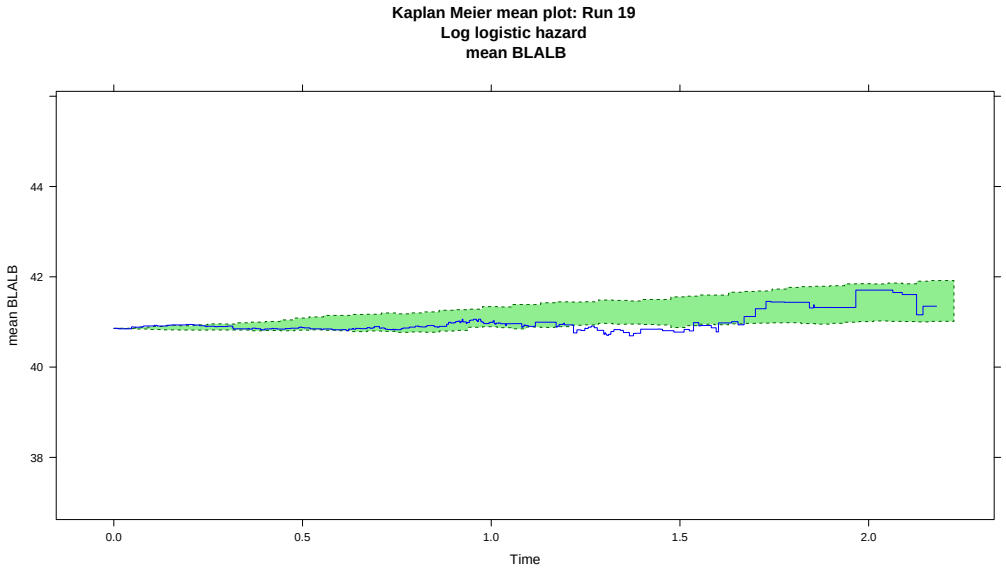


Figure 225: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

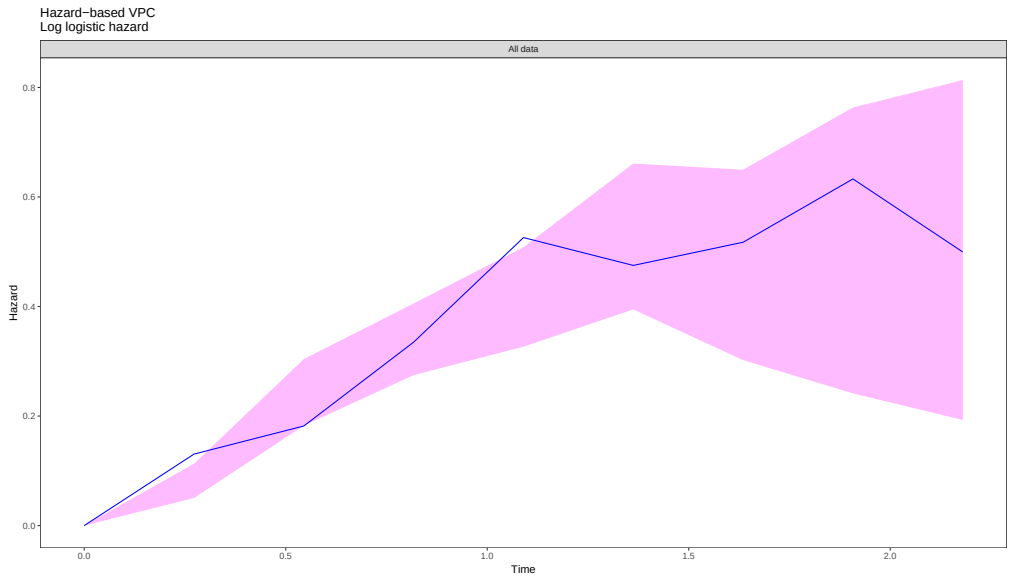


Figure 226: Simulation-based diagnostic: Hazard based VPC

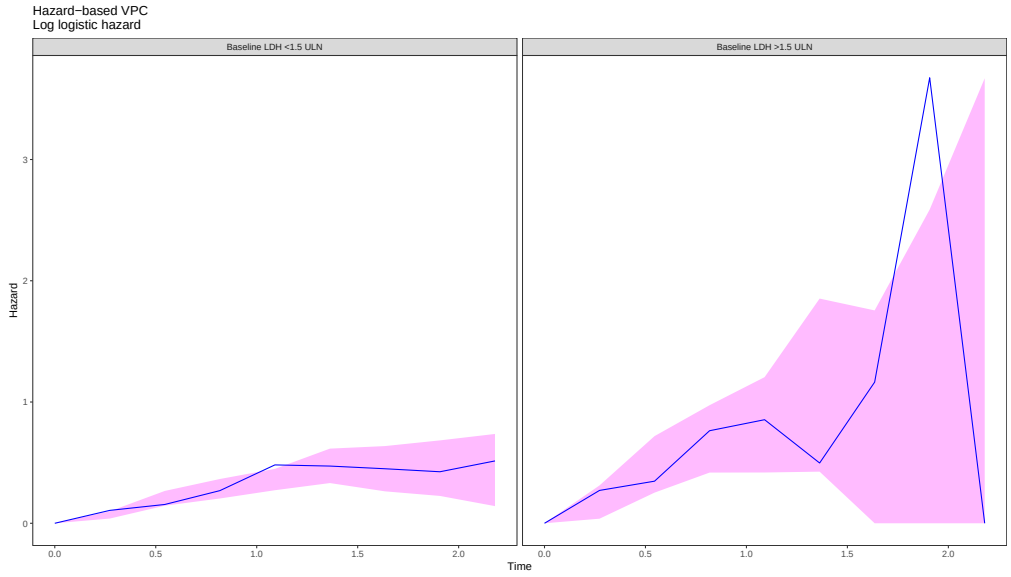


Figure 227: Simulation-based diagnostic: Hazard based VPC

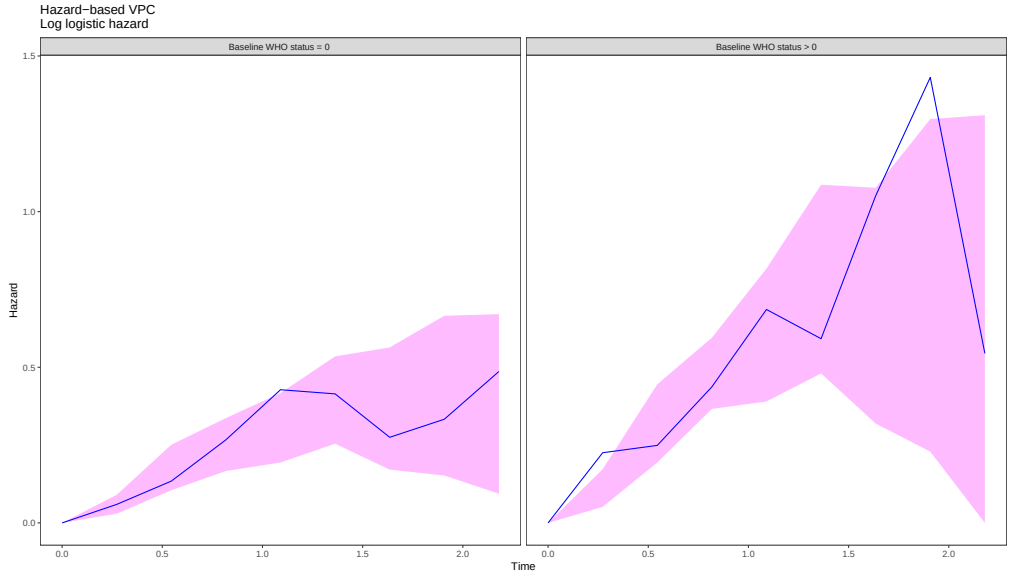


Figure 228: Simulation-based diagnostic: Hazard based VPC

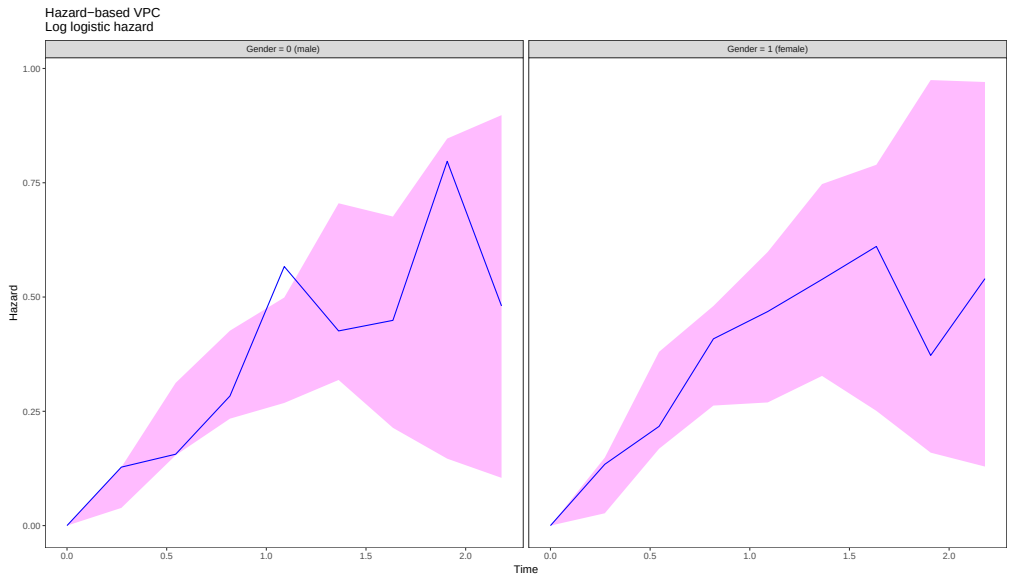


Figure 229: Simulation-based diagnostic: Hazard based VPC

12 Postamble

```
## R version 3.4.3 (2017-11-30)
## Platform: x86_64-pc-linux-gnu (64-bit)
## Running under: Red Hat Enterprise Linux Server release 6.5 (Santiago)
##
## Matrix products: default
## BLAS: /apps/phaser/prod/R-3.4.3/lib64/R/lib/libRblas.so
## LAPACK: /apps/phaser/prod/R-3.4.3/lib64/R/lib/libRlapack.so
##
## locale:
##  [1] LC_CTYPE=en_US.UTF-8       LC_NUMERIC=C
##  [3] LC_TIME=en_US.UTF-8        LC_COLLATE=en_US.UTF-8
##  [5] LC_MONETARY=en_US.UTF-8    LC_MESSAGES=en_US.UTF-8
##  [7] LC_PAPER=en_US.UTF-8       LC_NAME=C
##  [9] LC_ADDRESS=C               LC_TELEPHONE=C
## [11] LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C
##
## attached base packages:
## [1] grid      stats     graphics  grDevices utils     datasets  methods
## [8] base
##
## other attached packages:
##  [1] bindrcpp_0.2     xpose_0.4.1      xpose4_4.6.0     dplyr_0.7.4
##  [5] xtable_1.8-2     GGally_1.3.2     gridExtra_2.3    ggplot2_2.2.1
##  [9] metrumrg_5.55    MASS_7.3-47      XML_3.98-1.9     lattice_0.20-35
## [13] reshape_0.8.7    stringr_1.2.0    base64enc_0.1-3  rmarkdown_1.8
## [17] tidyselect_0.2.3 knitr_1.18       tidyr_0.7.2
##
## loaded via a namespace (and not attached):
##  [1] Rcpp_0.12.14       bindr_0.1          pillar_1.0.1
##  [4] compiler_3.4.3     RColorBrewer_1.1-2 plyr_1.8.4
##  [7] iterators_1.0.9    tools_3.4.3        digest_0.6.13
## [10] evaluate_0.10.1    tibble_1.4.1       gtable_0.2.0
## [13] pkgconfig_2.0.1    rlang_0.1.6        Matrix_1.2-12
## [16] foreach_1.4.4      yaml_2.1.16        rprojroot_1.3-2
## [19] glue_1.2.0         R6_2.2.2           survival_2.41-3
## [22] udunits2_0.13      tweenr_0.1.5       purrr_0.2.4
## [25] magrittr_1.5       units_0.5-1        codetools_0.2-15
## [28] splines_3.4.3      backports_1.1.2    scales_0.5.0
## [31] htmltools_0.3.6    assertthat_0.2.0   ggforce_0.1.1
## [34] colorspace_1.3-2   labeling_0.3       stringi_1.1.6
## [37] lazyeval_0.2.1     munsell_0.4.3      gam_1.14-4
```