

TTE Modeling History

Giselle Benitez

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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 upc

## 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/ProjectDataSphere.RData")
```

2 Objectives

1. Develop a base time to event model for AZ Cediranib data, ProjectDataSphere # 78
2. Assess the impact of categorical 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 BLHOSTAT 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 occurred 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, binary covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5 upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLHOSTAT, 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 BLAL
## ;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 BLHOSTAT 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)

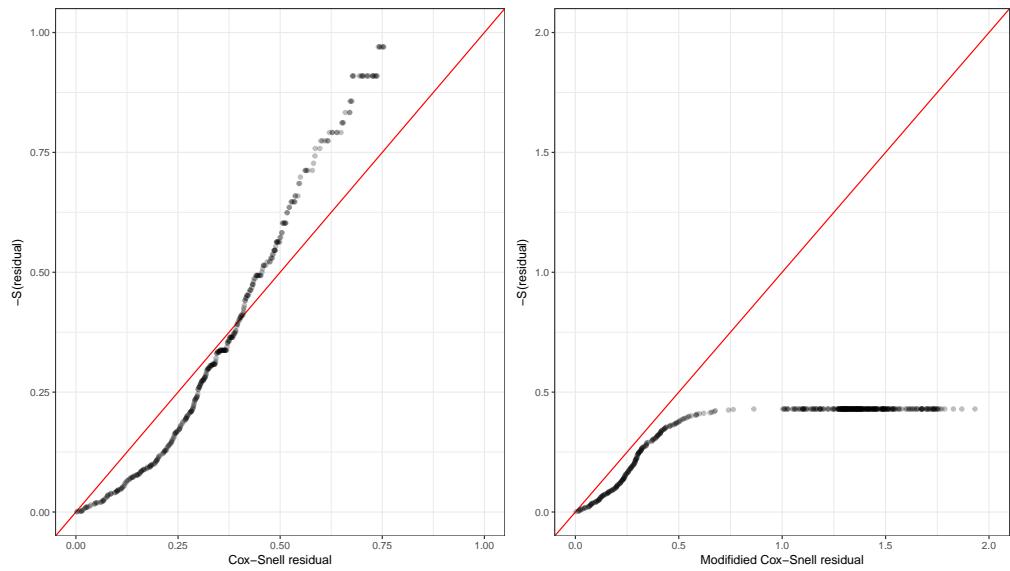


Figure 1: Residual-based diagnostics

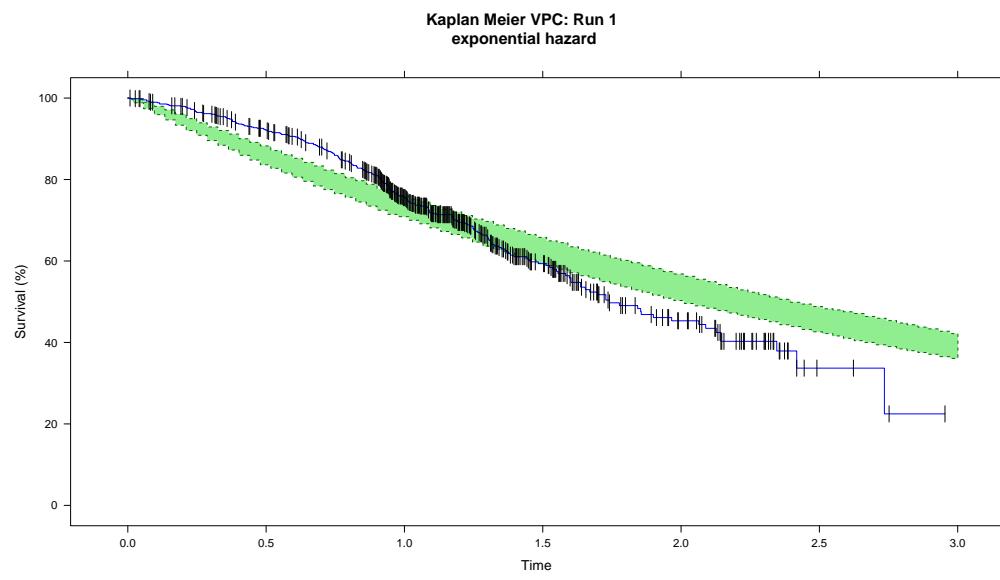


Figure 2: Simulation-based diagnostic: Kaplan Meier plot

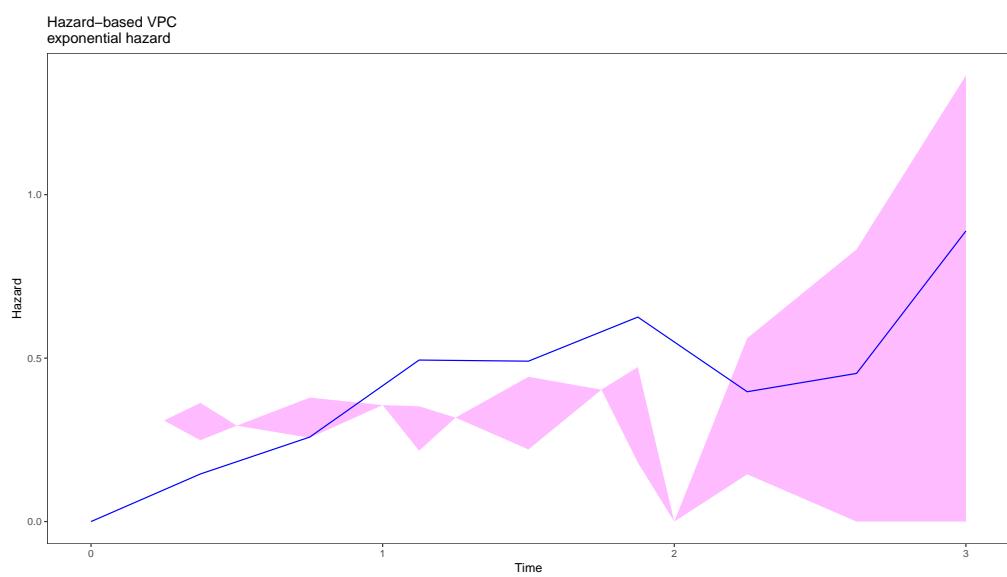


Figure 3: Simulation-based diagnostic: Hazard based VPC

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 BLHOSTAT BLALB BLALP BLWOLEVE
## ;
## ;-----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 occurred 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, binary 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 BLHOSTAT BLALB BLALP BLWOLEVEL 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 BLHOSTAT BLALB BLALP BLWOLEVEL
## 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"
## [6] "No rounding errors"
## [7] "No zero gradients"
## [8] "No final zero gradients"
## [9] "Hessian not reset"
## [10] "No parameter near boundary"
## [11] "Covariance step"
## [12] ""
## [13] "Condition number"
## [14] "Correlations"
## [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

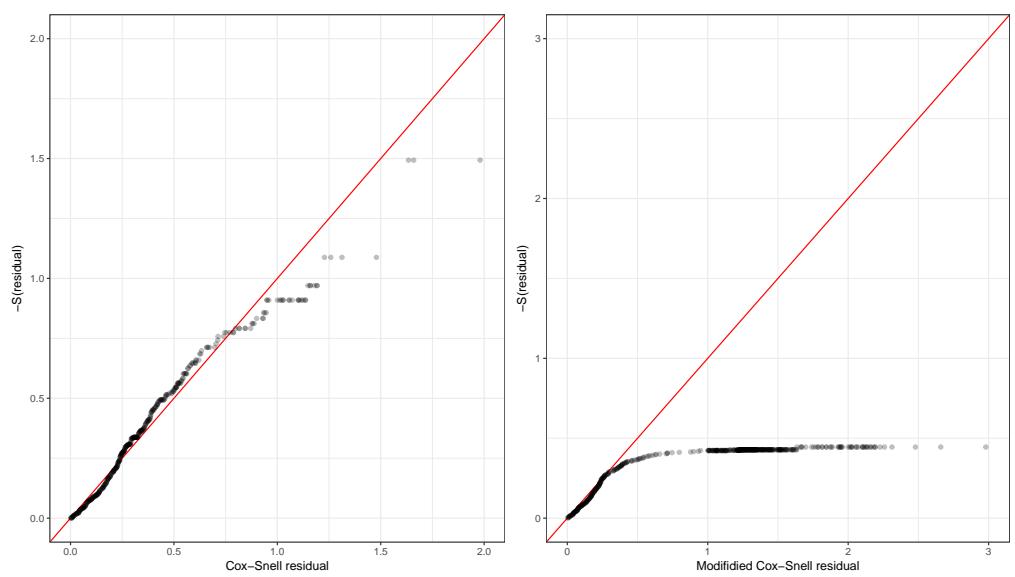


Figure 4: Residual-based diagnostics

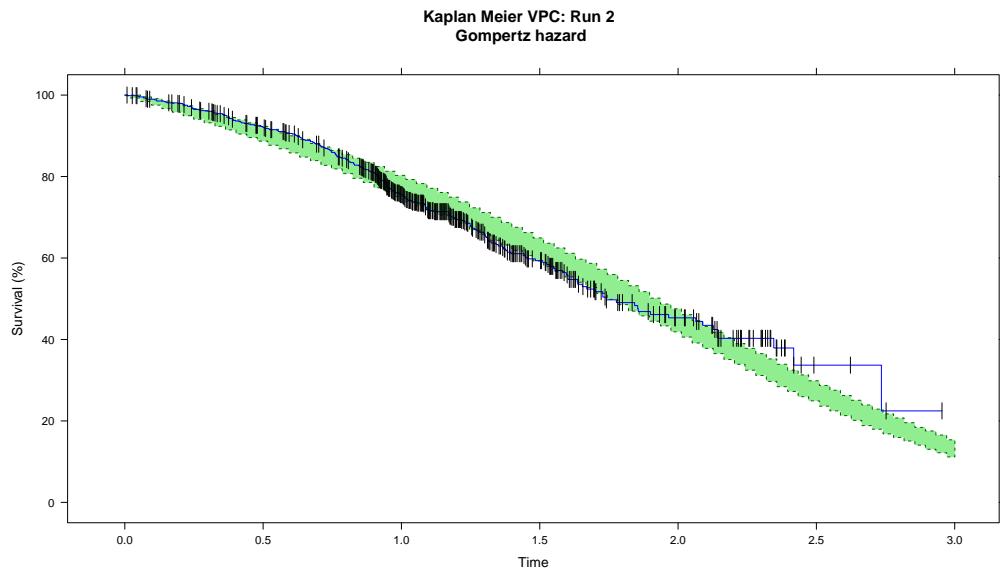


Figure 5: Simulation-based diagnostic

3.0.2.3 Evaluation of run 2

- Gompertz hazard better captures 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 inappropriate

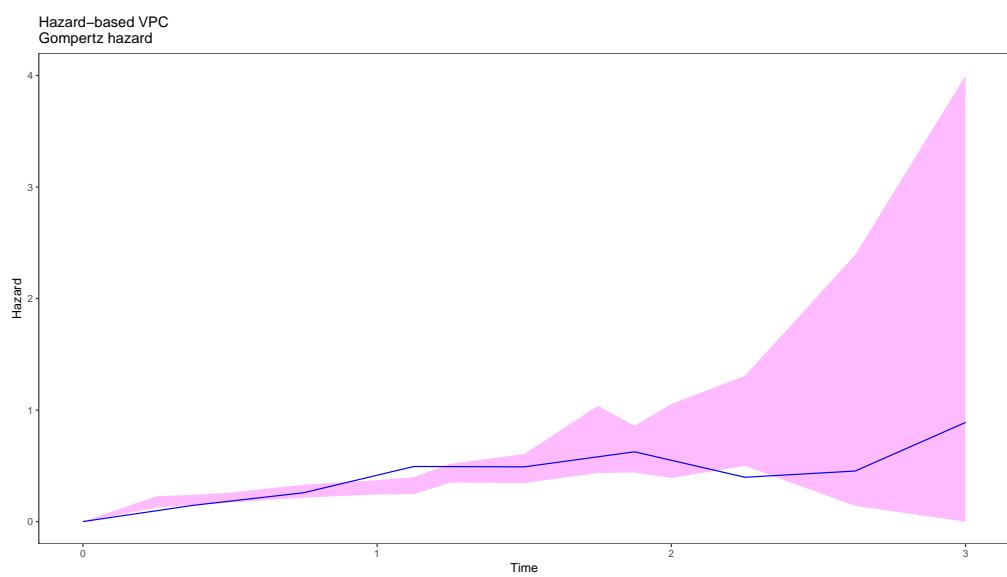


Figure 6: Simulation-based diagnostic: Hazard based VPC

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 BLALB BLALP BLWOLEVEL
##
## ;-----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 occurred 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, binary covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5 upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWOLEVEL, 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 BLDDH BLAGE BLWHOSTAT BLALB BLALP BLWLEVEL 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 BLDDH BLAGE BLWHOSTAT BLALB BLALP BLWLEVEL
##
## 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"
## [6] "No rounding errors"
## [7] "No zero gradients"
## [8] "No final zero gradients"
## [9] "Hessian not reset"
## [10] "No parameter near boundary"
## [11] "Covariance step"
## [12] ""
## [13] "Condition number"
## [14] "Correlations"
## [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

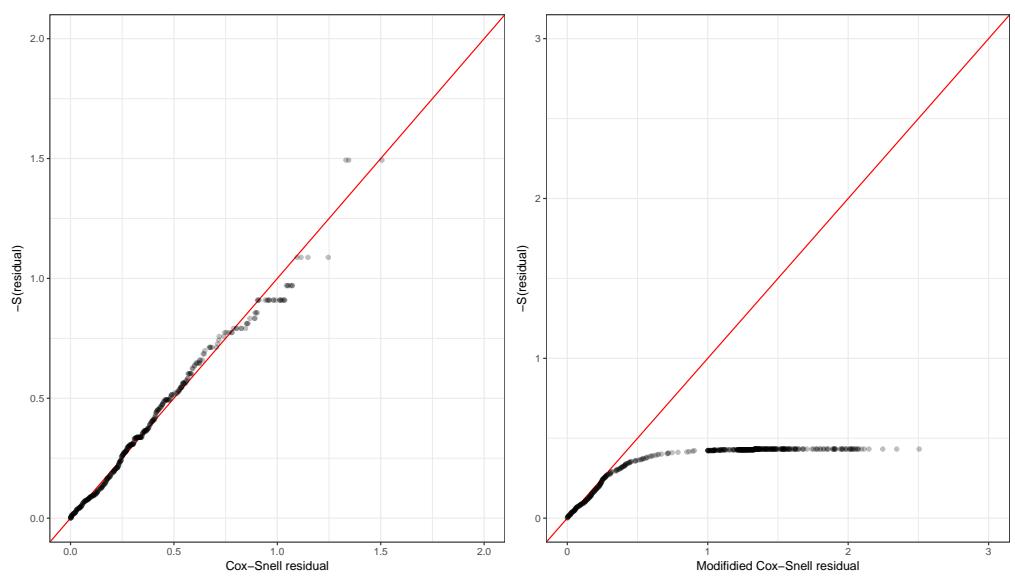


Figure 7: Residual-based diagnostics

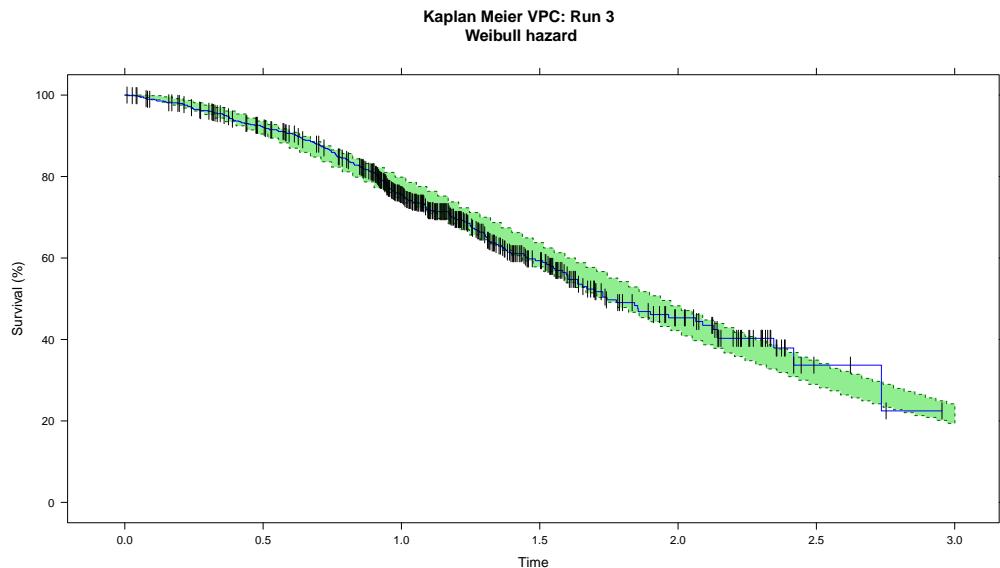


Figure 8: Simulation-based diagnostic

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.

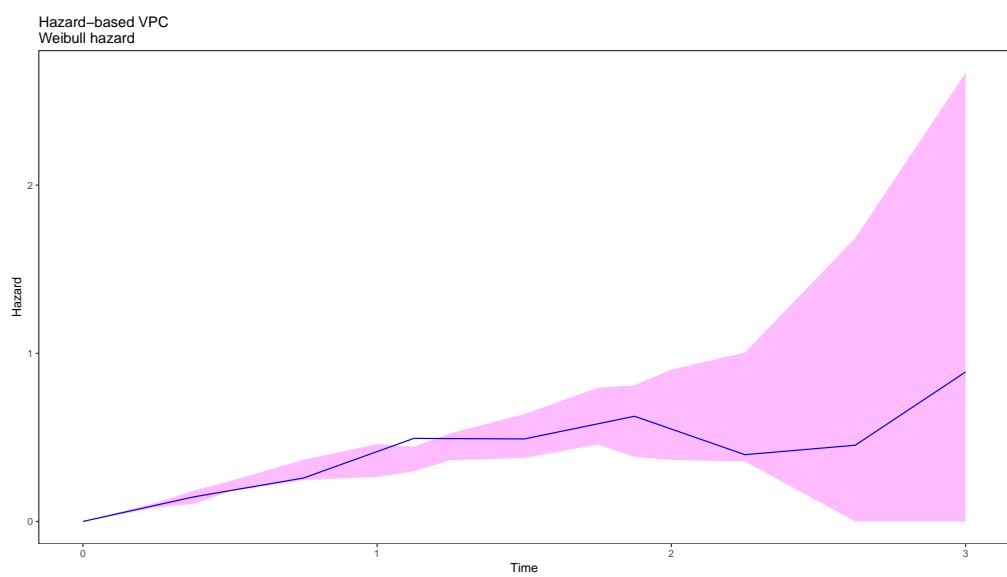


Figure 9: Simulation-based diagnostic: Hazard based VPC

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 BLALB BLALP BLWHOLEVEL
## ;
## ;-----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 occurred 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, binary covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5 upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLHOSTAT, 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 BLDDH BLAGE BLWHOSTAT BLALB BLALP BLWLEVEL 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 BLDDH BLAGE BLWHOSTAT BLALB BLALP BLWLEVEL
##
## 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"
## [6] "No rounding errors"
## [7] "No zero gradients"
## [8] "No final zero gradients"
## [9] "Hessian not reset"
## [10] "No parameter near boundary"
## [11] "Covariance step"
## [12] ""
## [13] "Condition number"
## [14] "Correlations"
## [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

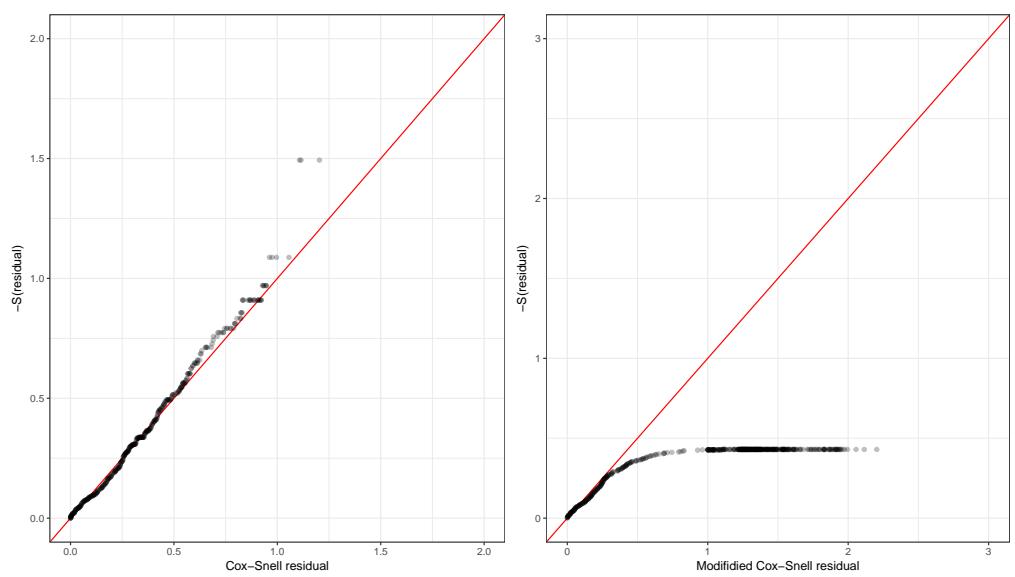


Figure 10: Residual-based diagnostics

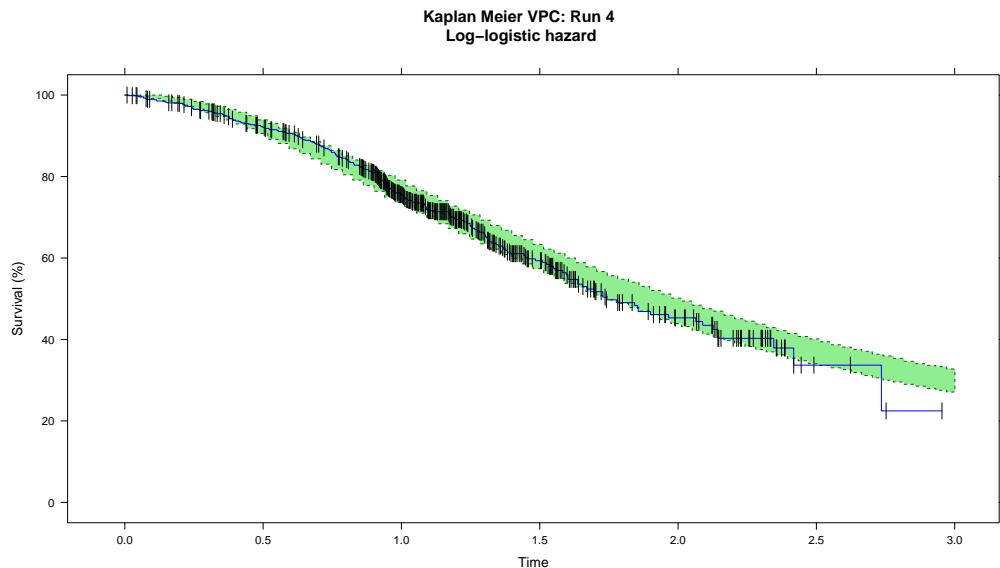


Figure 11: Simulation-based diagnostic

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)

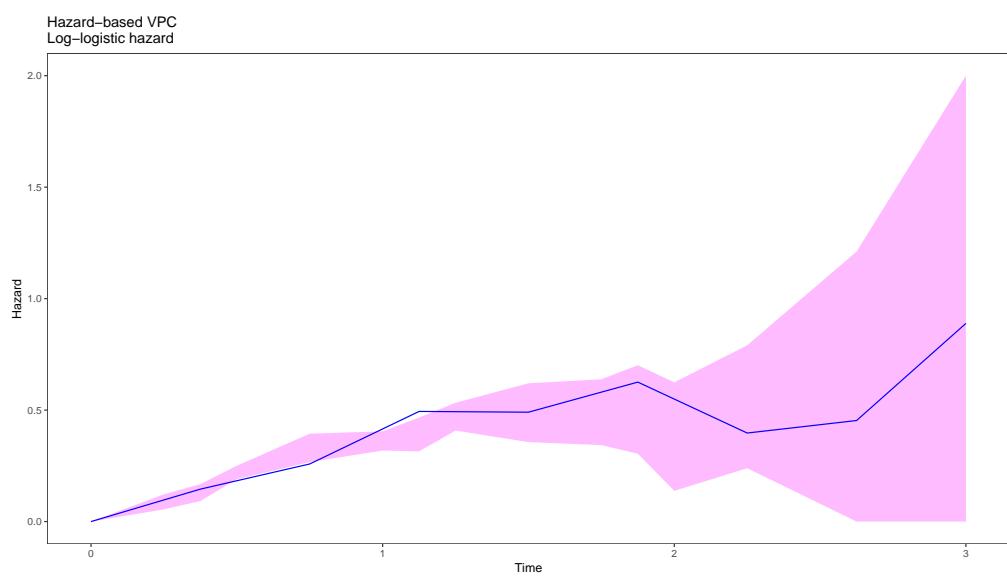


Figure 12: Simulation-based diagnostic: Hazard based VPC

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
##               BLHOSTAT 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 occurred 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, binary 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
##
## ; BLWOLEVEL, 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"
## [6] "No rounding errors"
## [7] "No zero gradients"
## [8] "No final zero gradients"
## [9] "Hessian not reset"
## [10] "No parameter near boundary"
## [11] "Covariance step"
## [12] ""
## [13] "Condition number"
## [14] "Correlations"
## [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

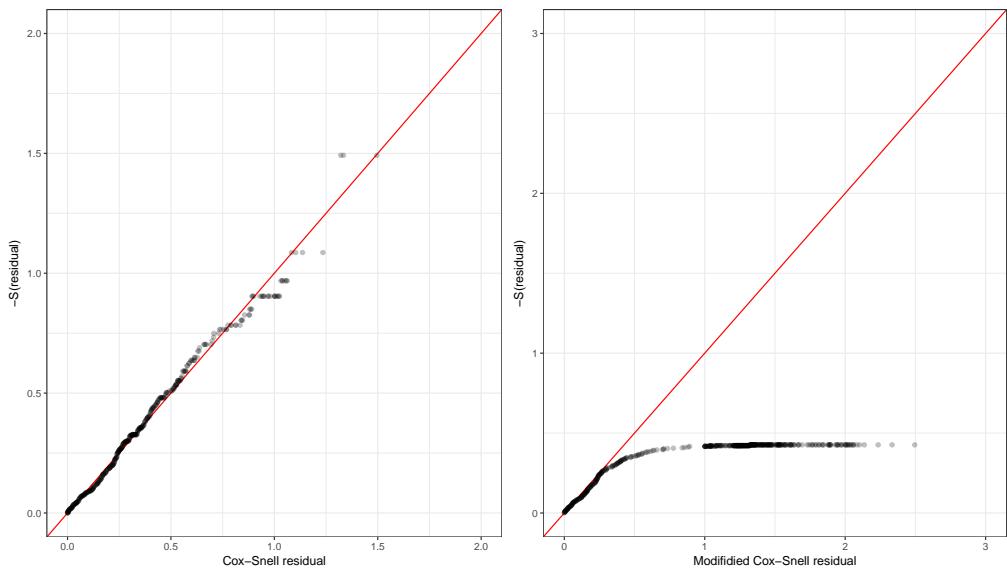


Figure 13: Residual-based diagnostics

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

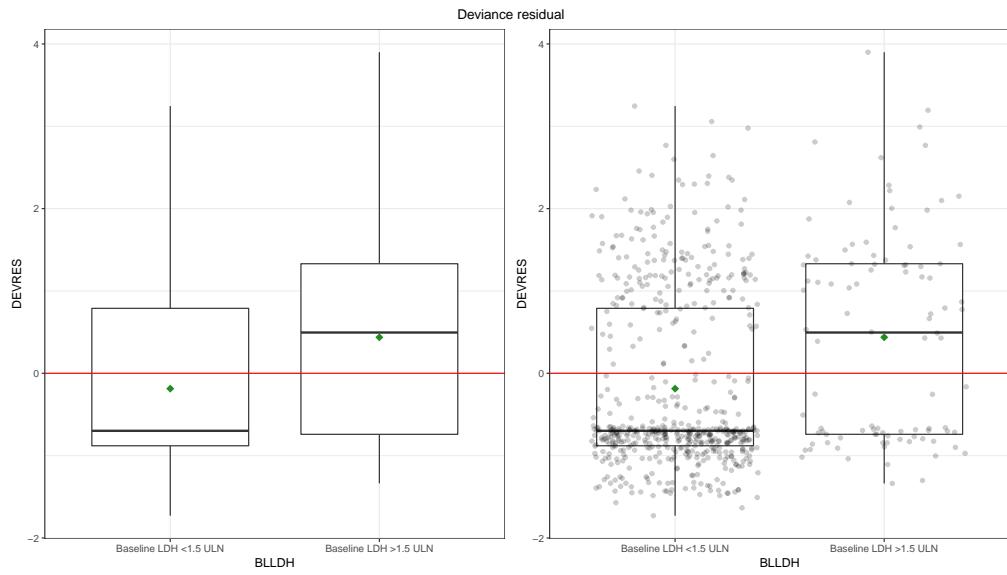


Figure 14: Residual-based diagnostics - Deviance plot

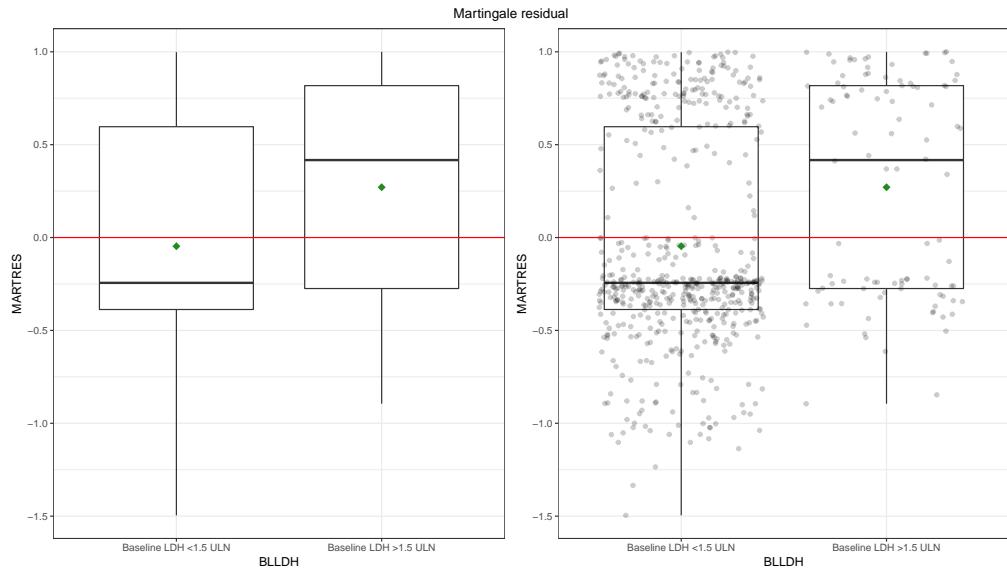


Figure 15: Residual-based diagnostics - Martingale plot

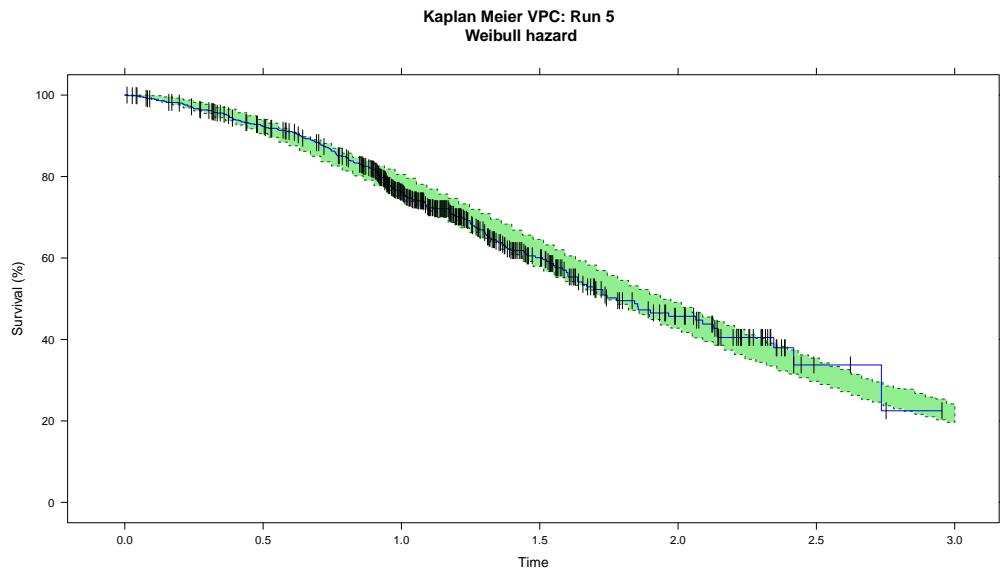


Figure 16: Simulation-based diagnostic

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 diagnostics (KM VPC, hbVPC and Cox-Snell residuals) do not appear to be impacted

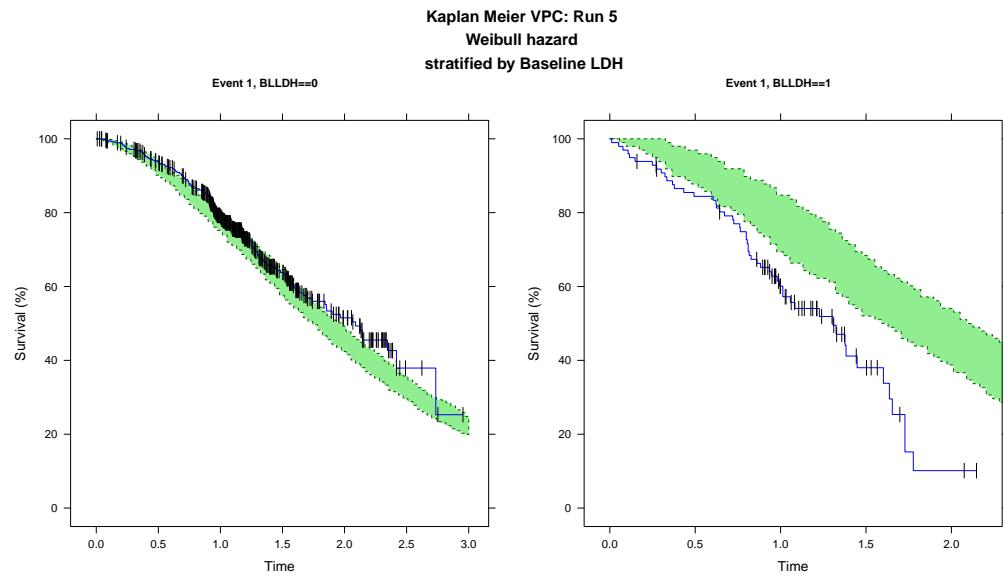


Figure 17: Simulation-based diagnostic - stratified by baseline LDH

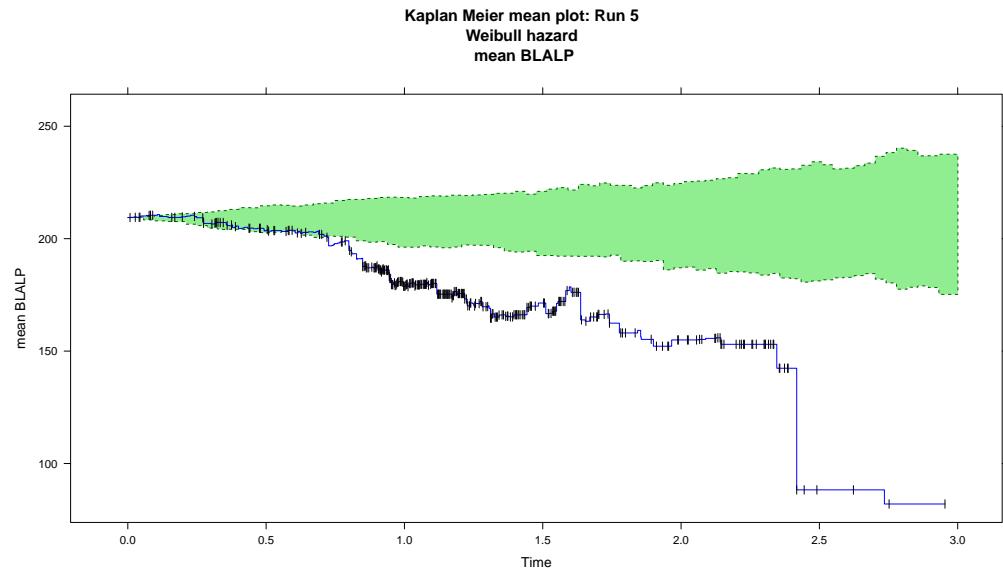


Figure 18: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

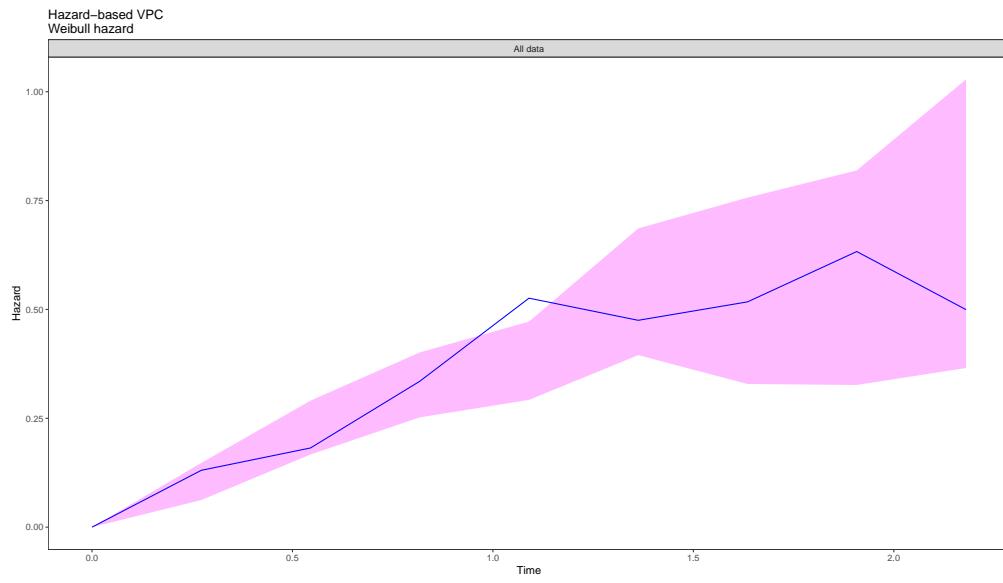


Figure 19: Simulation-based diagnostic: Hazard based VPC

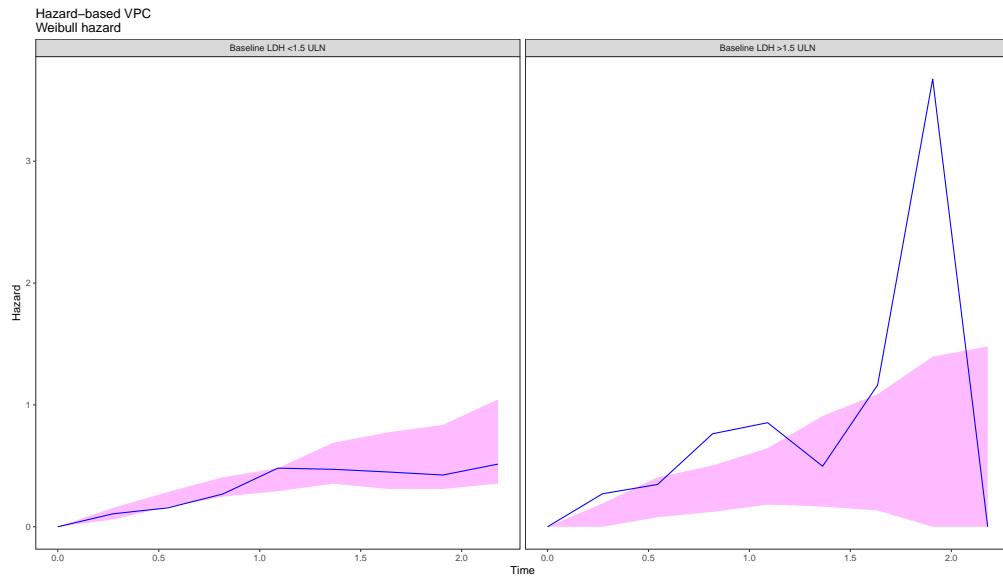


Figure 20: Simulation-based diagnostic: Hazard based VPC

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
##                 BLHOSTAT BLALB BLALP BLWOLEVEL 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 occurred 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, binary covariate (0=male,1=female)
##
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5 upper limit of normal
##
## ; BLAGE, categorical, age group in years
```

```

## ; BLHOSTAT, 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

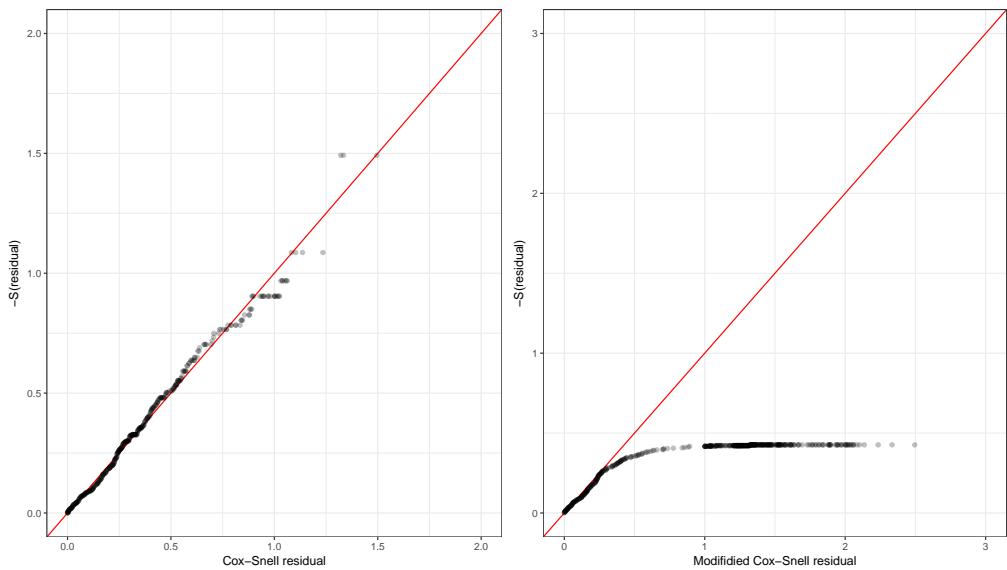


Figure 21: Residual-based diagnostics

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

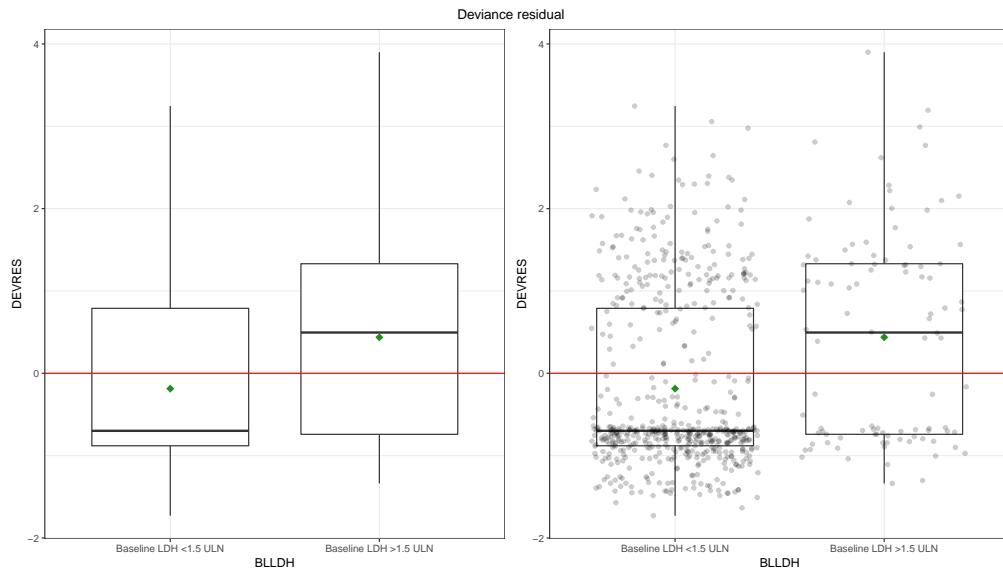


Figure 22: Residual-based diagnostics - Deviance plot

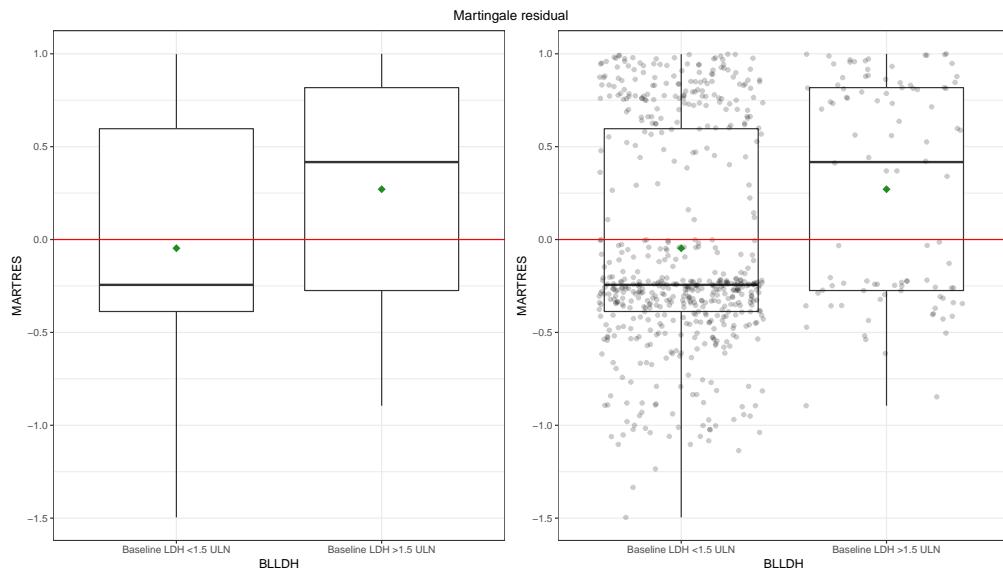


Figure 23: Residual-based diagnostics - Martingale plot

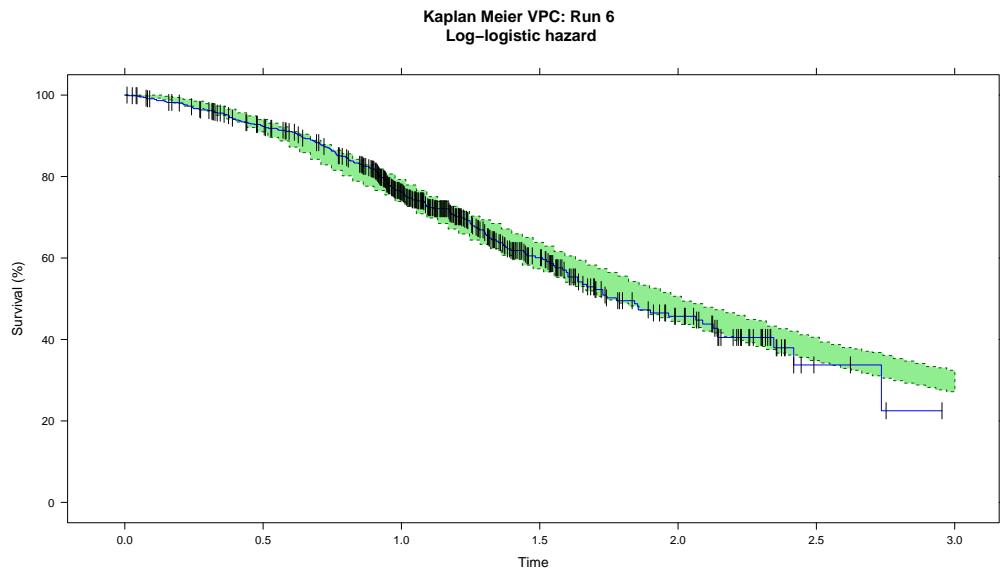


Figure 24: Simulation-based diagnostic

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 diagnostics (KM VPC, hbVPC and Cox-Snell residuals) do not appear to be impacted

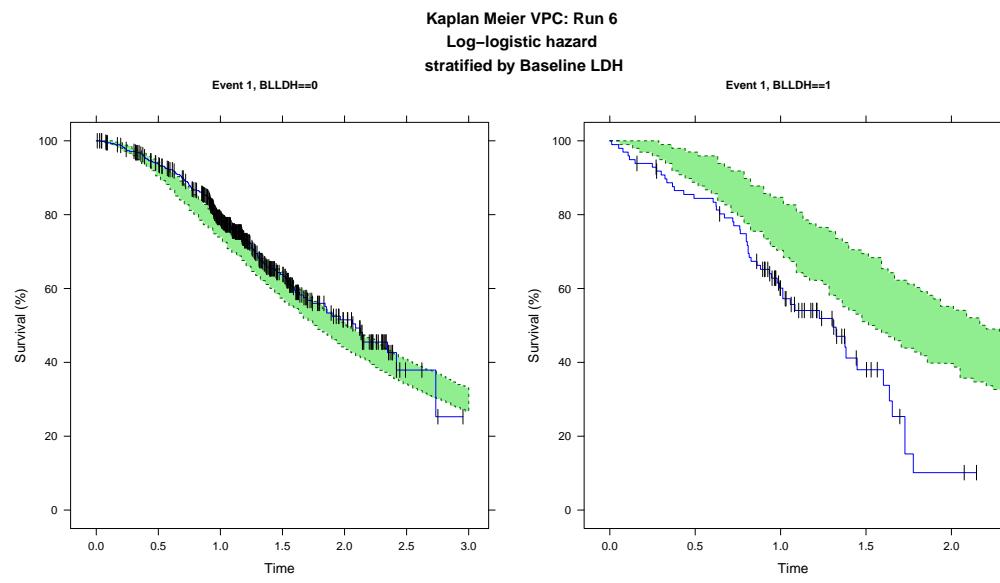


Figure 25: Simulation-based diagnostic - stratified by baseline LDH

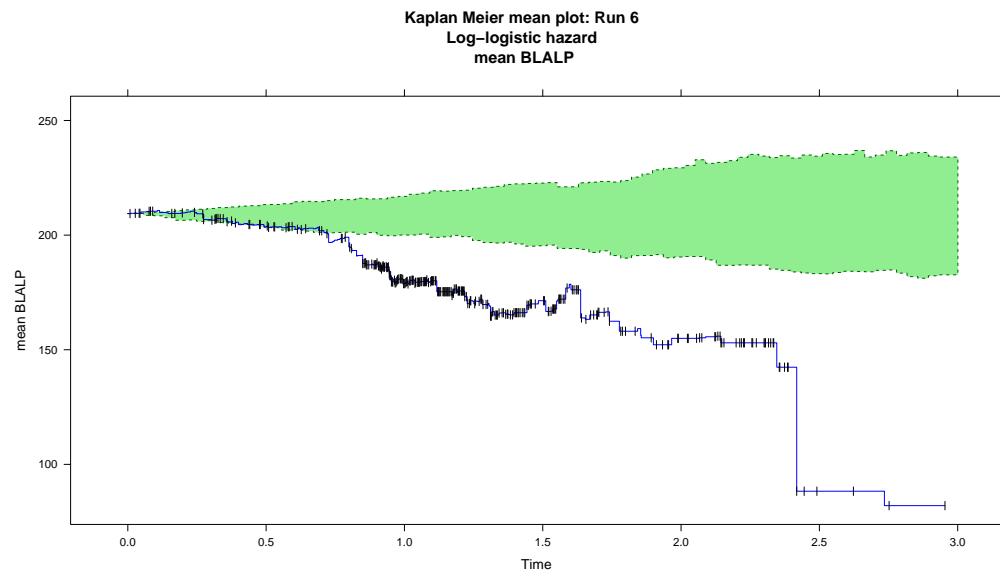


Figure 26: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

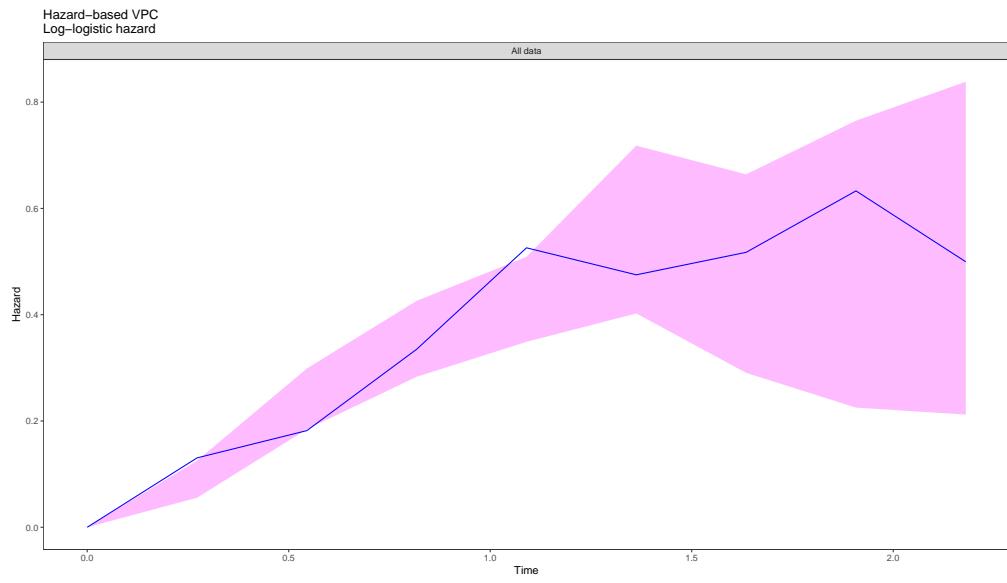


Figure 27: Simulation-based diagnostic: Hazard based VPC

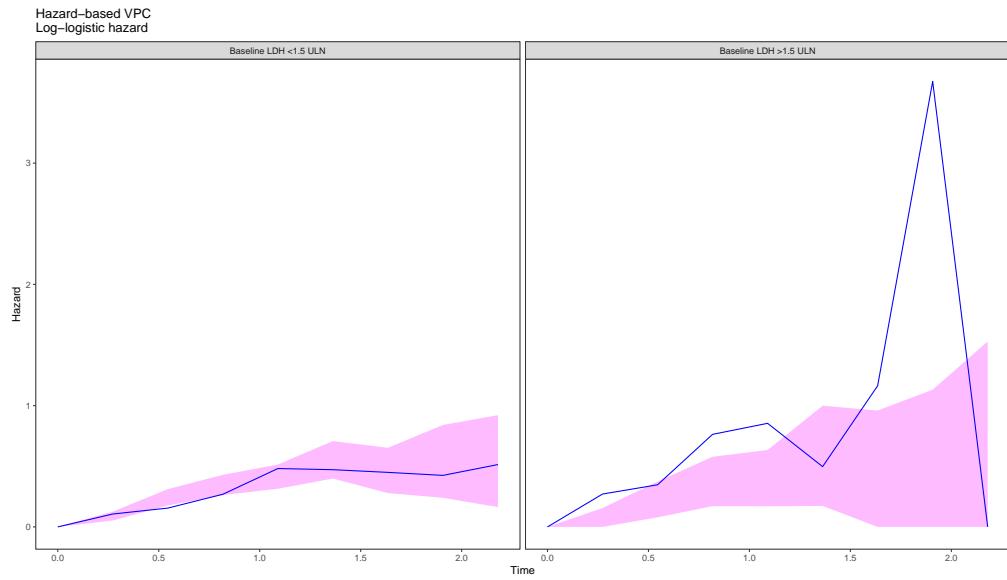


Figure 28: Simulation-based diagnostic: Hazard based VPC

5 Explore covariate relationships

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

```
## Emax model, baseline ALP (initial 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)

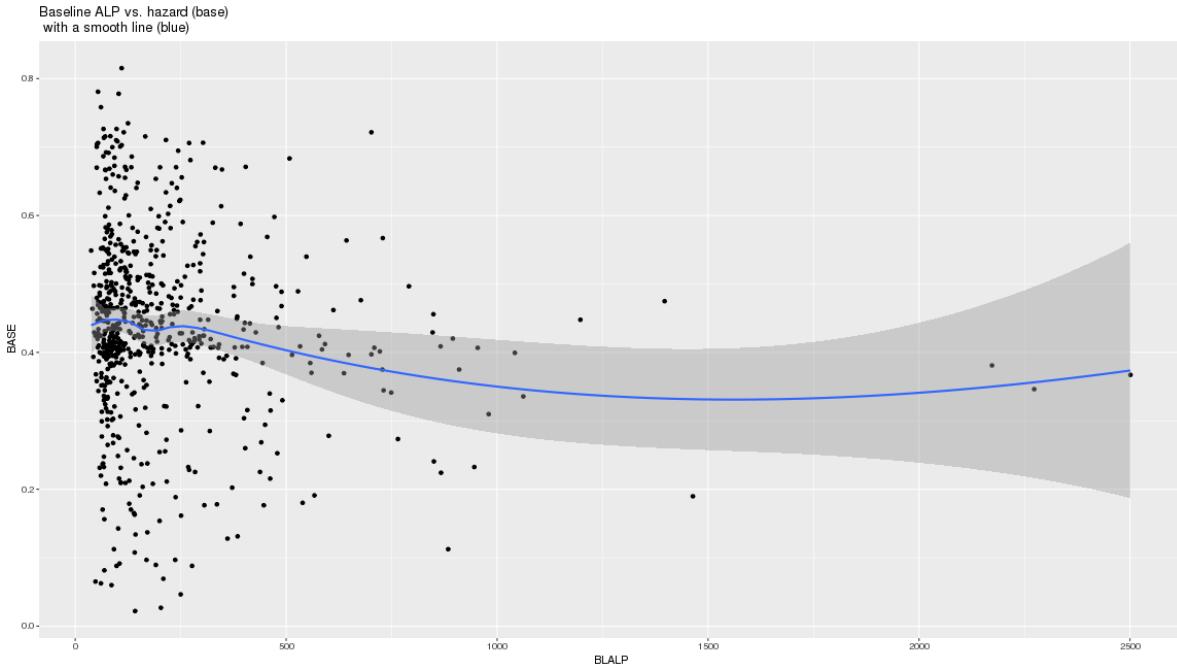
dat_in5.1 <- dat_in5 %>% select(ID, TIME, DV, BASE, LAMBDA, BLALP, BLLDH) %>%
  mutate(logBLALP = log(BLALP)) %>%
  mutate(LDH = factor(BLLDH, levels =c(0,1),
  labels=c('baseline LDH \n within normal range', 'baseline LDH \n > 1.5 ULN')))

##    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)))

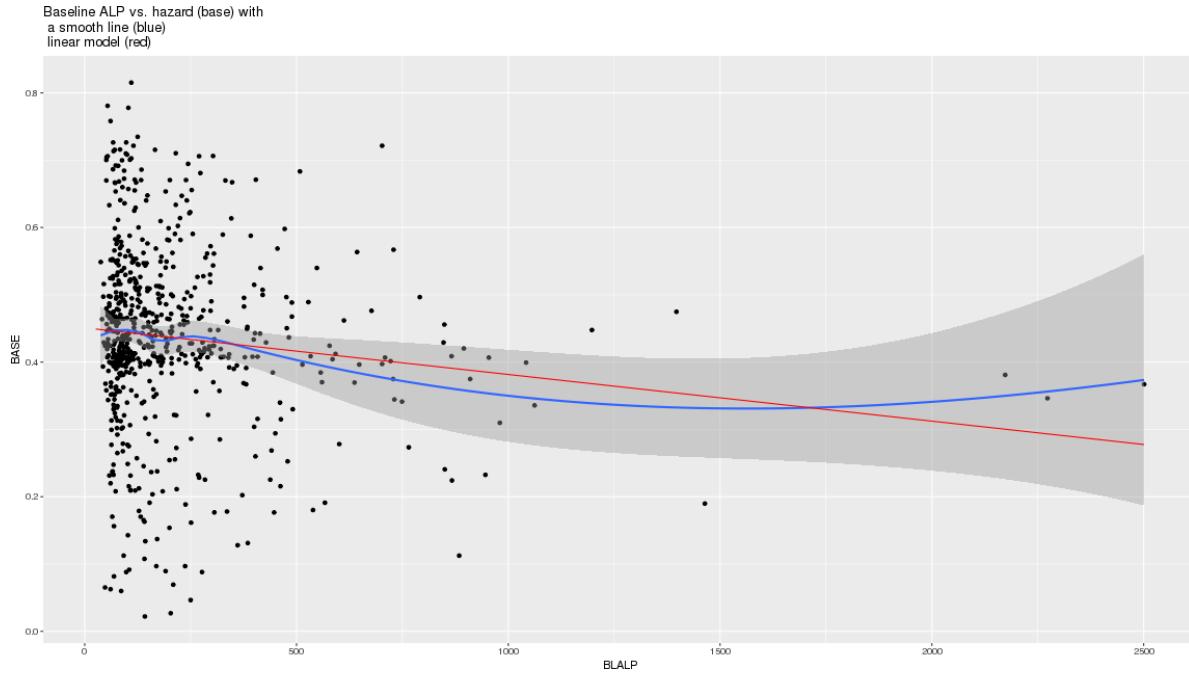
# linear model

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)')
```



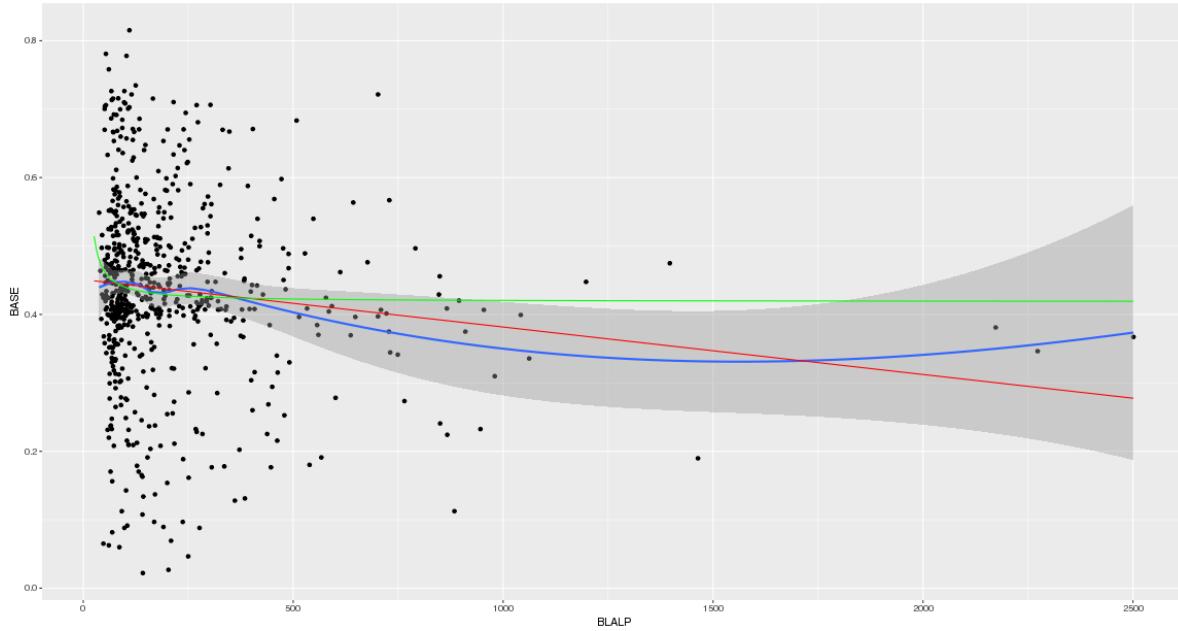
```
# Emax model
emax.mod <- nls(BASE ~ EMAX*BLALP/(EC50+BLALP), data=dat_in5.1, start=list(EC50=50, EMAX=100))
summary(emax.mod)
```

```
##
## 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
```

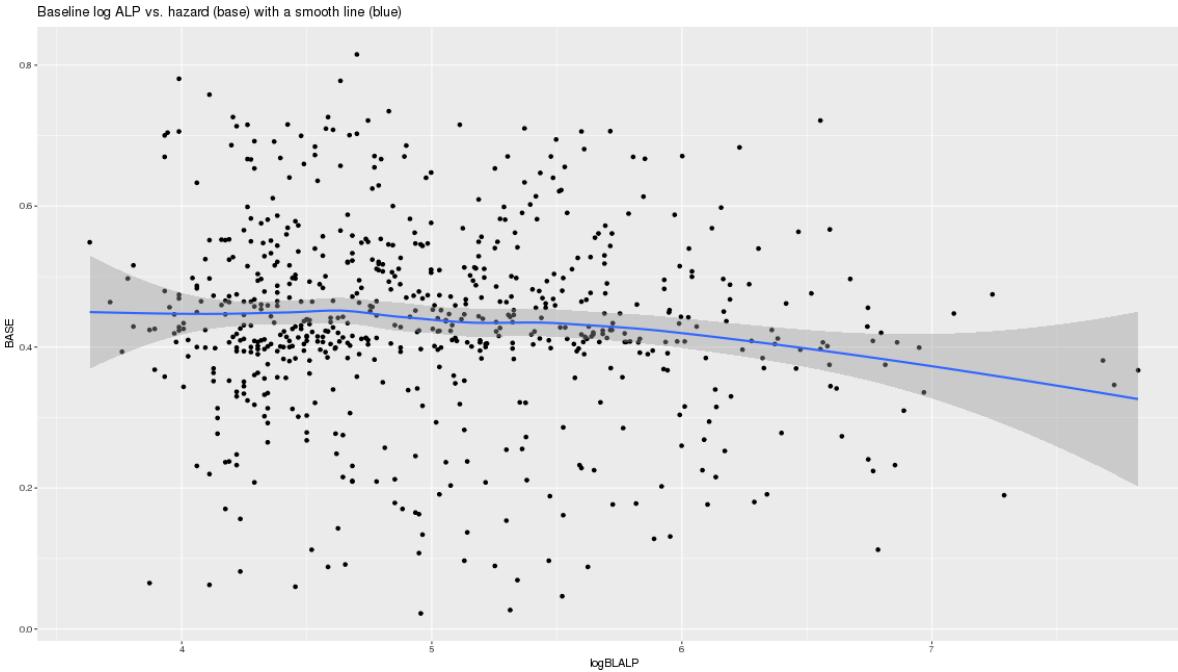
```
pred_alp_emax =within(pred,{
  PRED = predict(emax.mod, newdata=pred)
})
```

```
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
```

Baseline ALP vs. hazard (base) with: a smooth line (blue) linear model (red)
hyperbolic Emax model (green)



```
# 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)
```

##

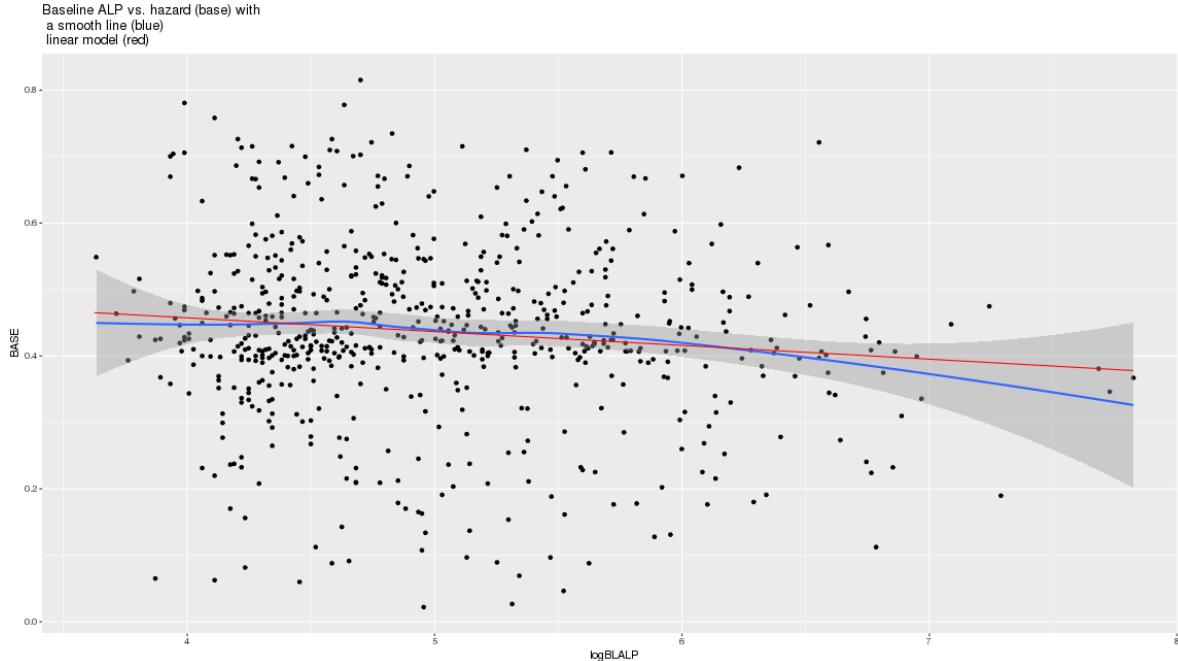
```

## 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:

```

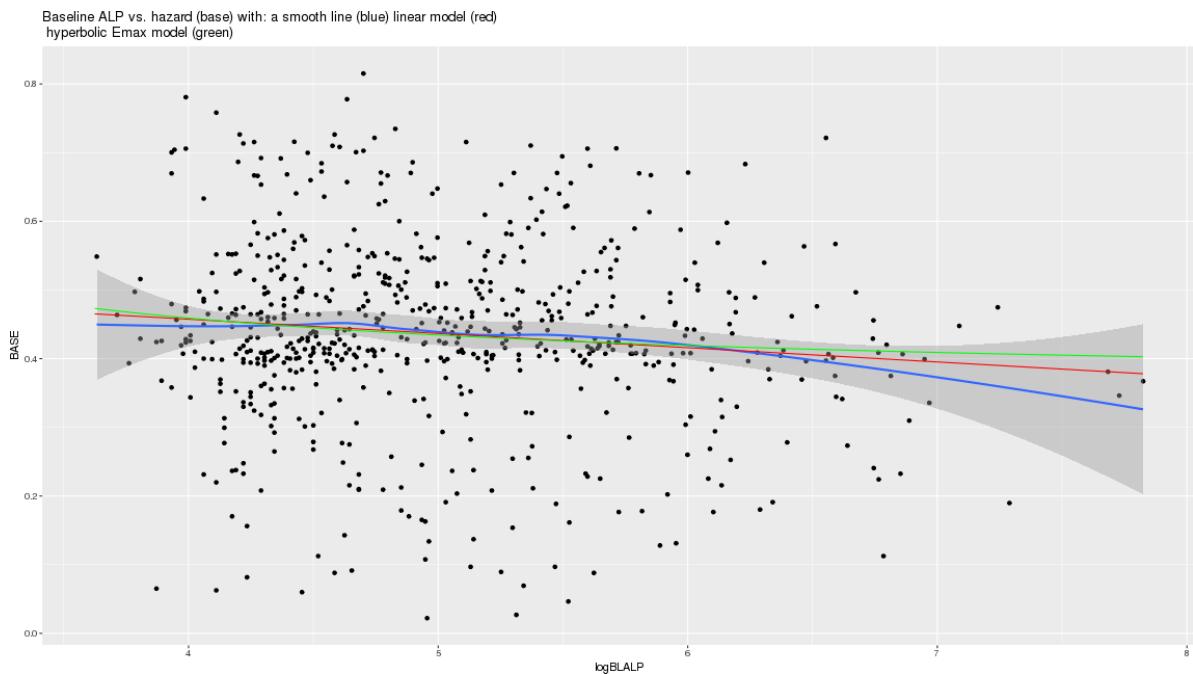
```

##      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)
})

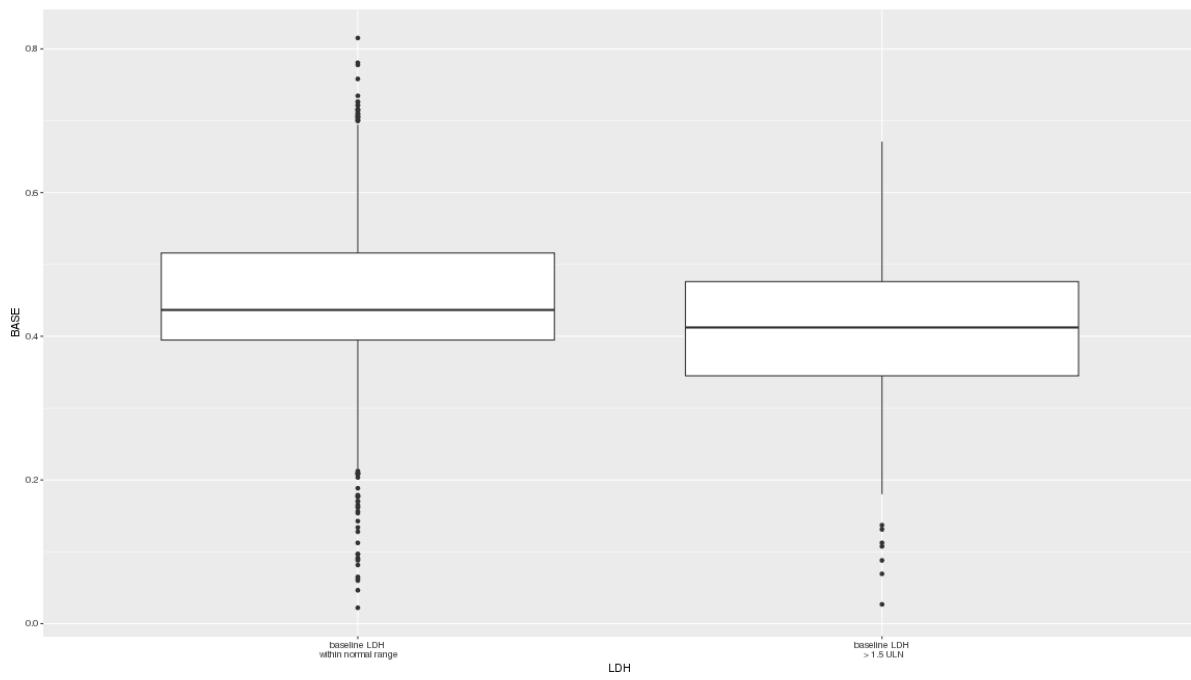
pl.base.log + geom_line(data=pred_alp_log.lnr, aes(x=logBLALP, y=PRED), color='red')+
  geom_line(data=logpred_alp_emax, aes(x=logBLALP, y=PRED), color='green')+
  ggtitle('Baseline ALP vs. hazard (base) with: a smooth line (blue) linear model (red) \n hyperbolic Emax model (green)')

```



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

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



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
##           BLHOSTAT 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 occurred 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, binary covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5 upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWOLEVEL, 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"
## [6] "No rounding errors"
## [7] "No zero gradients"
## [8] "No final zero gradients"
## [9] "Hessian not reset"
## [10] "No parameter near boundary"
## [11] "Covariance step"
## [12] ""
## [13] "Condition number"
## [14] "Correlations"
## [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

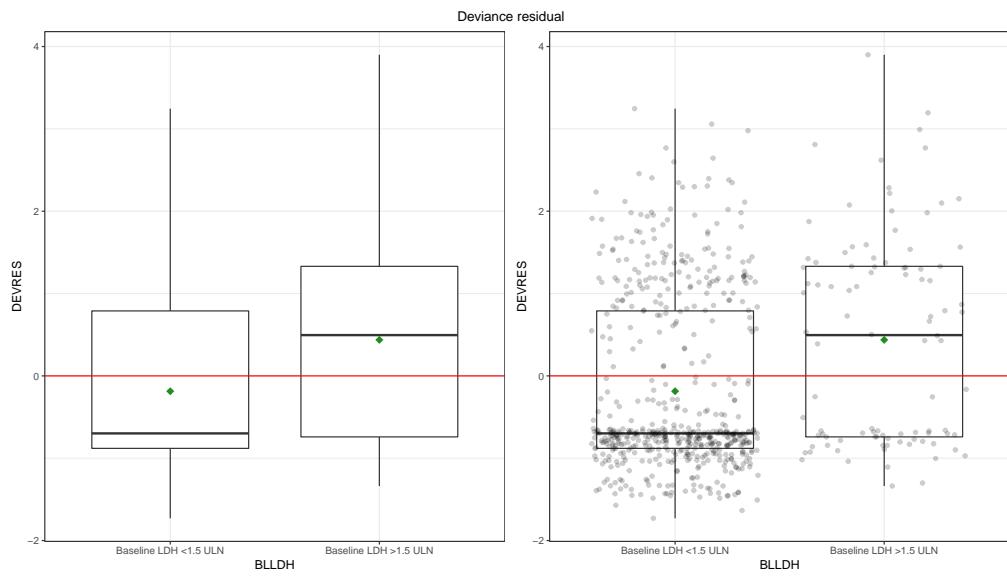


Figure 29: Residual-based diagnostics - Deviance plot

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

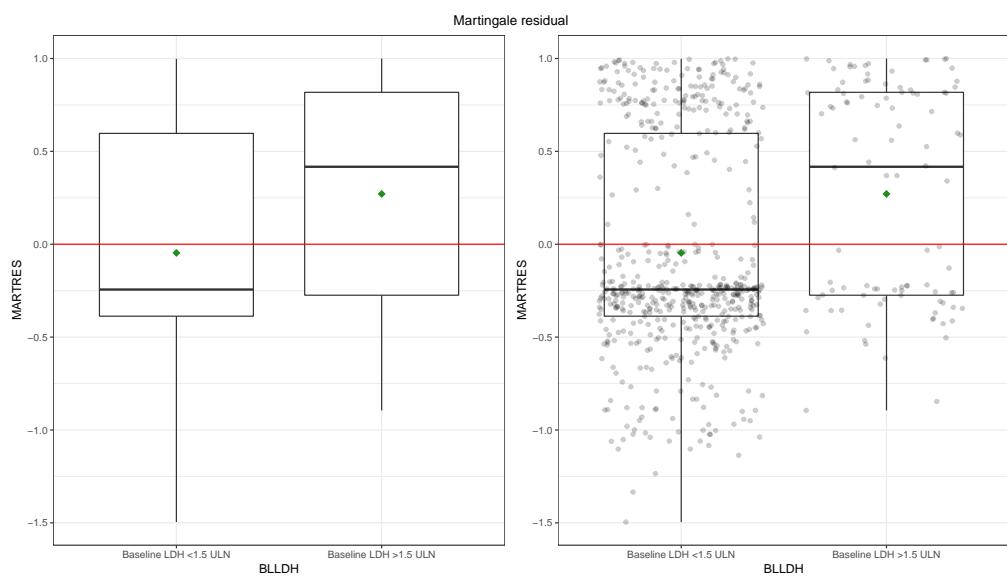
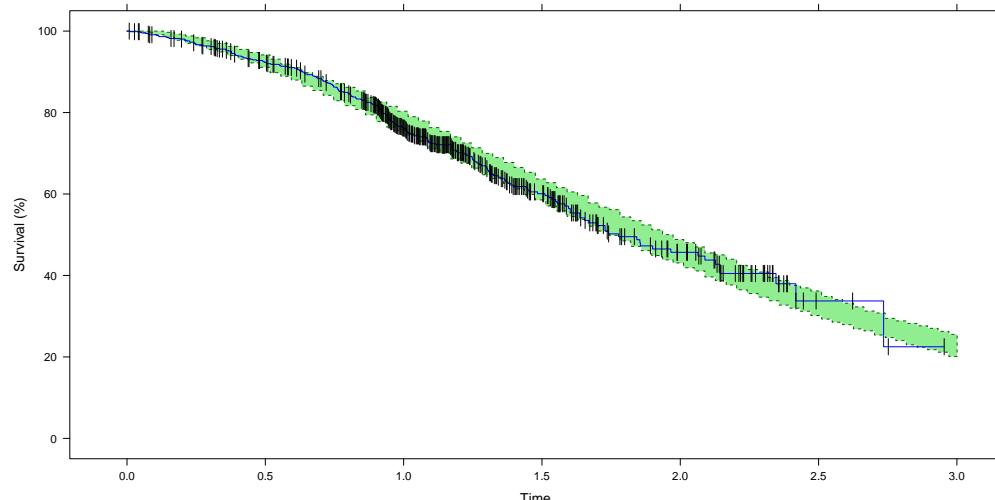
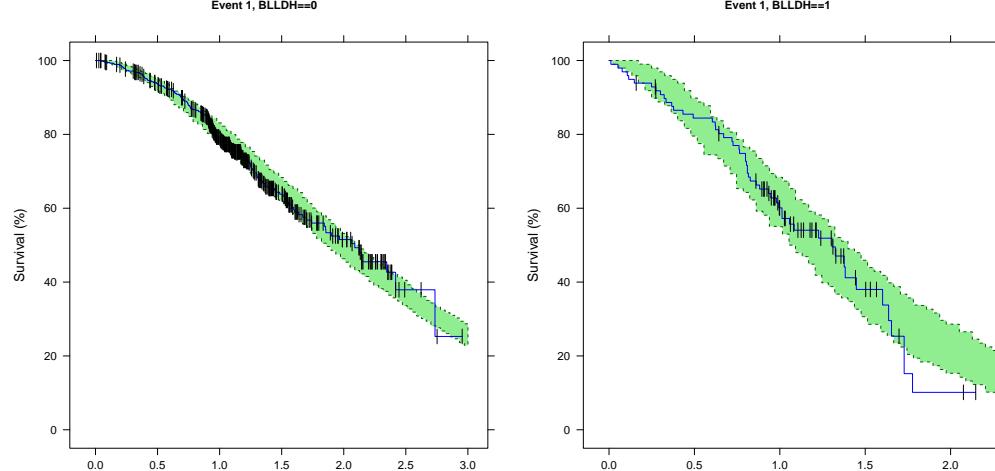


Figure 30: Residual-based diagnostics - Martingale plot

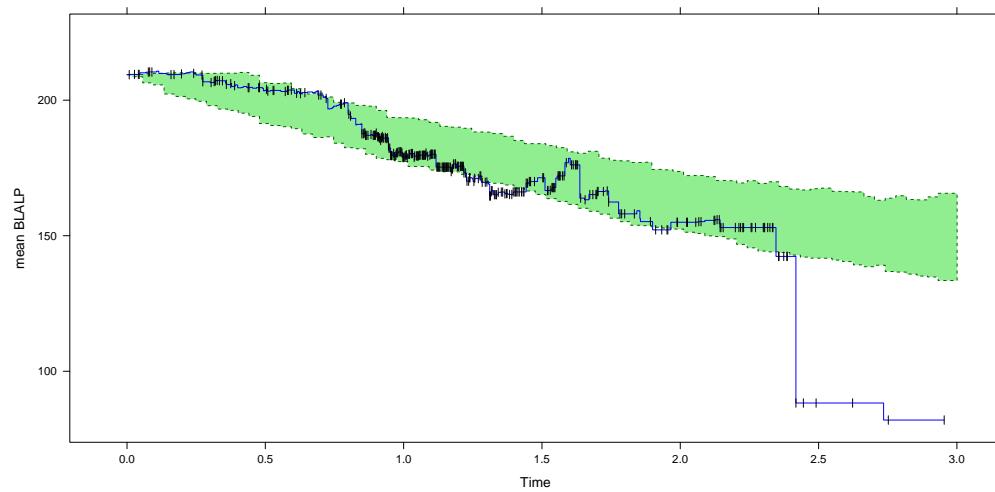
Kaplan Meier VPC: Run 7
Weibull hazard



Kaplan Meier VPC: Run 7
Weibull hazard
stratified by Baseline LDH



Kaplan Meier mean plot: Run 7
Weibull hazard
mean BLALP



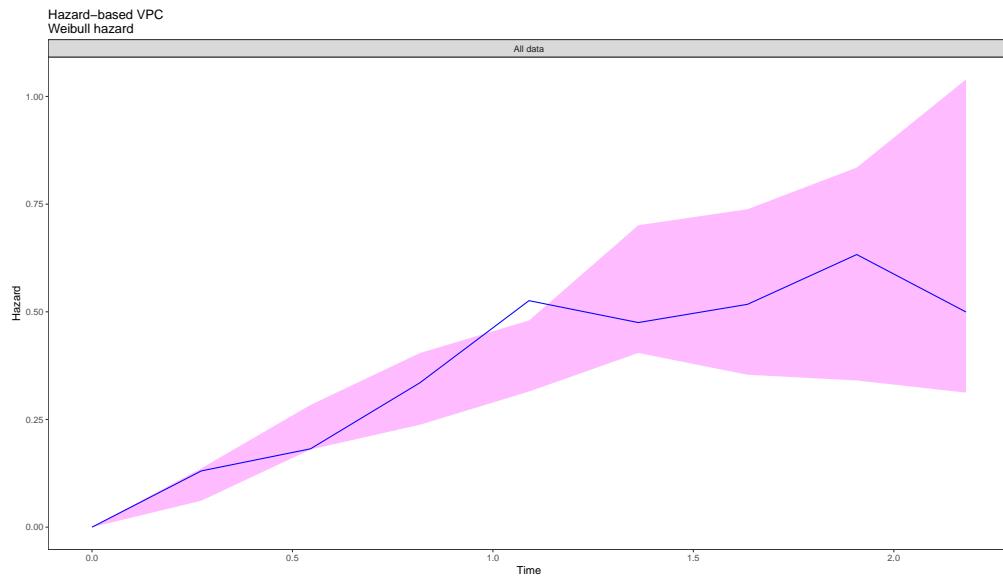


Figure 31: Simulation-based diagnostic: Hazard based VPC

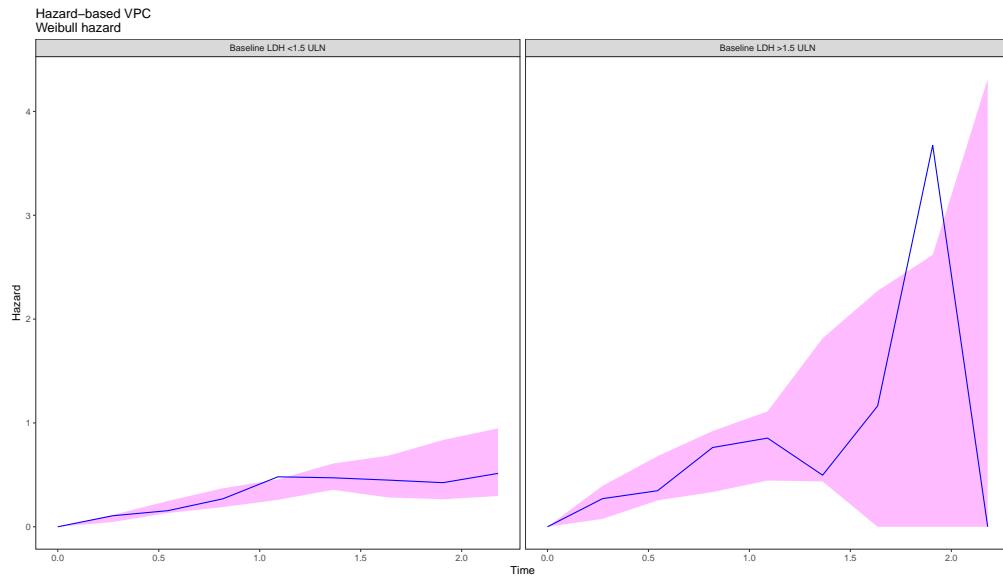


Figure 32: Simulation-based diagnostic: Hazard based VPC

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
##             BLHOSTAT 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 occurred 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, binary covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5 upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLHOSTAT, 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
##                 BLWHEOLEVEL 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"
## [6] "No rounding errors"
## [7] "No zero gradients"
## [8] "No final zero gradients"
## [9] "Hessian not reset"
## [10] "No parameter near boundary"
## [11] "Covariance step"
## [12] ""
## [13] "Condition number"
## [14] "Correlations"
## [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

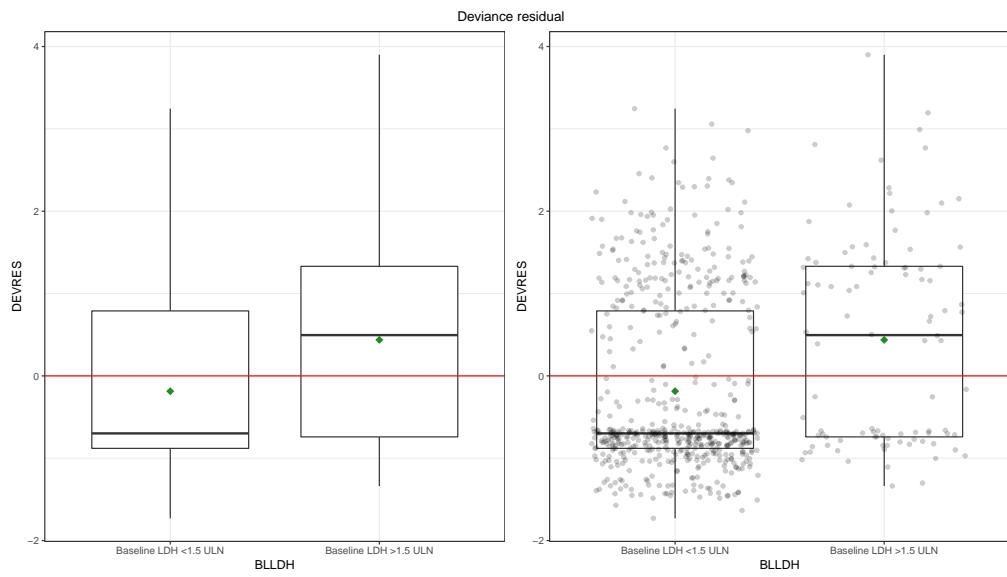


Figure 33: Residual-based diagnostics - Deviance plot

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

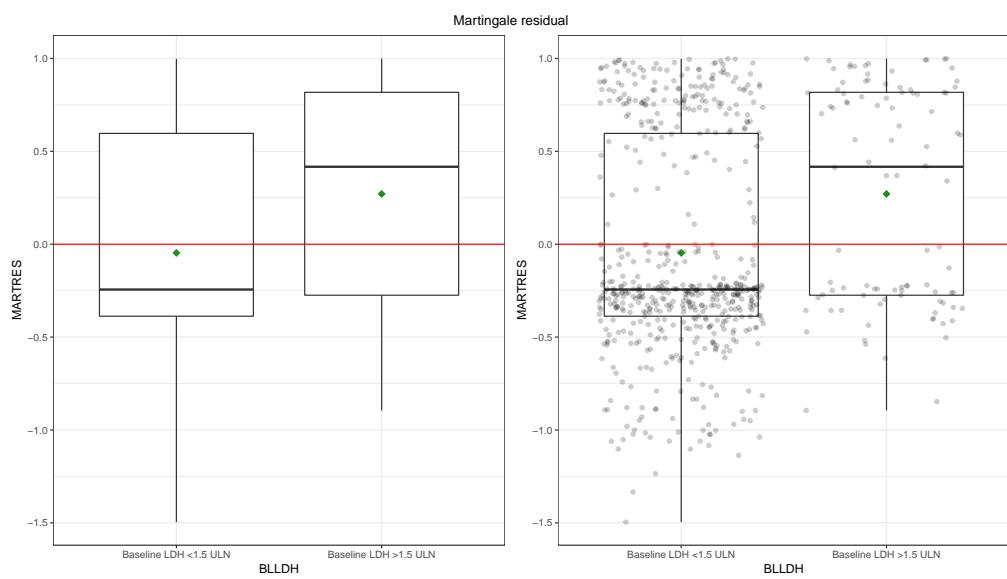


Figure 34: Residual-based diagnostics - Martingale plot

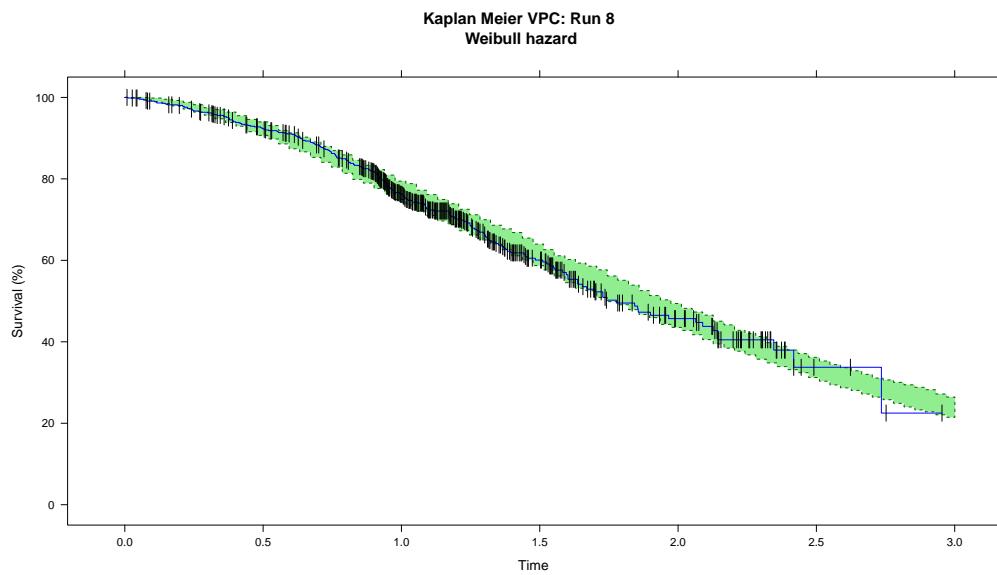


Figure 35: Simulation-based diagnostic

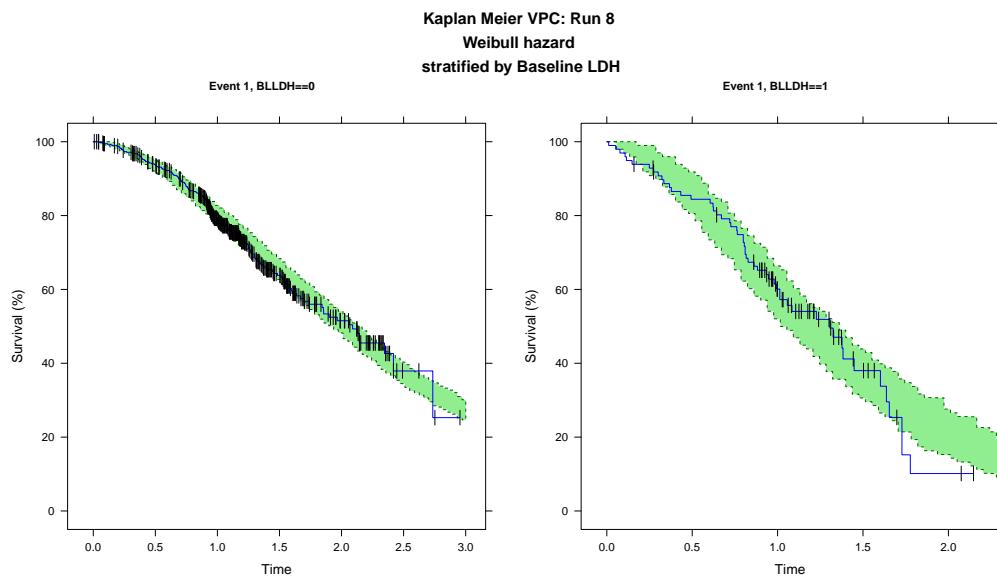


Figure 36: Simulation-based diagnostic - stratified by baseline LDH

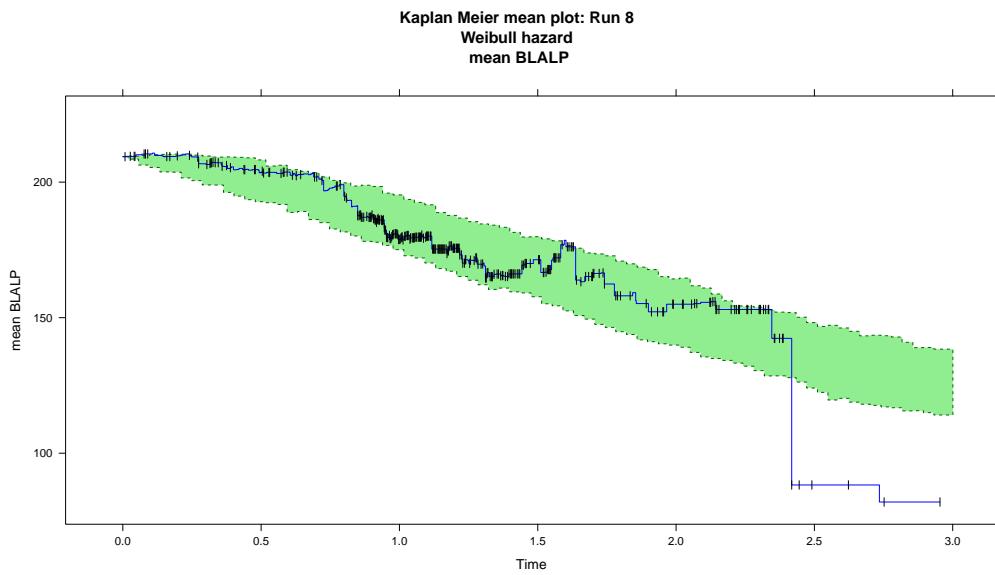


Figure 37: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

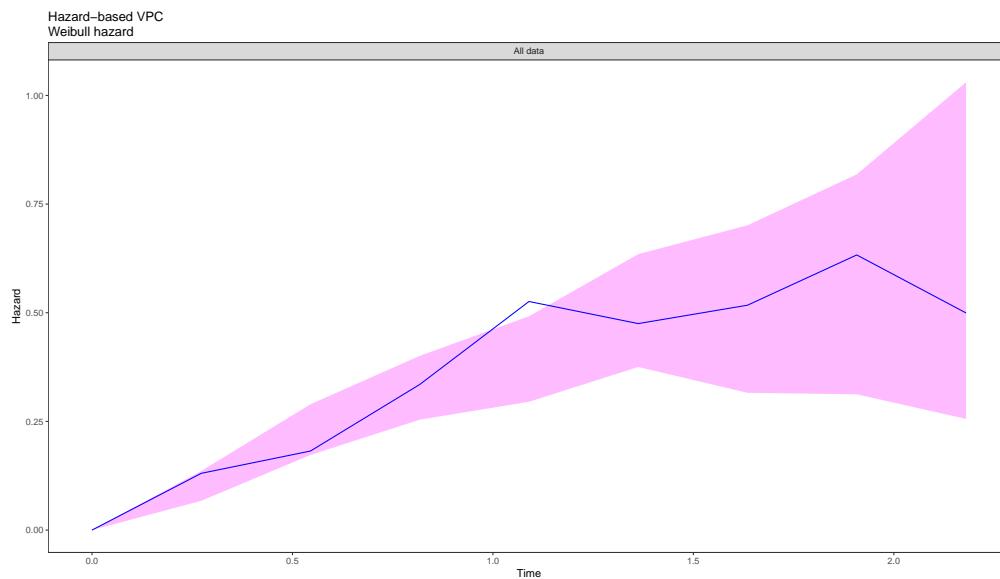


Figure 38: Simulation-based diagnostic: Hazard based VPC

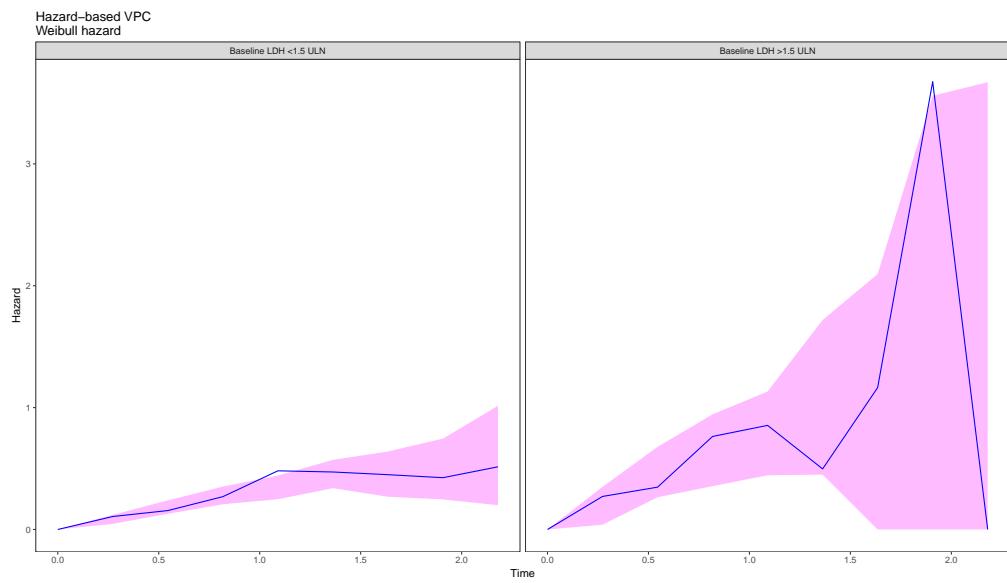


Figure 39: Simulation-based diagnostic: Hazard based VPC

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 occurred 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, binary 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

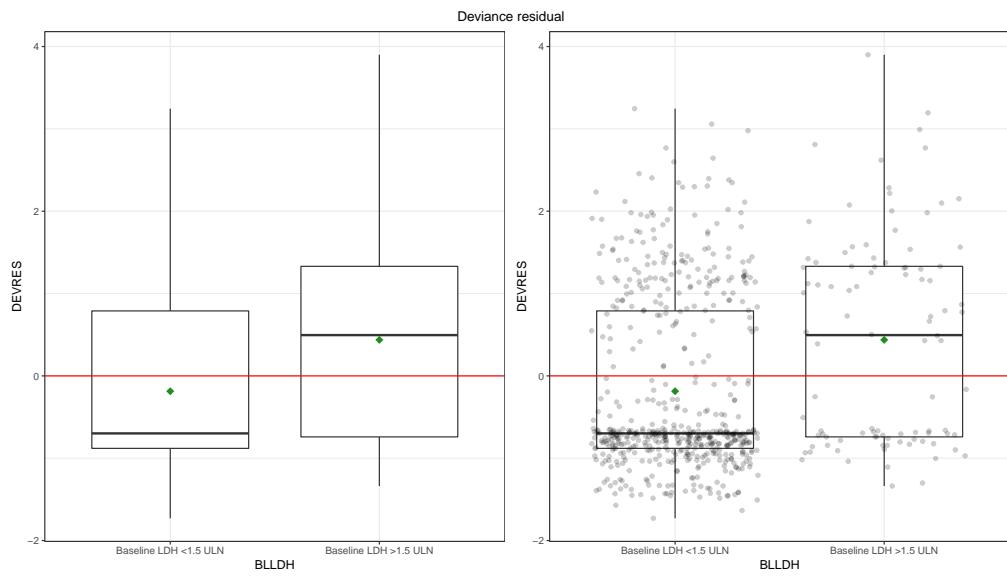


Figure 40: Residual-based diagnostics - Deviance plot

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

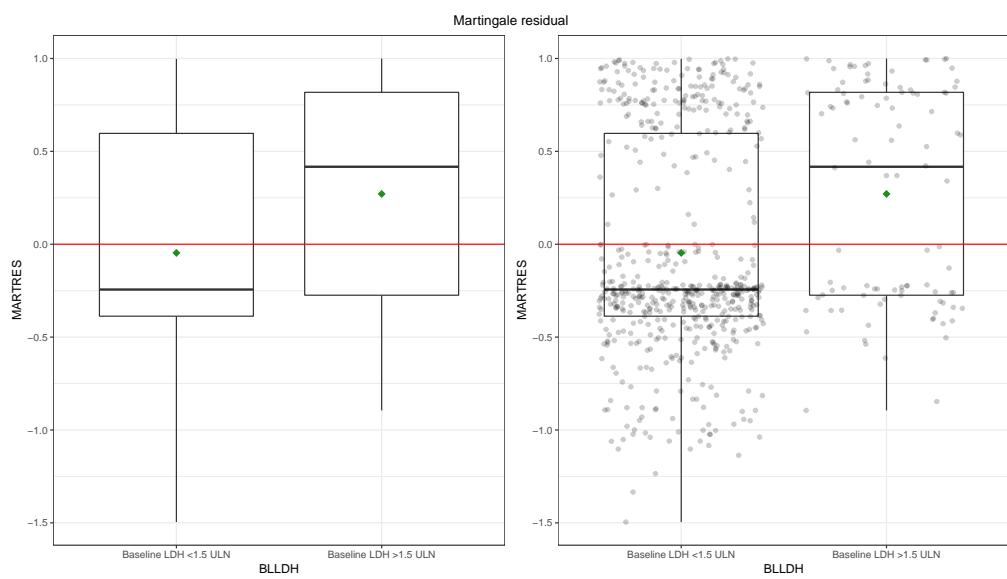
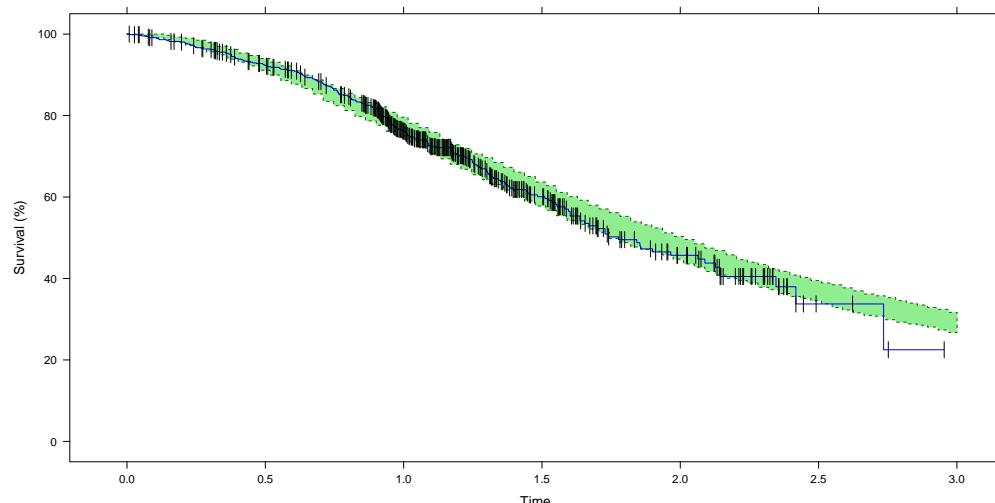
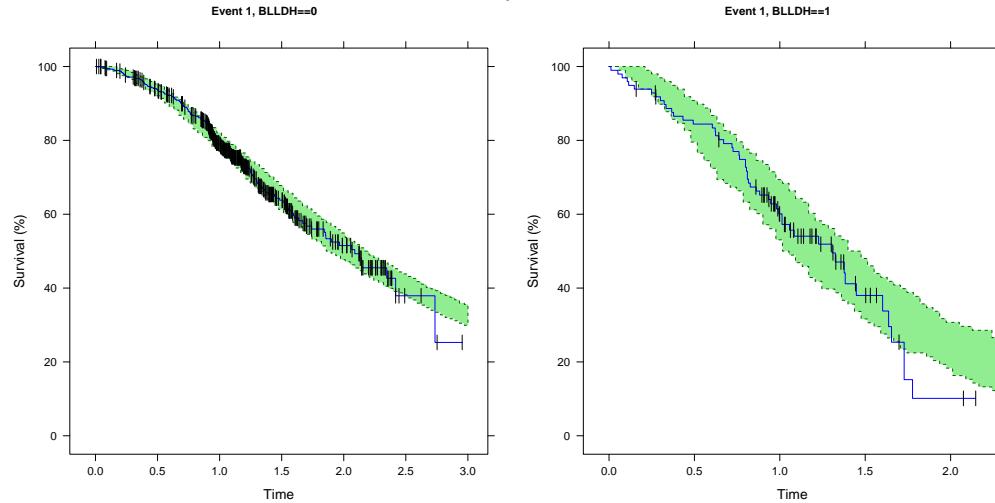


Figure 41: Residual-based diagnostics - Martingale plot

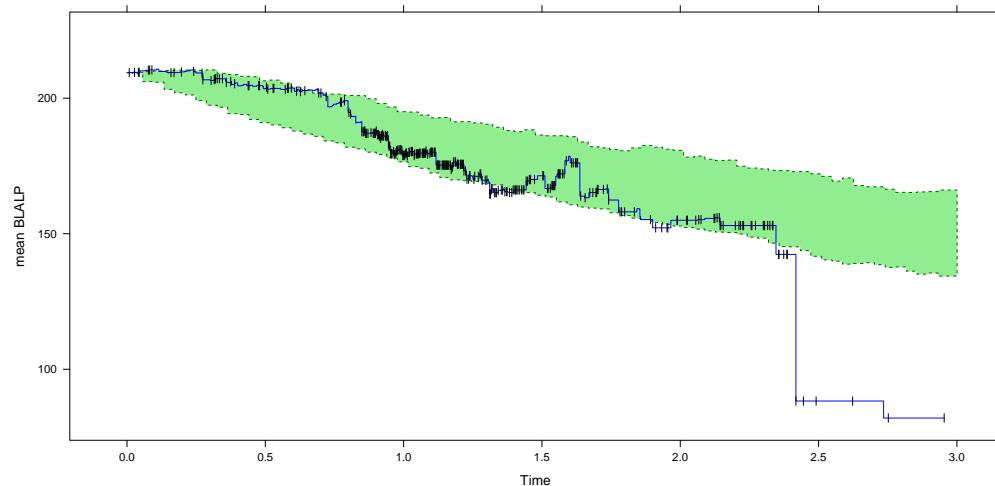
Kaplan Meier VPC: Run 9
Log-logistic hazard



Kaplan Meier VPC: Run 9
Log-logistic hazard
stratified by Baseline LDH



Kaplan Meier mean plot: Run 9
Log-logistic hazard
mean BLALP



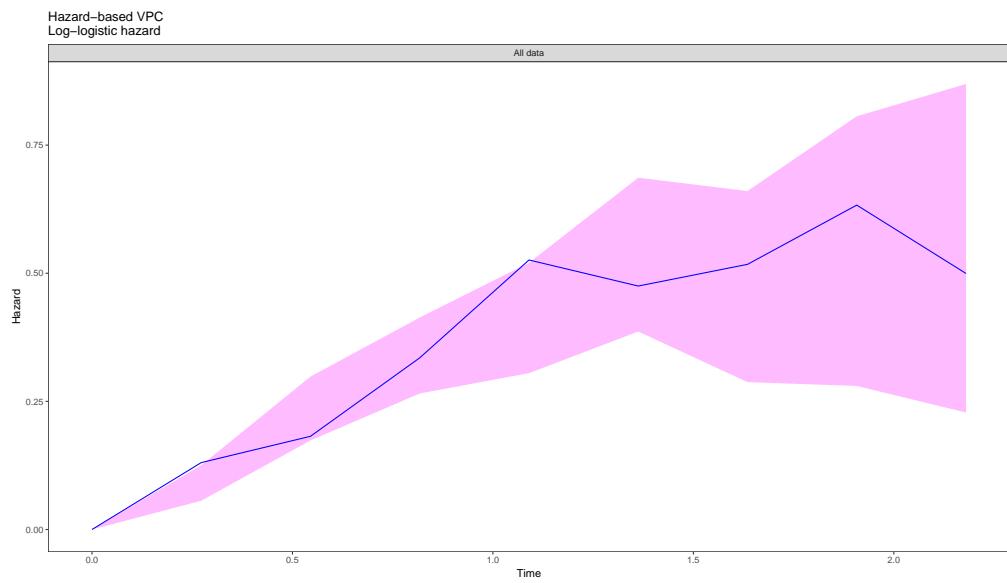
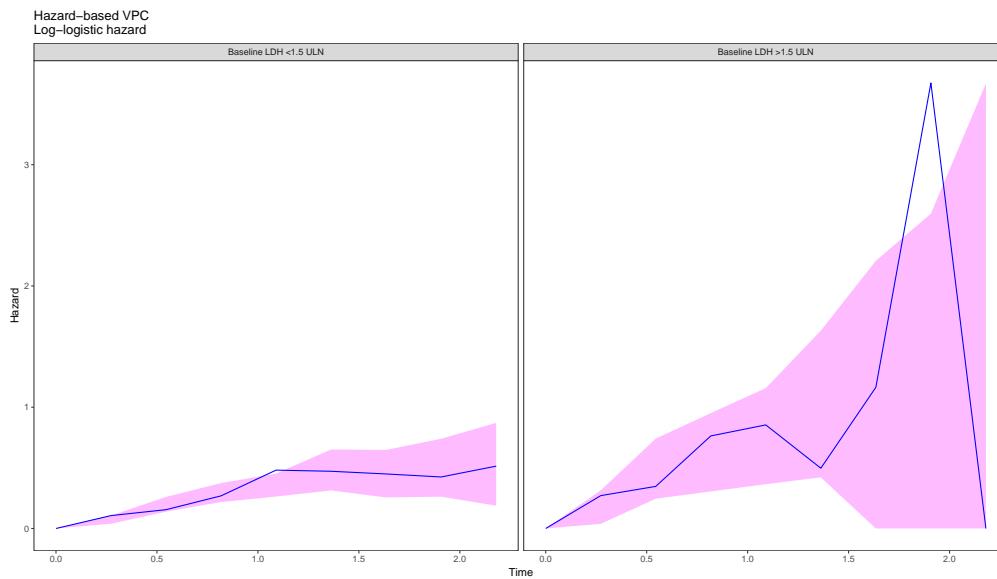


Figure 42: Simulation-based diagnostic: Hazard based VPC



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
##             BLHOSTAT 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 occurred 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, binary 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
##
## ; BLWOLEVEL, 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
## BLWOLEVEL 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"
## [6] "No rounding errors"
## [7] "No zero gradients"
## [8] "No final zero gradients"
## [9] "Hessian not reset"
## [10] "No parameter near boundary"
## [11] "Covariance step"
## [12] ""
## [13] "Condition number"
## [14] "Large correlations between parameter estimates found"
## [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

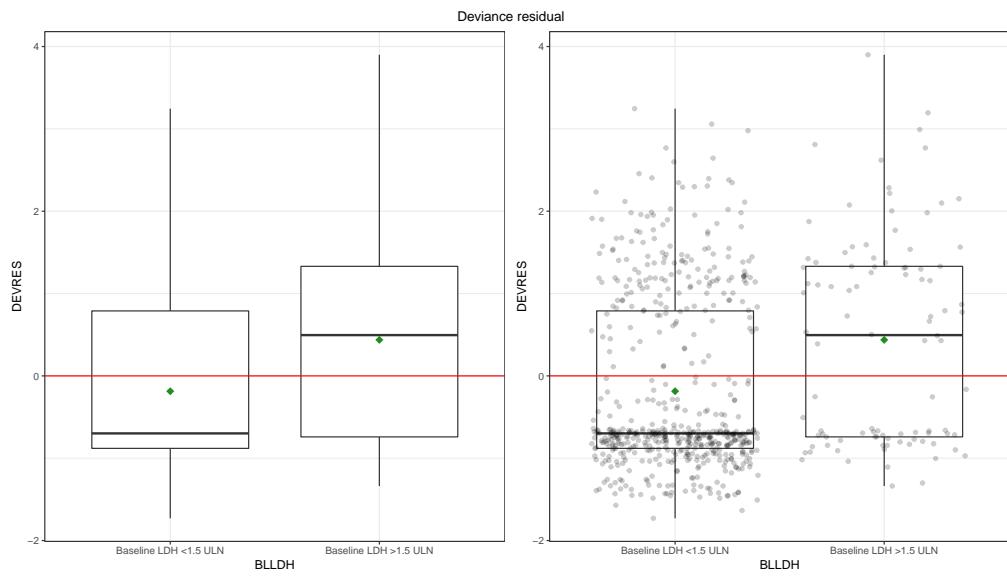


Figure 43: Residual-based diagnostics - Deviance plot

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

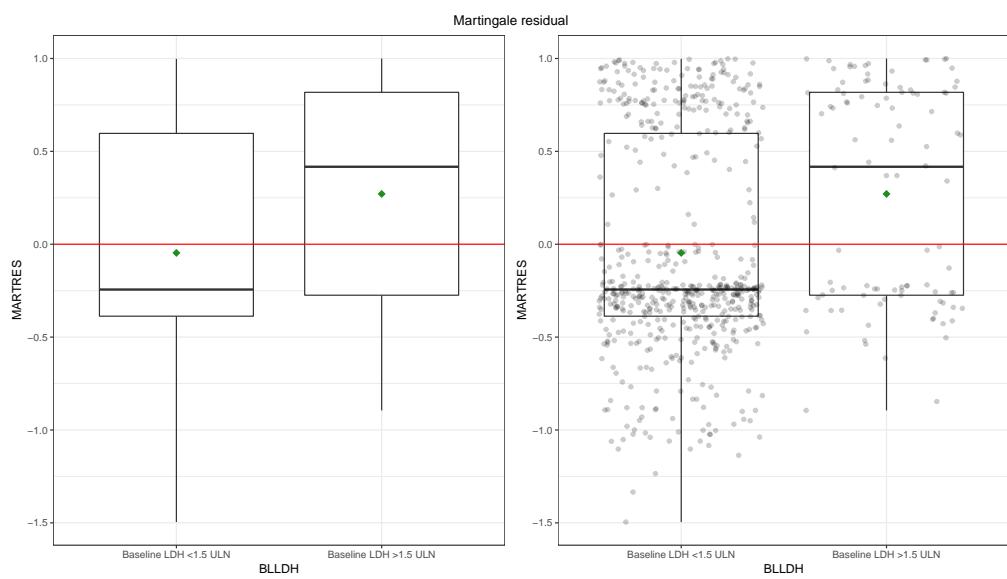
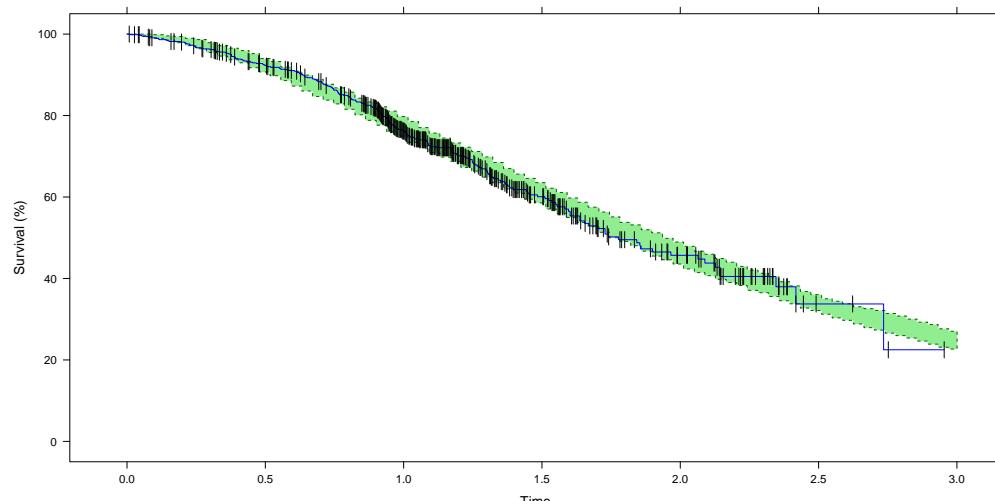
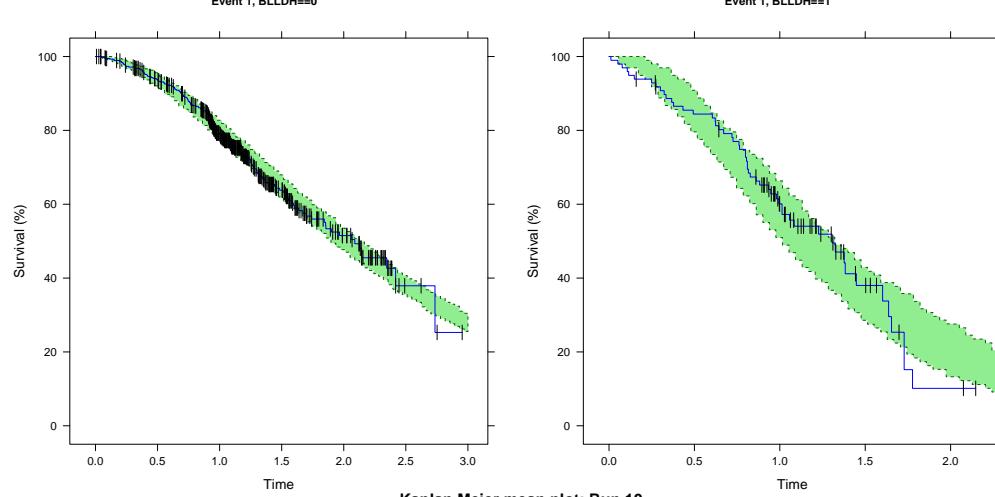


Figure 44: Residual-based diagnostics - Martingale plot

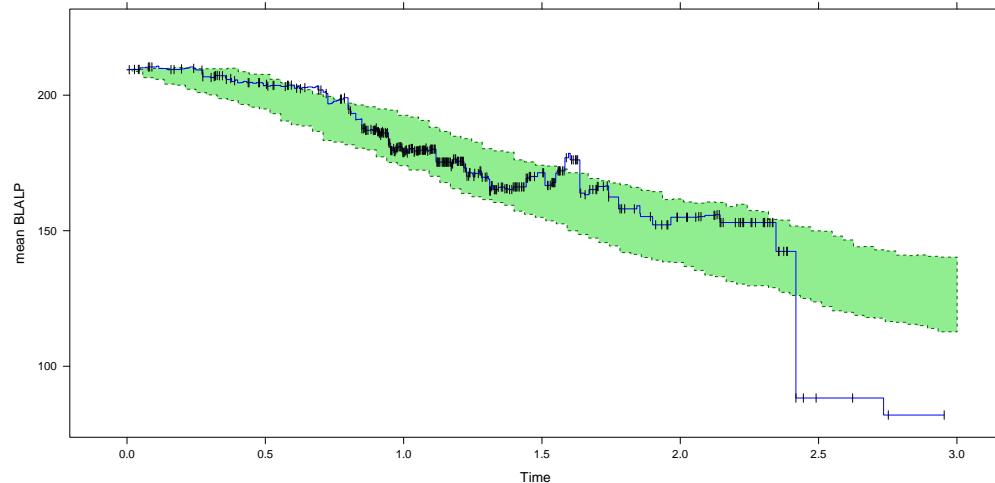
Kaplan Meier VPC: Run 10
Log-logistic hazard



Kaplan Meier VPC: Run 10
Log-logistic hazard
stratified by Baseline LDH



Kaplan Meier mean plot: Run 10
Log-logistic hazard
mean BLALP



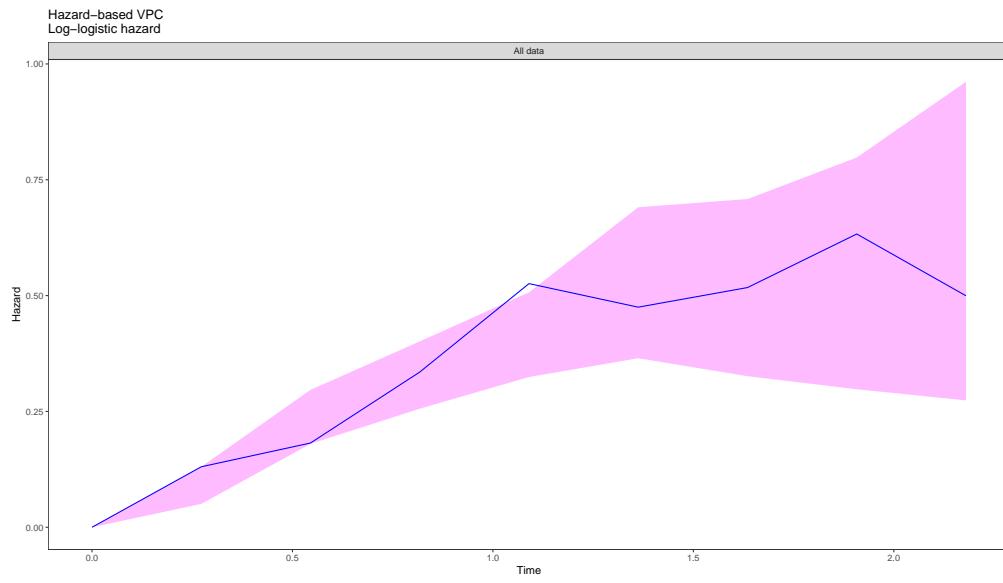


Figure 45: Simulation-based diagnostic: Hazard based VPC

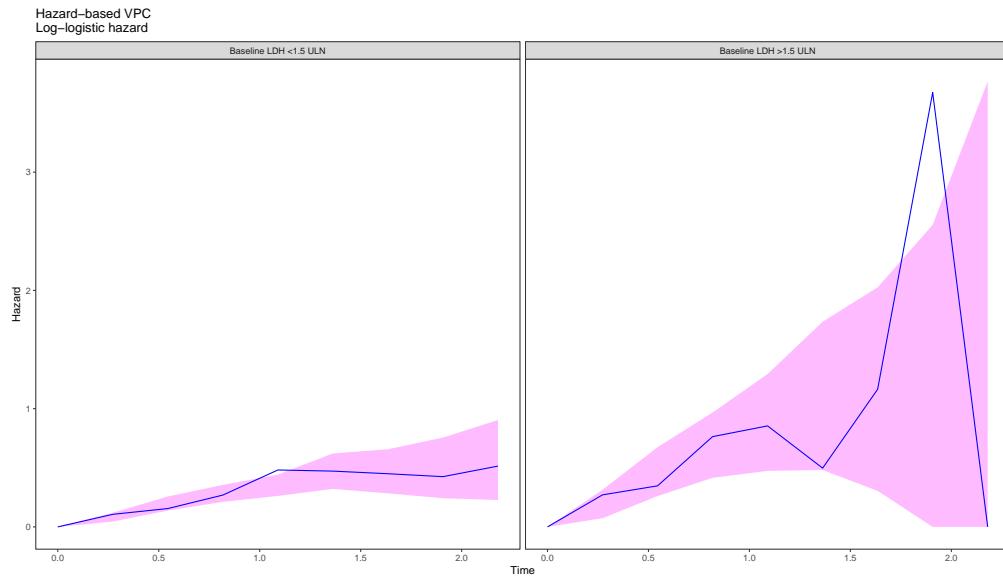
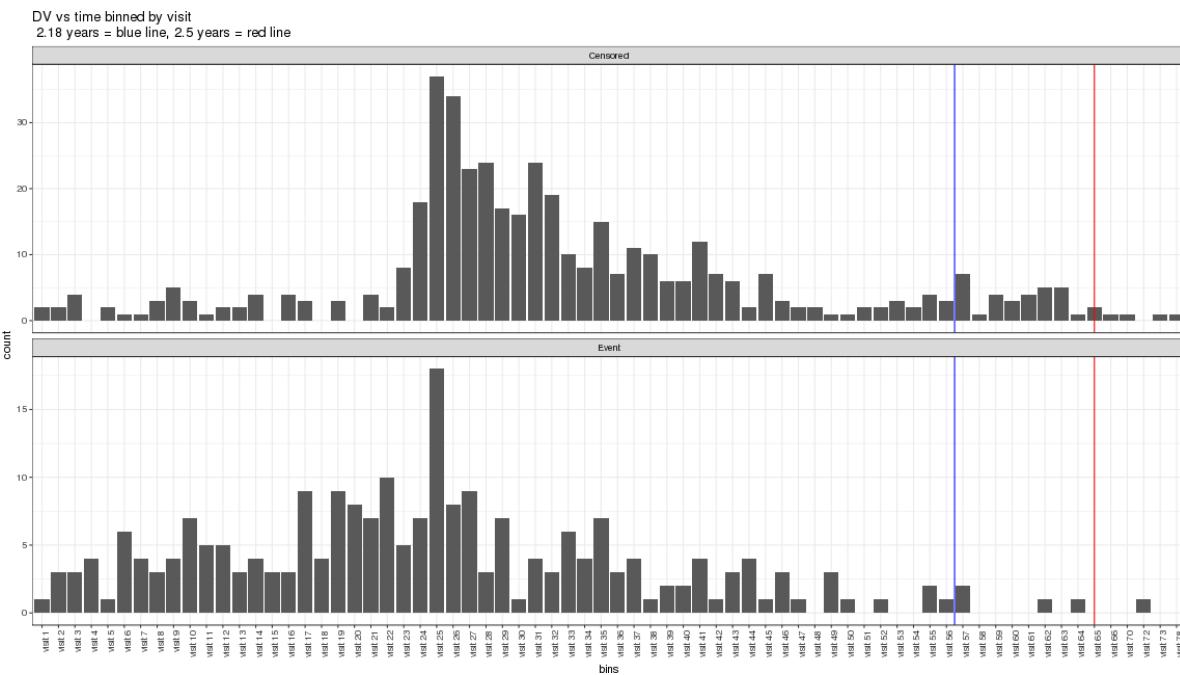
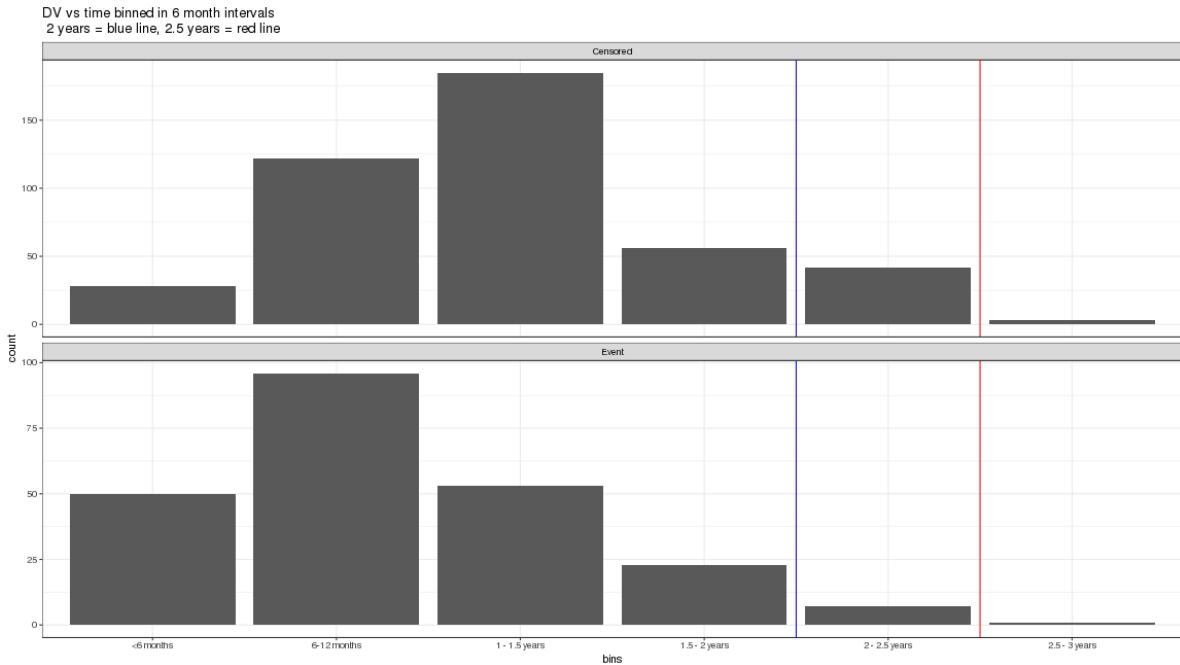


Figure 46: Simulation-based diagnostic: Hazard based VPC

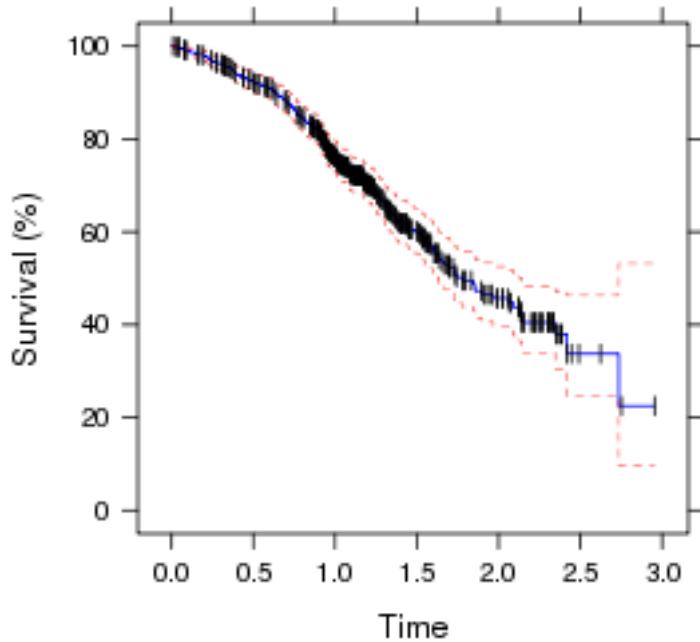
8 Data mining

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

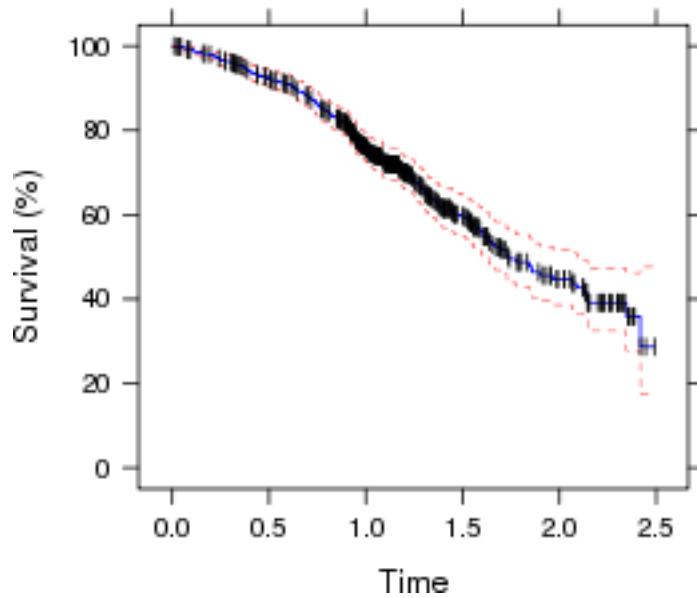
- Data within the last year of this study is mostly censored (%censored = 84.91)
- Past visit 57 (2.18 years), 3/16 records are events.
- Over 2.5 years 1/4 records is an event.
- Suggestion: ignore data over 2.5 years



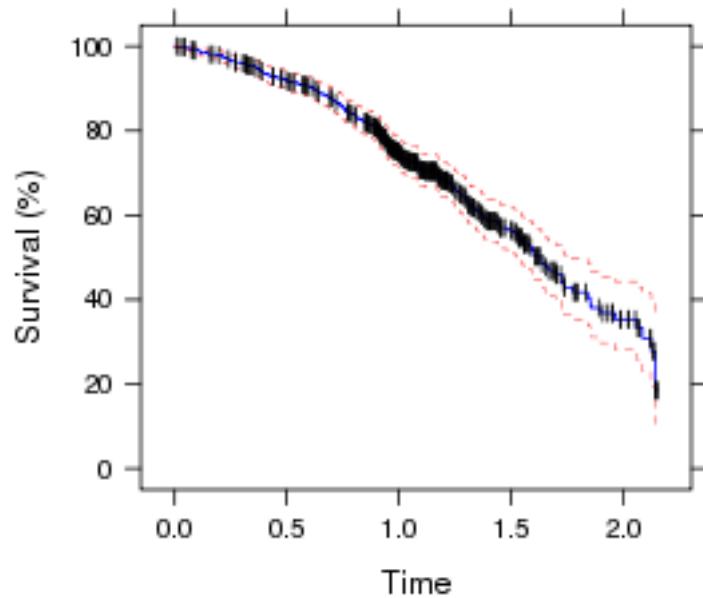
Kaplan-Meier plot for event 1



**Kaplan-Meier plot for event 1
[TIME<=2.5]**



**Kaplan-Meier plot for event 1
[TIME<=2.18]**



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

```



```

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)

```

# 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 occurred 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, binary 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
##
## ; BLWHEOLEVEL, 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
## BLWOLEVEL 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] ""                                         [ OK   ] "
## [13] "Condition number                            [ OK   ] "
## [14] "Correlations                                [ OK   ] "
## [15] ""                                         [ OK   ] "
## [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

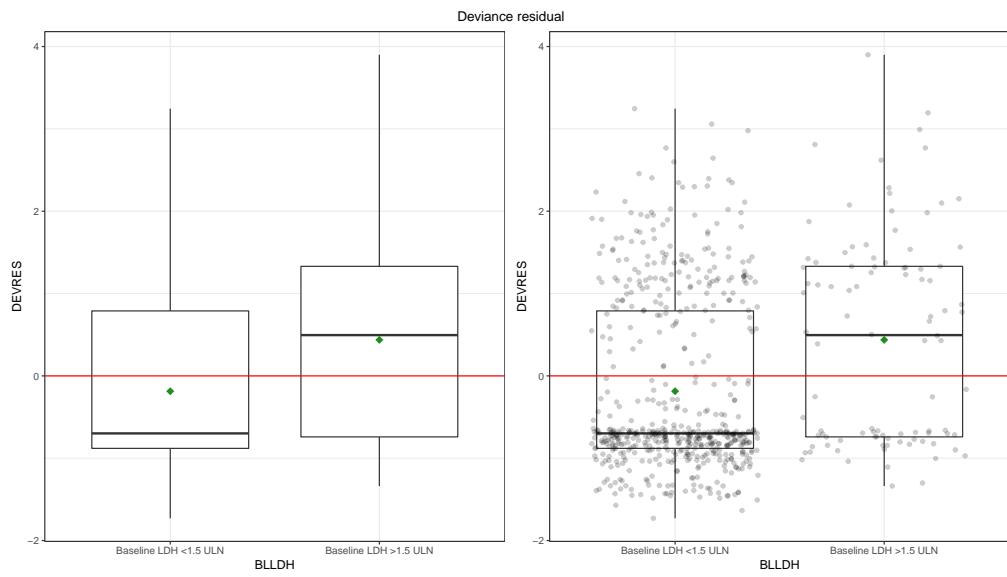


Figure 47: Residual-based diagnostics - Deviance plot

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

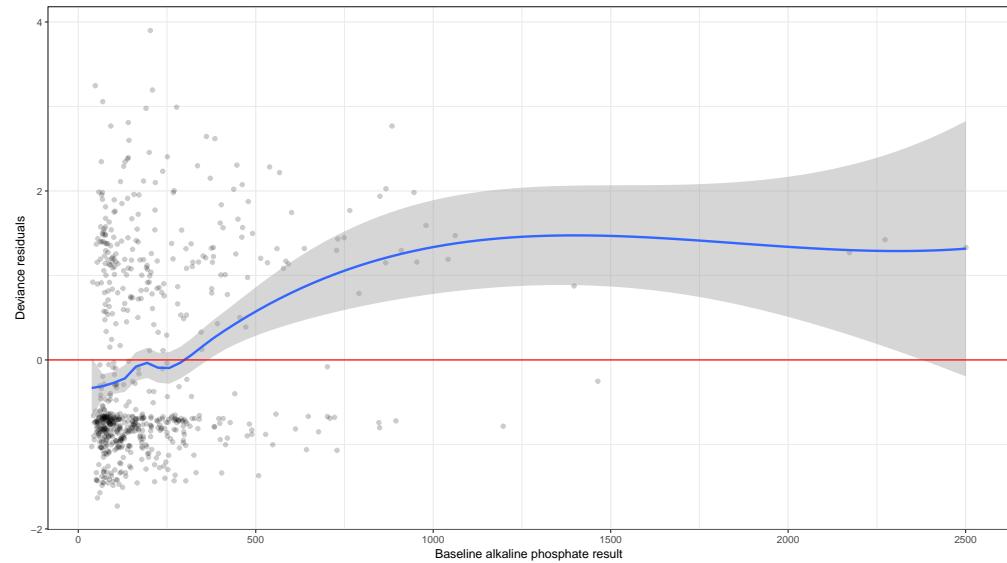


Figure 48: Residual-based diagnostics - Deviance plot

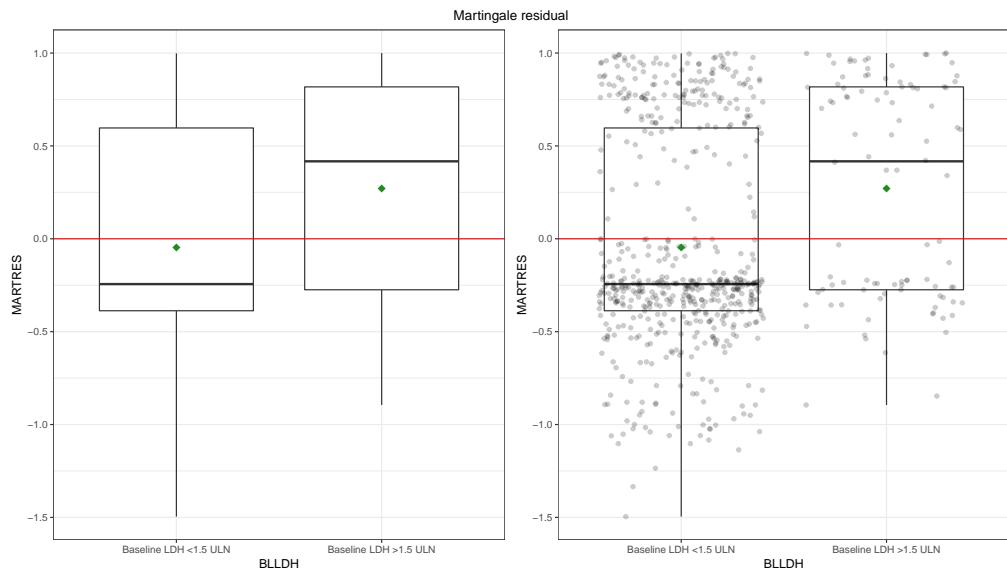


Figure 49: Residual-based diagnostics - Martingale plot

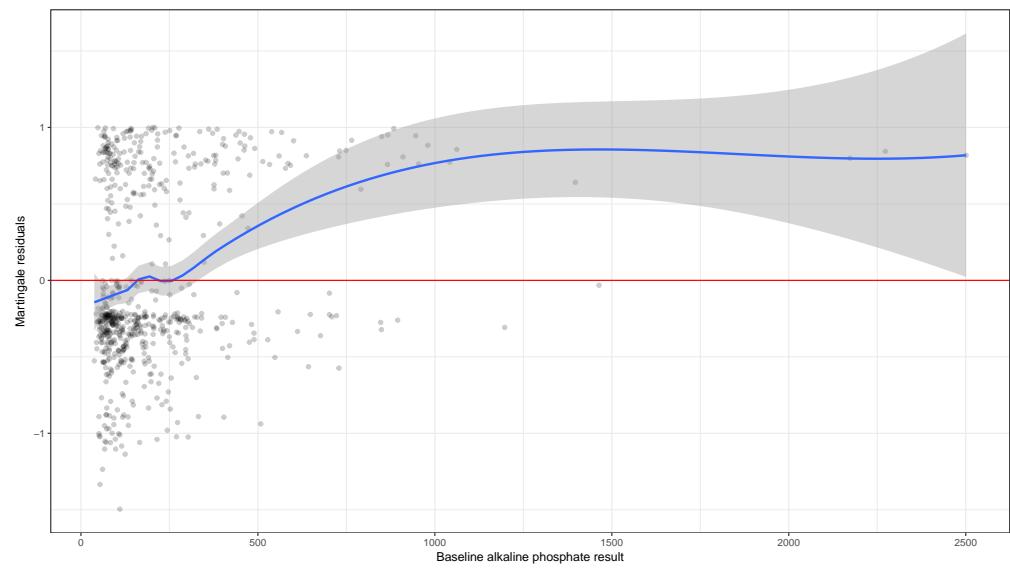
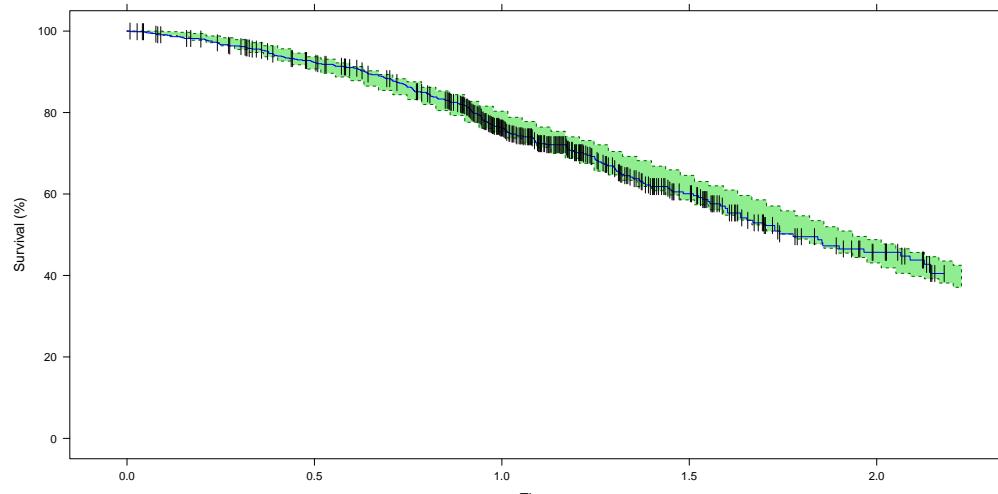
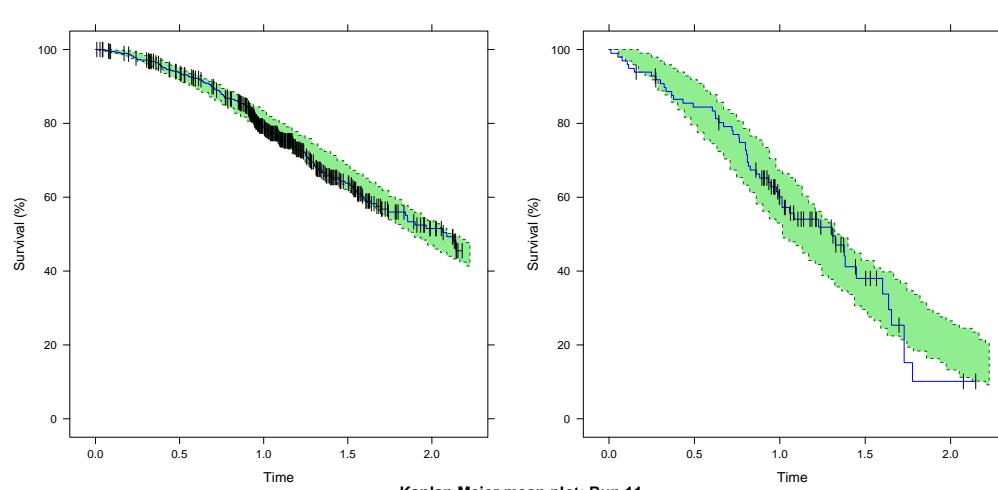


Figure 50: Residual-based diagnostics - Martingale plot

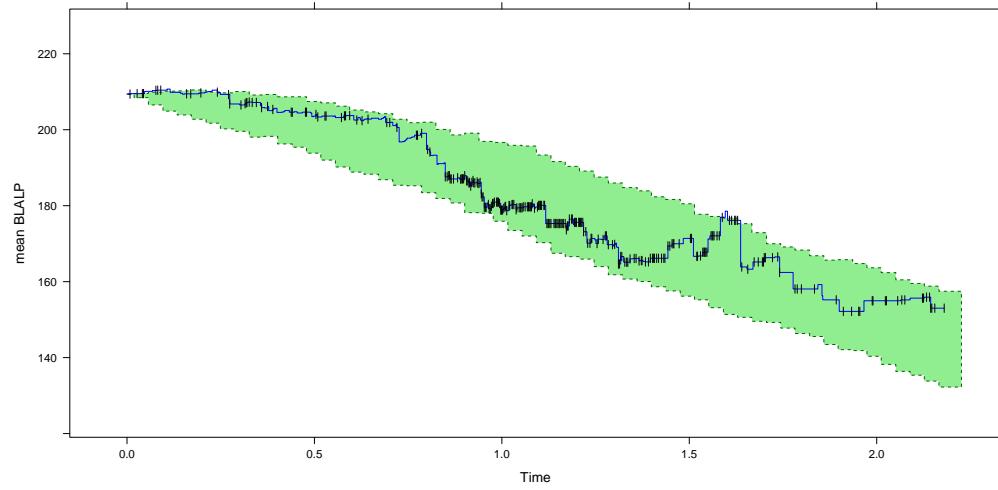
Kaplan Meier VPC: Run 11
Weibull hazard



Kaplan Meier VPC: Run 11
Weibull hazard
stratified by Baseline LDH



Kaplan Meier mean plot: Run 11
Weibull hazard
mean BLALP



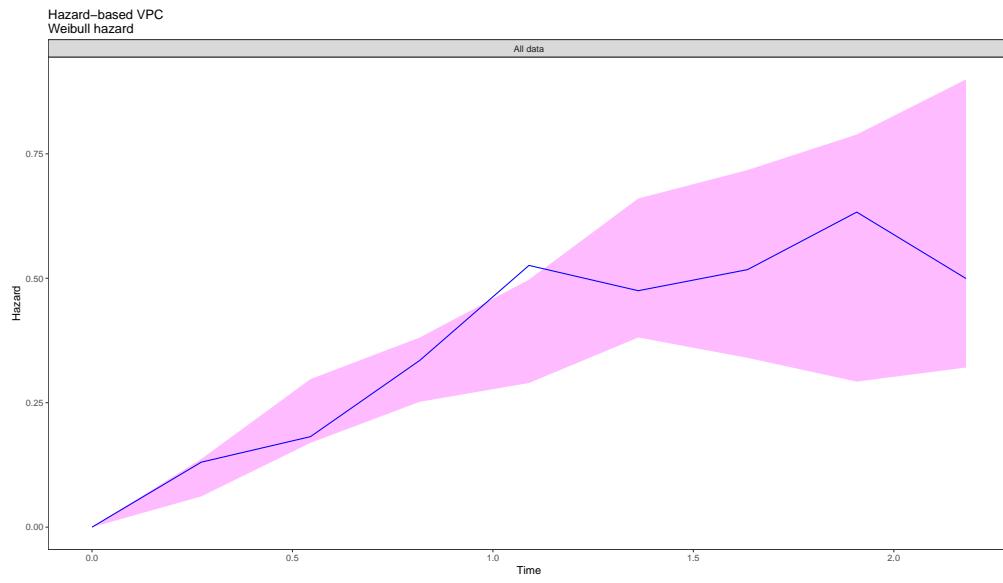


Figure 51: Simulation-based diagnostic: Hazard based VPC

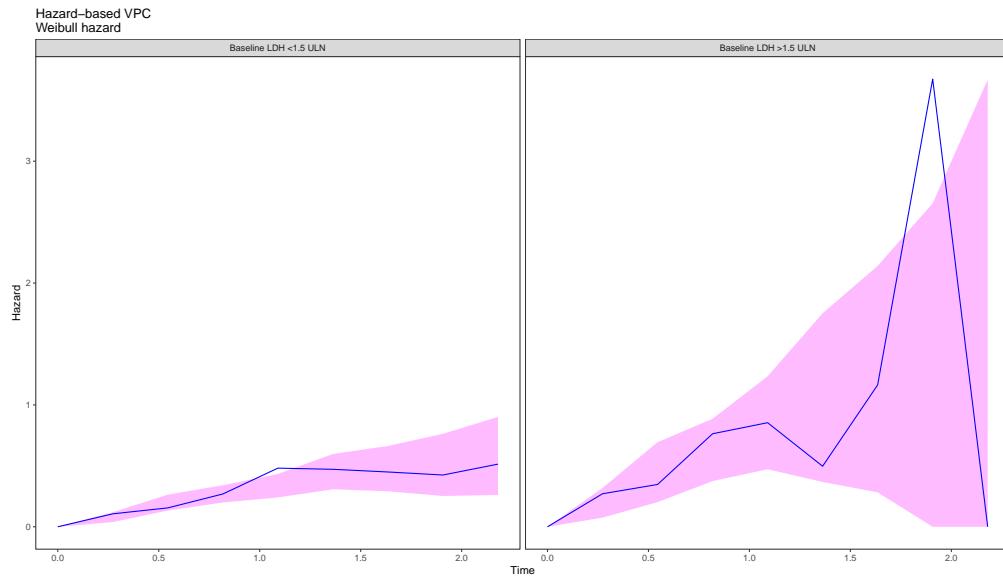


Figure 52: Simulation-based diagnostic: Hazard based VPC

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. Interoccassion 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
##             BLHOSTAT 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 occurred 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, binary covariate (0=male,1=female)
##
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5 upper limit of normal
##
## ; BLAGE, categorical, age group in years
##
## ; BLHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
##

```

```

## ; BLALB, continuous, ALB test values at baseline
##
## ; BLALP, continuous, ALP test values at baseline
##
## ; BLWHEOLEVEL, 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"
## [6] "No rounding errors"
## [7] "No zero gradients"
## [8] "No final zero gradients"
## [9] "Hessian not reset"
## [10] "No parameter near boundary"
## [11] "Covariance step"
## [12] ""
## [13] "Condition number"
## [14] "Large correlations between parameter estimates found"
## [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

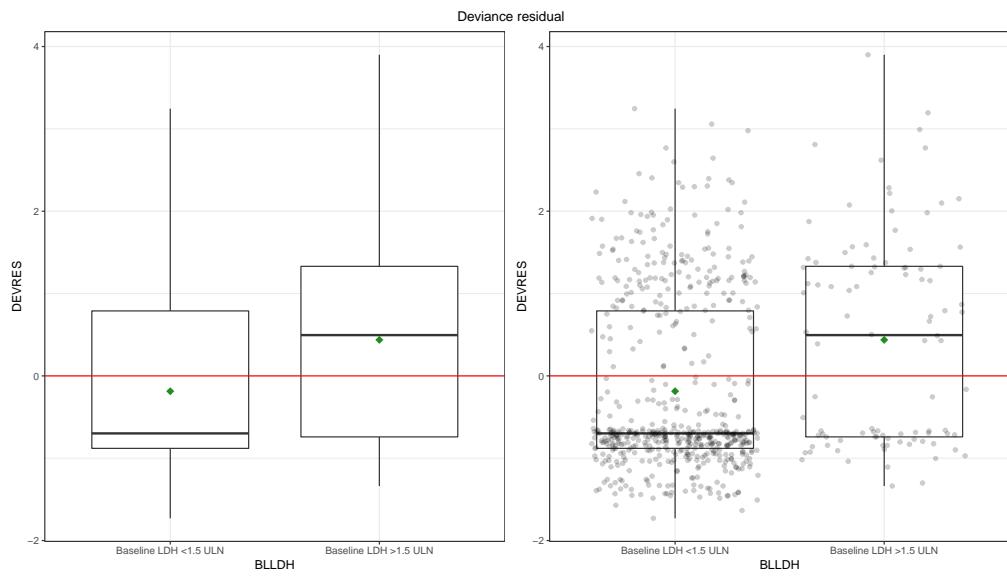


Figure 53: Residual-based diagnostics - Deviance plot

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

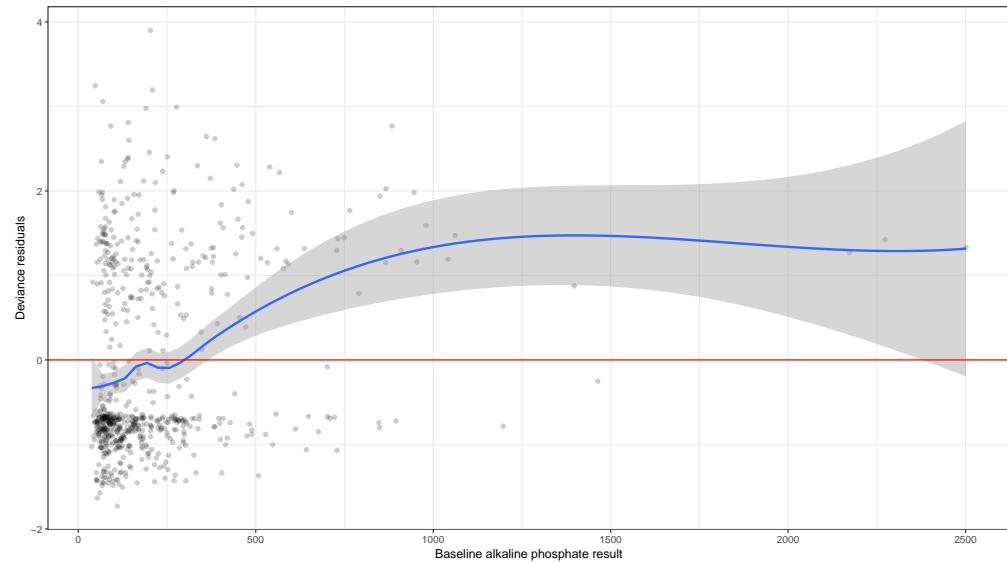


Figure 54: Residual-based diagnostics - Deviance plot

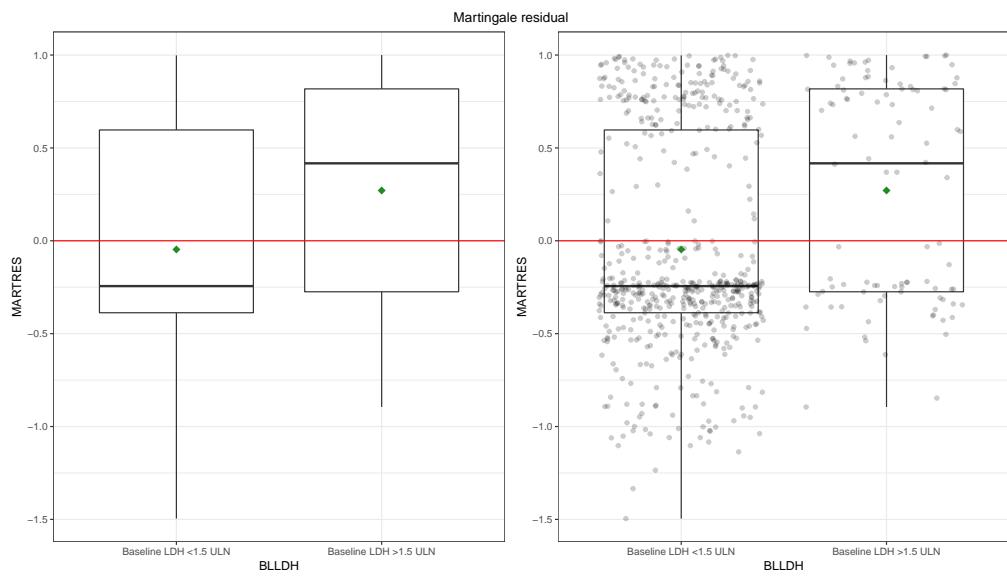


Figure 55: Residual-based diagnostics - Martingale plot

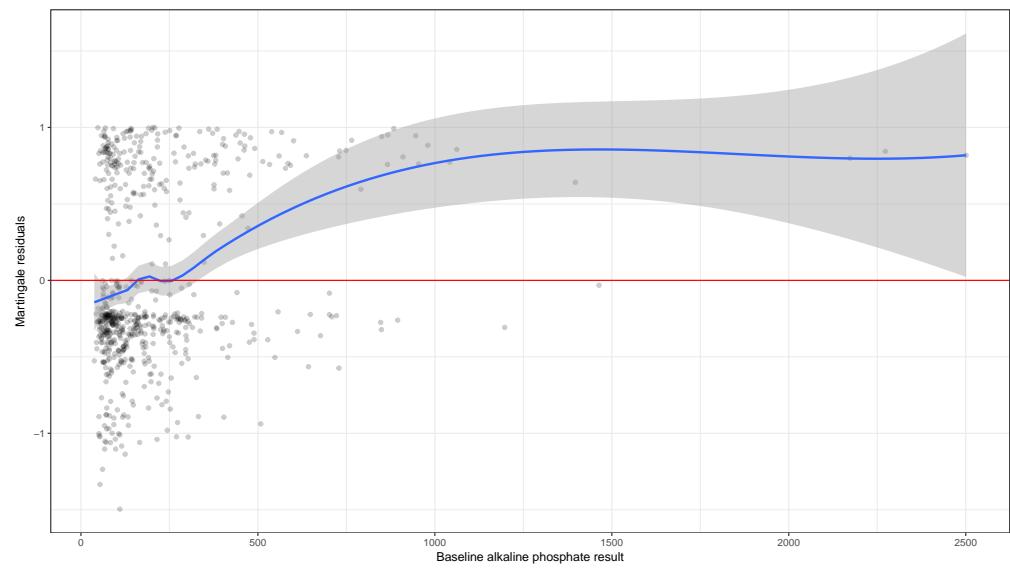
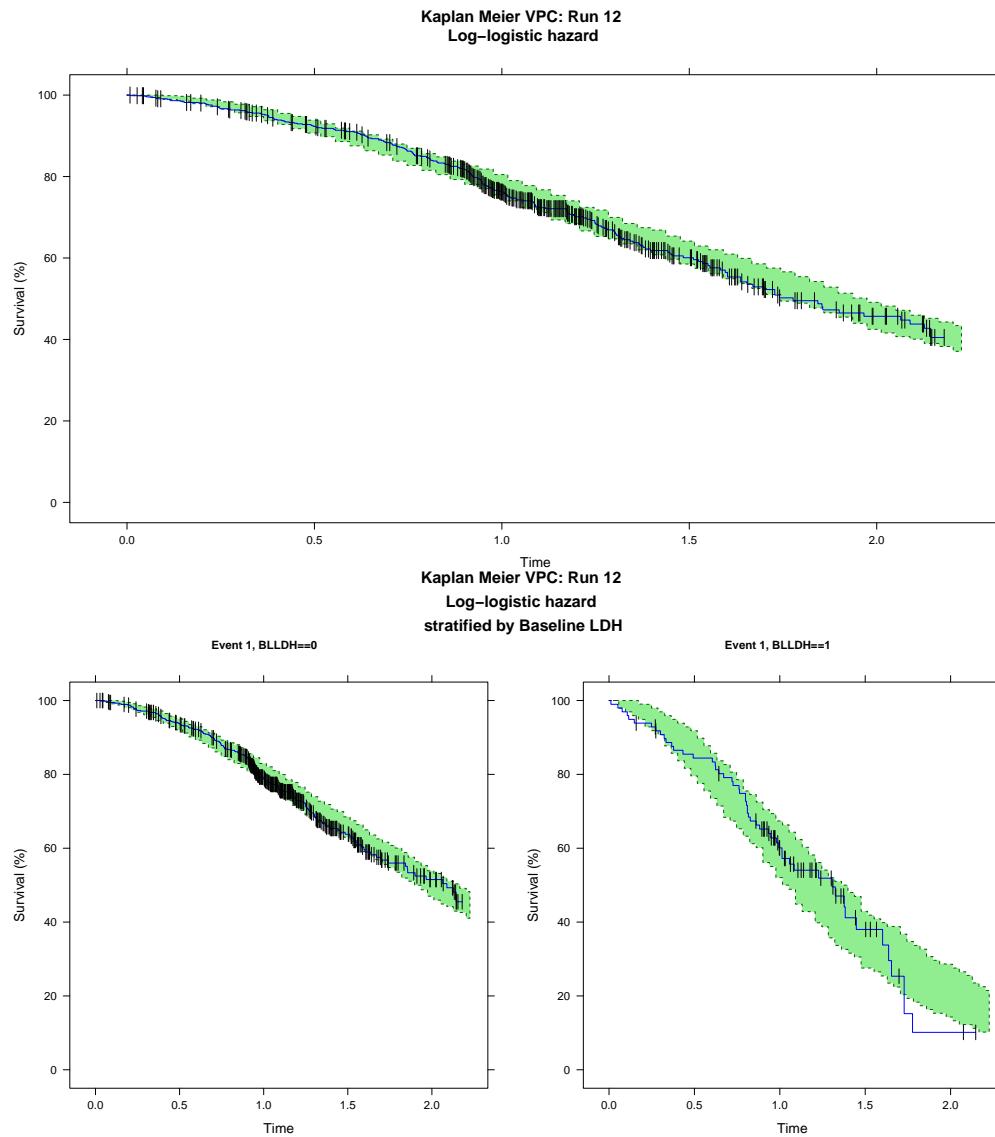


Figure 56: Residual-based diagnostics - Martingale plot



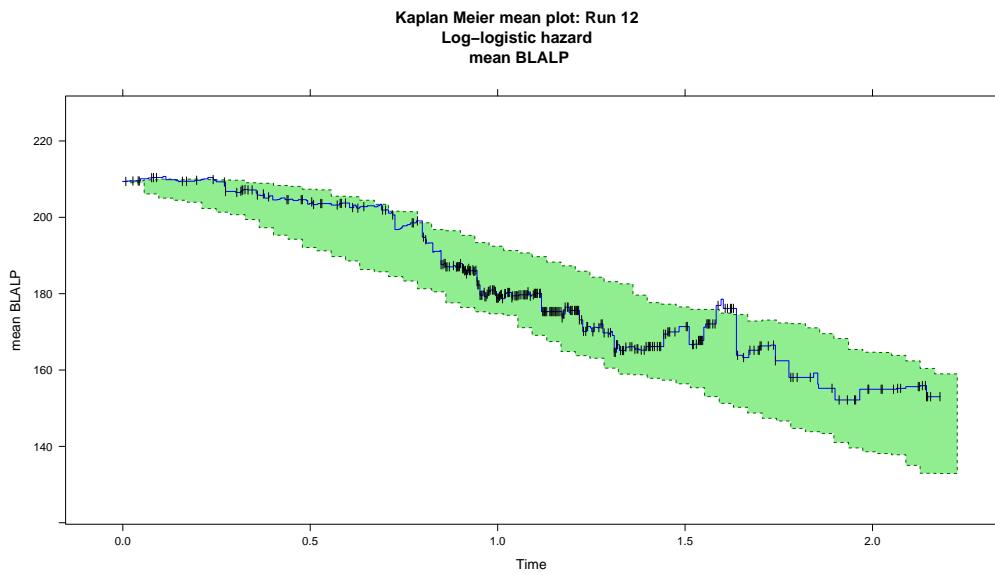


Figure 57: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

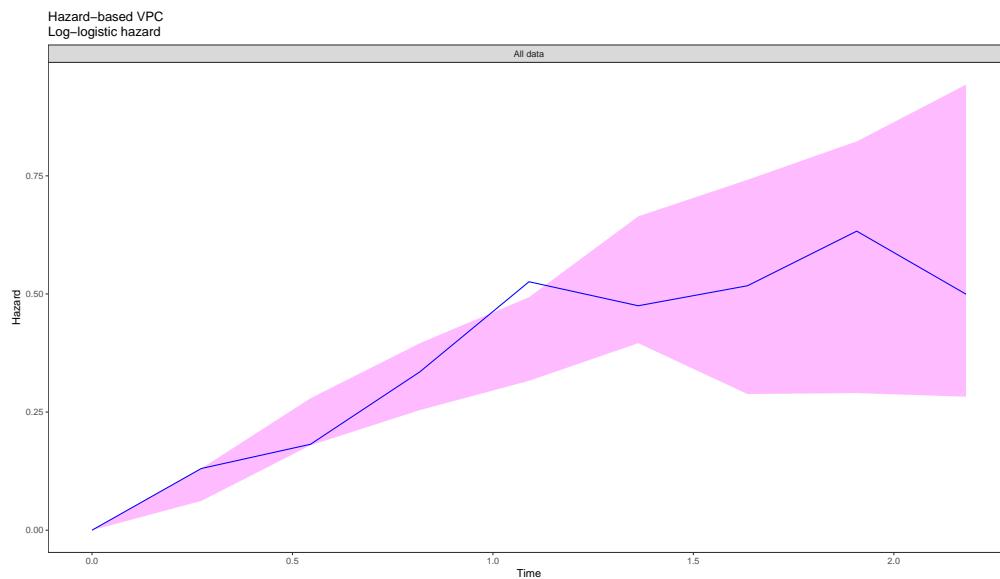


Figure 58: Simulation-based diagnostic: Hazard based VPC

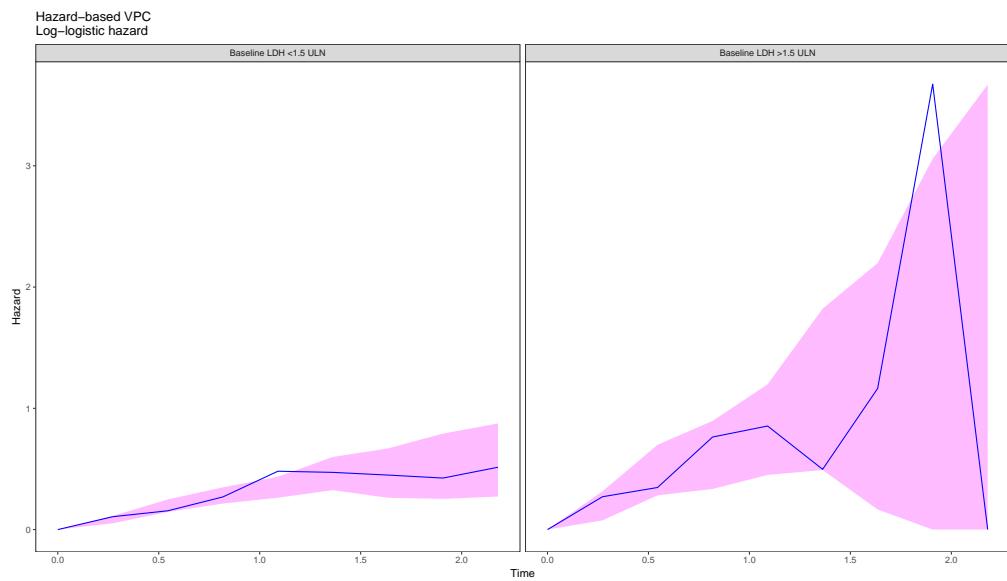


Figure 59: Simulation-based diagnostic: Hazard based VPC

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. Interoccassion 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
##                 BLHOSTAT 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 occurred 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, binary covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5 upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLHOSTAT, 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
## BLWOLEVEL 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"
## [6] "No rounding errors"
## [7] "No zero gradients"
## [8] "No final zero gradients"
## [9] "Hessian not reset"
## [10] "No parameter near boundary"
## [11] "Covariance step"
## [12] ""
## [13] "Condition number"
## [14] "Correlations"
## [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

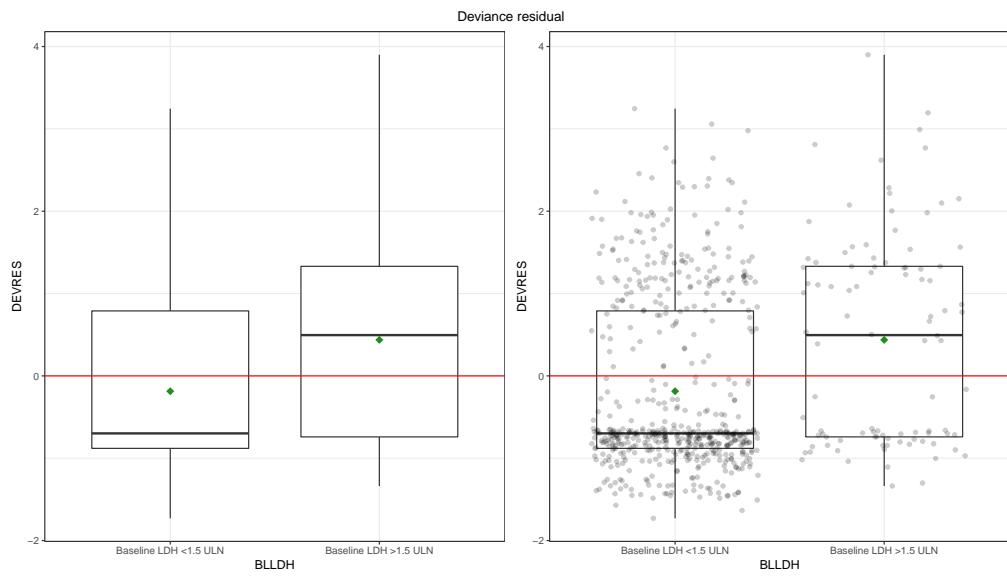


Figure 60: Residual-based diagnostics - Deviance plot

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

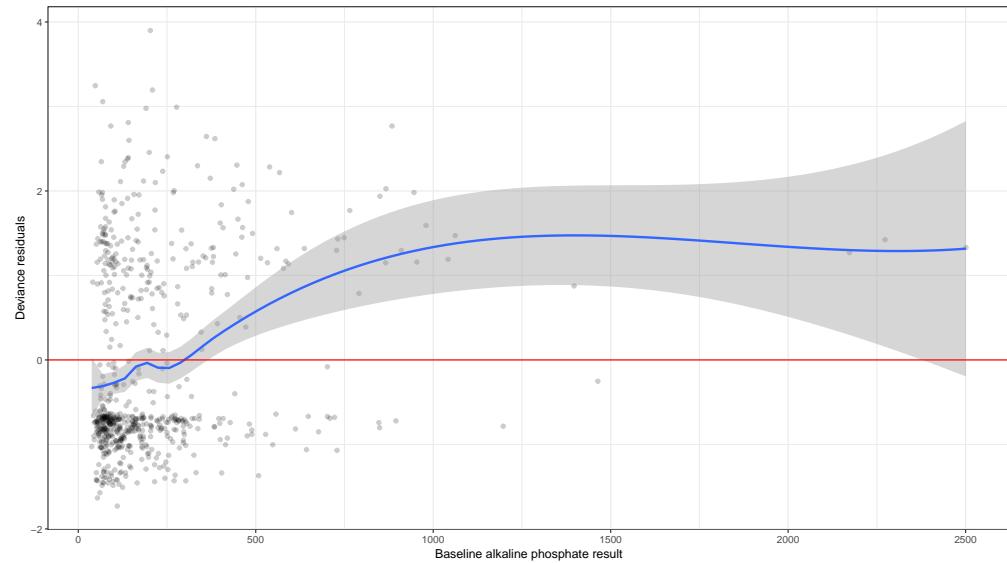


Figure 61: Residual-based diagnostics - Deviance plot

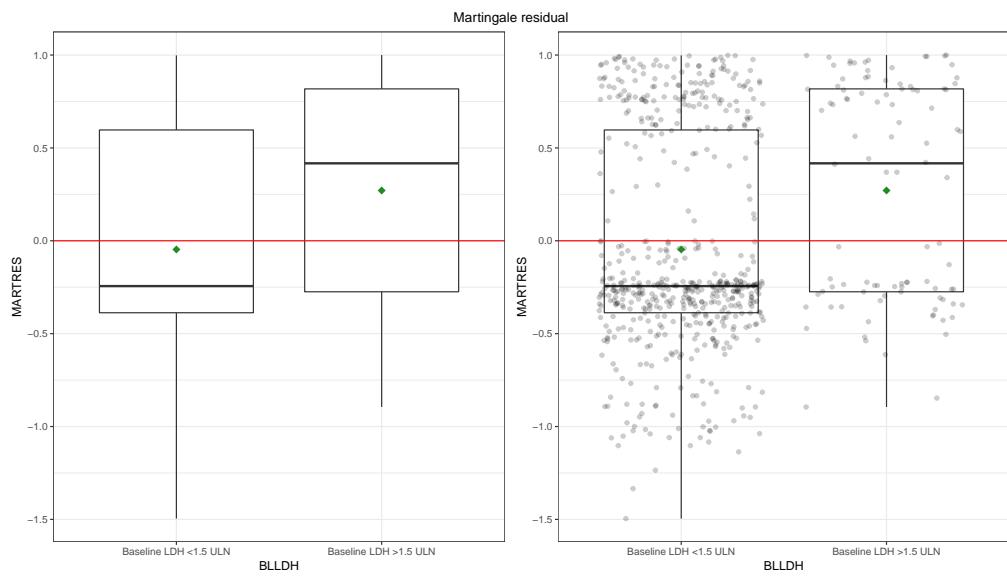


Figure 62: Residual-based diagnostics - Martingale plot

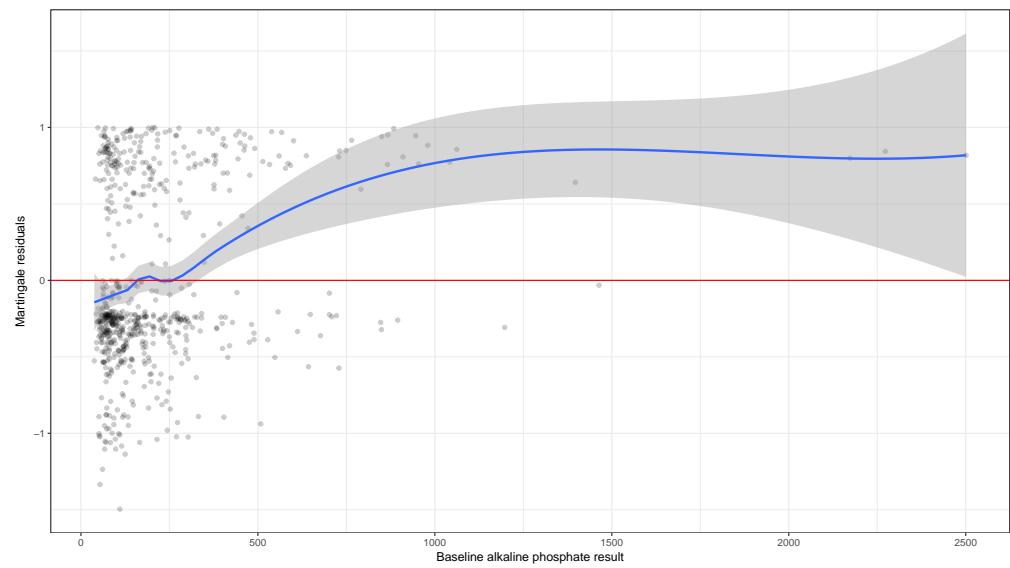
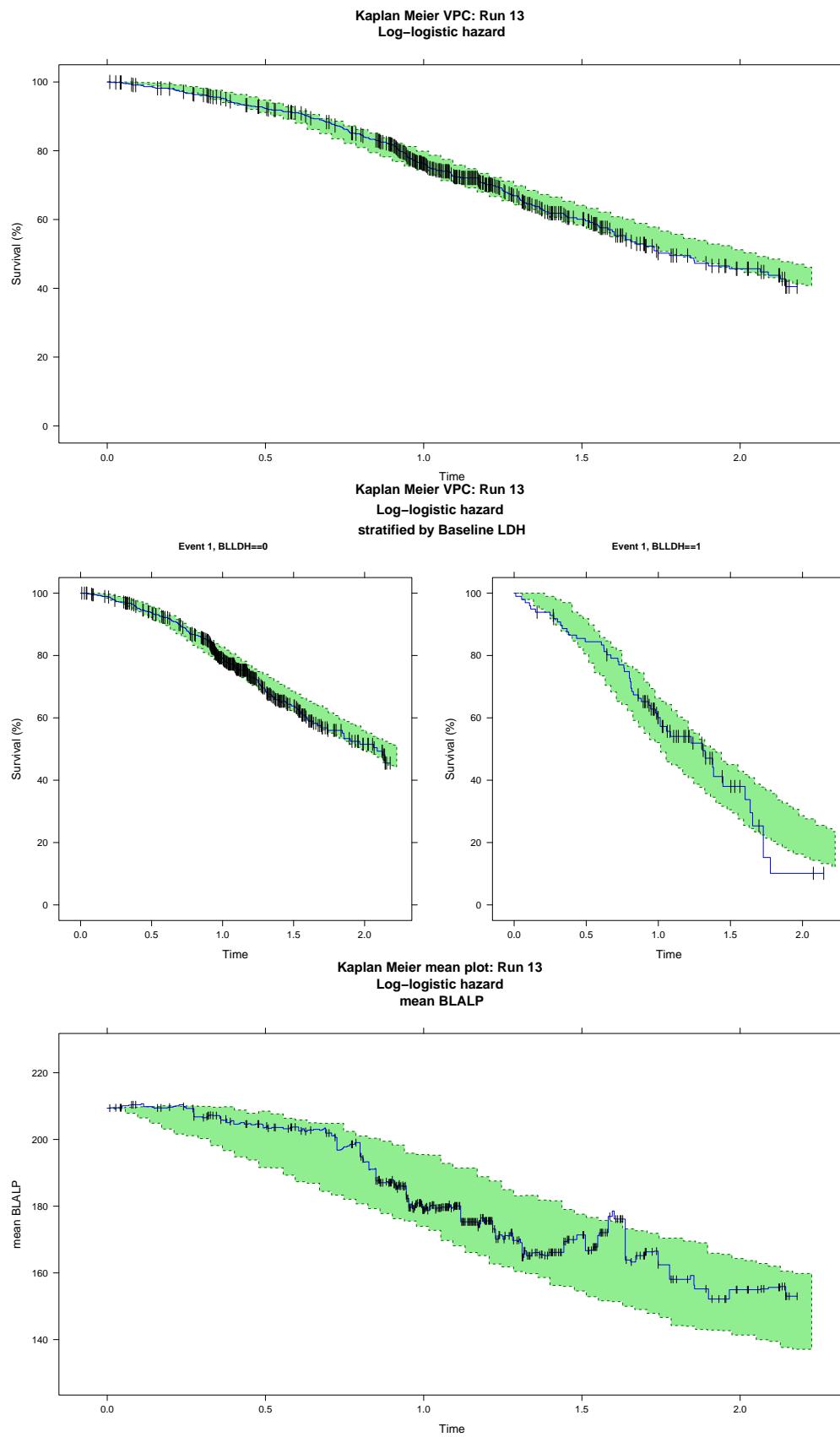


Figure 63: Residual-based diagnostics - Martingale plot



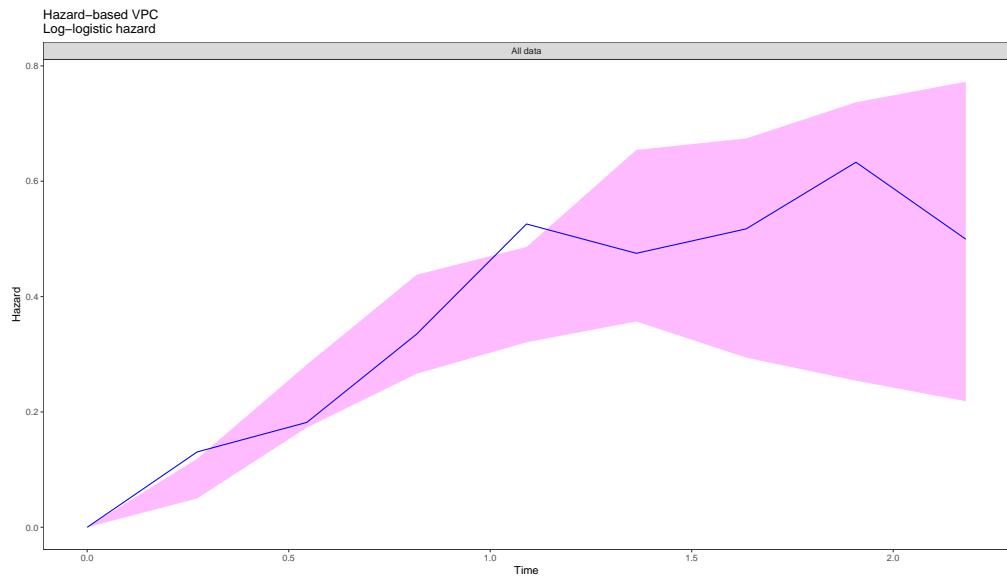


Figure 64: Simulation-based diagnostic: Hazard based VPC

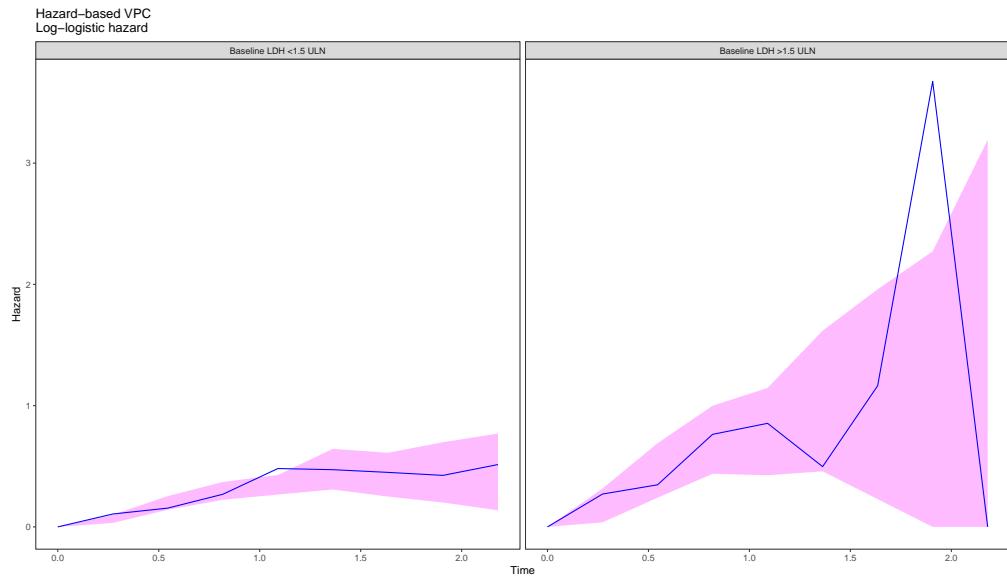


Figure 65: Simulation-based diagnostic: Hazard based VPC

11 Selected models for publication

Notes:

- subjects missing baseline covariates are excluded
- events occurring after 2.18 years are censored
- continuous 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
##             BLHOSTAT 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 occurred 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
## ; BLHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWHEOLEVEL, 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  

## BLWOLEVEL 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

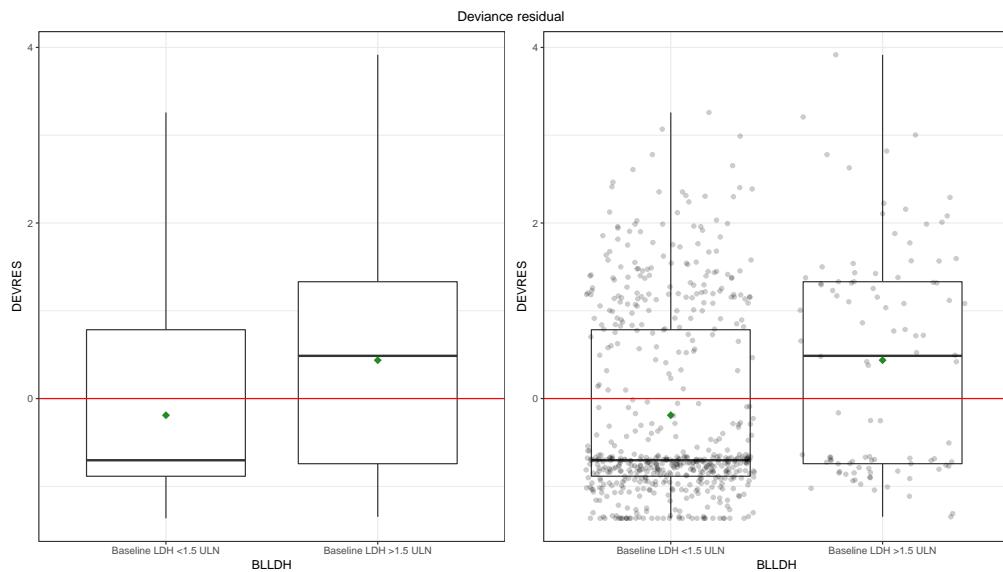


Figure 66: Residual-based diagnostics - Deviance plot

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

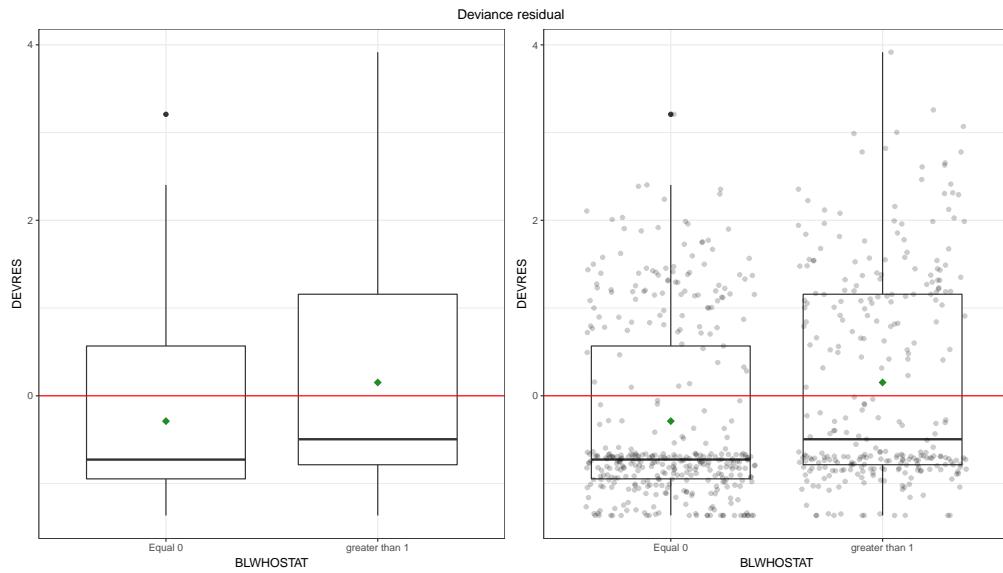


Figure 67: Residual-based diagnostics - Deviance plot

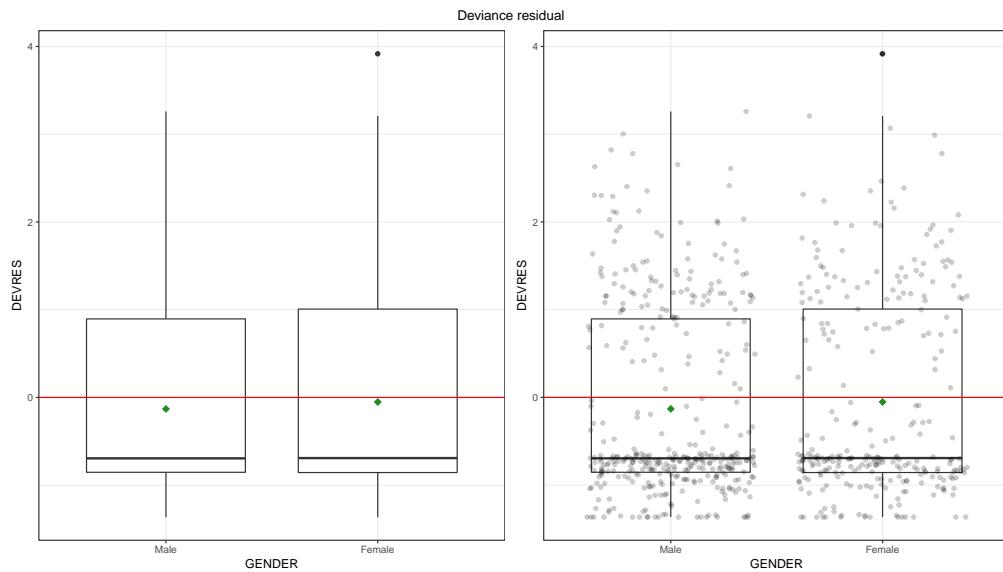


Figure 68: Residual-based diagnostics - Deviance plot

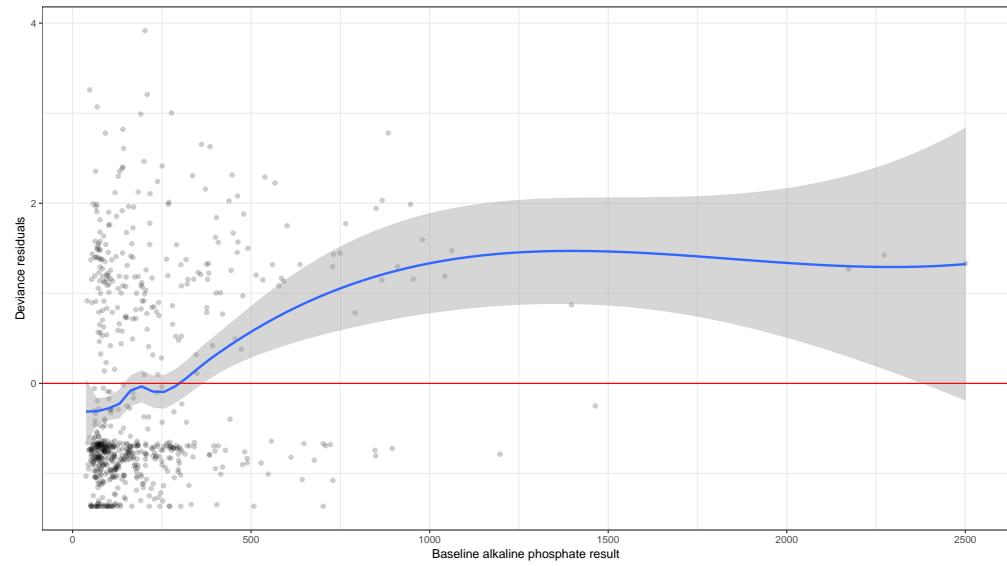


Figure 69: Residual-based diagnostics - Deviance plot

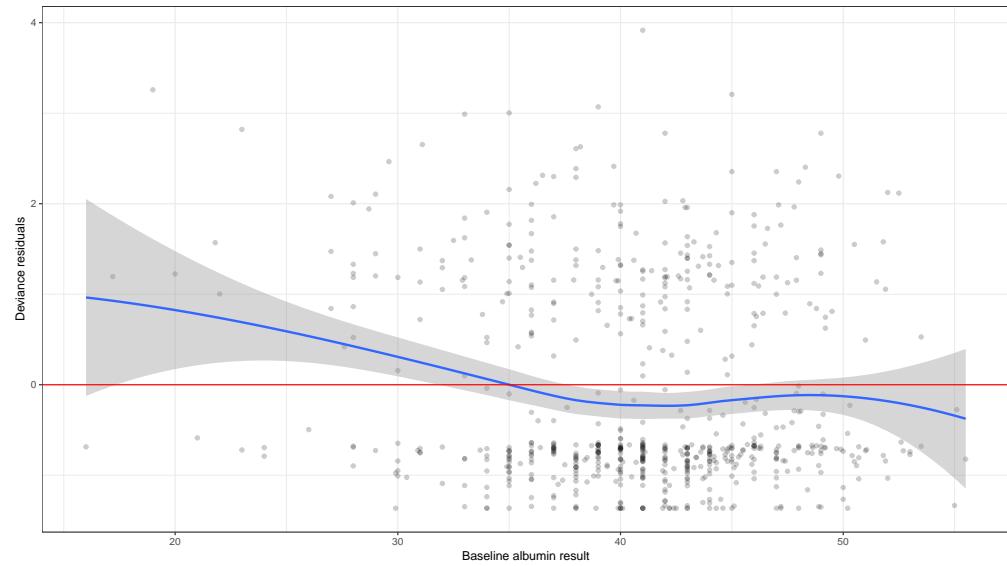


Figure 70: Residual-based diagnostics - Deviance plot

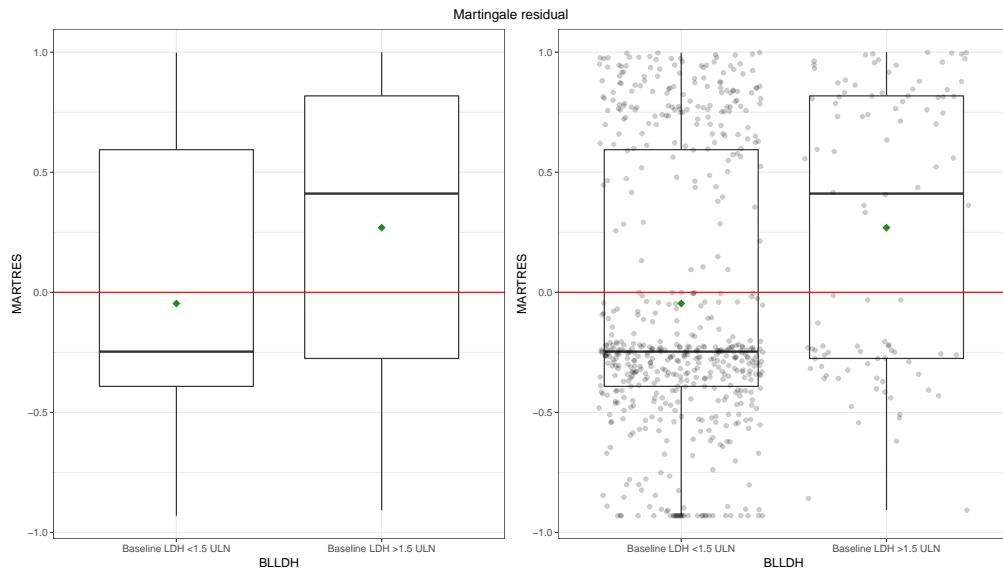


Figure 71: Residual-based diagnostics - Martingale plot

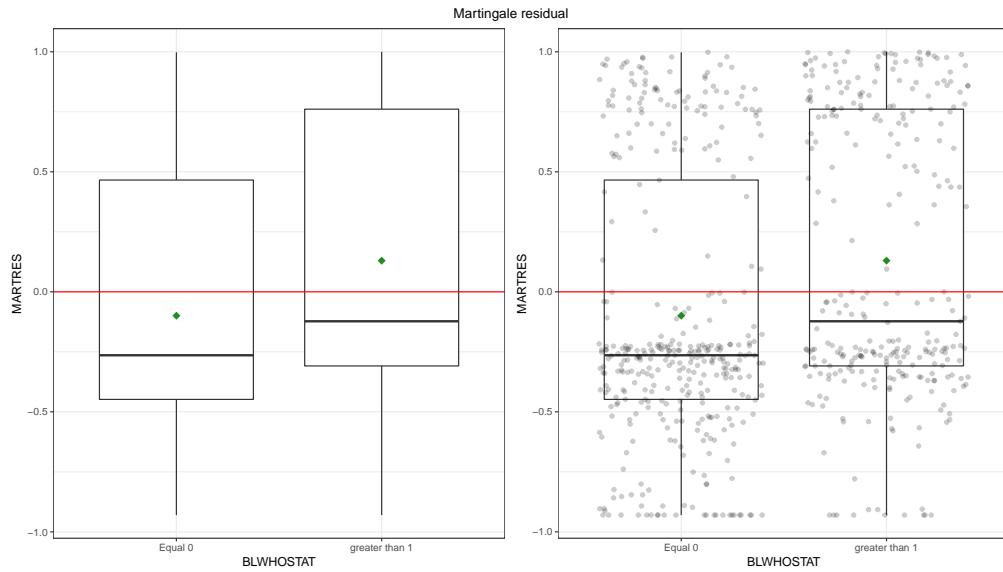


Figure 72: Residual-based diagnostics - Martingale plot

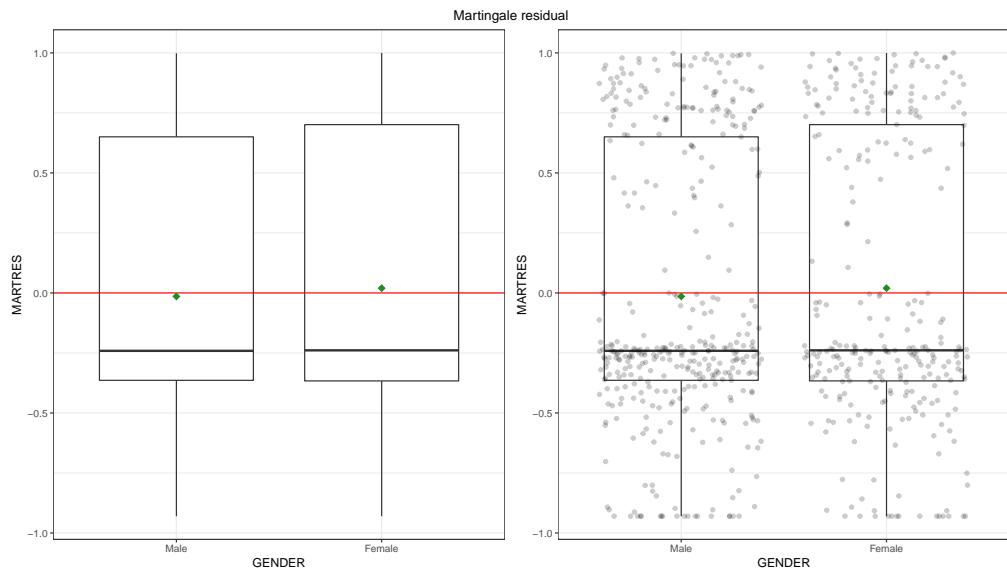


Figure 73: Residual-based diagnostics - Martingale plot

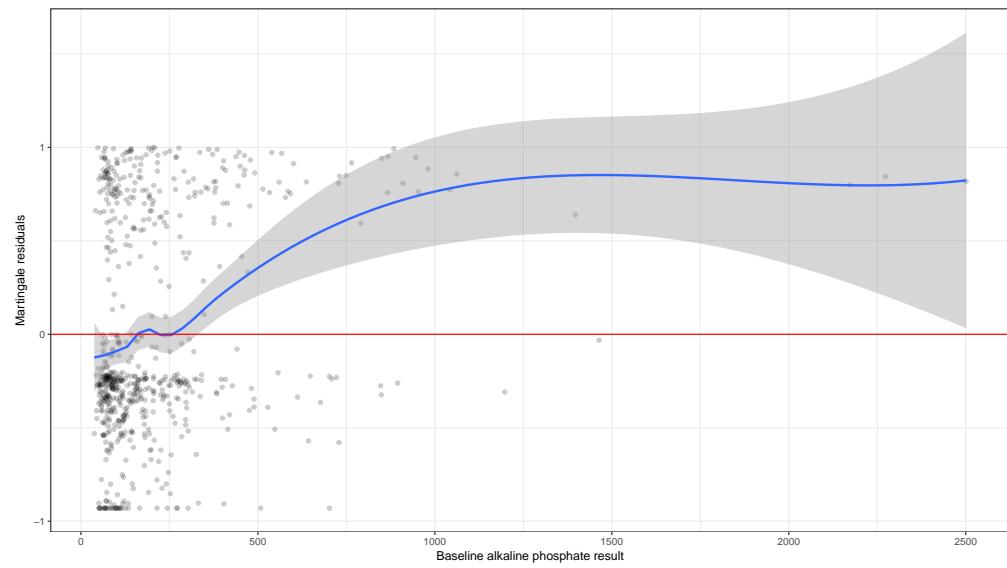


Figure 74: Residual-based diagnostics - Martingale plot

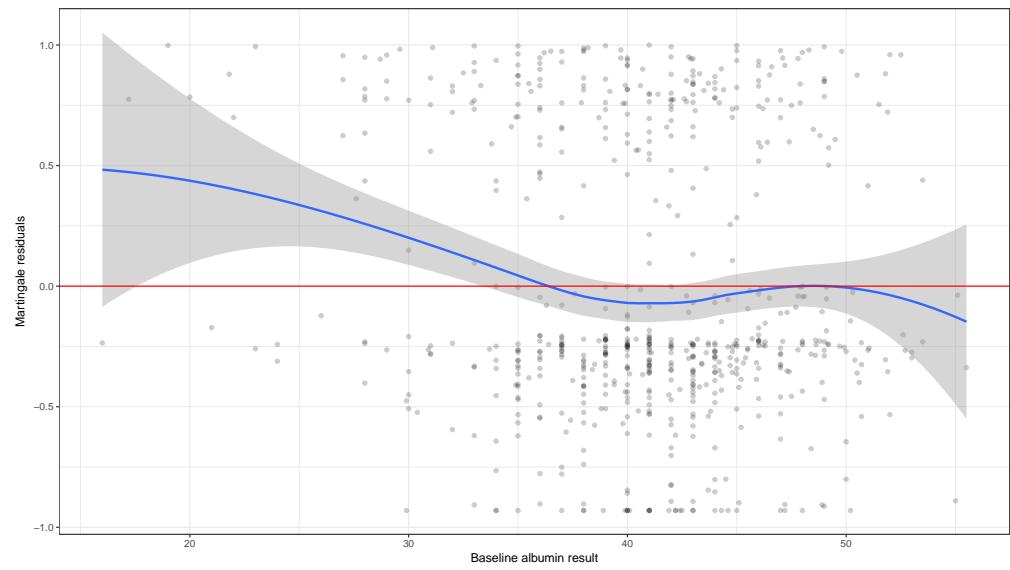


Figure 75: Residual-based diagnostics - Martingale plot

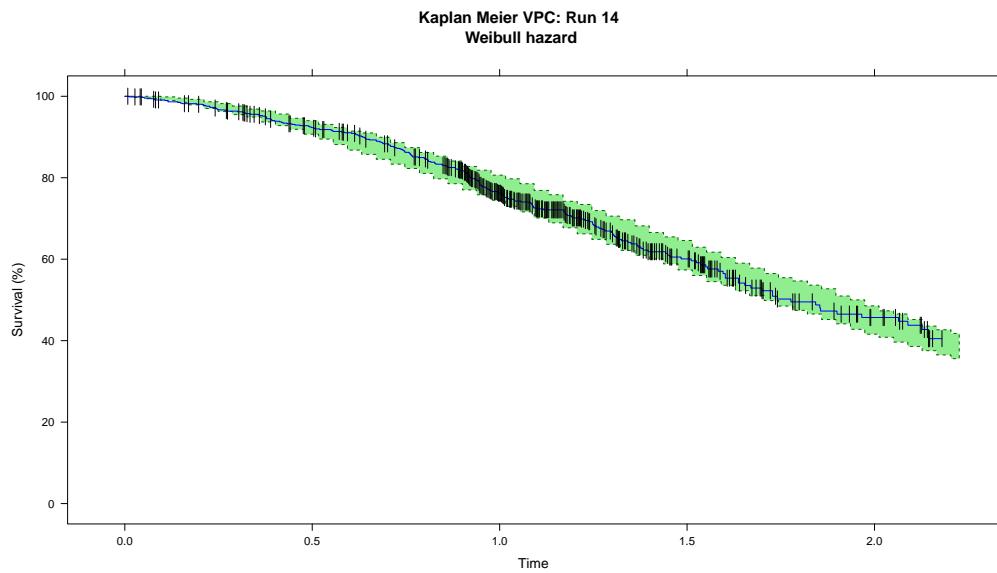


Figure 76: Simulation-based diagnostic

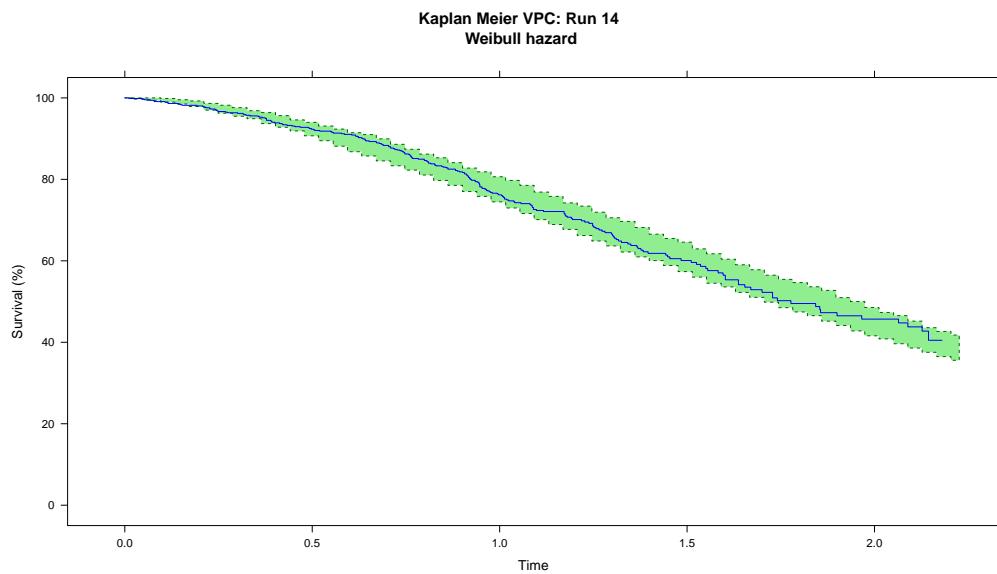


Figure 77: Simulation-based diagnostic

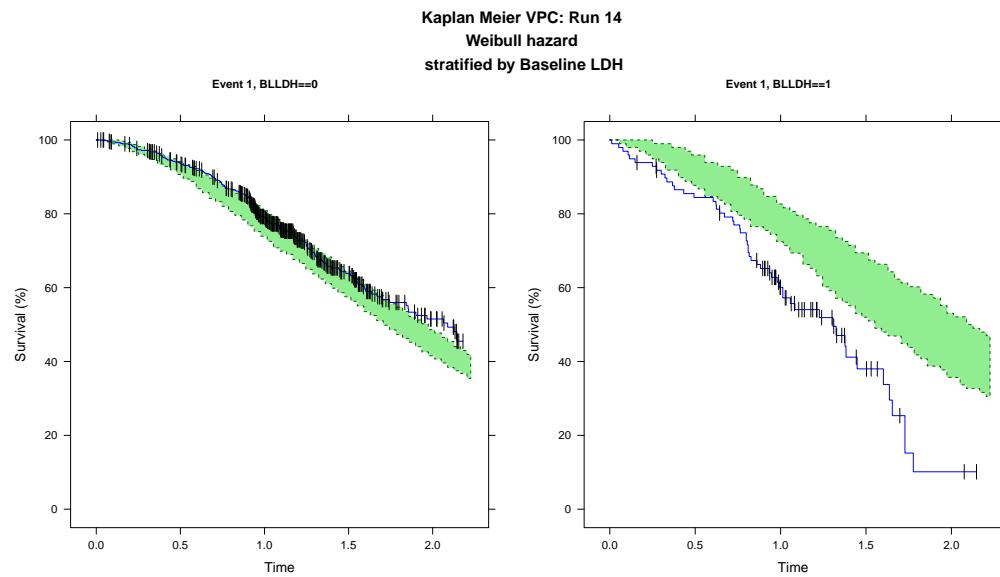


Figure 78: Simulation-based diagnostic - stratified by baseline LDH

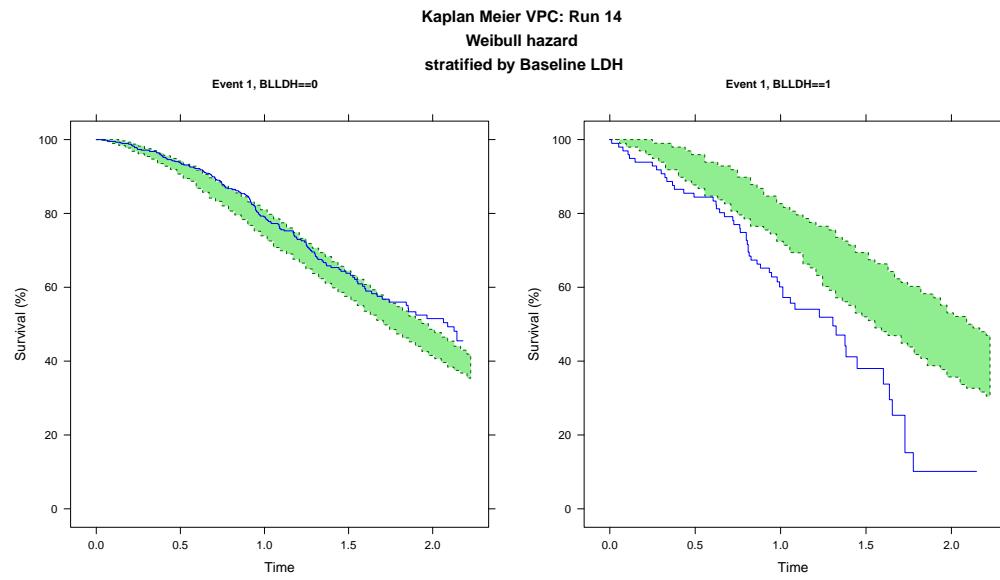


Figure 79: Simulation-based diagnostic - stratified by baseline LDH

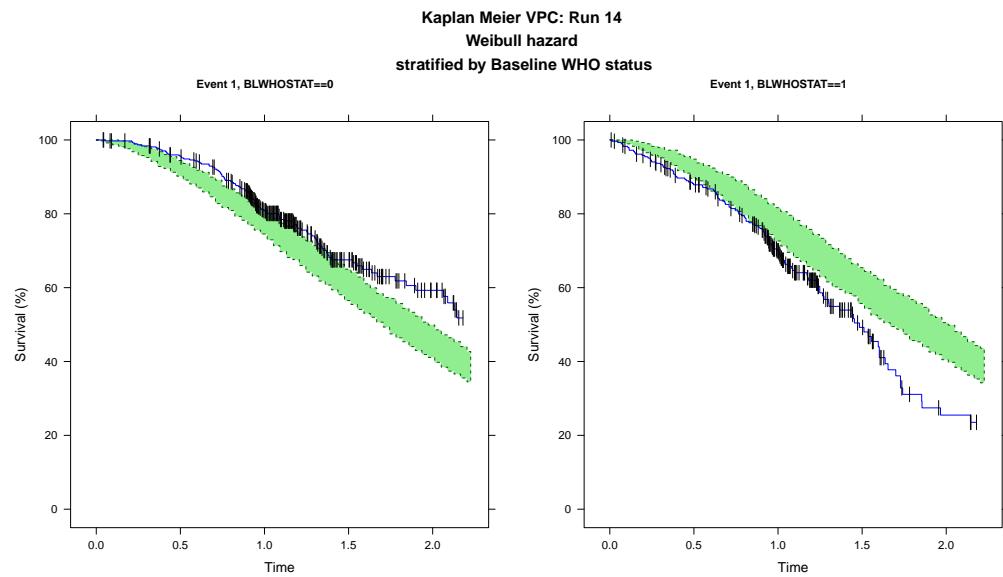


Figure 80: Simulation-based diagnostic - stratified by baseline WHO status

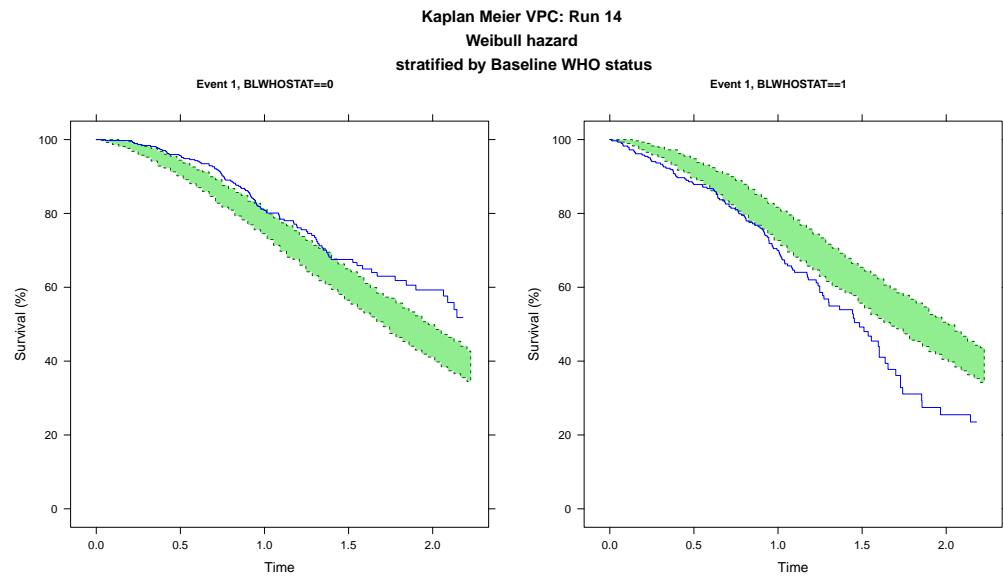


Figure 81: Simulation-based diagnostic - stratified by baseline WHO status

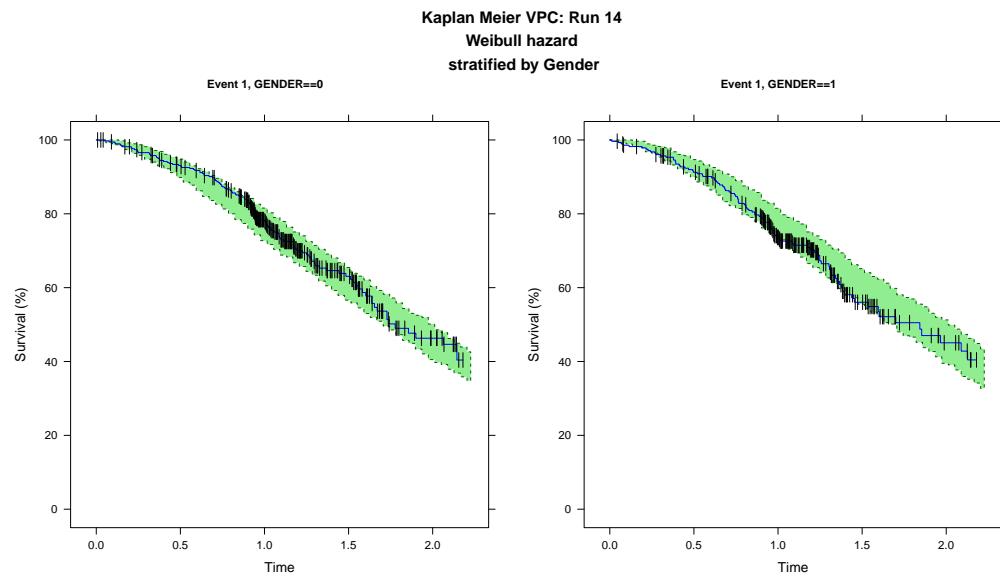


Figure 82: Simulation-based diagnostic - stratified by baseline Gender

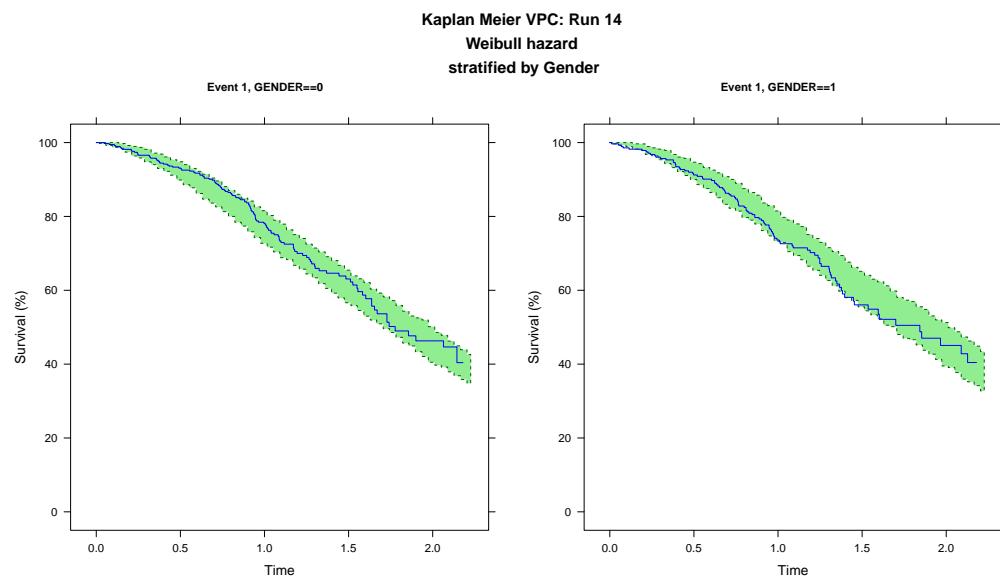


Figure 83: Simulation-based diagnostic - stratified by baseline Gender

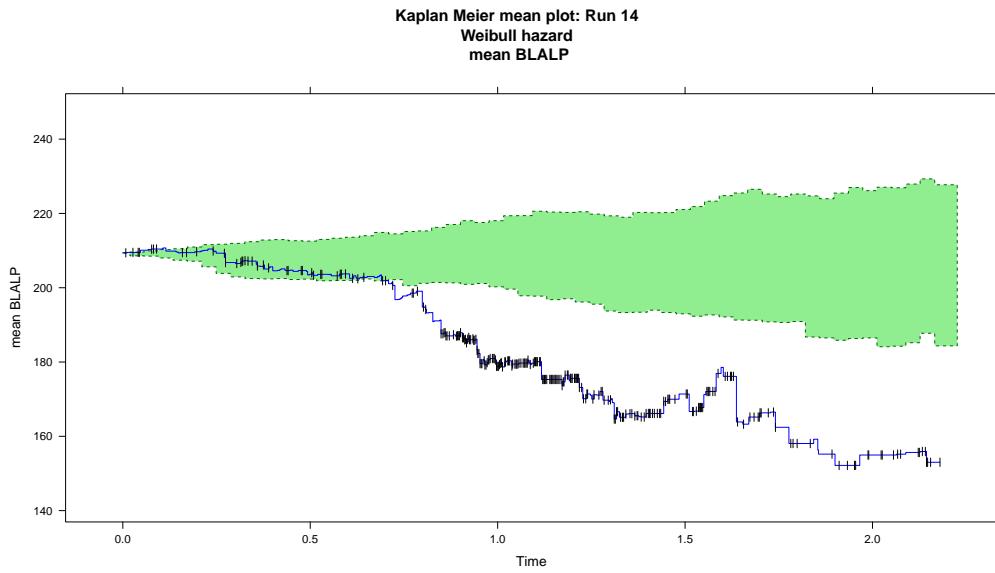


Figure 84: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

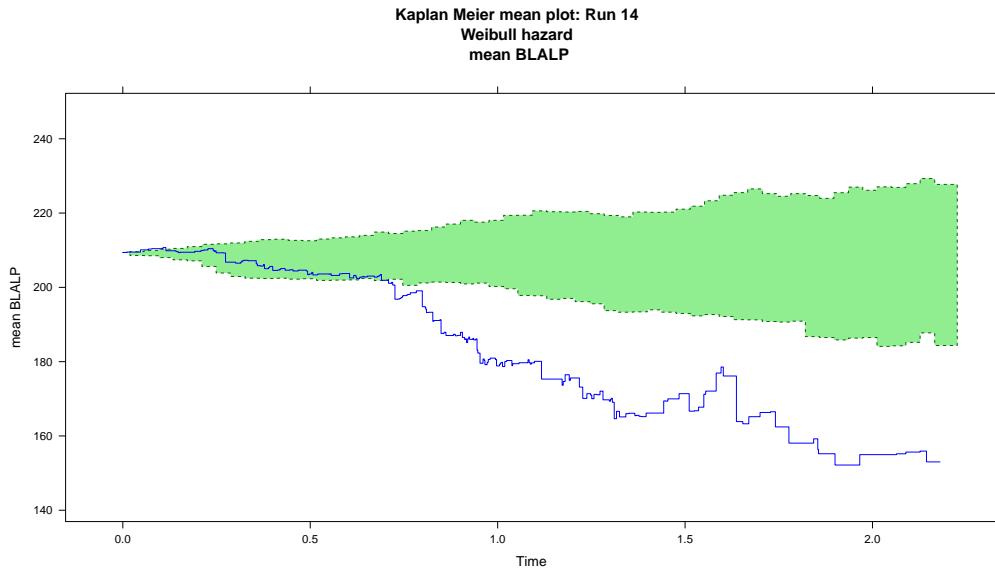


Figure 85: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

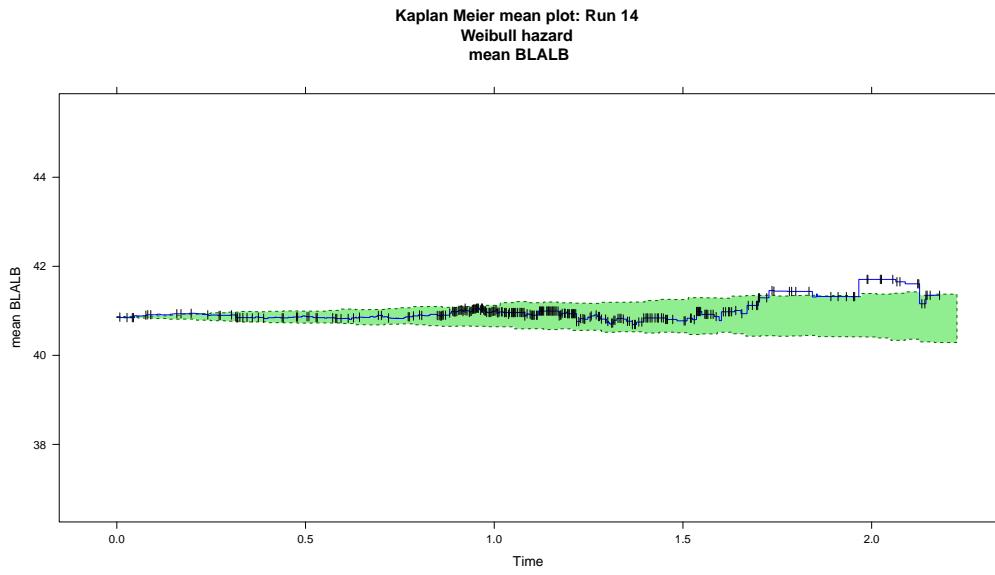


Figure 86: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

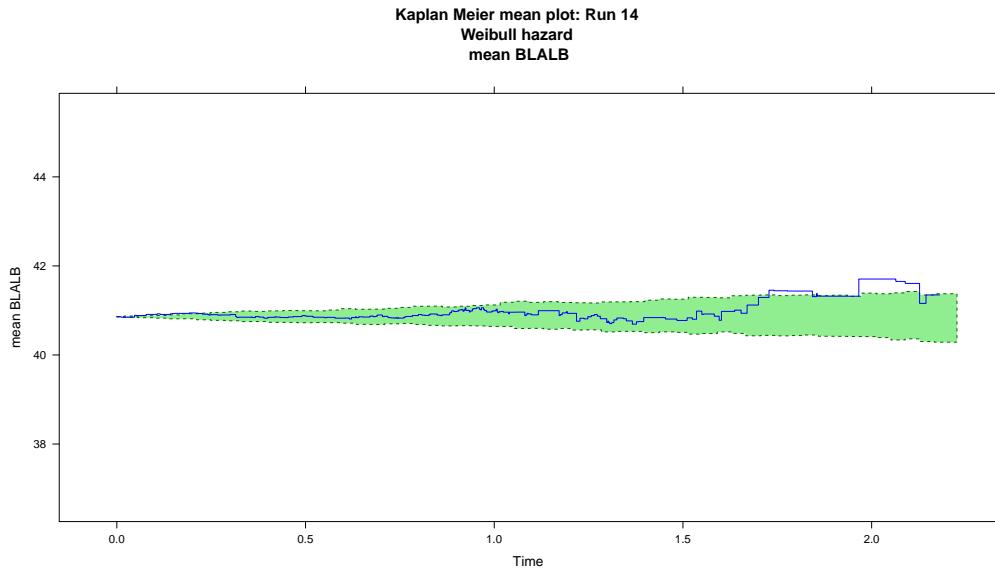


Figure 87: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

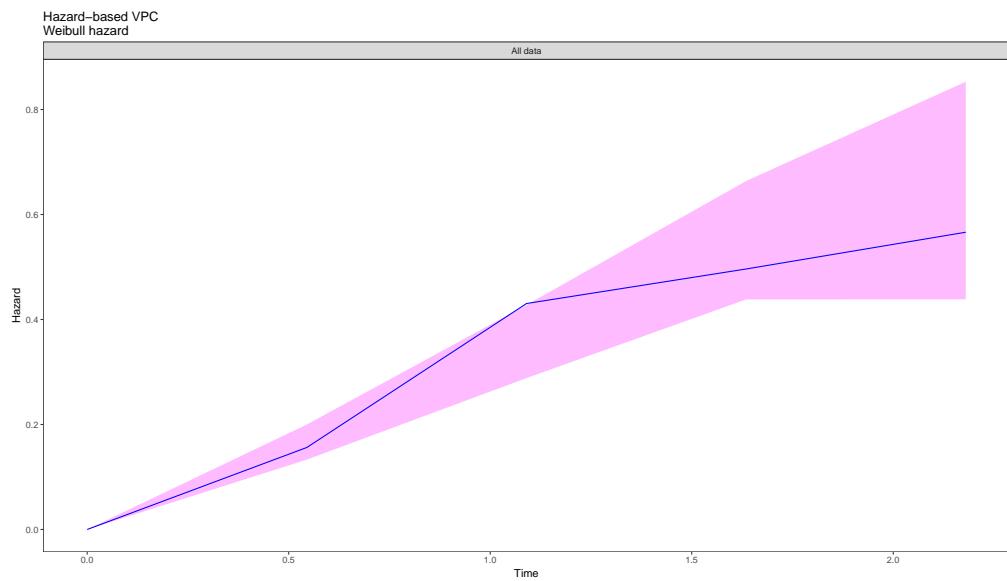


Figure 88: Simulation-based diagnostic: Hazard based VPC

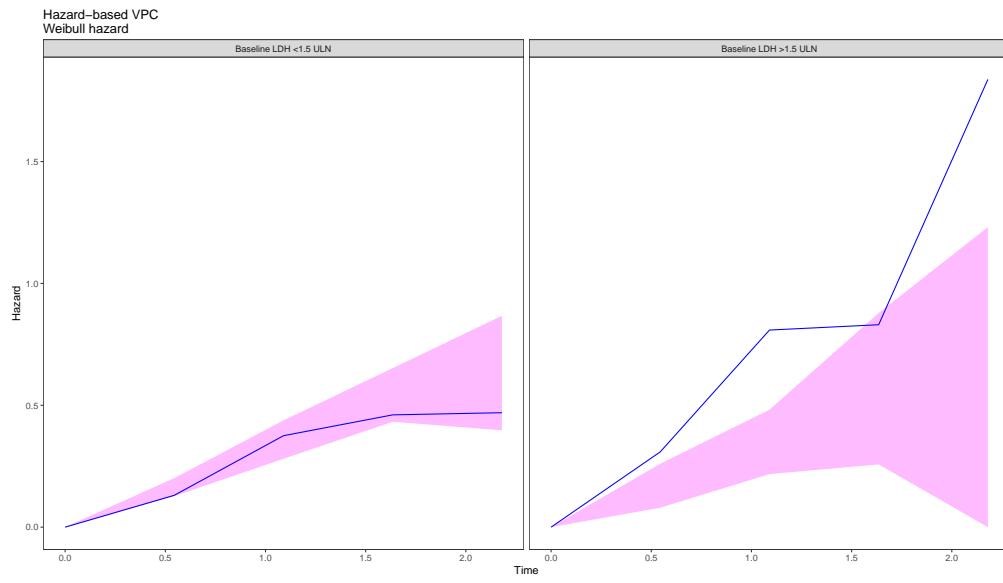


Figure 89: Simulation-based diagnostic: Hazard based VPC

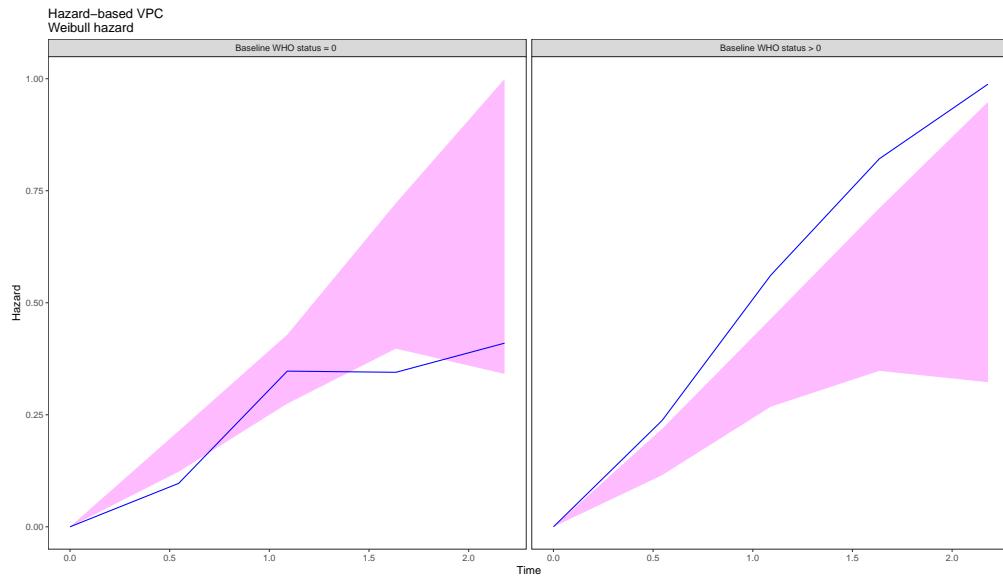


Figure 90: Simulation-based diagnostic: Hazard based VPC

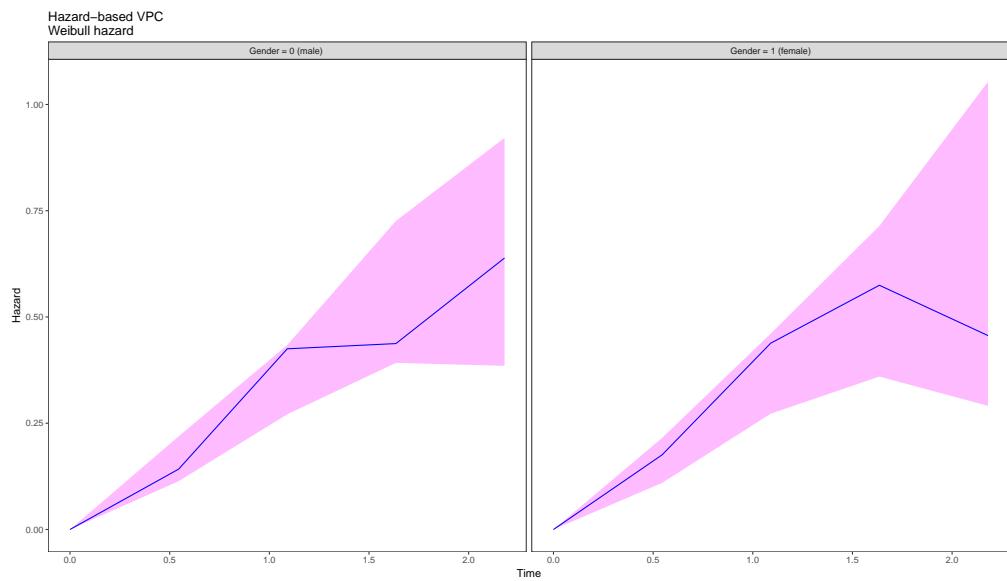


Figure 91: Simulation-based diagnostic: Hazard based VPC

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 occurred 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, binary 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=0
```

```

## 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 BLWLEVEL
## 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"
## [6] "No rounding errors"
## [7] "No zero gradients"
## [8] "No final zero gradients"
## [9] "Hessian not reset"
## [10] "No parameter near boundary"
## [11] "Covariance step"
## [12] ""
## [13] "Condition number"
## [14] "Correlations"
## [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

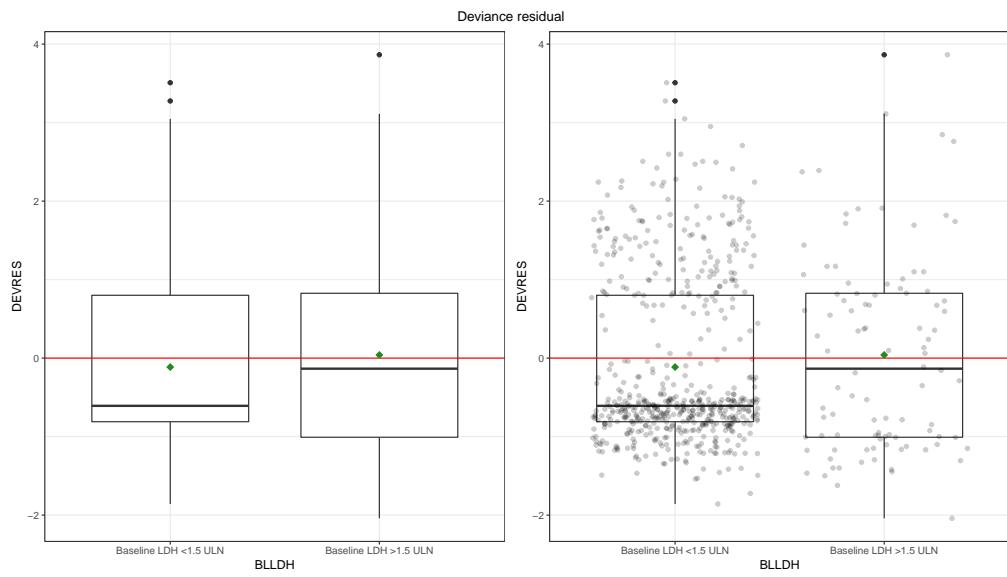


Figure 92: Residual-based diagnostics - Deviance plot

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

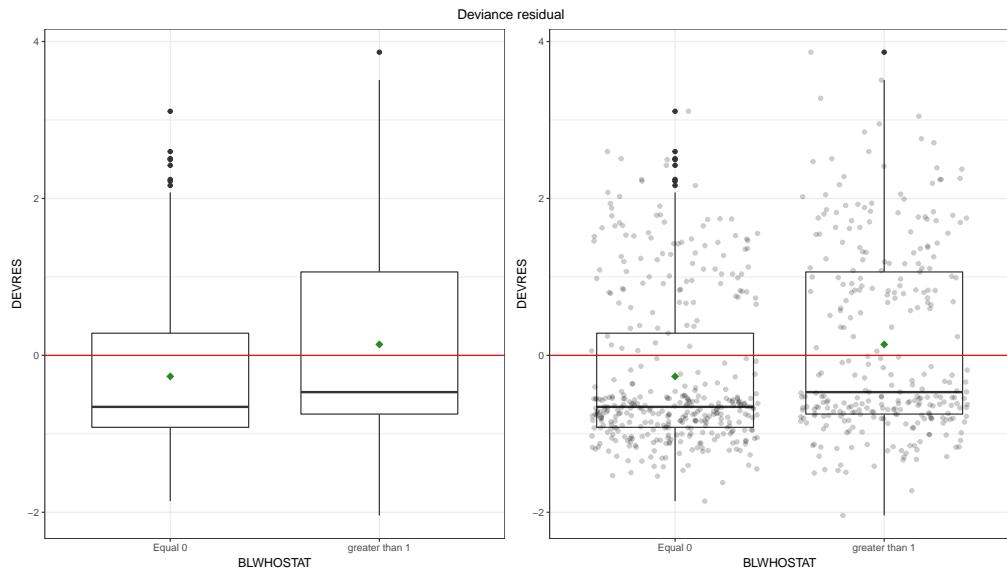


Figure 93: Residual-based diagnostics - Deviance plot

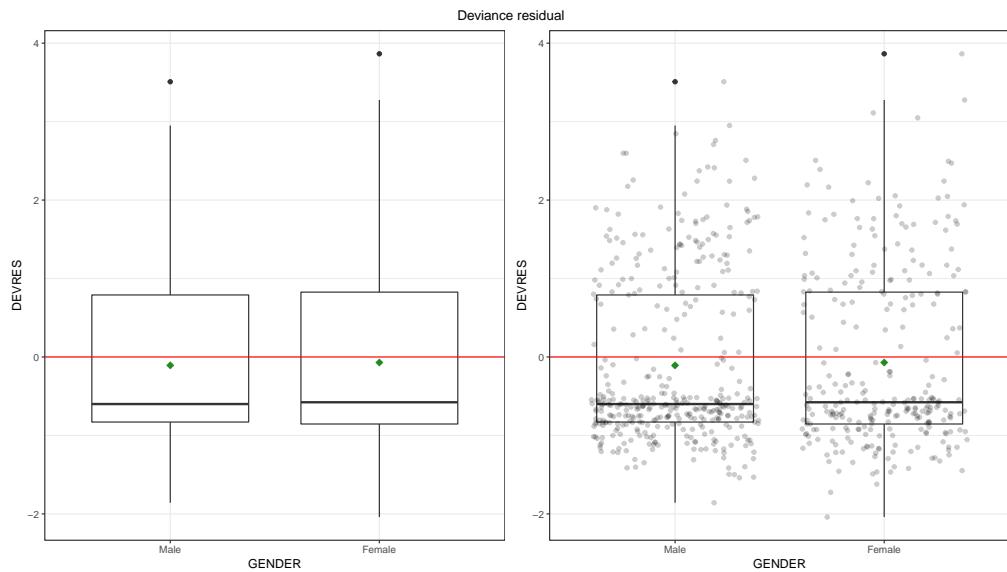


Figure 94: Residual-based diagnostics - Deviance plot

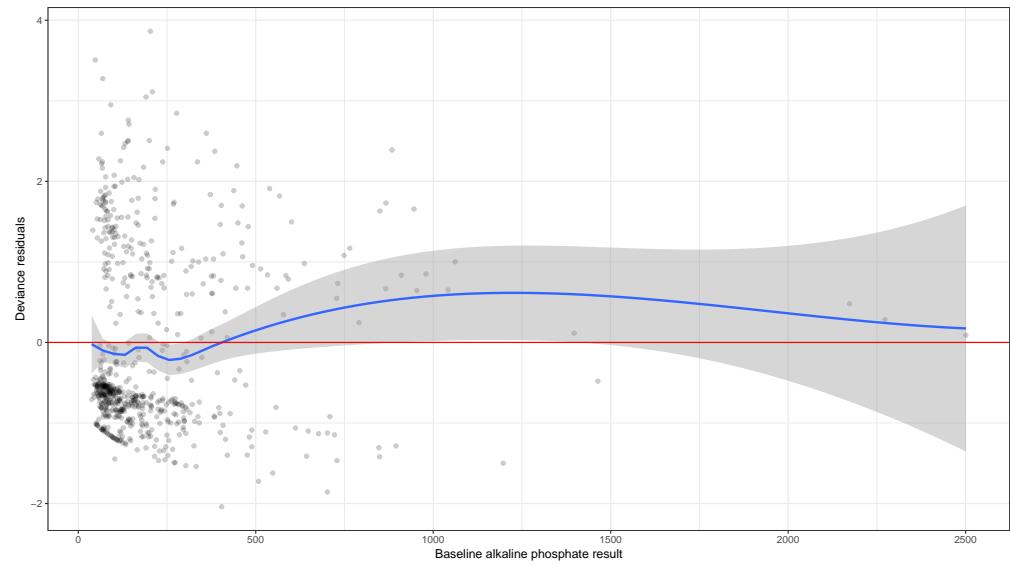


Figure 95: Residual-based diagnostics - Deviance plot

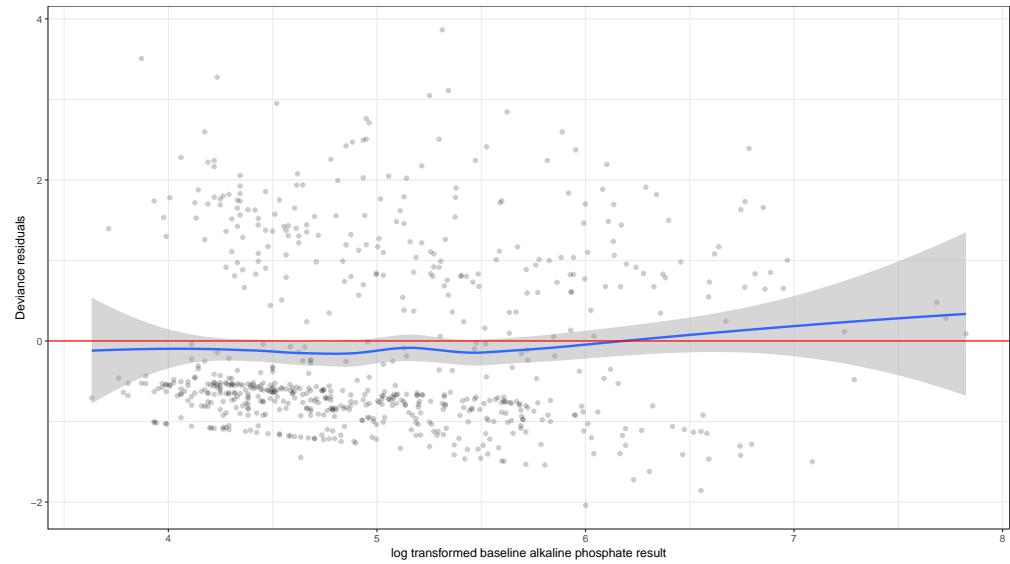


Figure 96: Residual-based diagnostics - Deviance plot

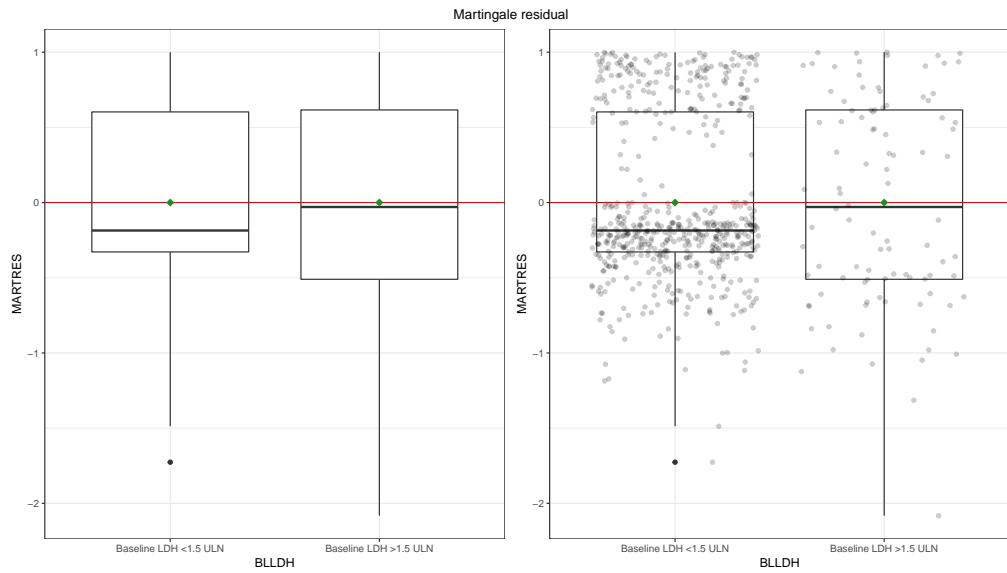


Figure 97: Residual-based diagnostics - Martingale plot

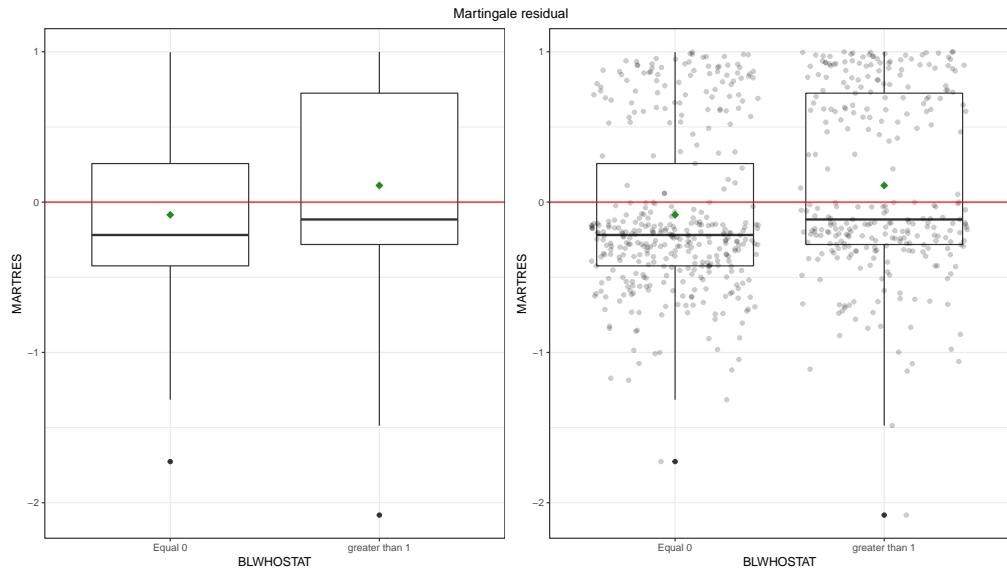


Figure 98: Residual-based diagnostics - Martingale plot

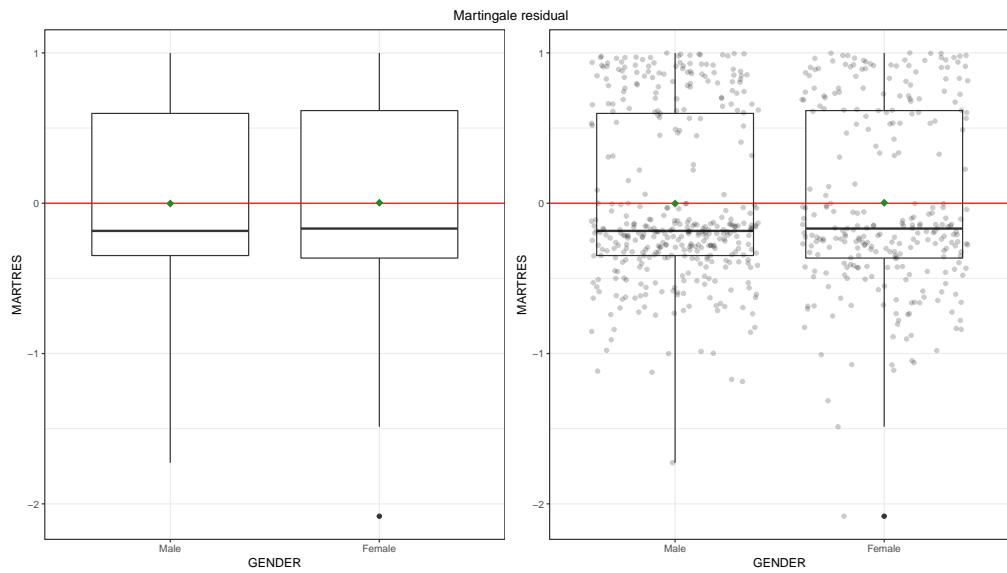


Figure 99: Residual-based diagnostics - Martingale plot

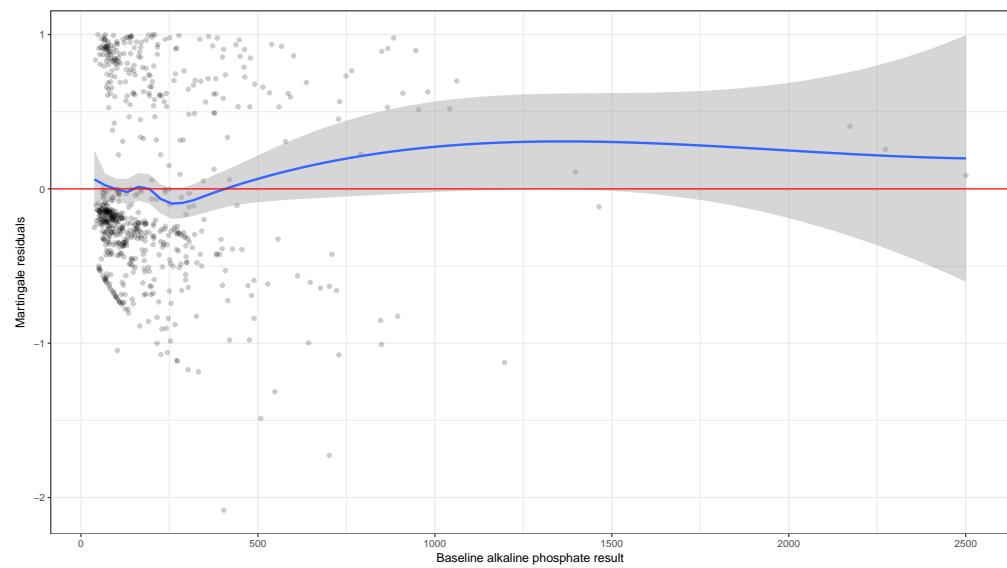


Figure 100: Residual-based diagnostics - Martingale plot

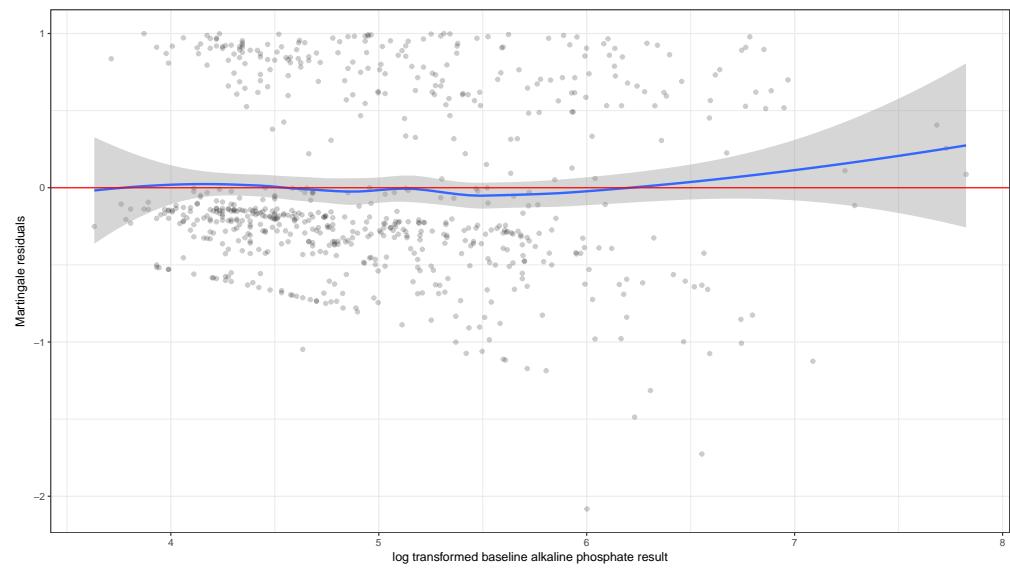


Figure 101: Residual-based diagnostics - Martingale plot

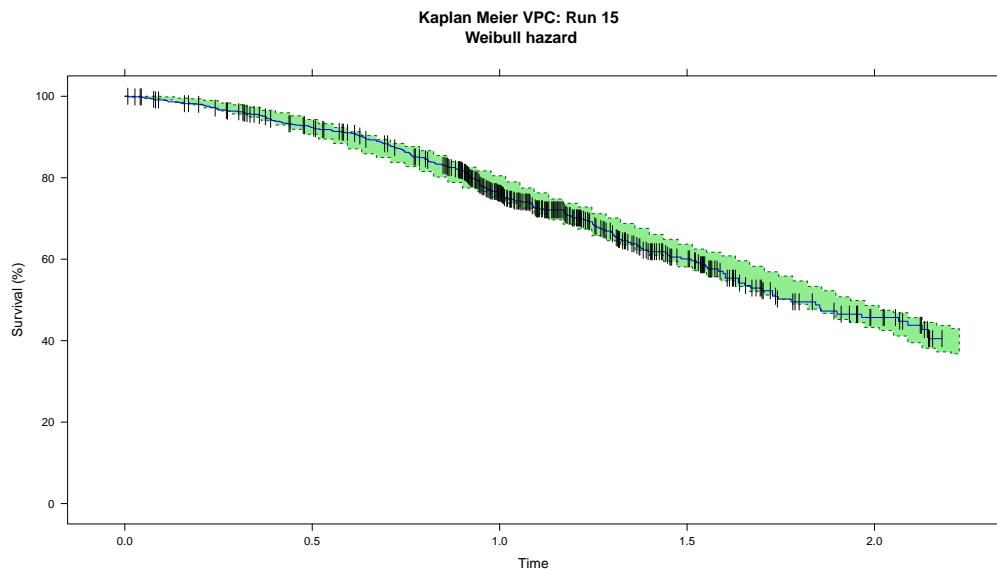


Figure 102: Simulation-based diagnostic

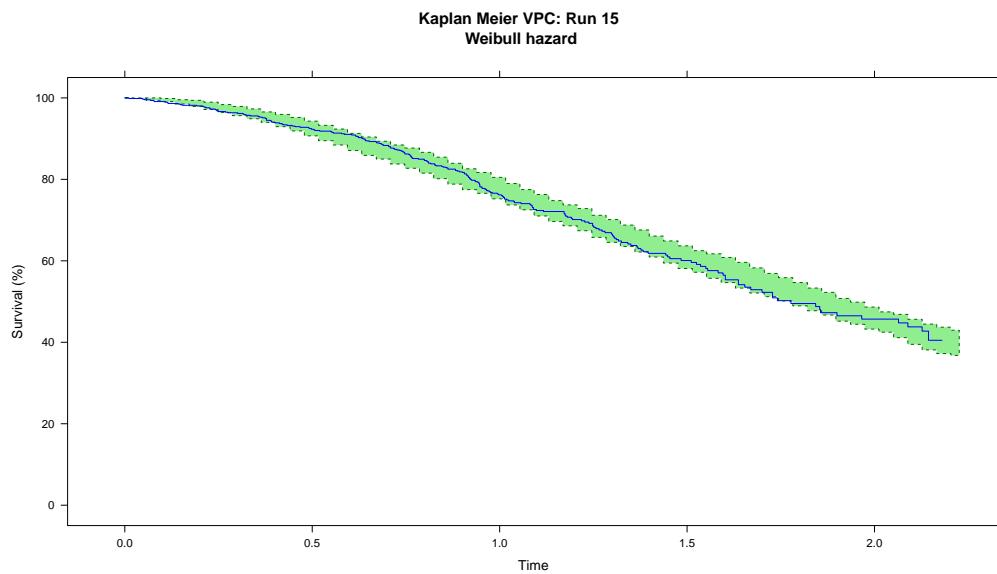


Figure 103: Simulation-based diagnostic

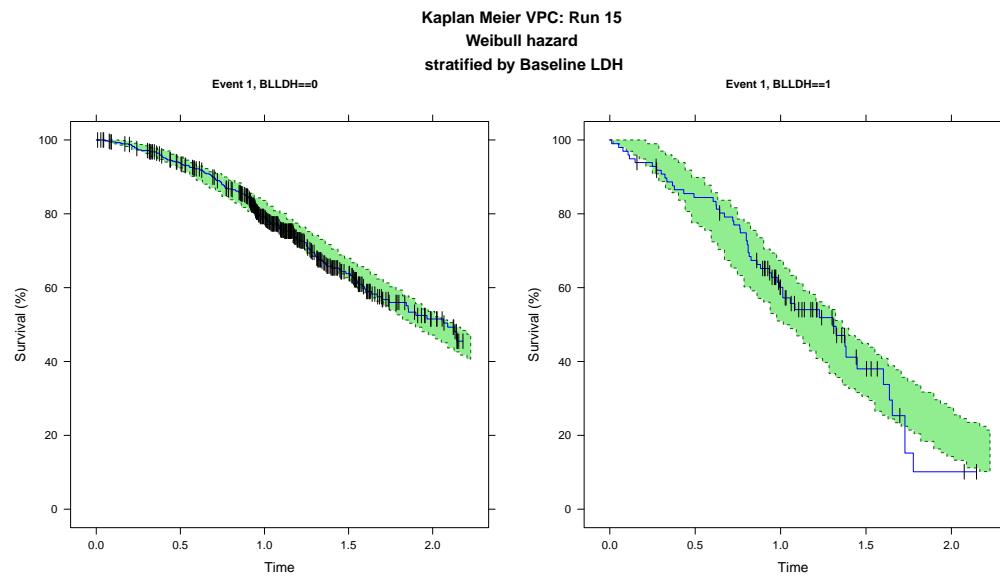


Figure 104: Simulation-based diagnostic - stratified by baseline LDH

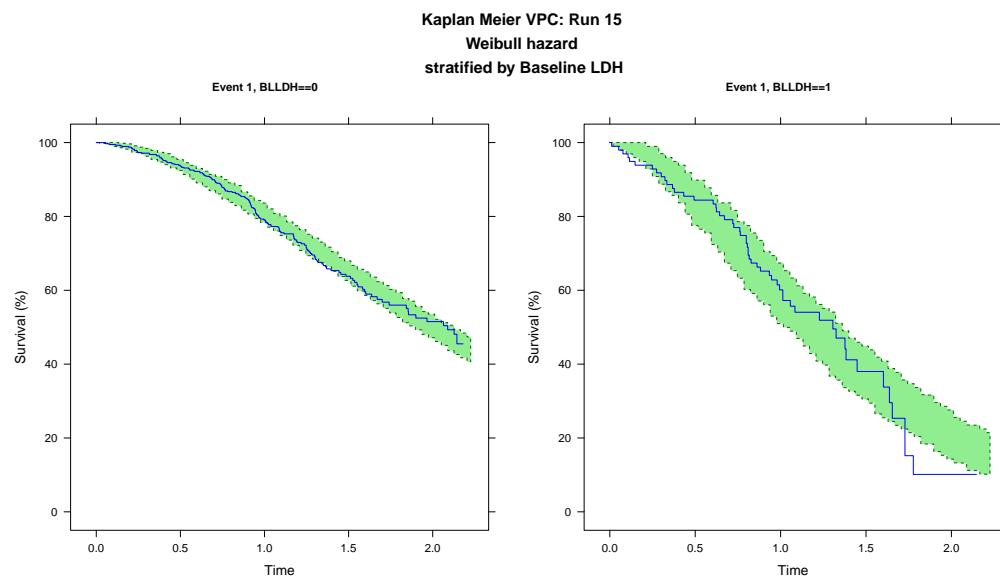


Figure 105: Simulation-based diagnostic - stratified by baseline LDH

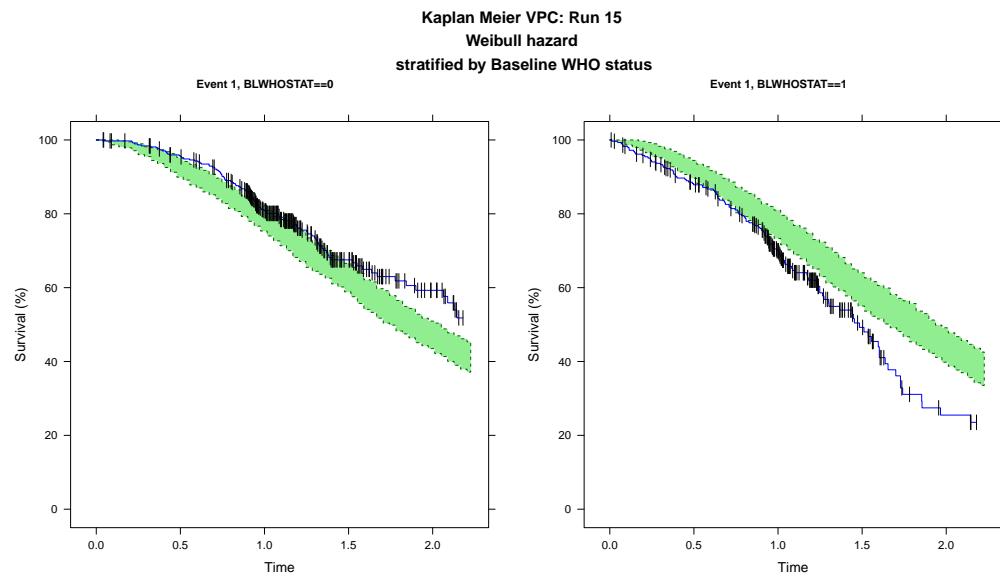


Figure 106: Simulation-based diagnostic - stratified by baseline WHO status

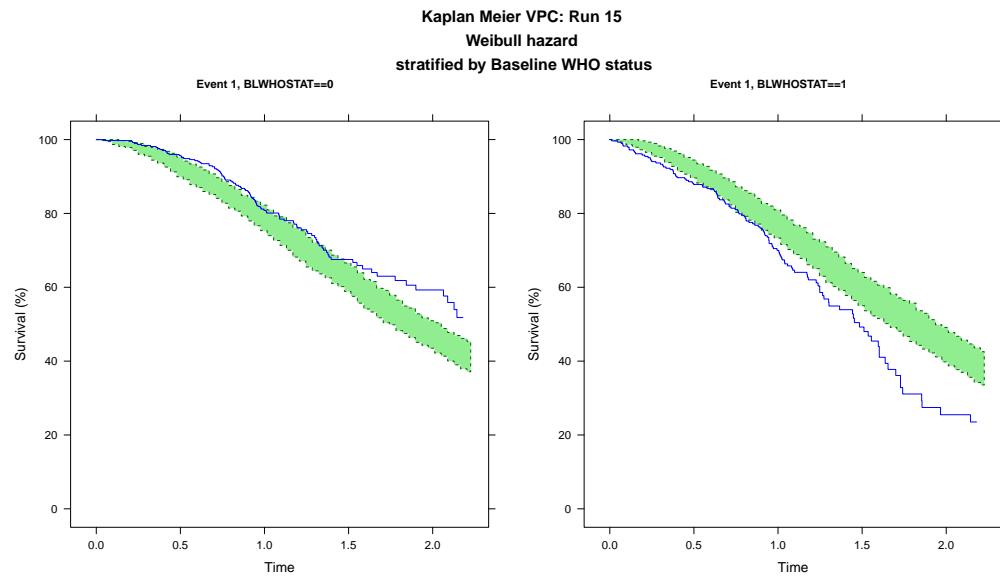


Figure 107: Simulation-based diagnostic - stratified by baseline WHO status

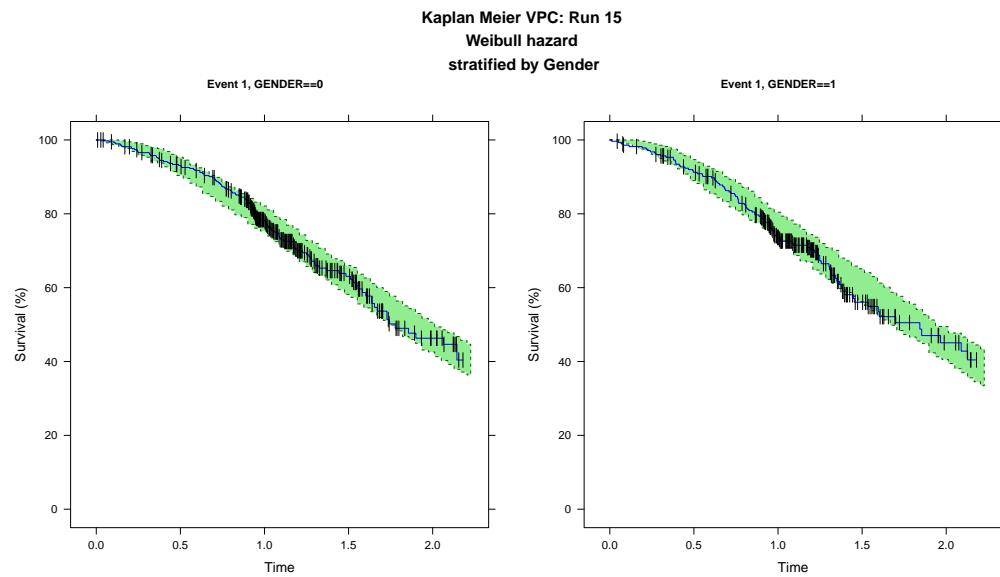


Figure 108: Simulation-based diagnostic - stratified by baseline Gender

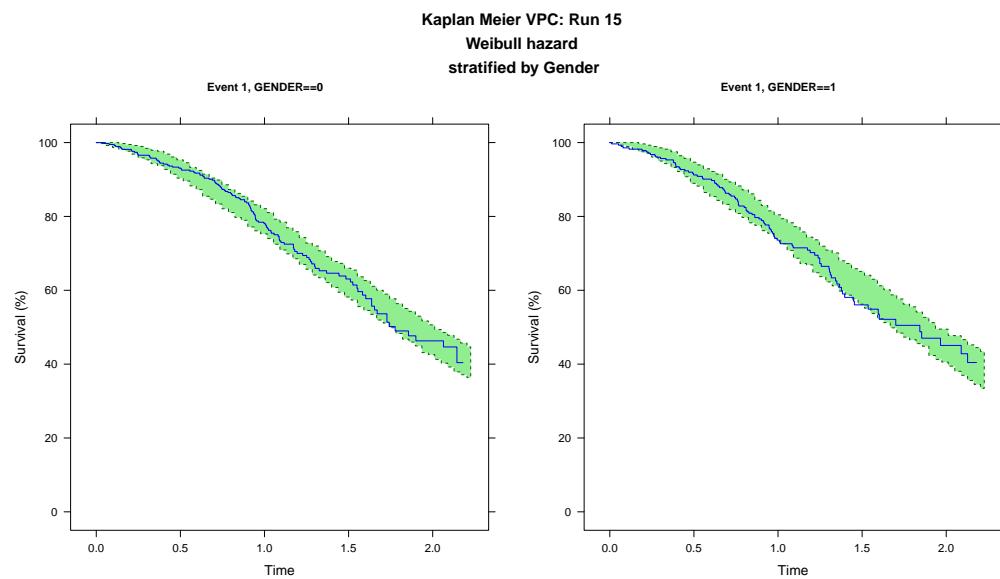


Figure 109: Simulation-based diagnostic - stratified by baseline Gender

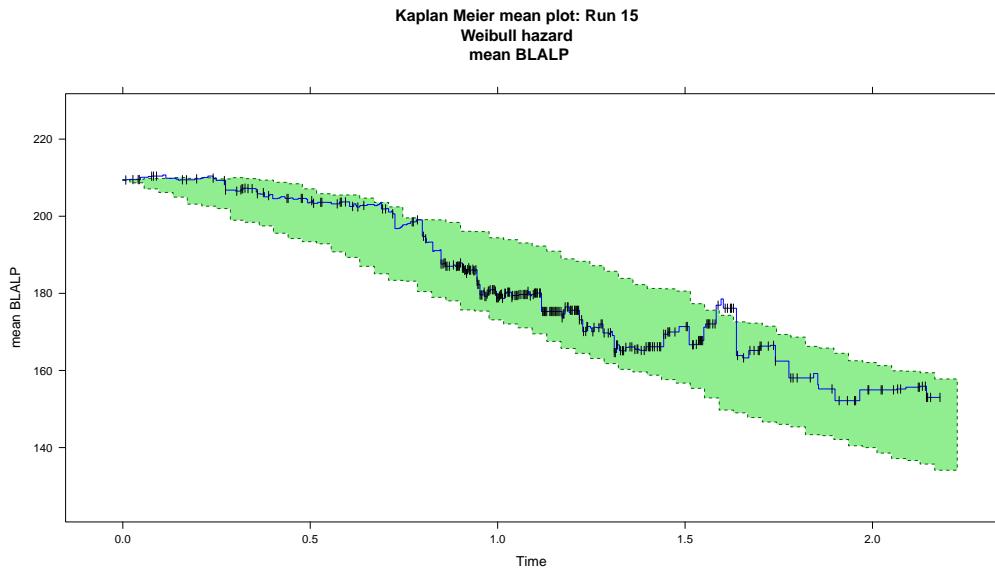


Figure 110: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

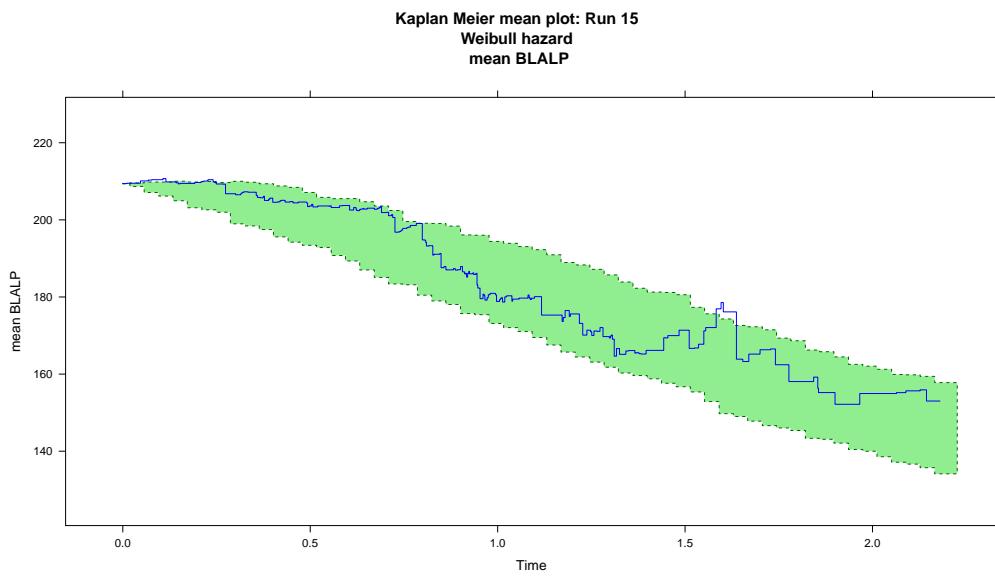


Figure 111: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

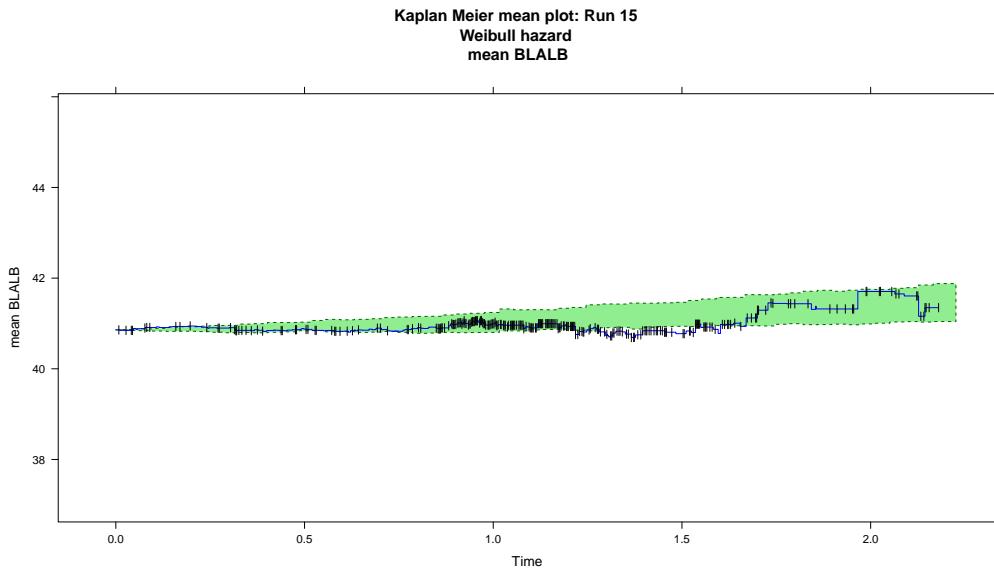


Figure 112: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

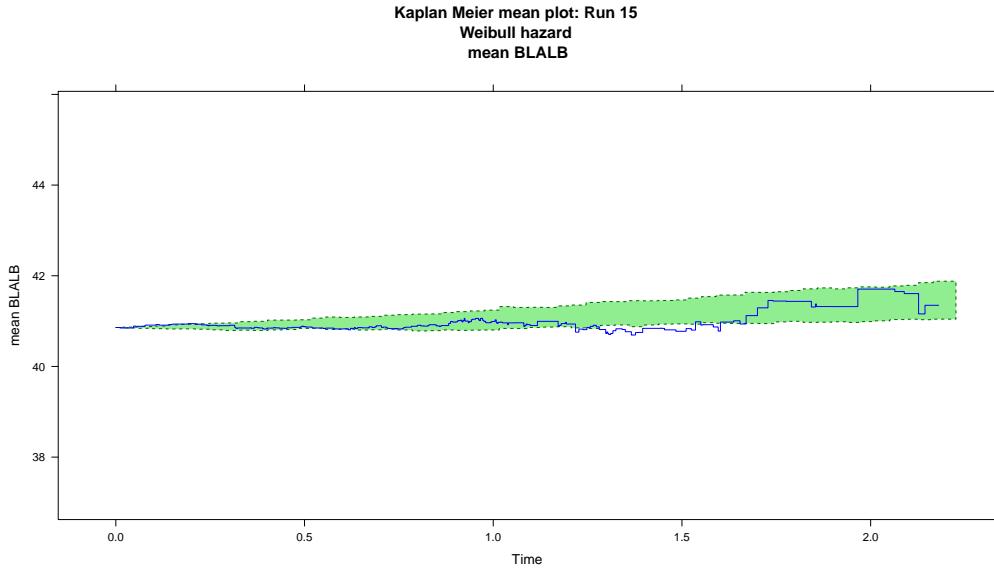


Figure 113: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

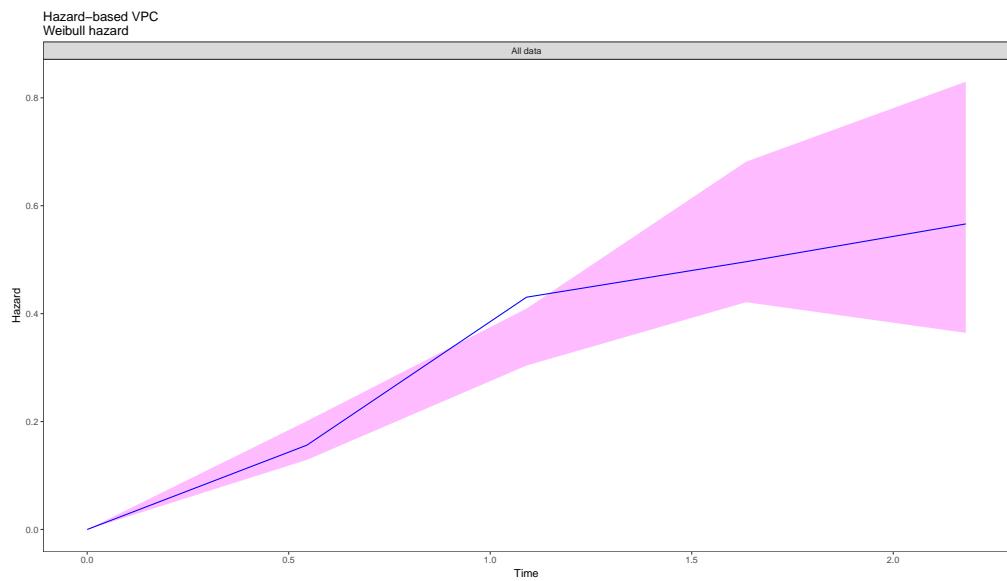


Figure 114: Simulation-based diagnostic: Hazard based VPC

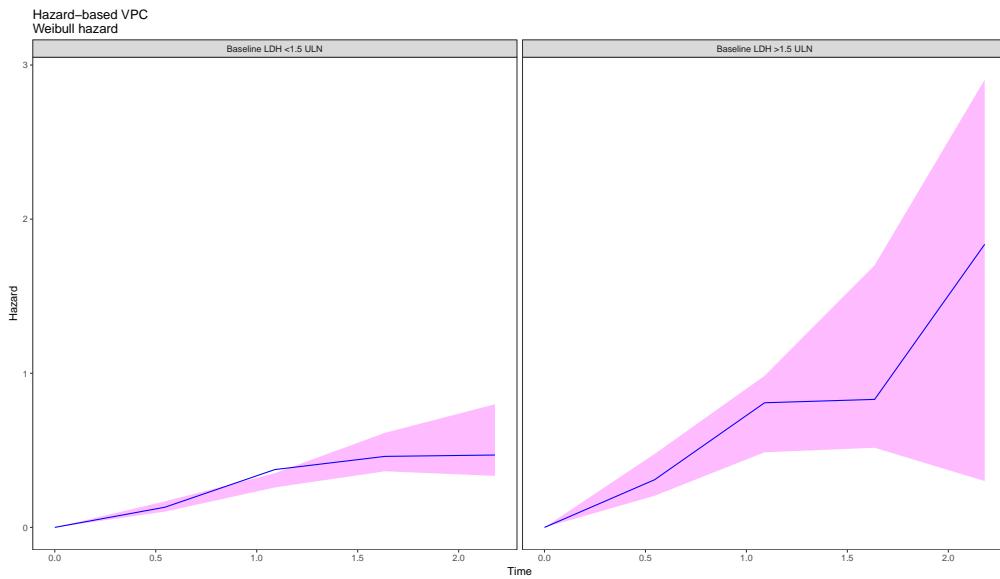


Figure 115: Simulation-based diagnostic: Hazard based VPC

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
##
```

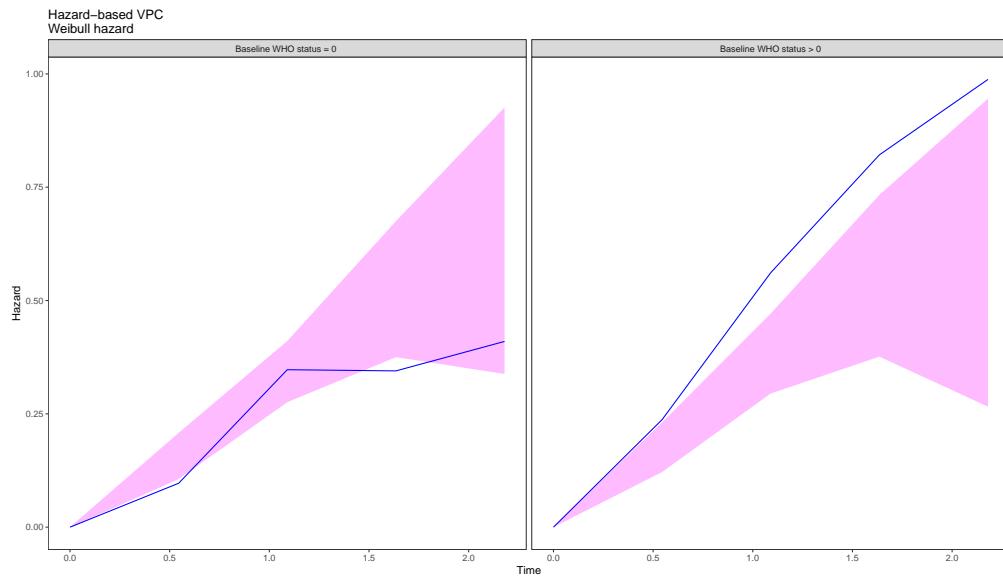


Figure 116: Simulation-based diagnostic: Hazard based VPC

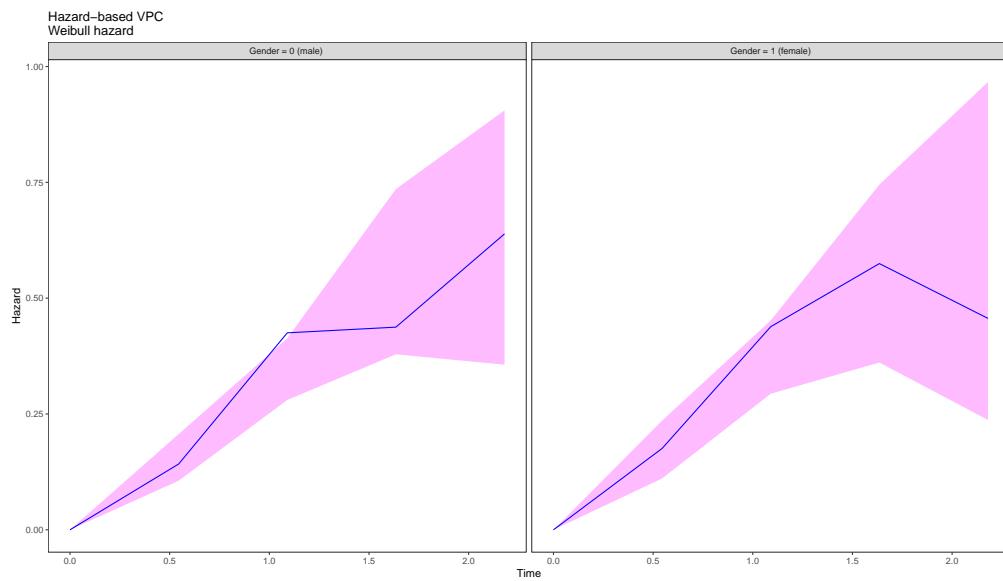


Figure 117: Simulation-based diagnostic: Hazard based VPC

```

## ;-----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 occurred 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, binary 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
## ; BLWHEOLEVEL, 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*BLHOSTAT ; 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 BLDH BLWHOSTAT BLALB BLALP BLWLEVEL
## 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"
## [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

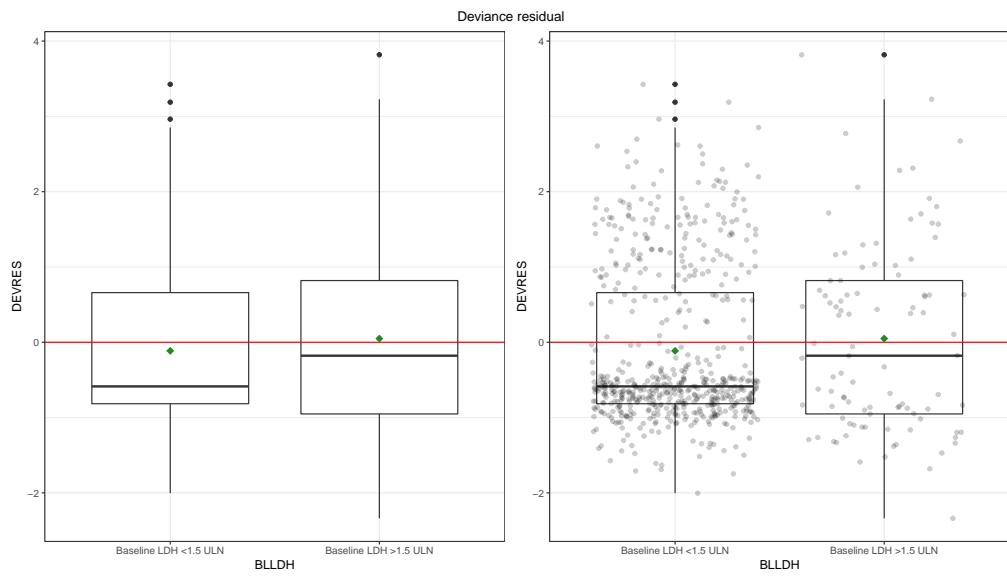


Figure 118: Residual-based diagnostics - Deviance plot

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

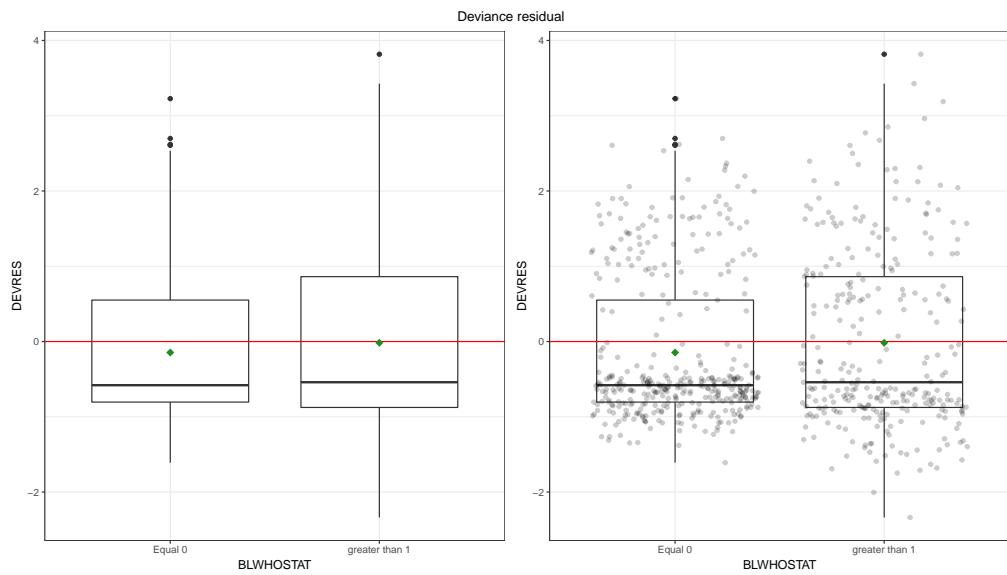


Figure 119: Residual-based diagnostics - Deviance plot

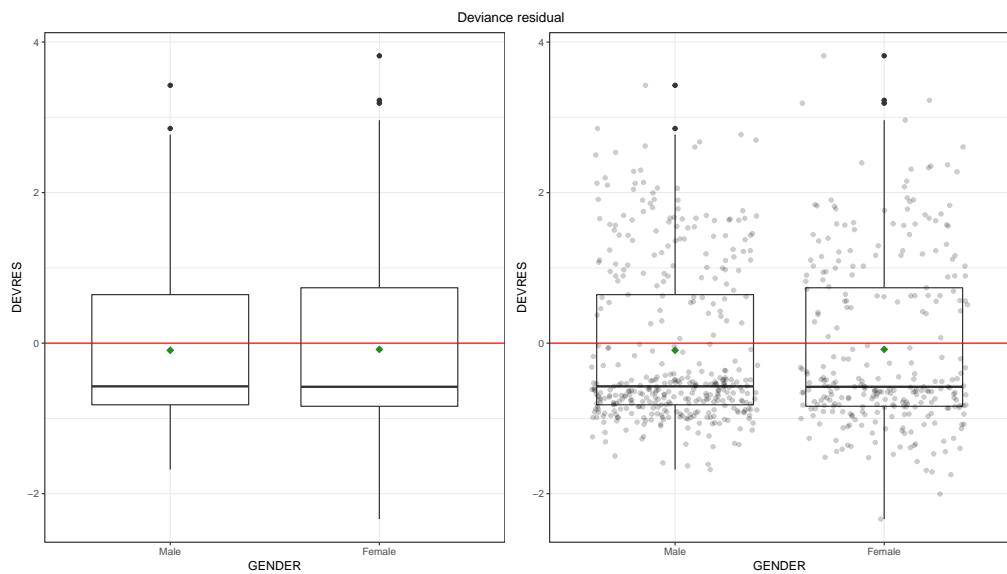


Figure 120: Residual-based diagnostics - Deviance plot

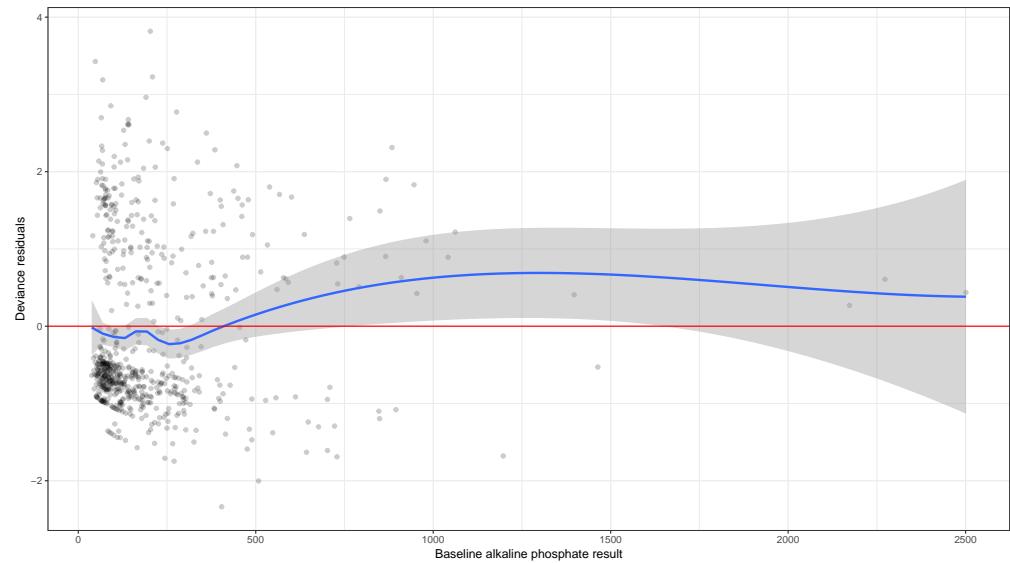


Figure 121: Residual-based diagnostics - Deviance plot

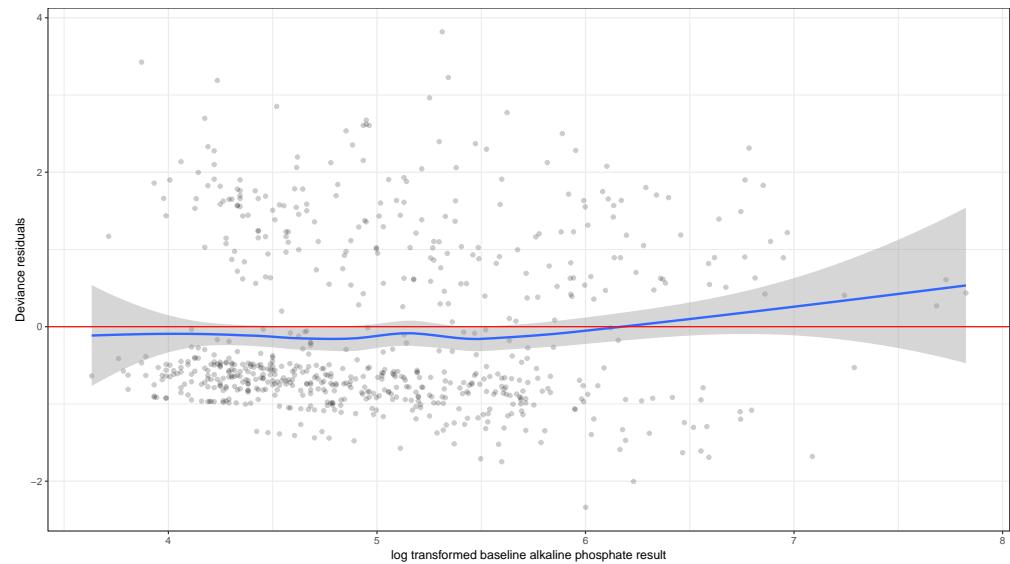


Figure 122: Residual-based diagnostics - Deviance plot

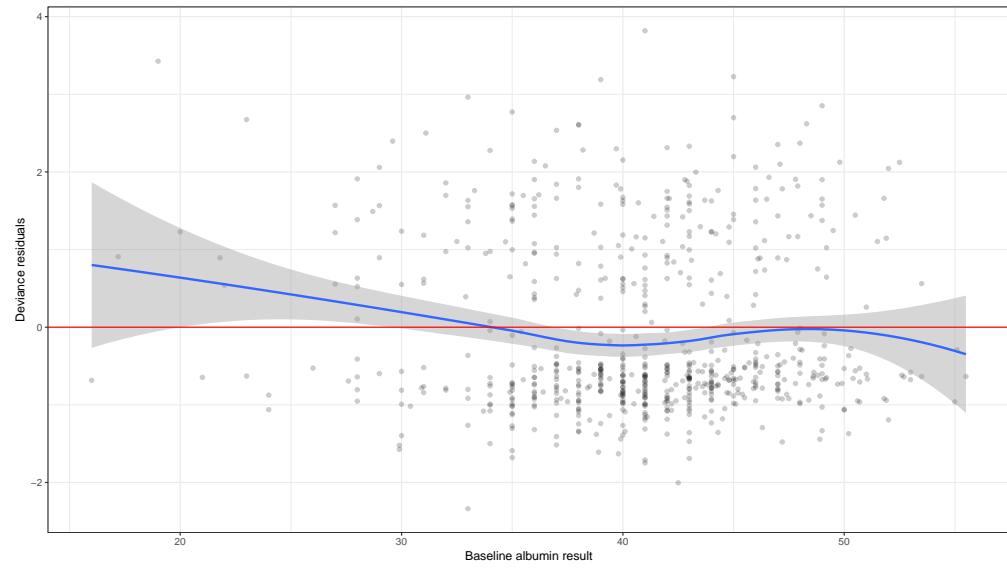


Figure 123: Residual-based diagnostics - Deviance plot

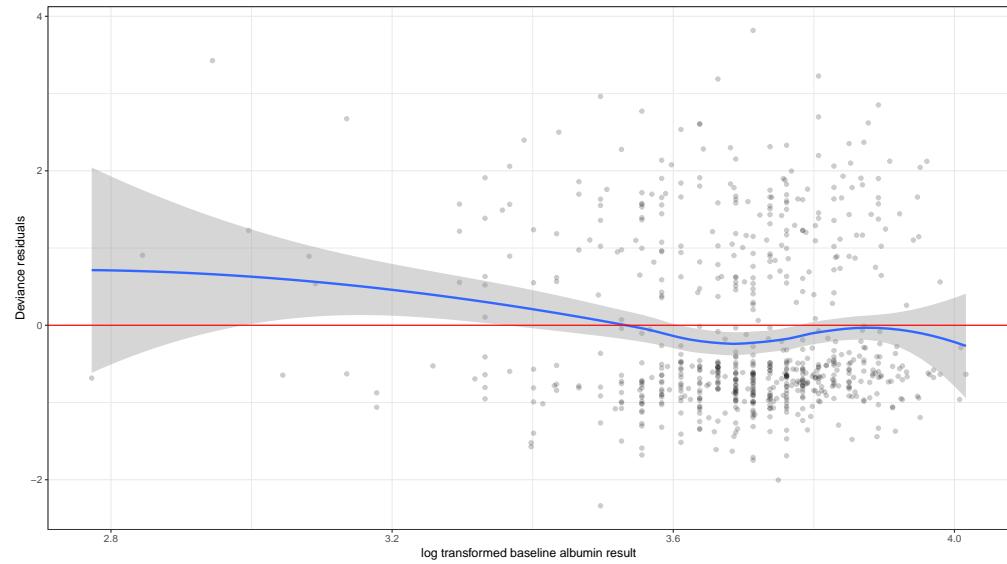


Figure 124: Residual-based diagnostics - Deviance plot

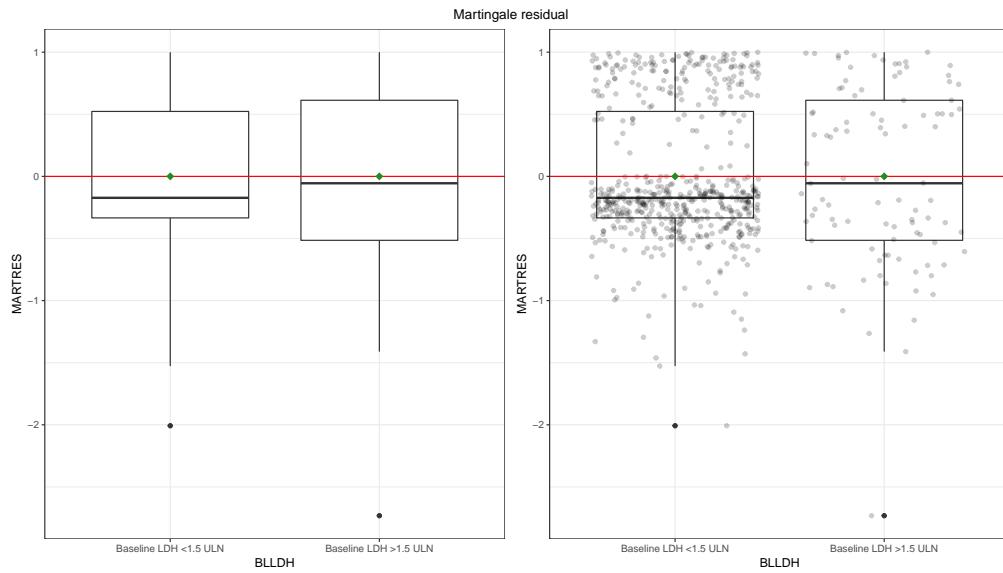


Figure 125: Residual-based diagnostics - Martingale plot

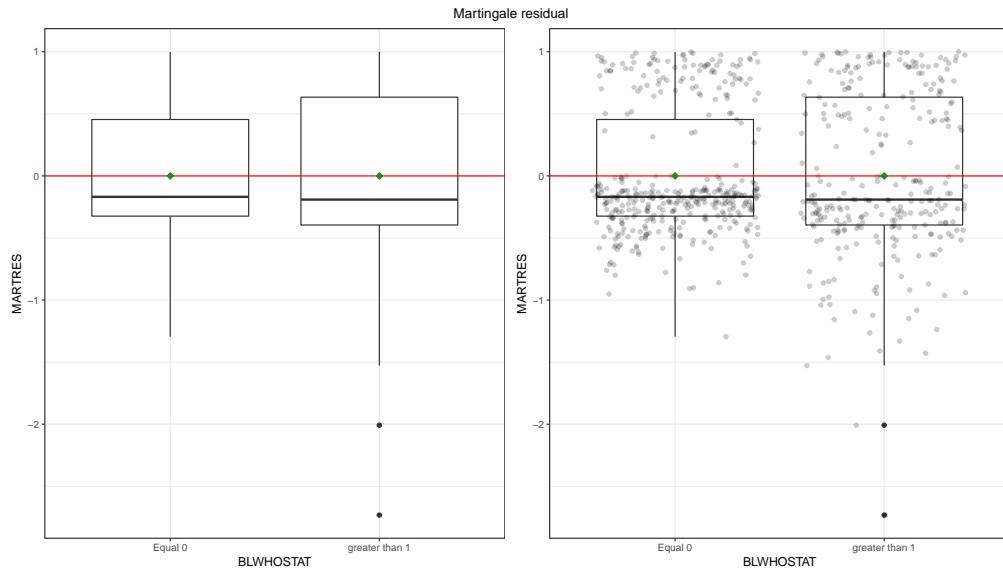


Figure 126: Residual-based diagnostics - Martingale plot

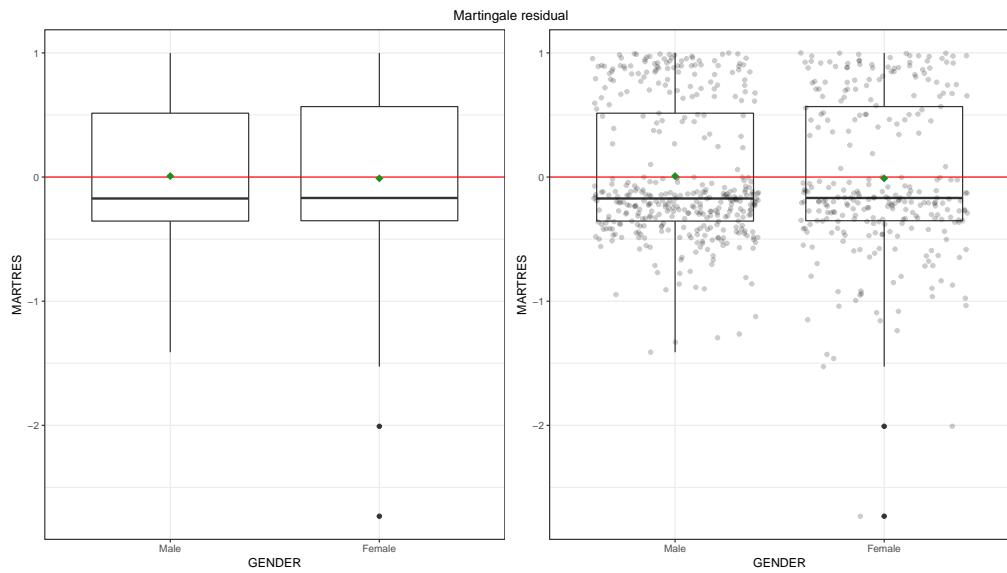


Figure 127: Residual-based diagnostics - Martingale plot

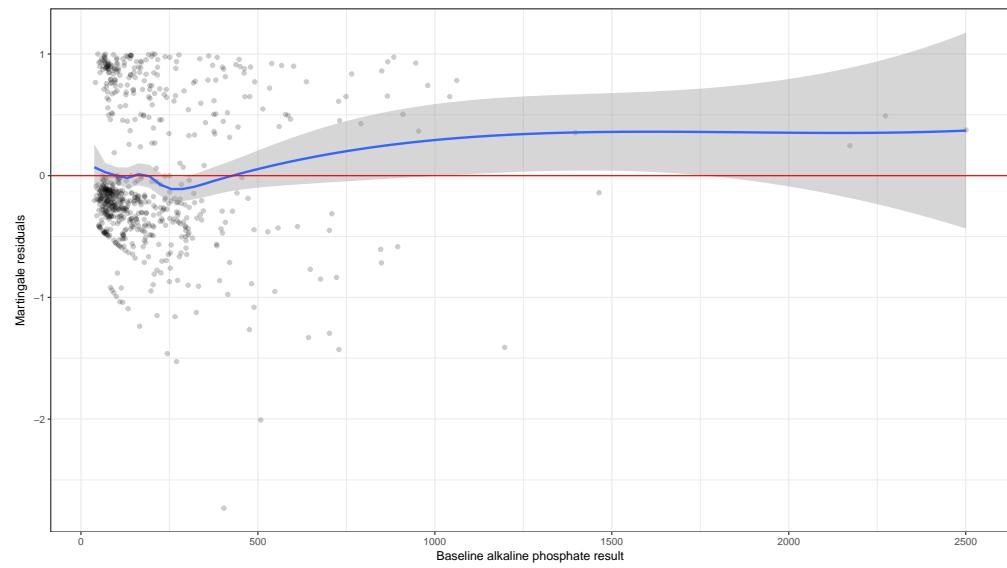
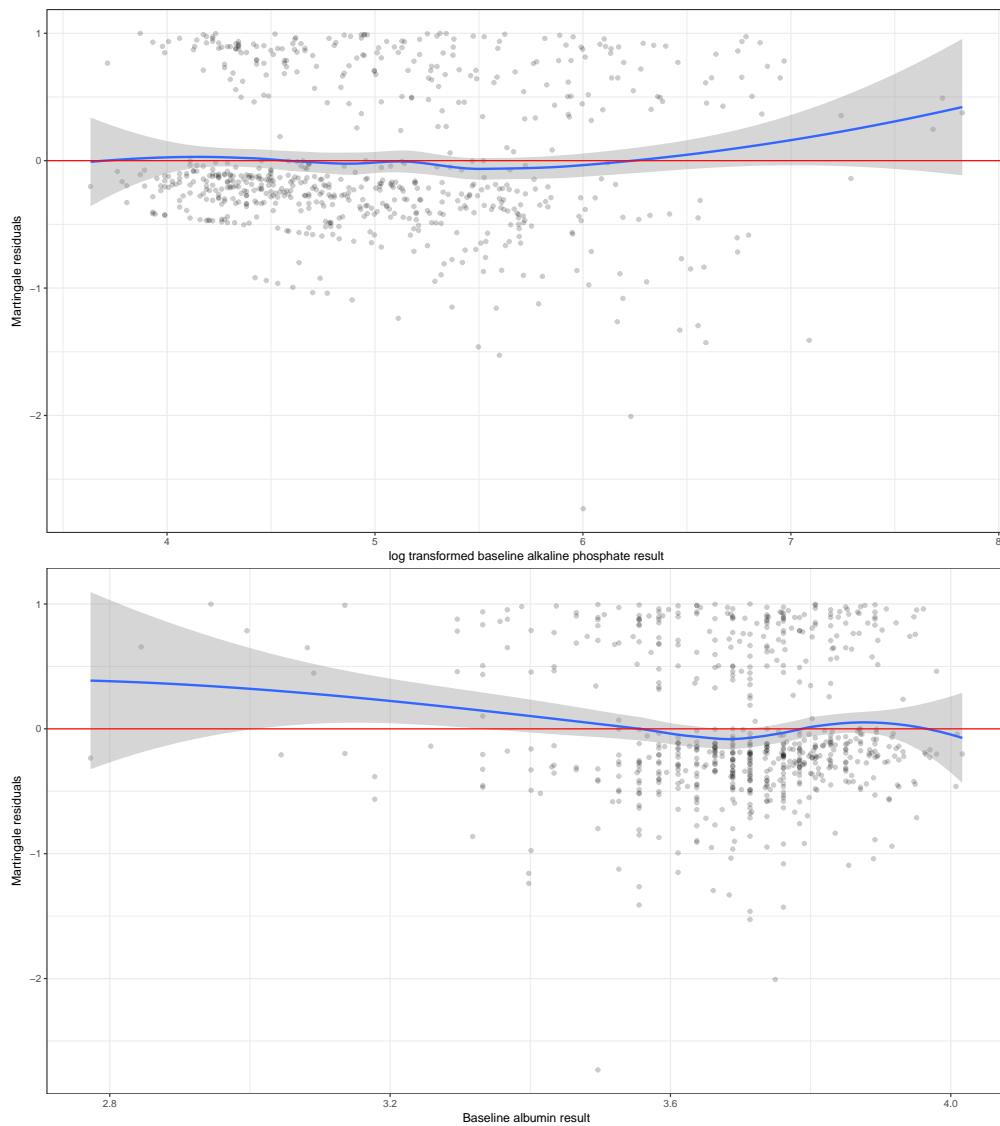


Figure 128: Residual-based diagnostics - Martingale plot



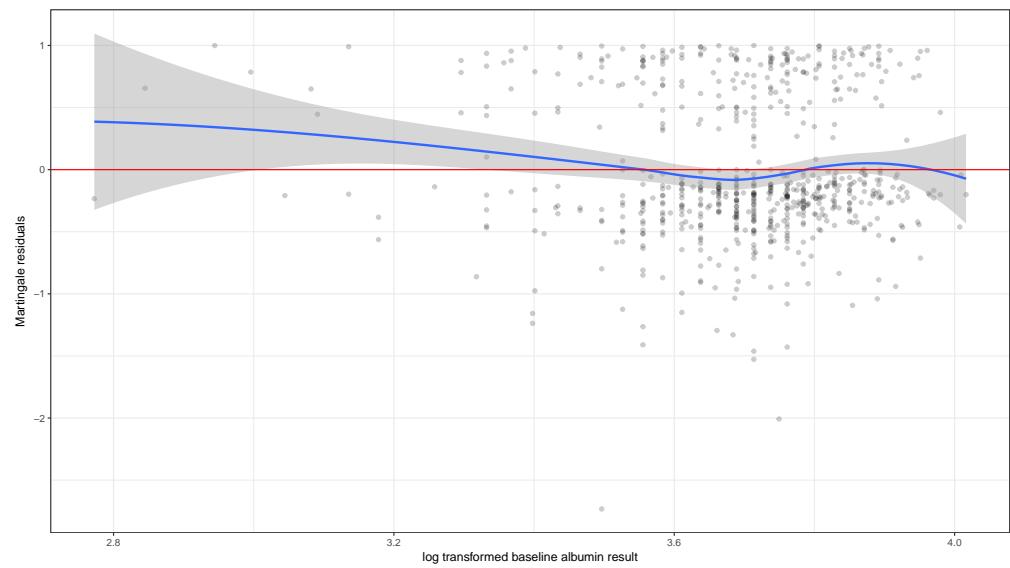


Figure 129: Residual-based diagnostics - Martingale plot

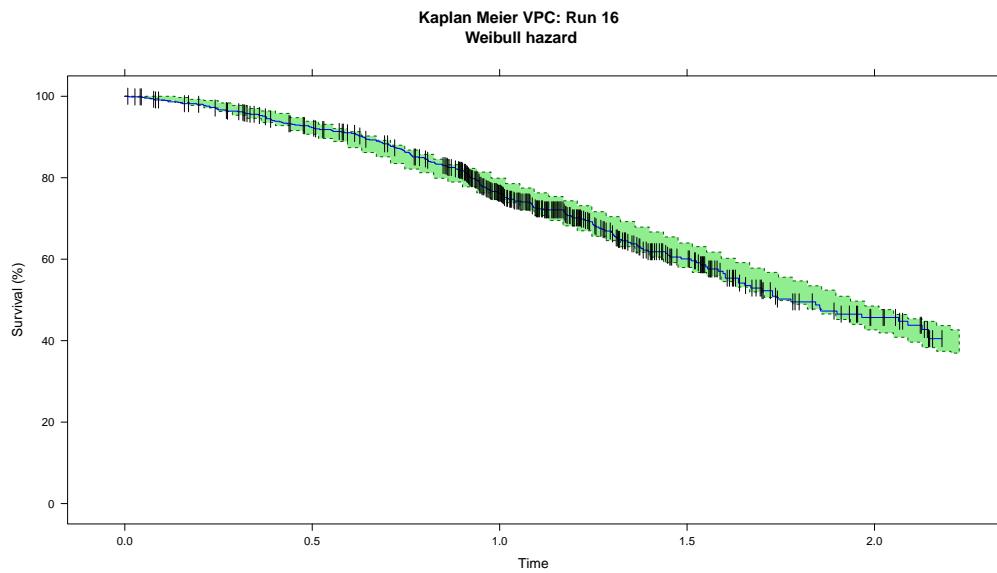


Figure 130: Simulation-based diagnostic

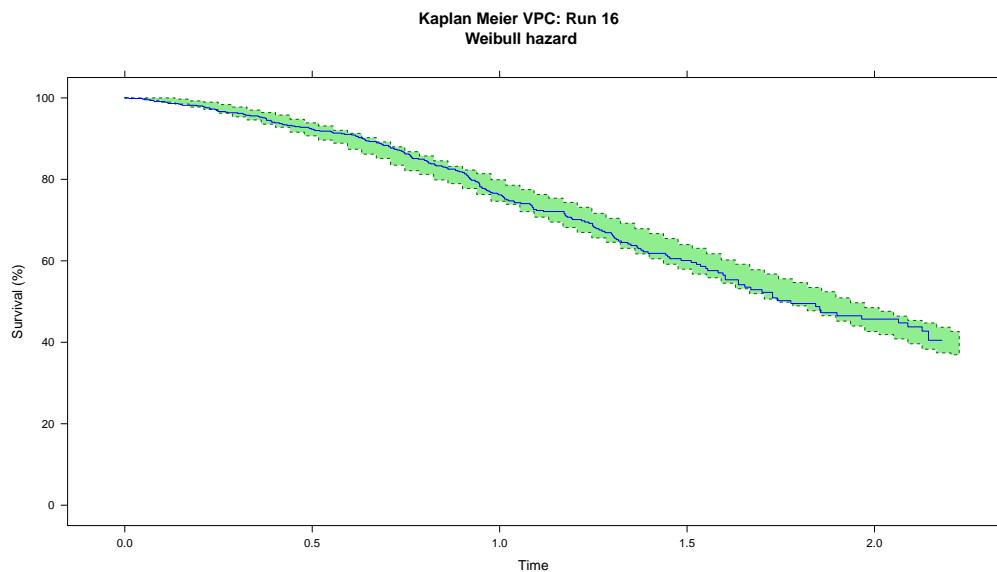


Figure 131: Simulation-based diagnostic

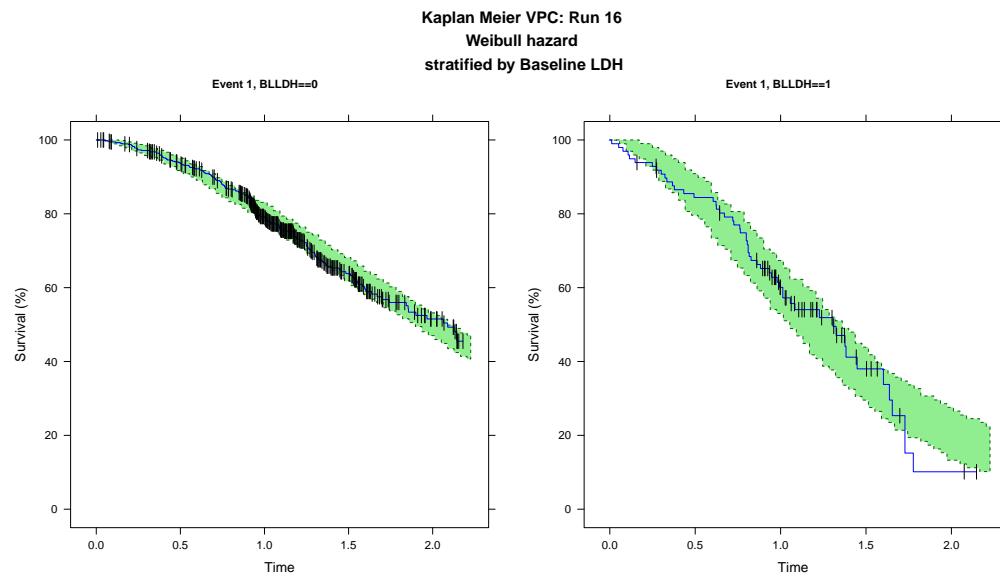


Figure 132: Simulation-based diagnostic - stratified by baseline LDH

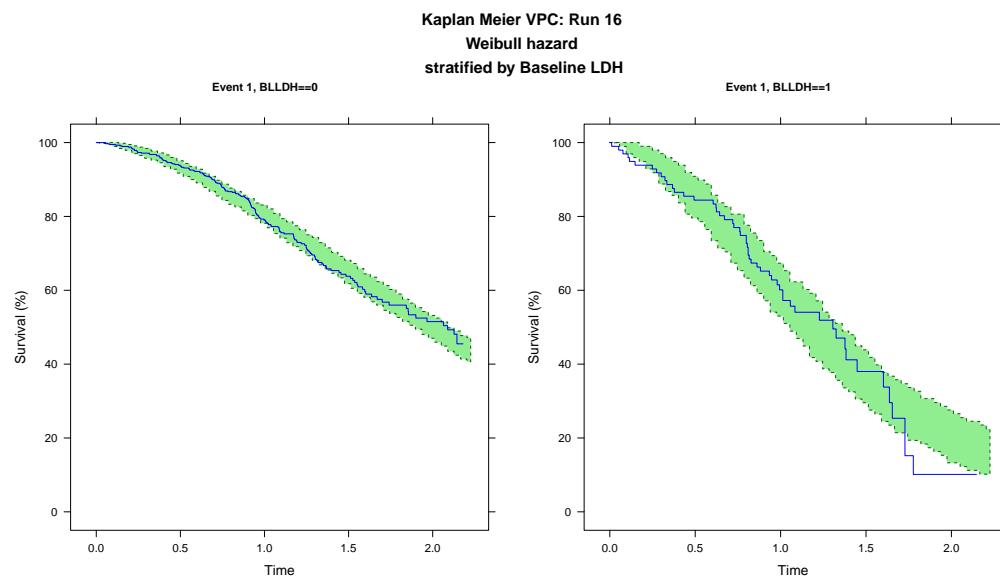


Figure 133: Simulation-based diagnostic - stratified by baseline LDH

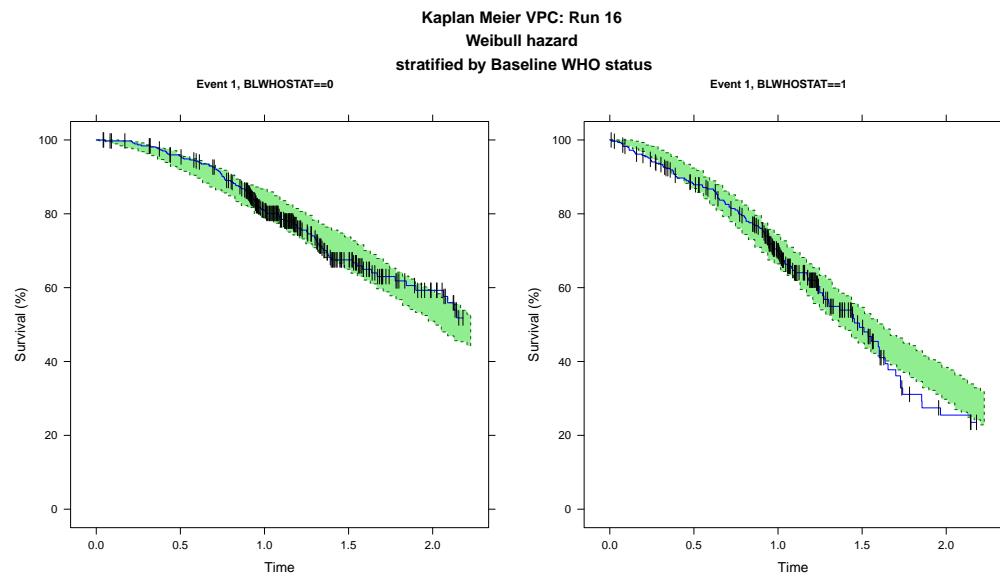


Figure 134: Simulation-based diagnostic - stratified by baseline WHO status

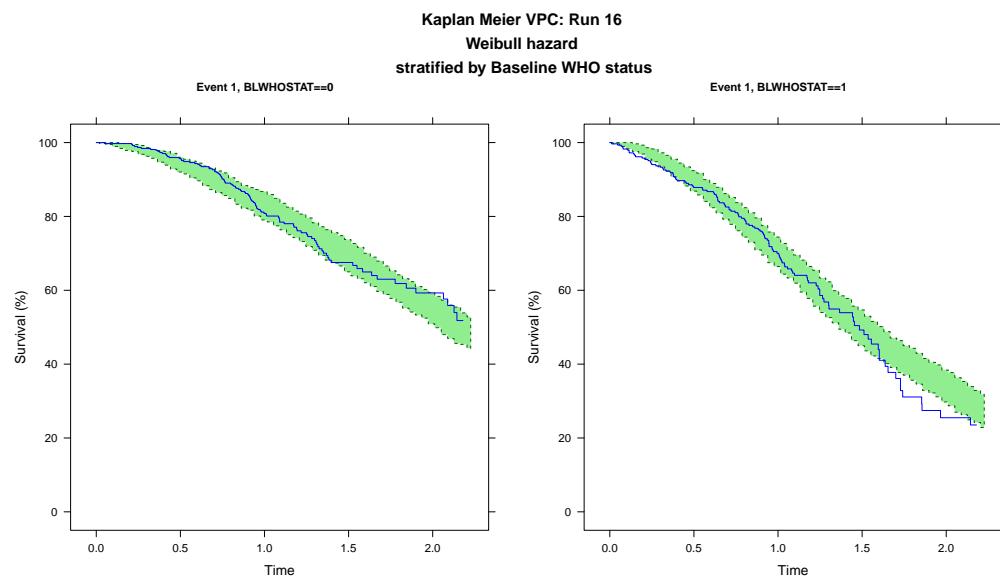


Figure 135: Simulation-based diagnostic - stratified by baseline WHO status

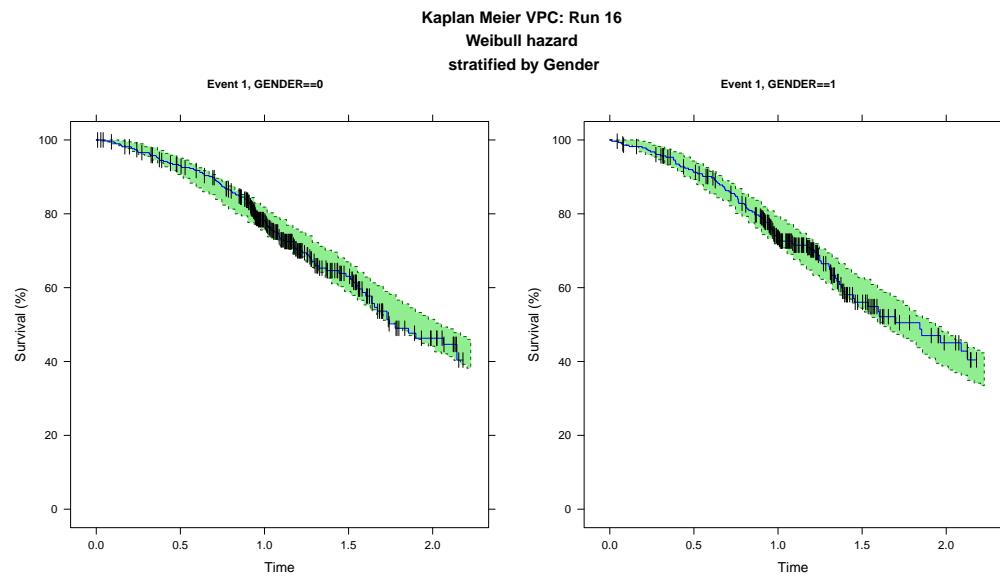


Figure 136: Simulation-based diagnostic - stratified by baseline Gender

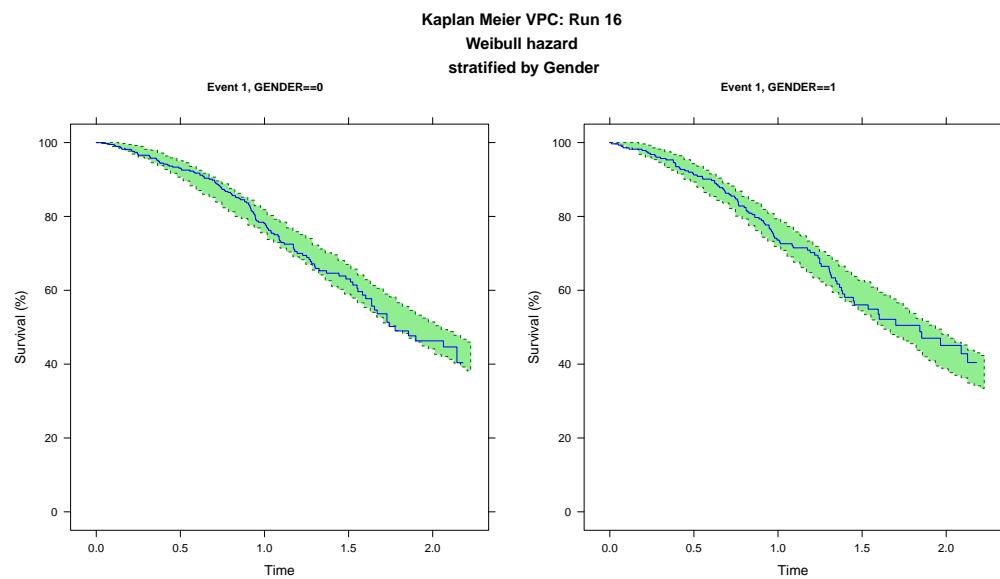


Figure 137: Simulation-based diagnostic - stratified by baseline Gender

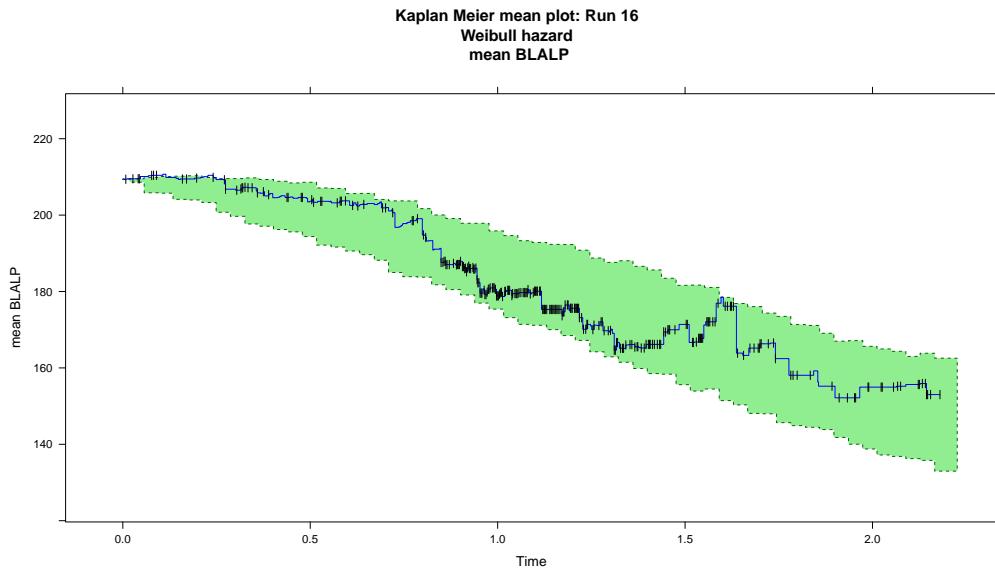


Figure 138: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

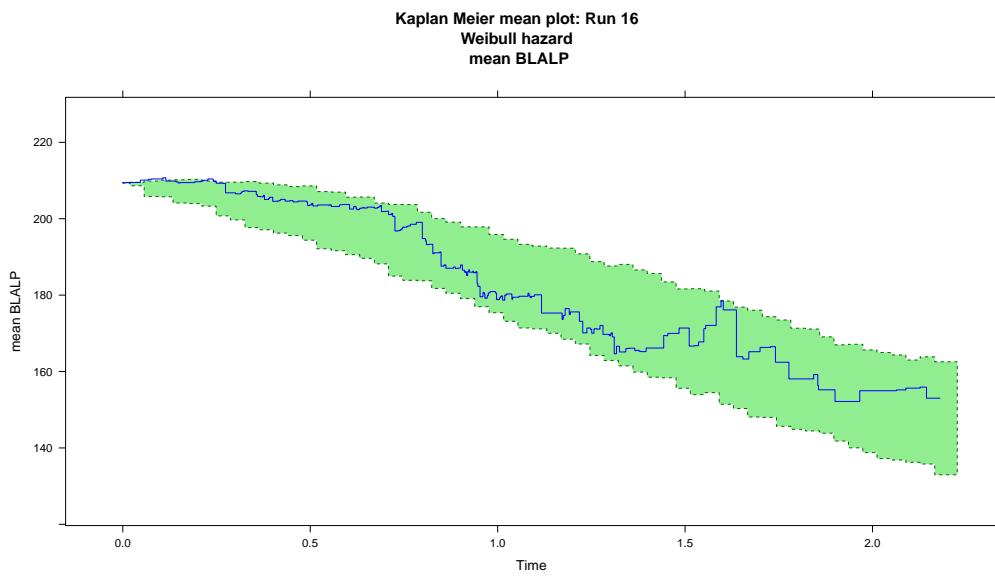


Figure 139: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

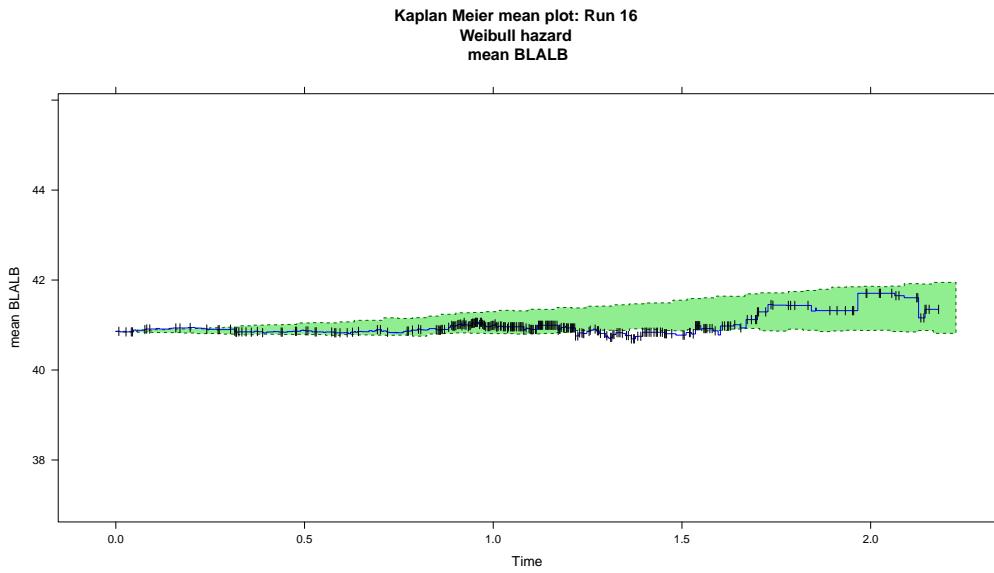


Figure 140: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

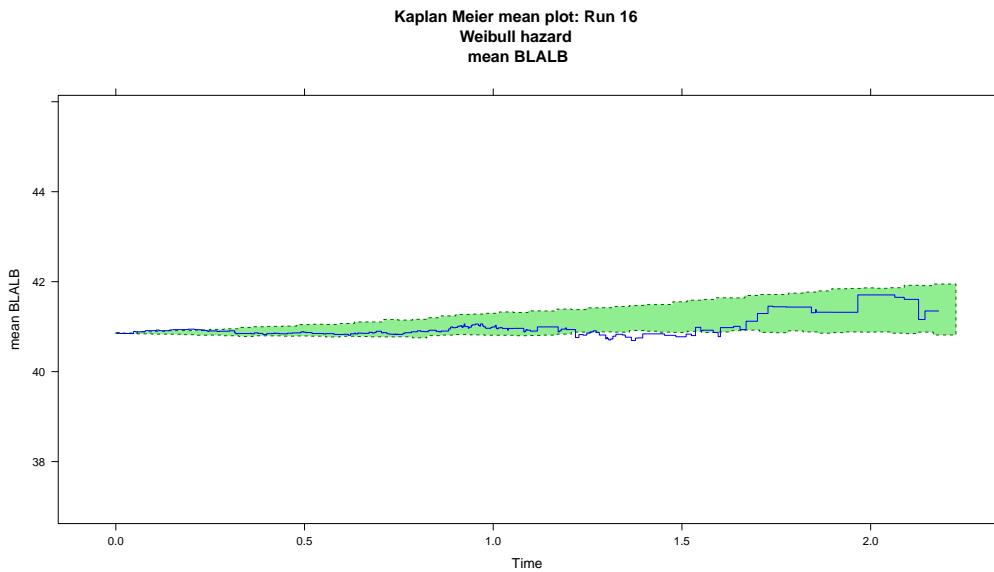


Figure 141: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

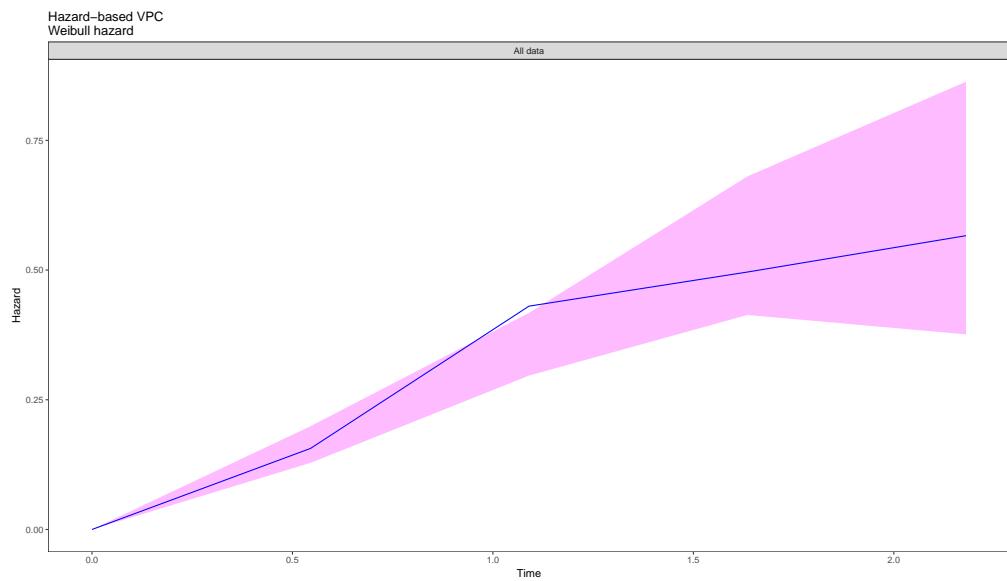


Figure 142: Simulation-based diagnostic: Hazard based VPC

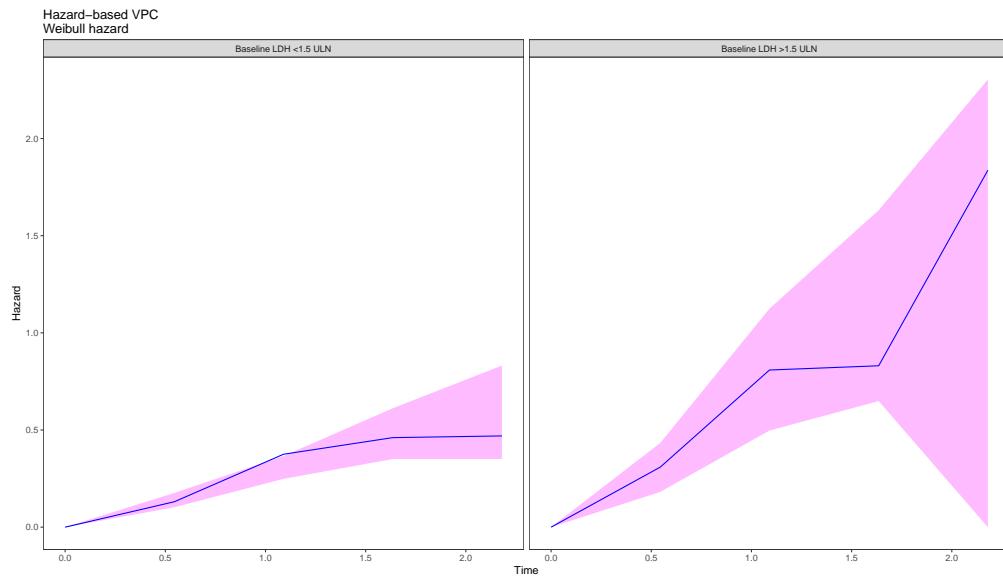


Figure 143: Simulation-based diagnostic: Hazard based VPC

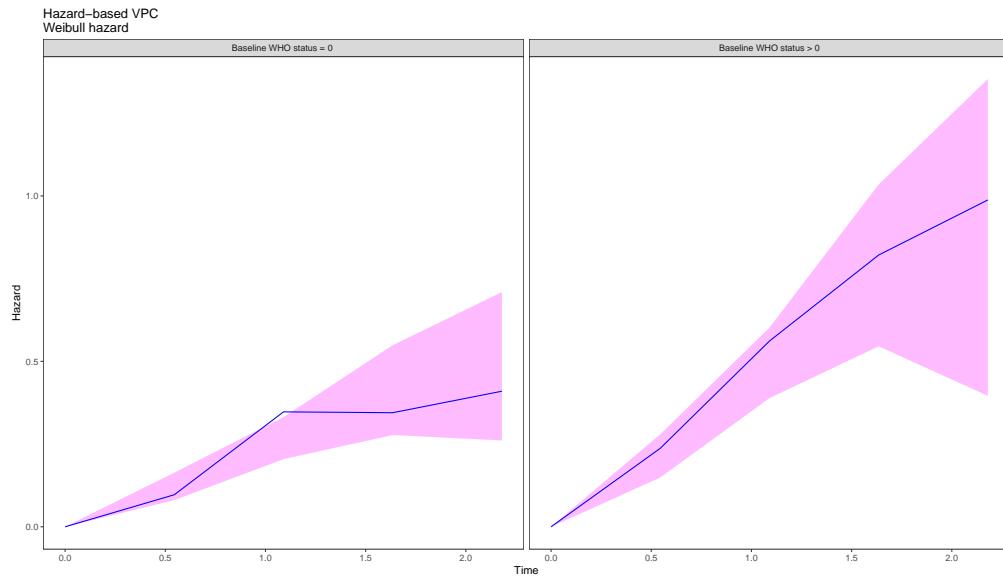


Figure 144: Simulation-based diagnostic: Hazard based VPC

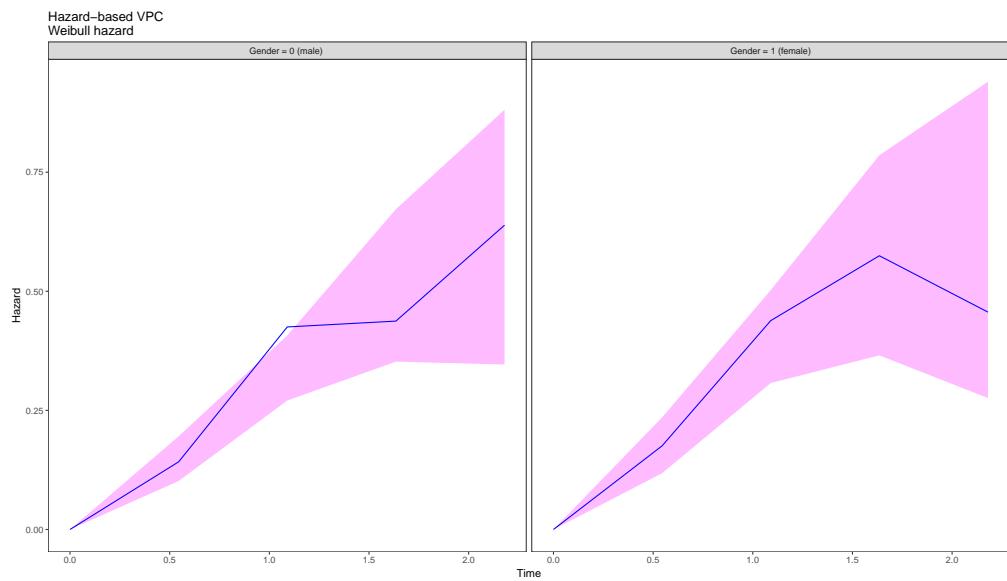


Figure 145: Simulation-based diagnostic: Hazard based VPC

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. Interoccassion 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 occurred 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, binary 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"
## [6] "No rounding errors"
## [7] "No zero gradients"
## [8] "No final zero gradients"
## [9] "Hessian not reset"
## [10] "No parameter near boundary"
## [11] "Covariance step"
## [12] ""
## [13] "Condition number"
## [14] "Correlations"
## [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

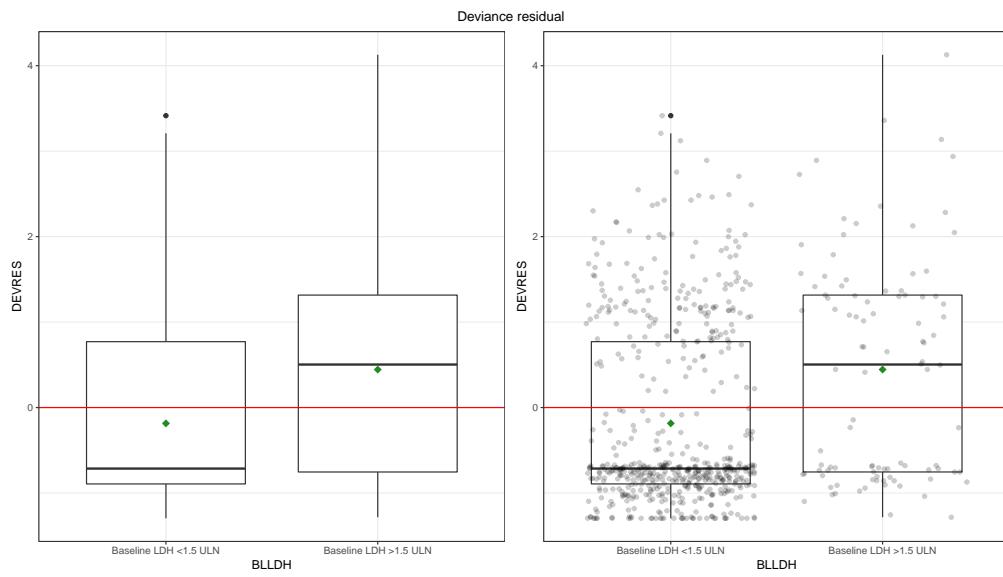


Figure 146: Residual-based diagnostics - Deviance plot

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

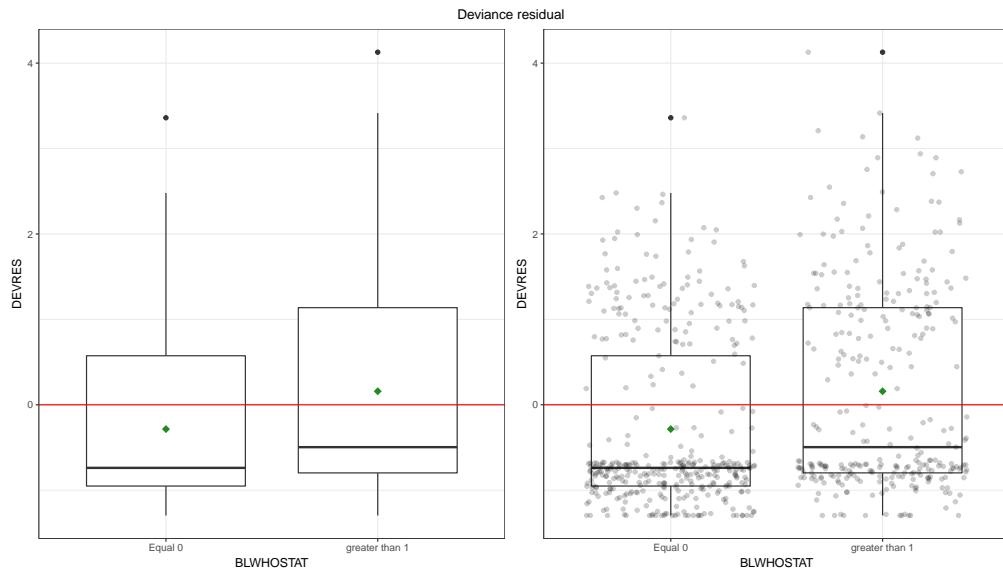


Figure 147: Residual-based diagnostics - Deviance plot

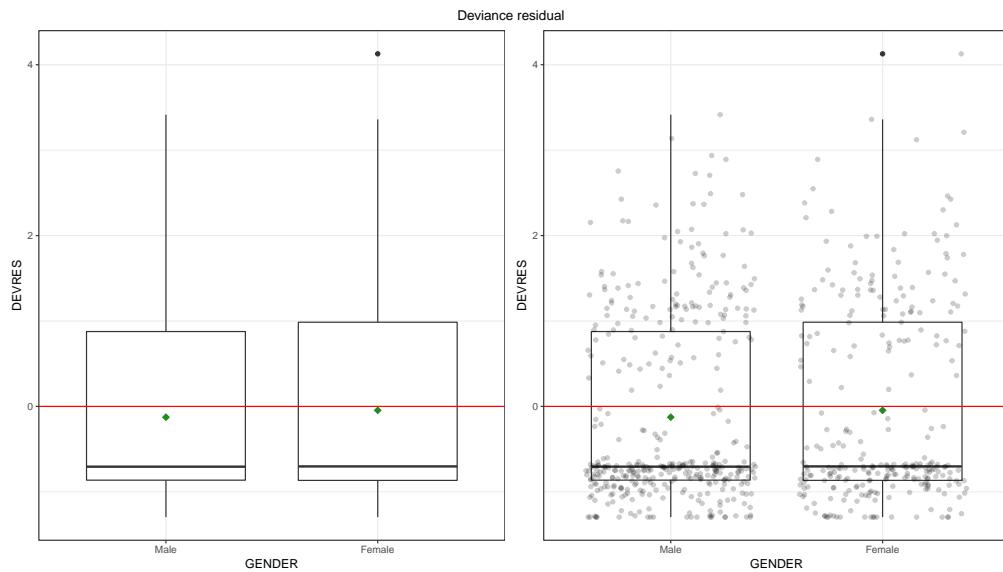


Figure 148: Residual-based diagnostics - Deviance plot

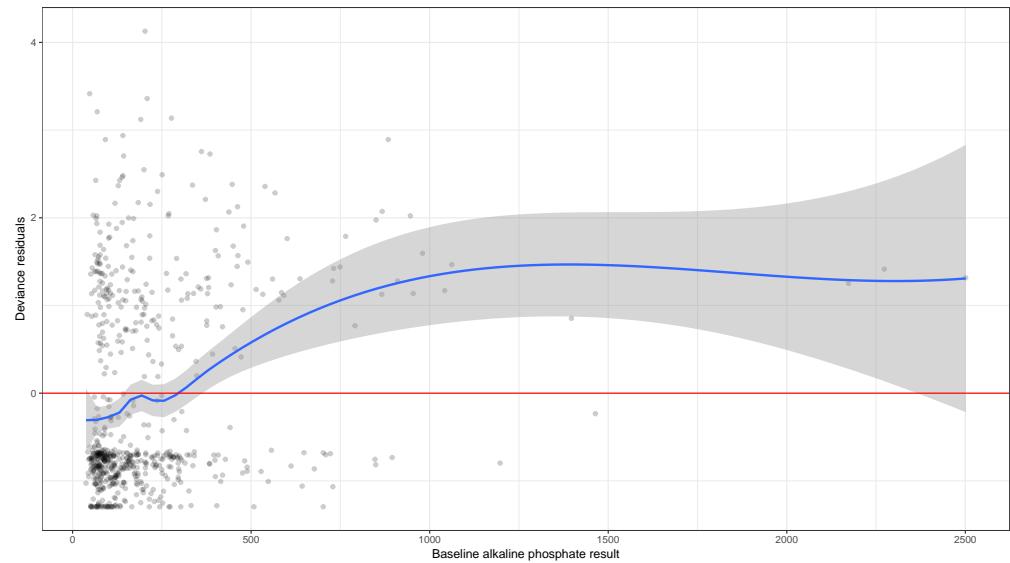


Figure 149: Residual-based diagnostics - Deviance plot

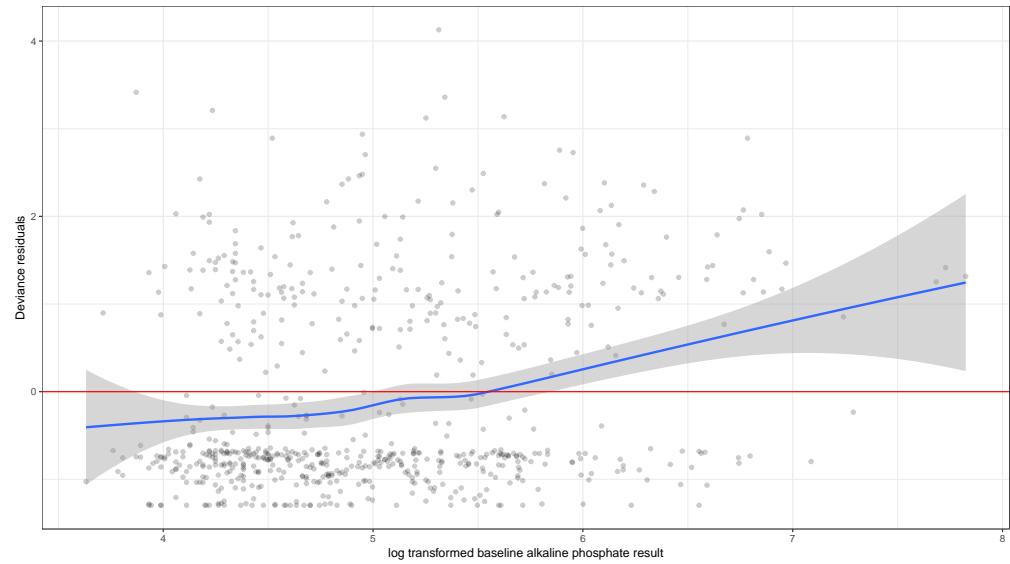


Figure 150: Residual-based diagnostics - Deviance plot

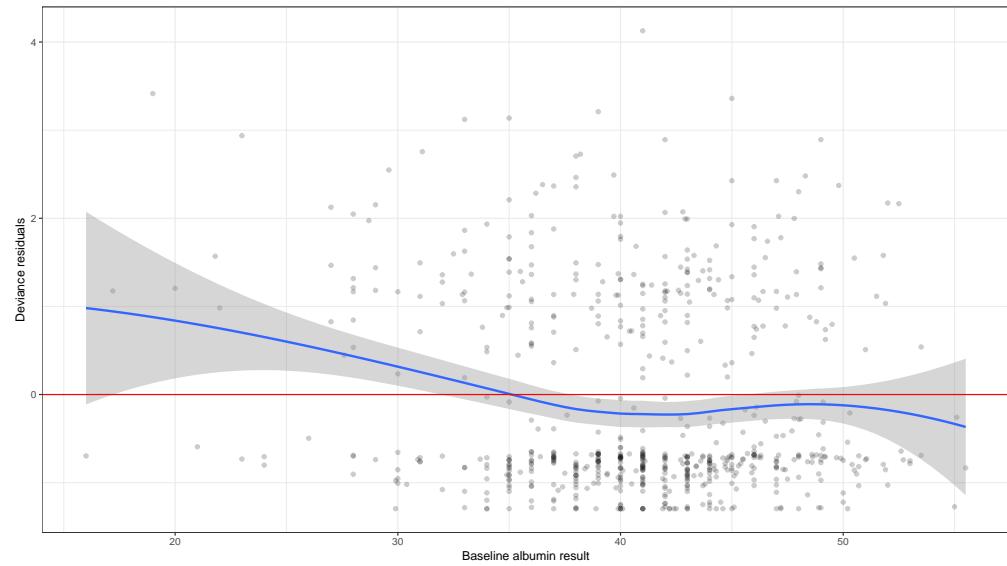


Figure 151: Residual-based diagnostics - Deviance plot

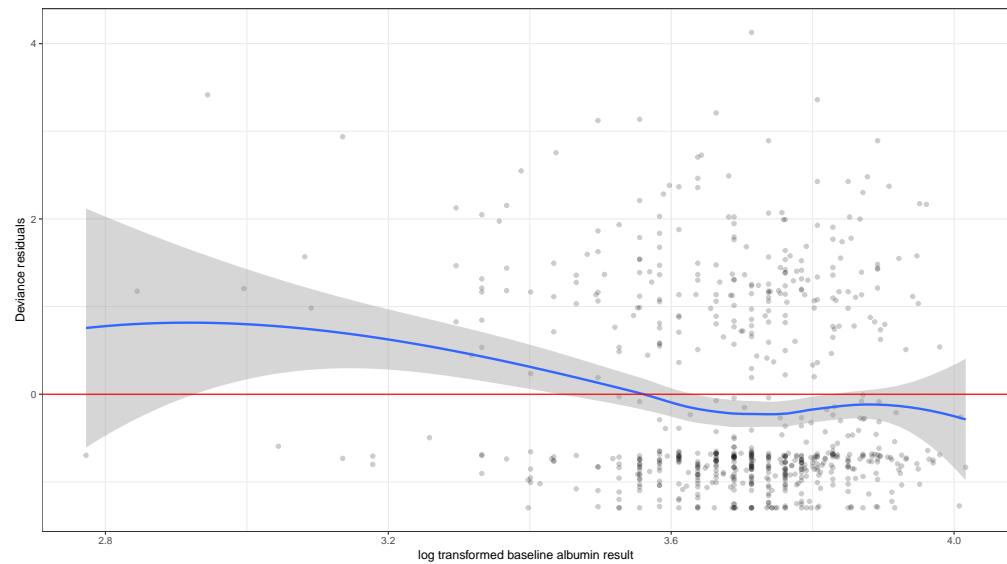


Figure 152: Residual-based diagnostics - Deviance plot

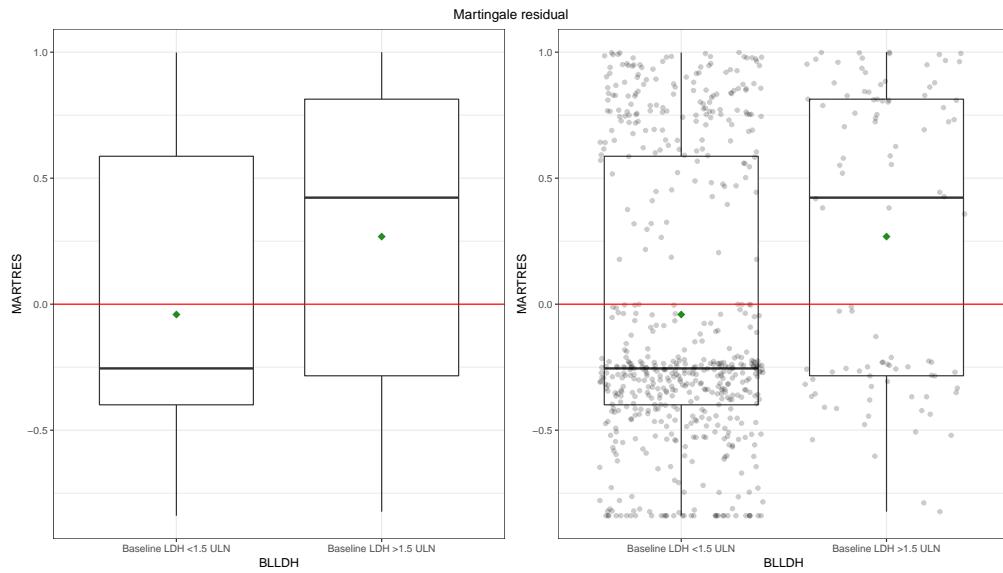


Figure 153: Residual-based diagnostics - Martingale plot

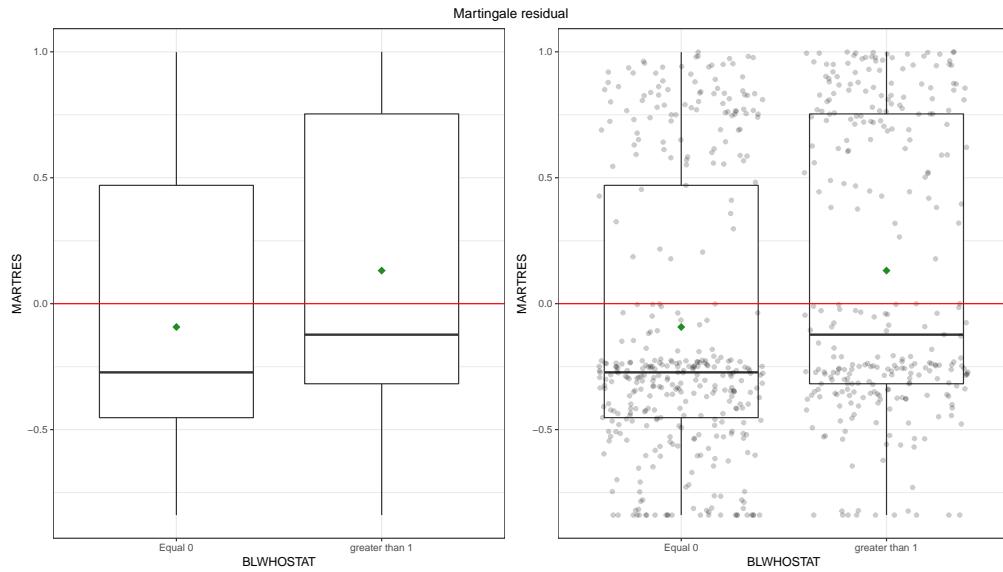


Figure 154: Residual-based diagnostics - Martingale plot

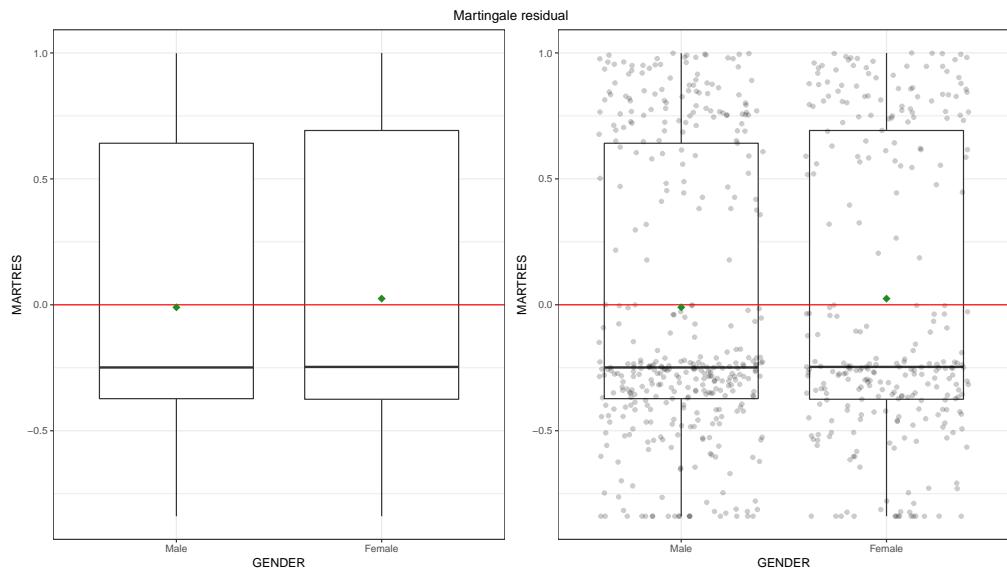


Figure 155: Residual-based diagnostics - Martingale plot

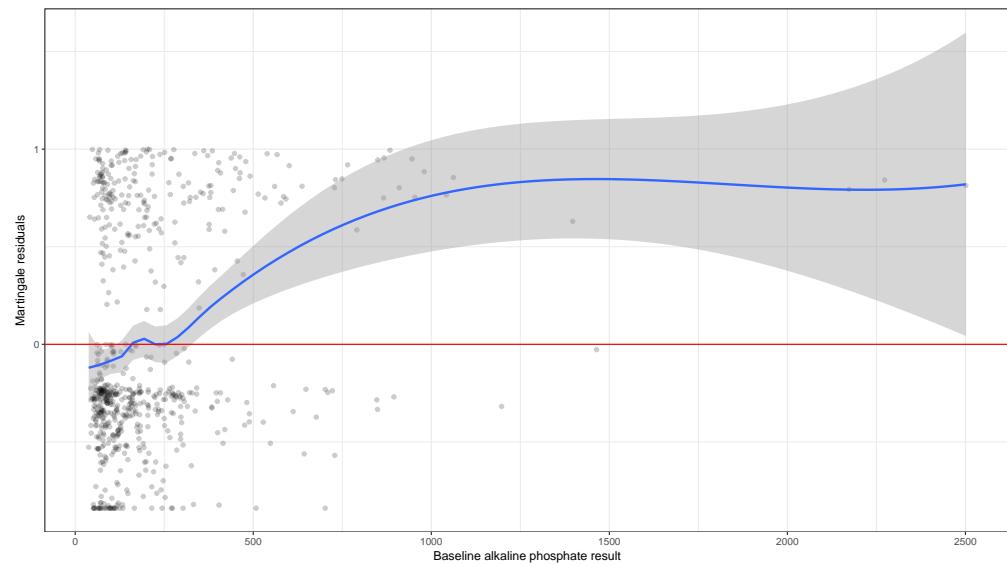
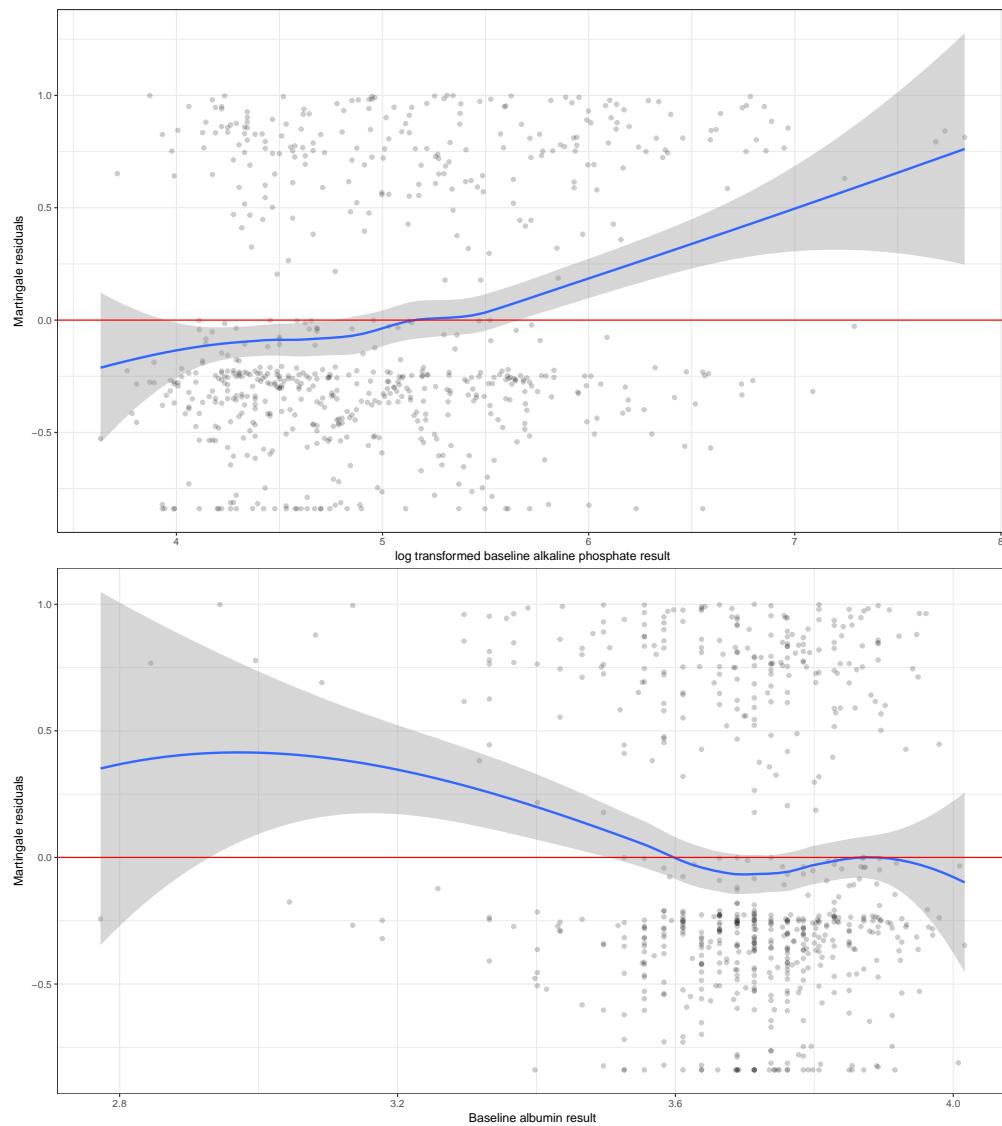


Figure 156: Residual-based diagnostics - Martingale plot



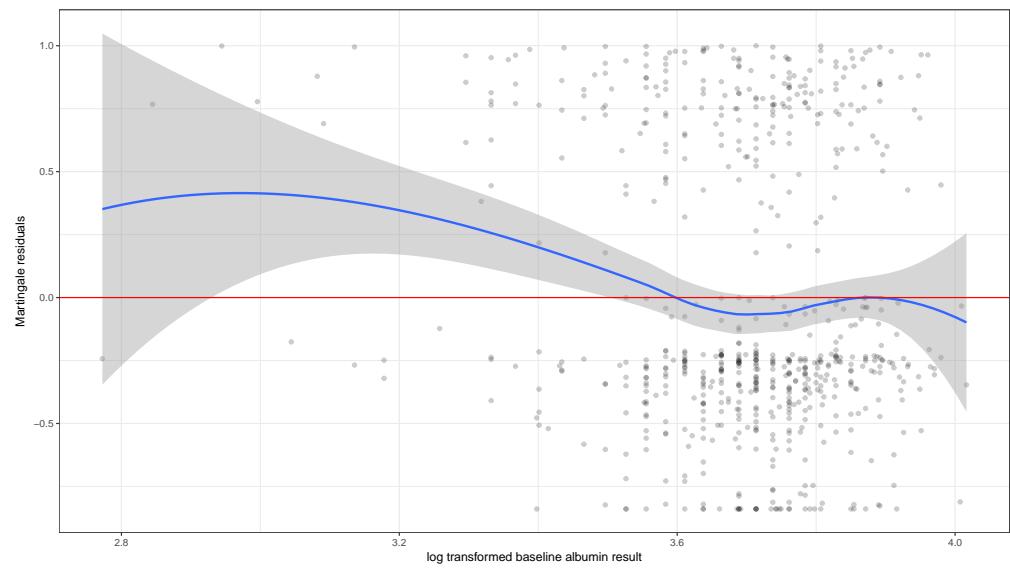


Figure 157: Residual-based diagnostics - Martingale plot

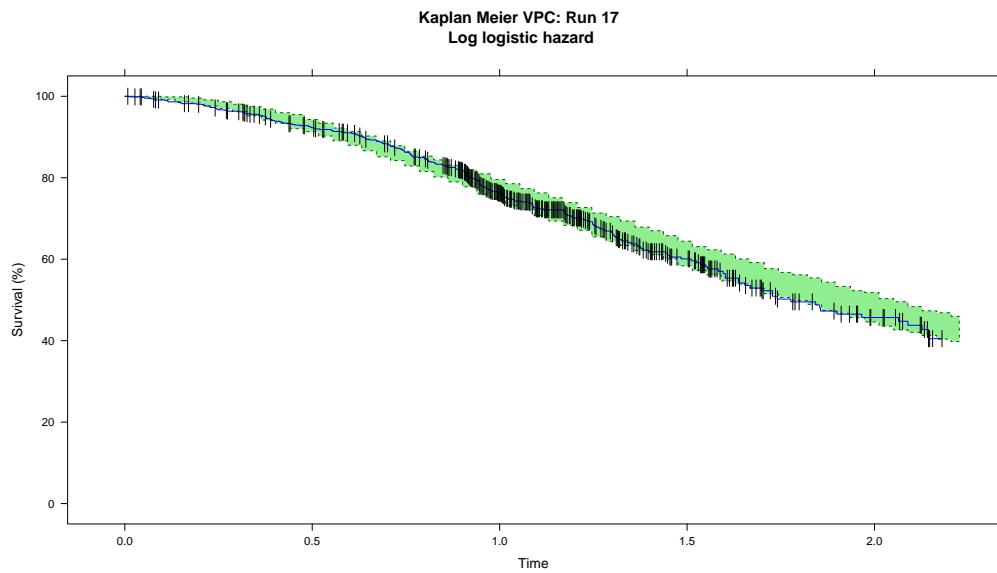


Figure 158: Simulation-based diagnostic

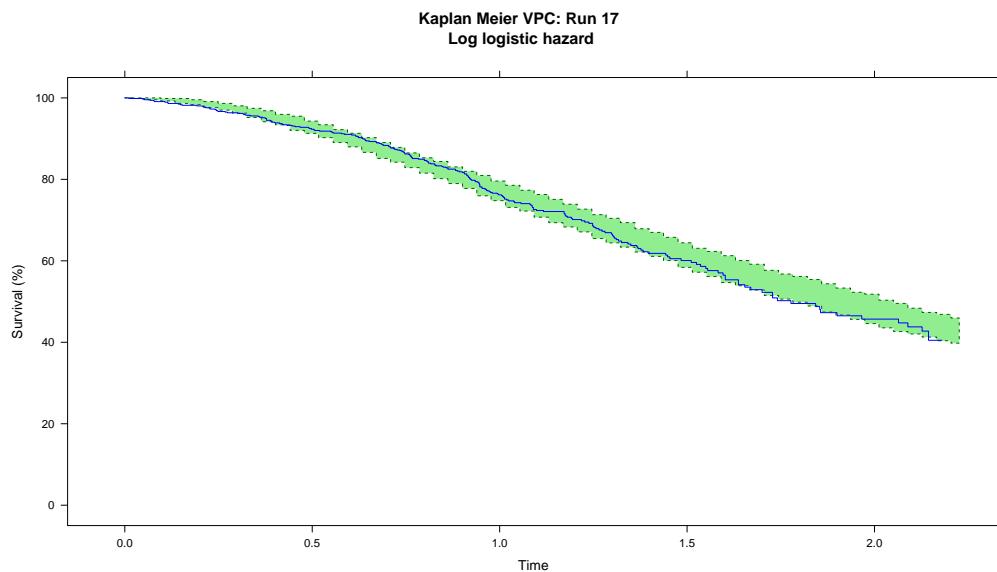


Figure 159: Simulation-based diagnostic

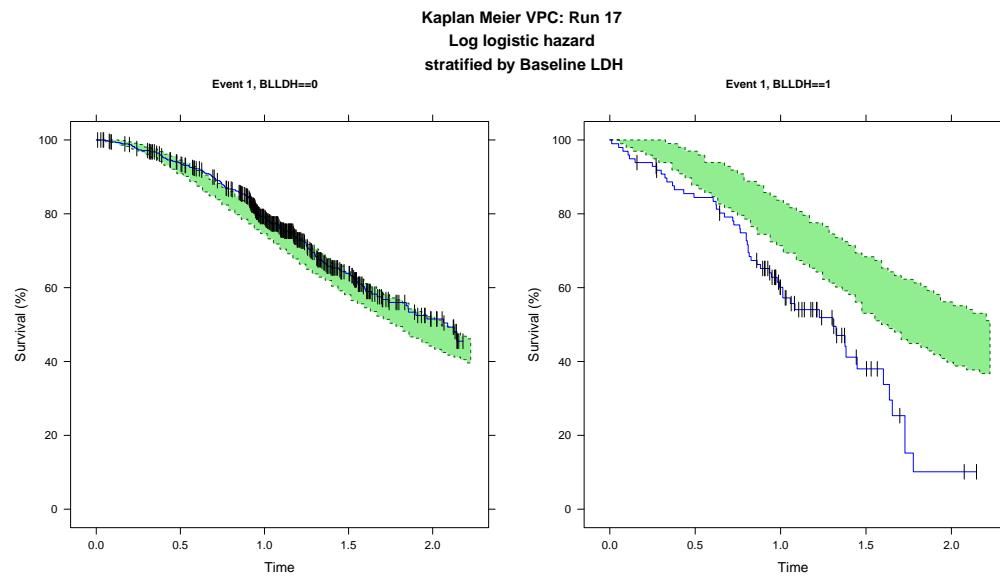


Figure 160: Simulation-based diagnostic - stratified by baseline LDH

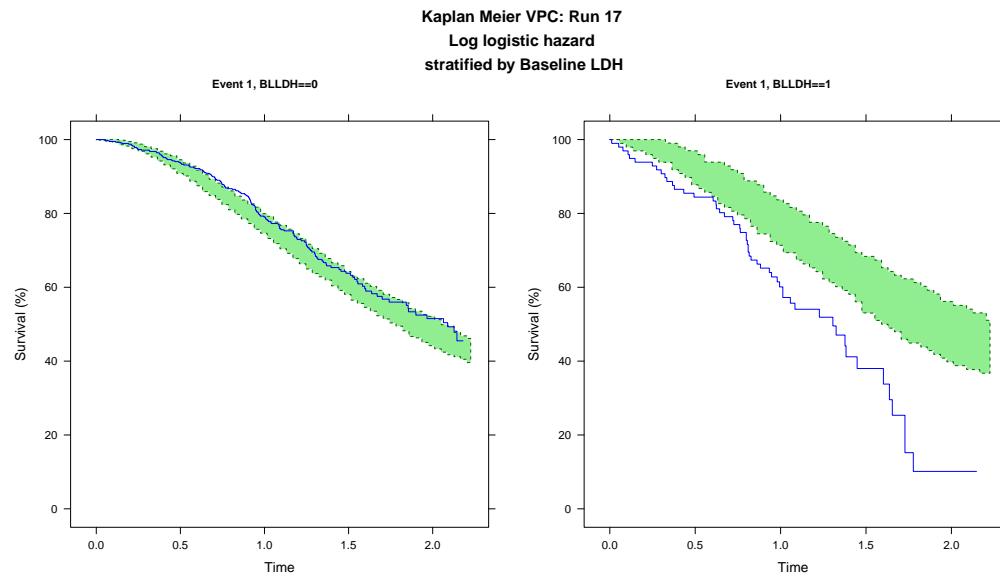


Figure 161: Simulation-based diagnostic - stratified by baseline LDH

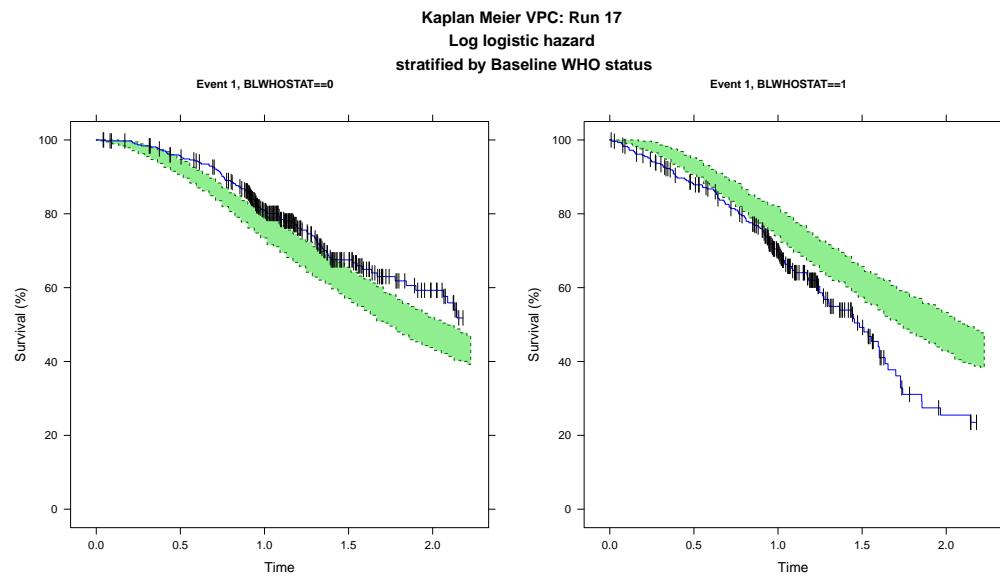


Figure 162: Simulation-based diagnostic - stratified by baseline WHO status

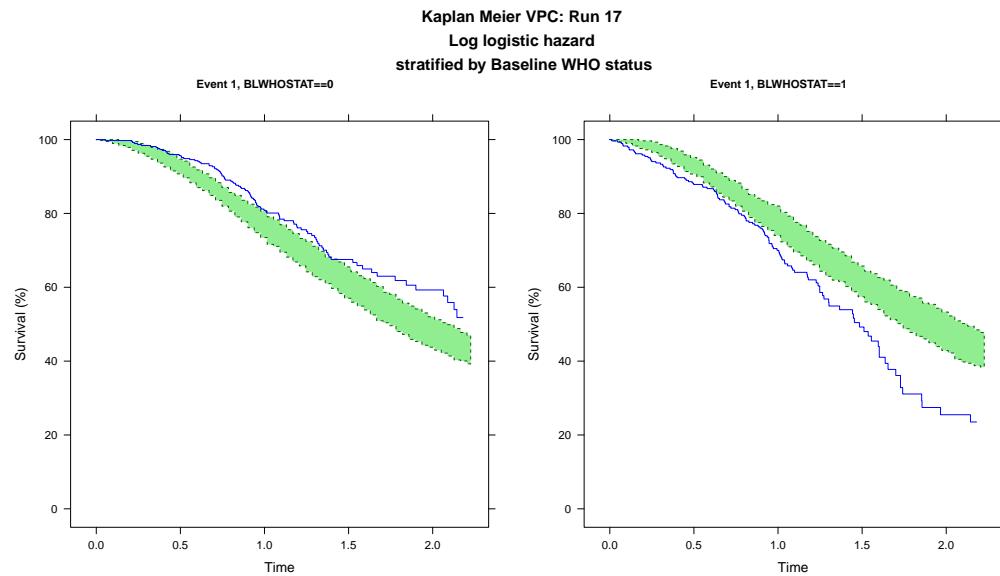


Figure 163: Simulation-based diagnostic - stratified by baseline WHO status

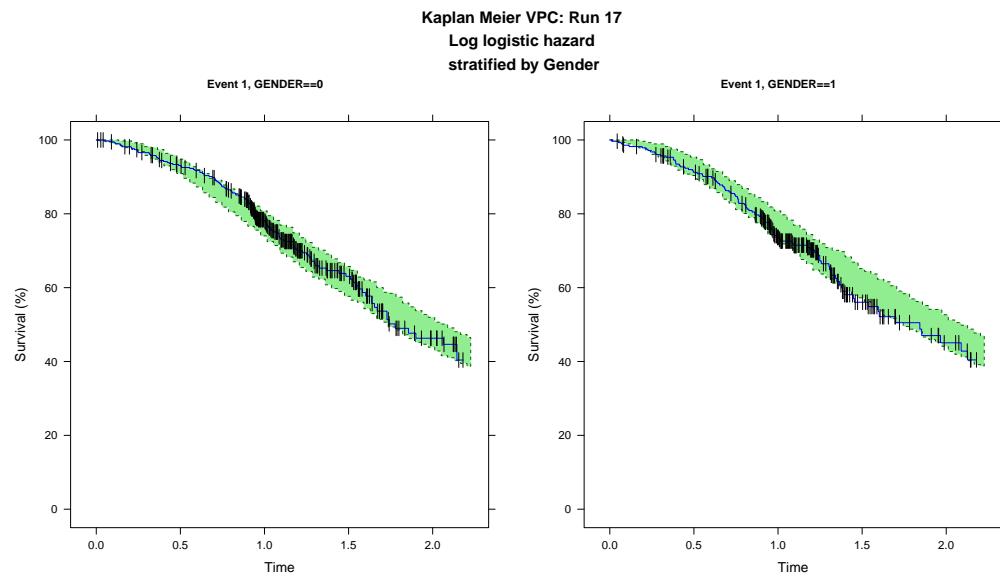


Figure 164: Simulation-based diagnostic - stratified by baseline Gender

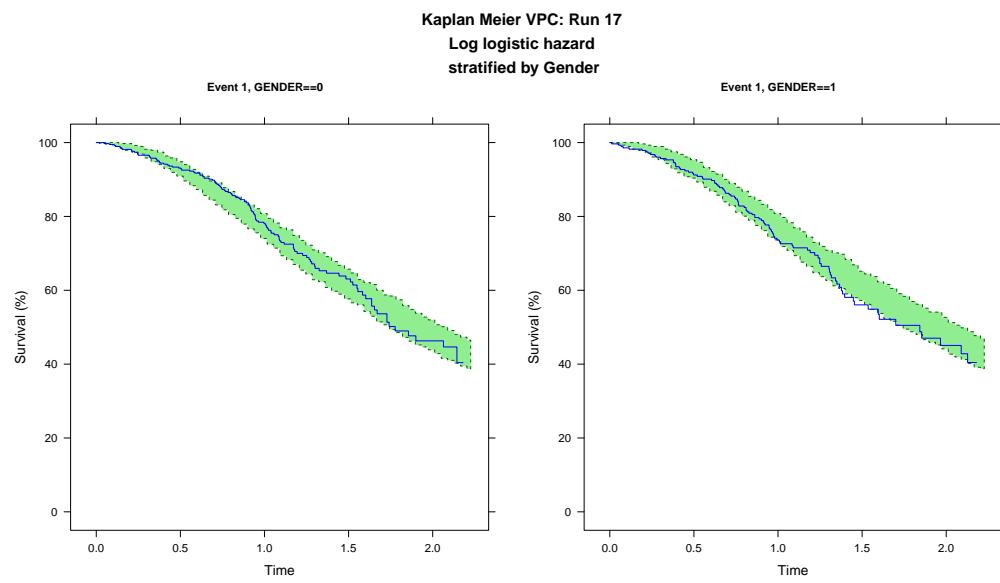


Figure 165: Simulation-based diagnostic - stratified by baseline Gender

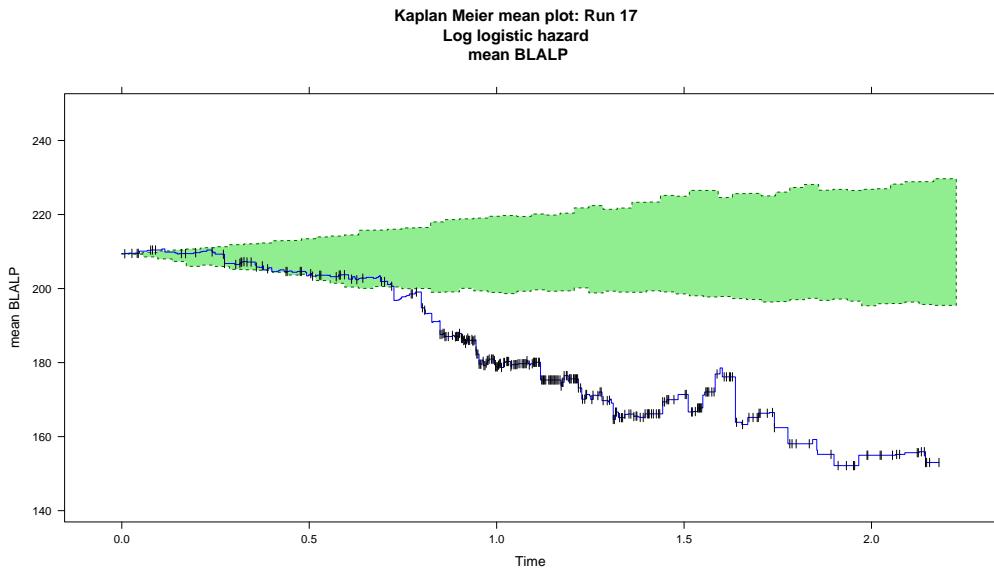


Figure 166: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

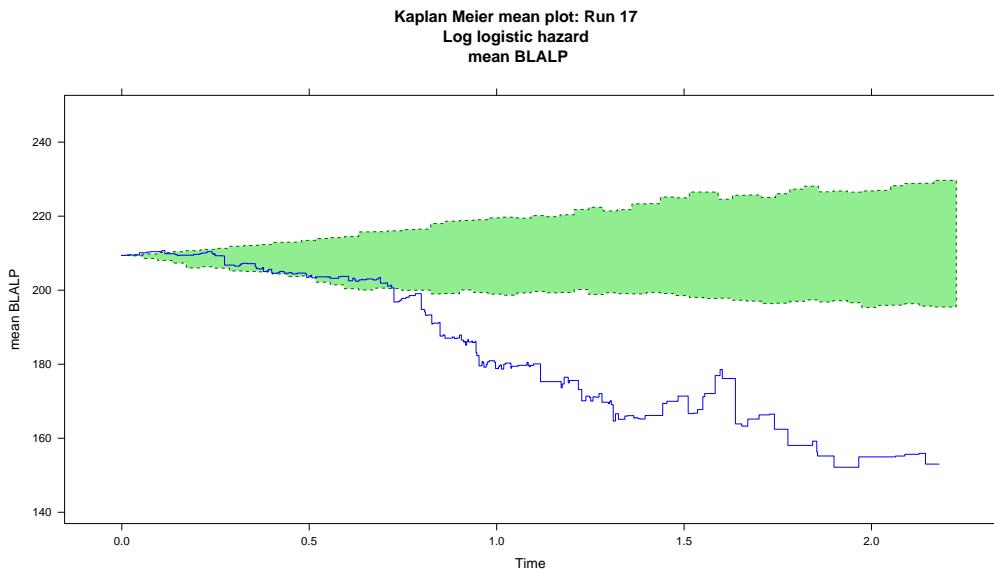


Figure 167: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

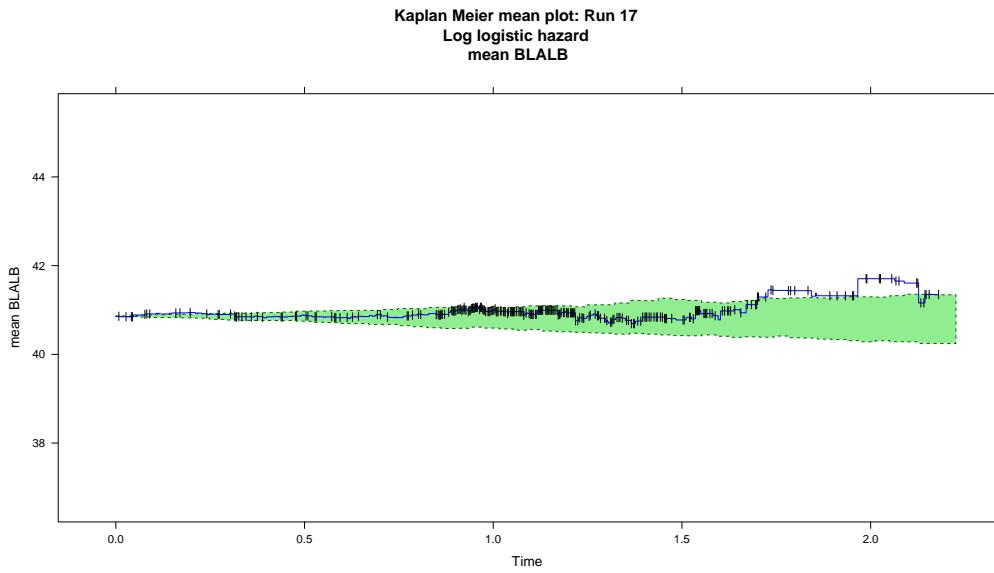


Figure 168: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

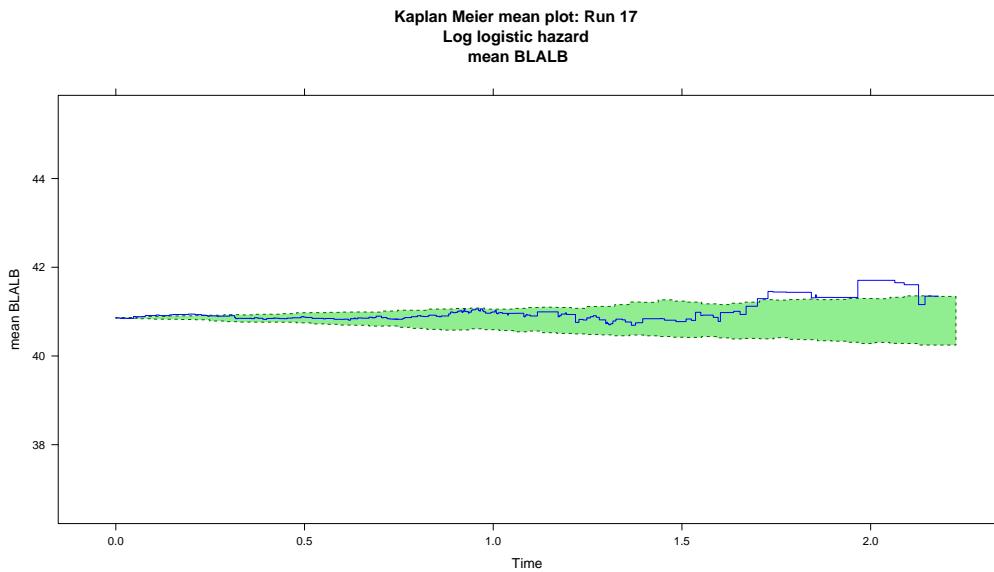


Figure 169: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

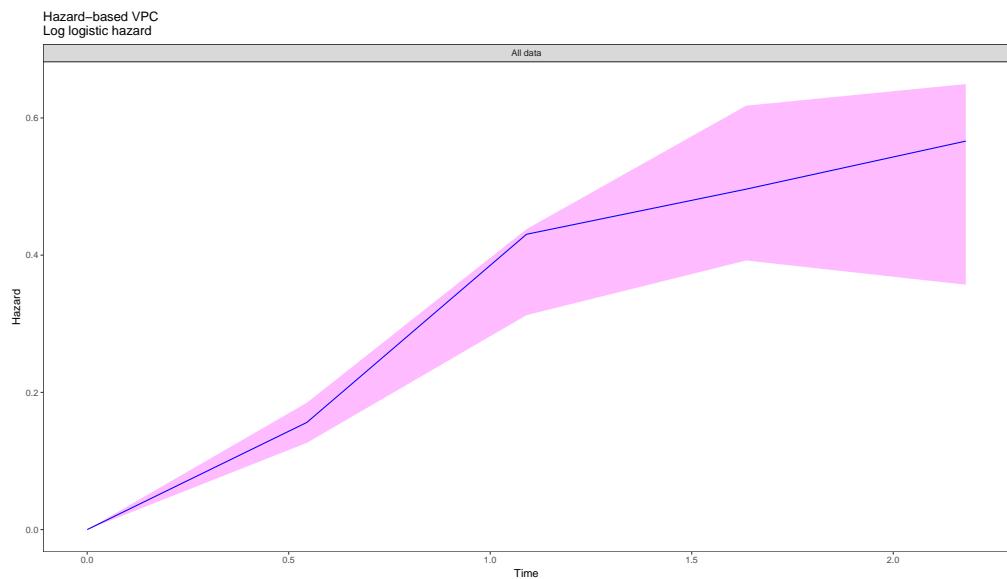


Figure 170: Simulation-based diagnostic: Hazard based VPC

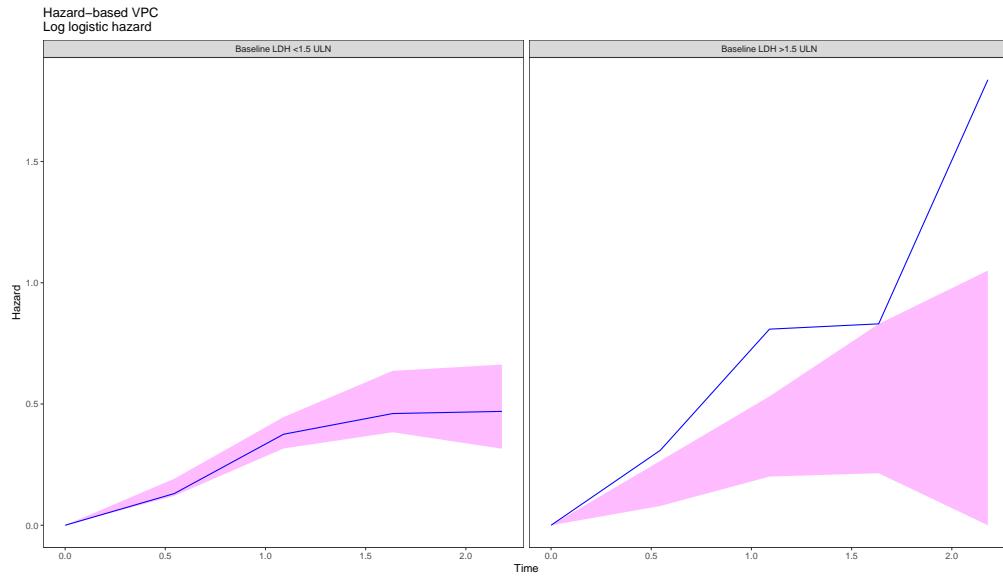


Figure 171: Simulation-based diagnostic: Hazard based VPC

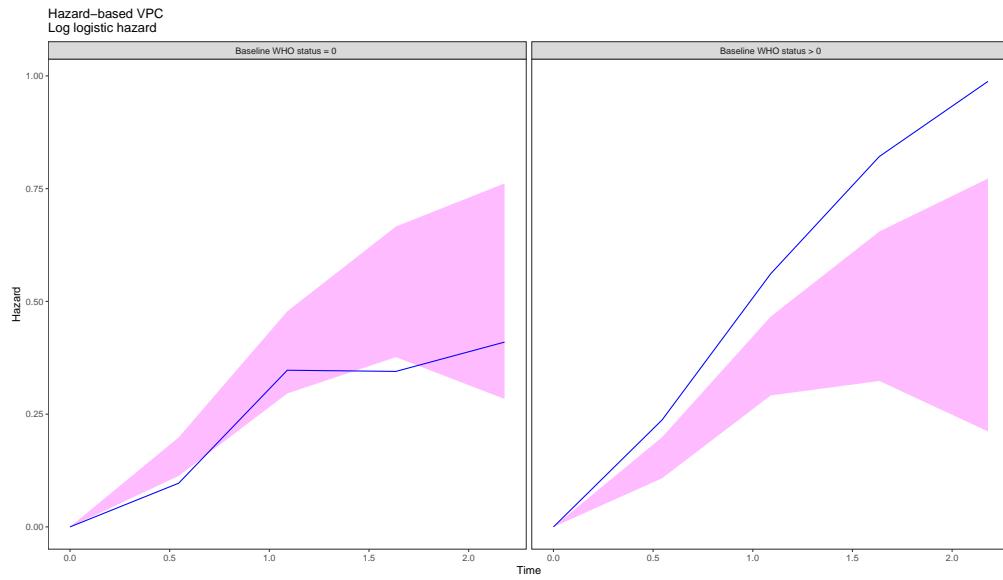


Figure 172: Simulation-based diagnostic: Hazard based VPC

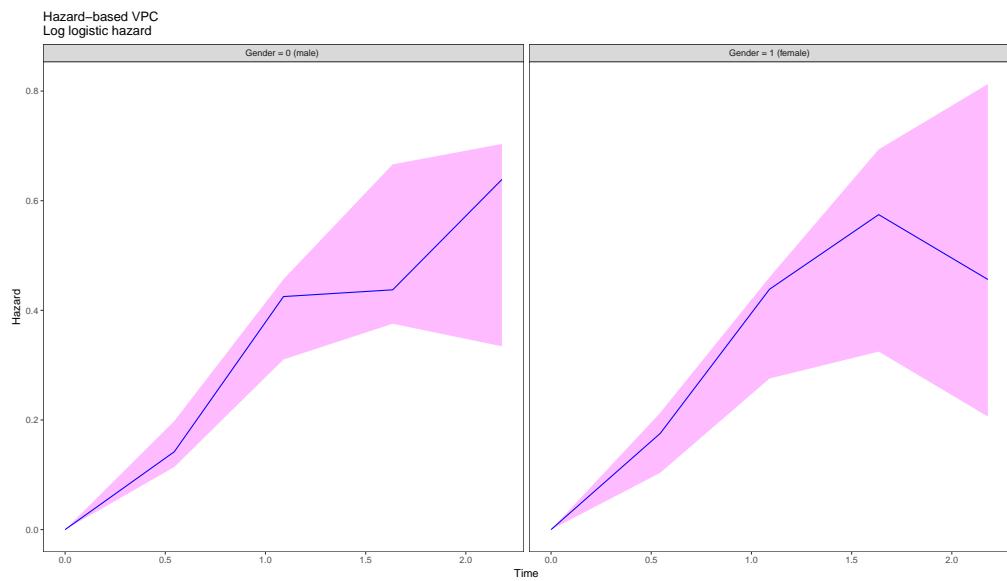


Figure 173: Simulation-based diagnostic: Hazard based VPC

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 occurred 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, binary 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 BLWOLEVEL 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"
## [6] "No rounding errors"
## [7] "No zero gradients"
## [8] "No final zero gradients"
## [9] "Hessian not reset"
## [10] "No parameter near boundary"
## [11] "Covariance step"
## [12] ""
## [13] "Condition number"
## [14] "Correlations"
## [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

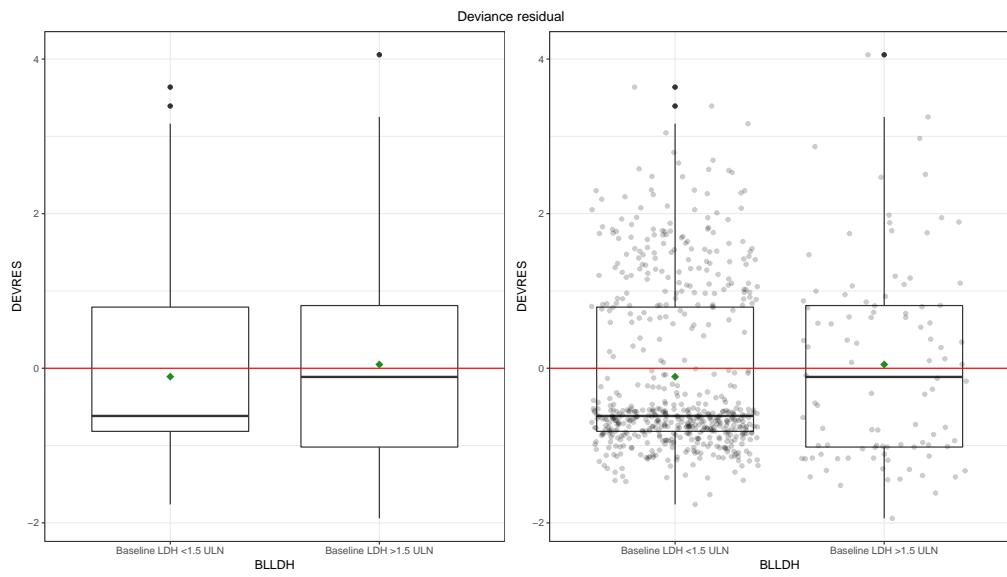


Figure 174: Residual-based diagnostics - Deviance plot

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

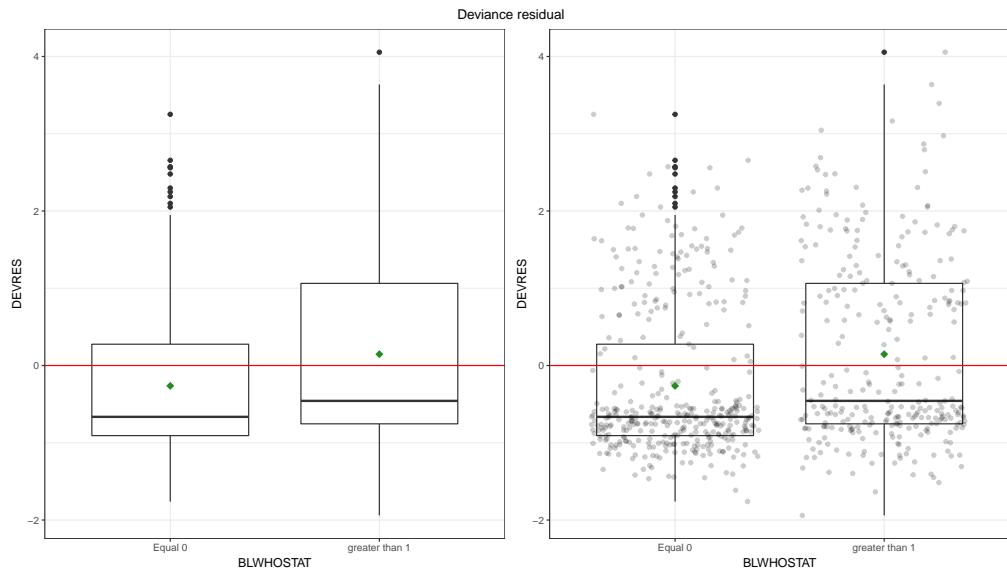


Figure 175: Residual-based diagnostics - Deviance plot

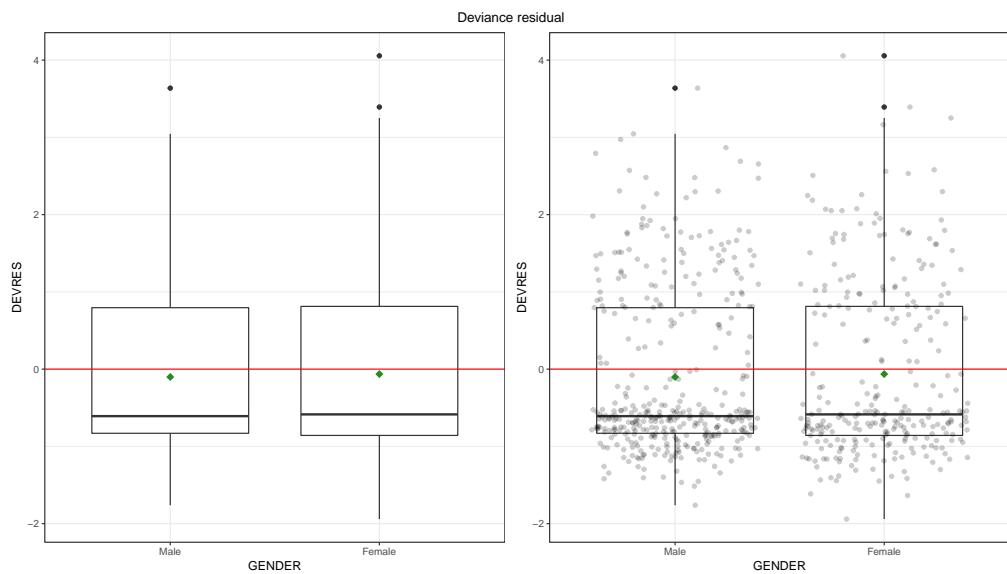


Figure 176: Residual-based diagnostics - Deviance plot

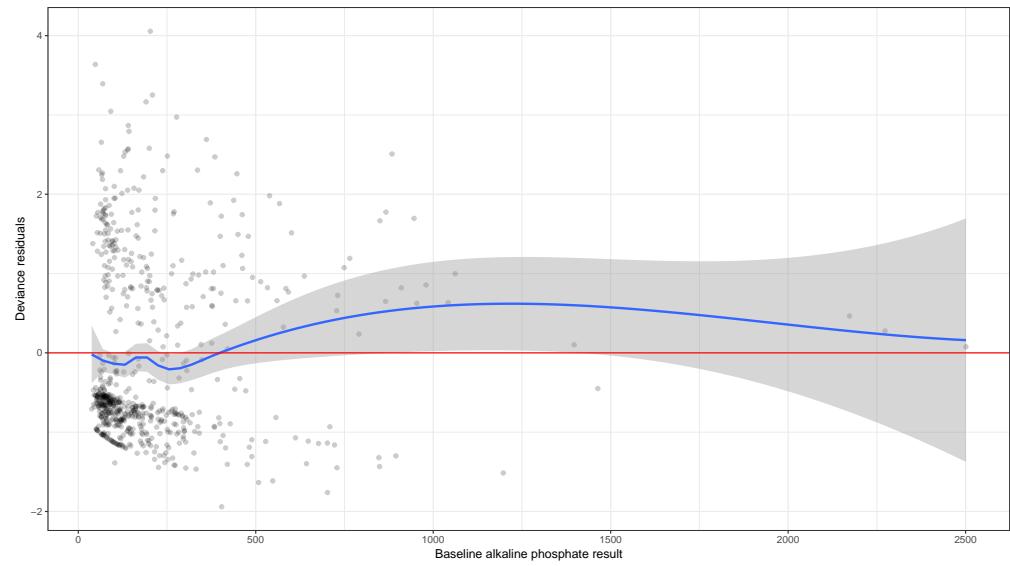


Figure 177: Residual-based diagnostics - Deviance plot

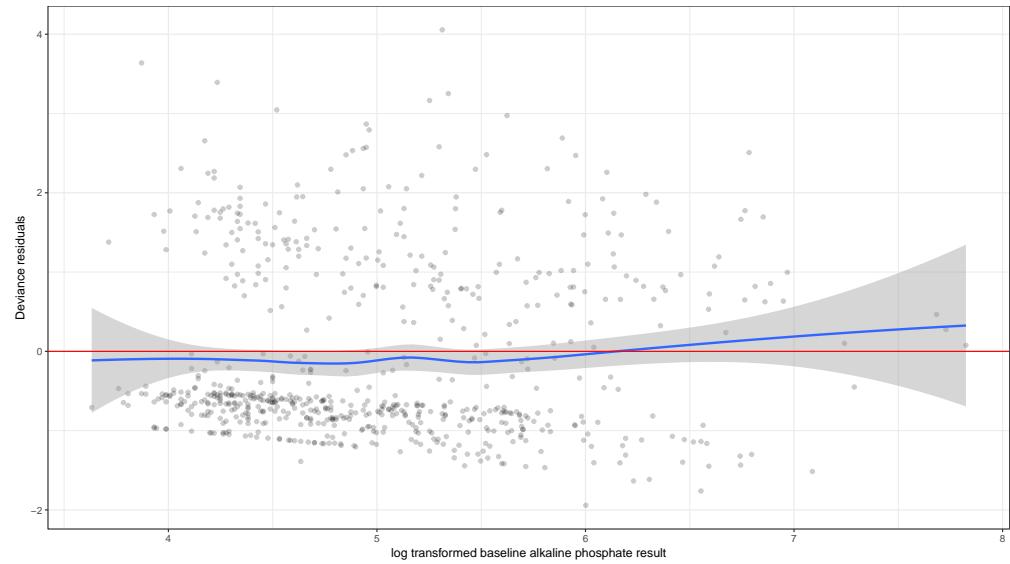


Figure 178: Residual-based diagnostics - Deviance plot

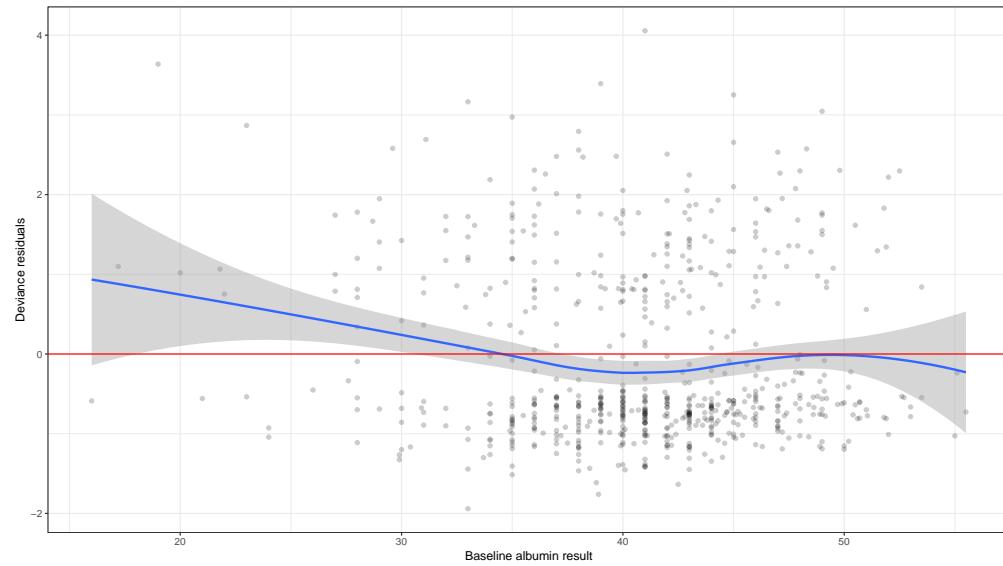


Figure 179: Residual-based diagnostics - Deviance plot

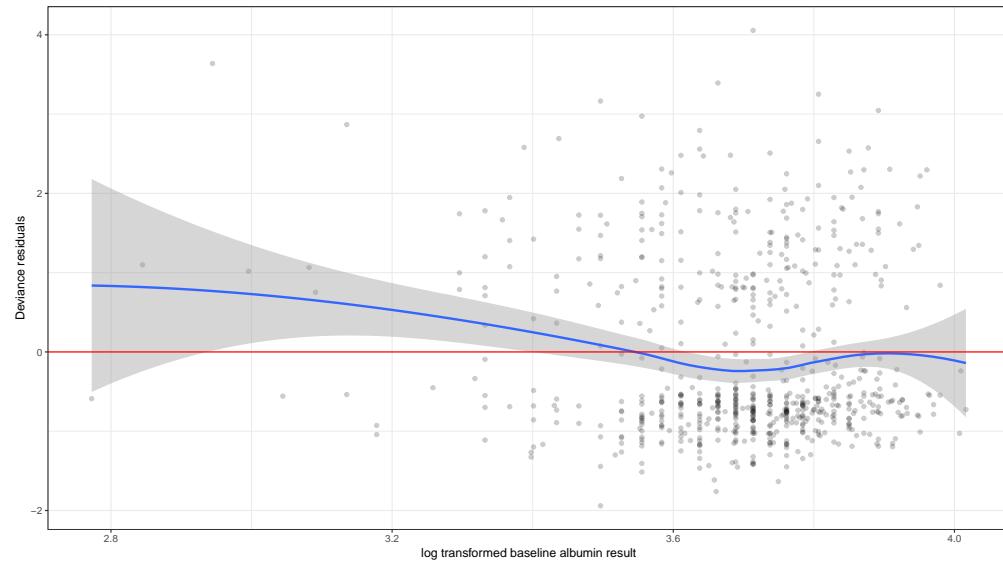


Figure 180: Residual-based diagnostics - Deviance plot

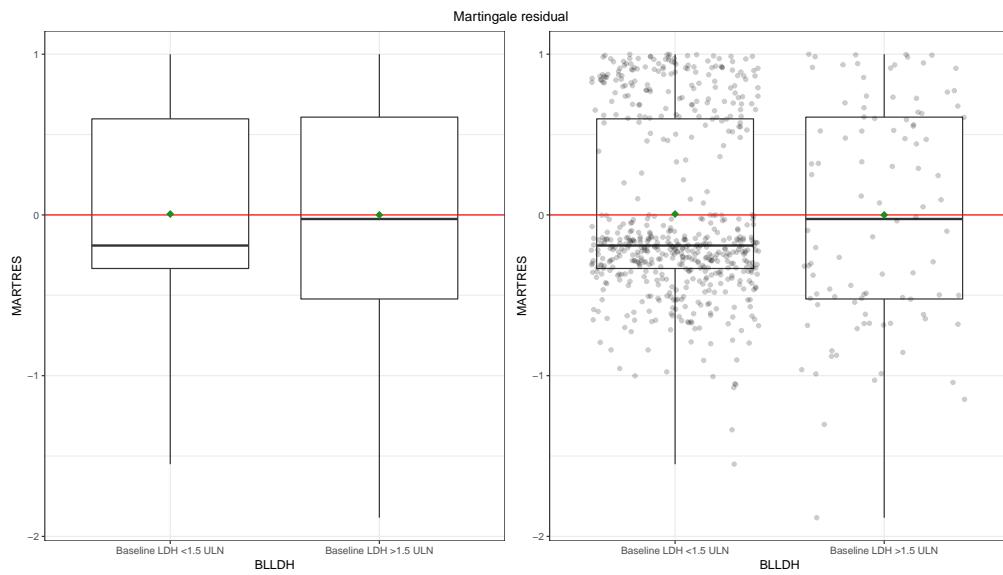


Figure 181: Residual-based diagnostics - Martingale plot

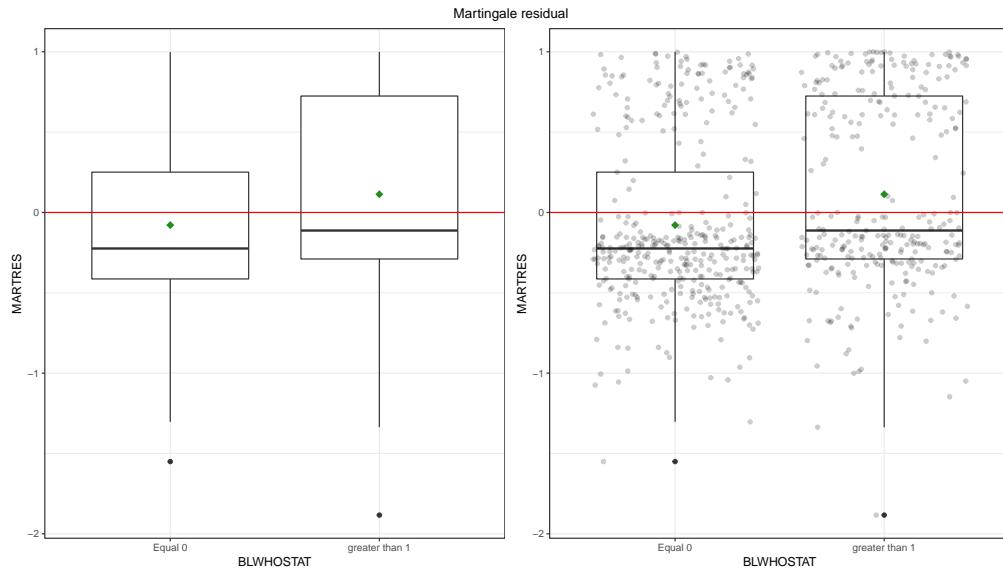


Figure 182: Residual-based diagnostics - Martingale plot

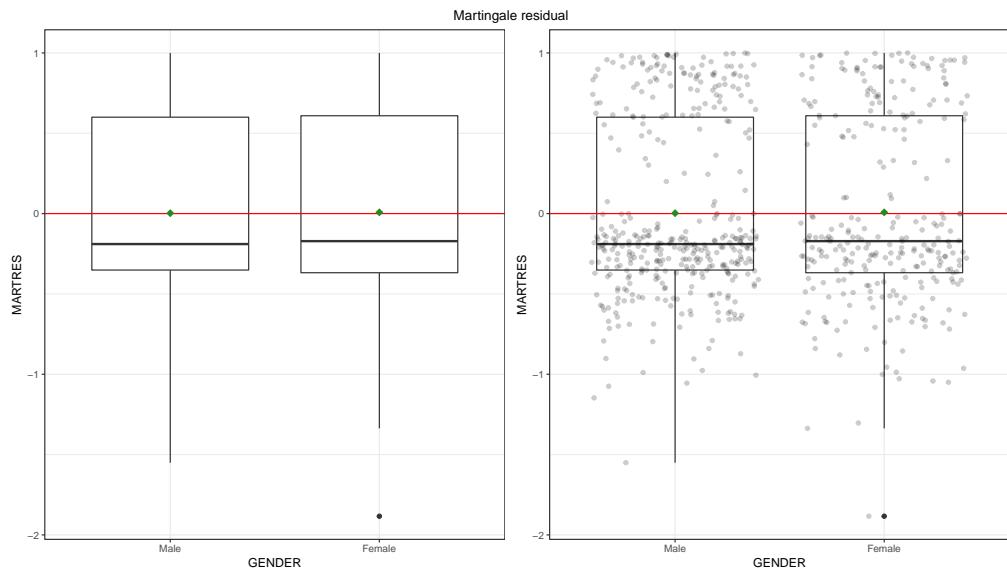


Figure 183: Residual-based diagnostics - Martingale plot

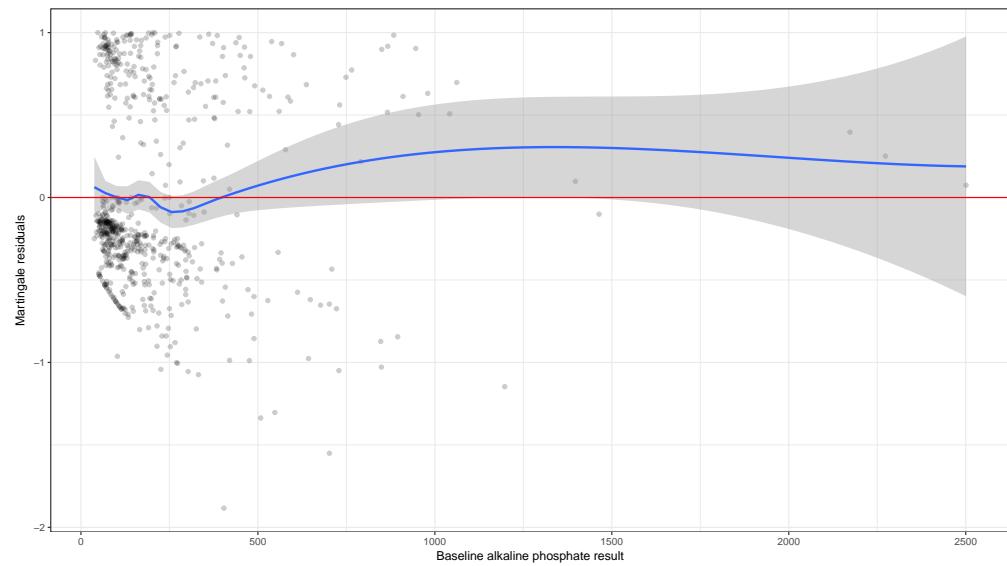
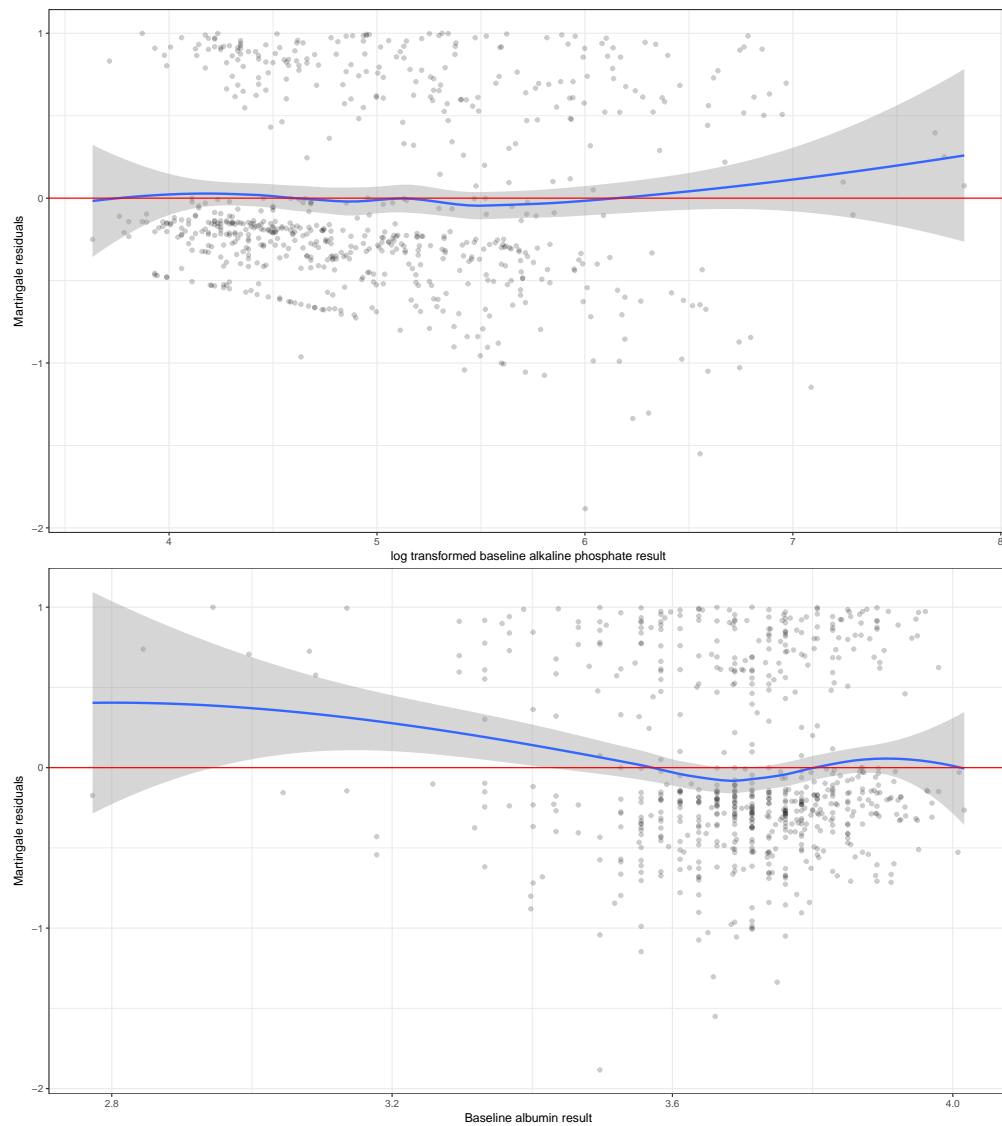


Figure 184: Residual-based diagnostics - Martingale plot



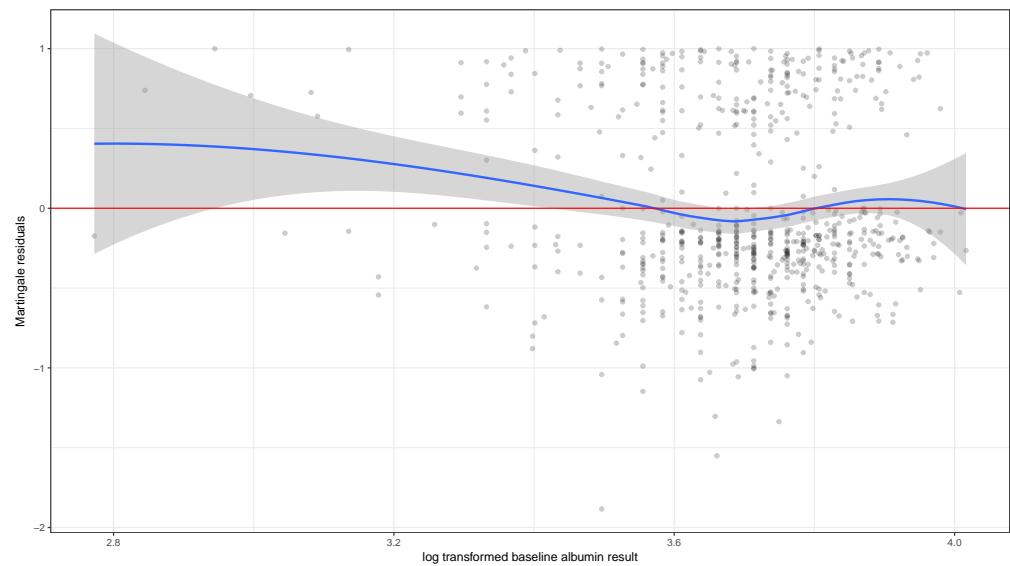


Figure 185: Residual-based diagnostics - Martingale plot

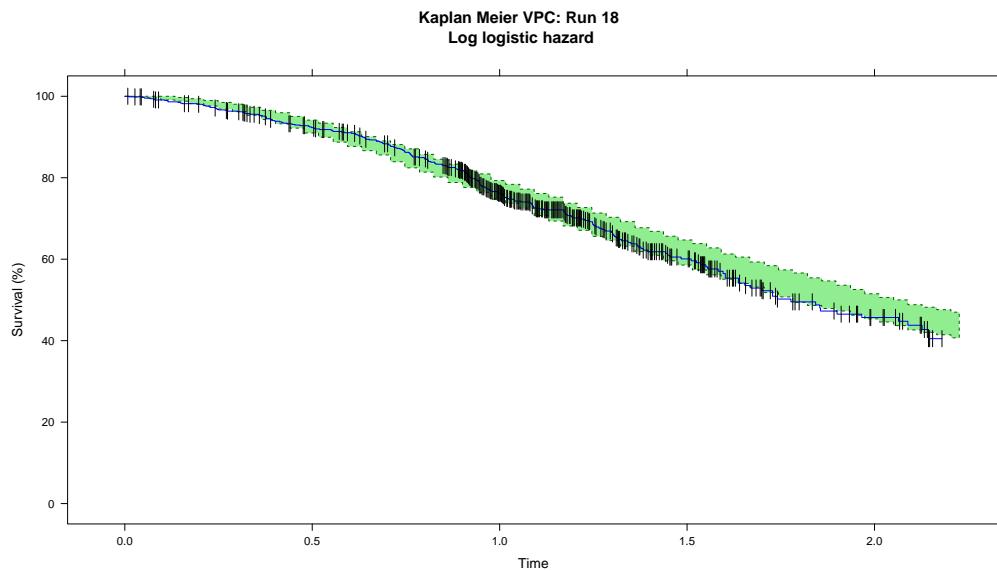


Figure 186: Simulation-based diagnostic

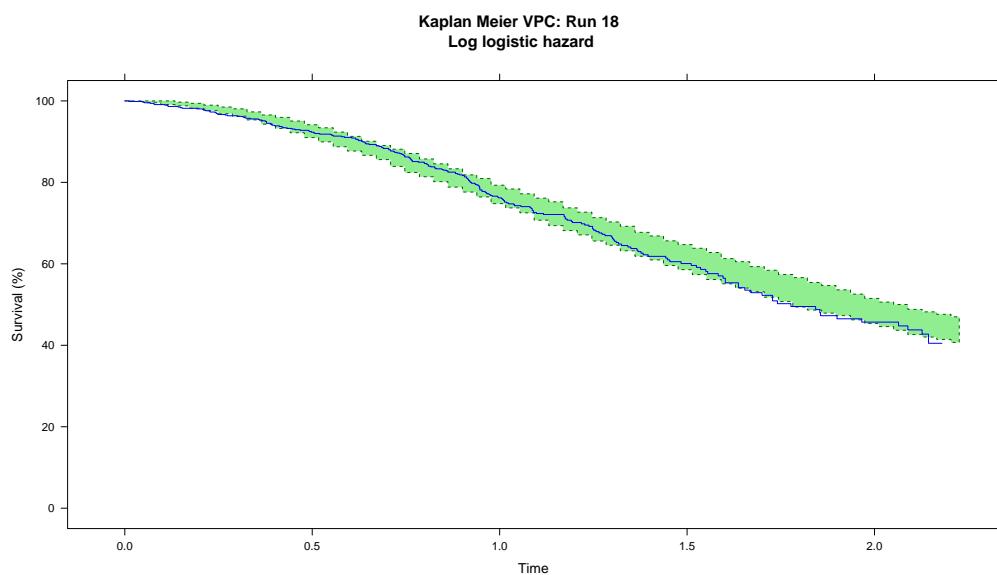


Figure 187: Simulation-based diagnostic

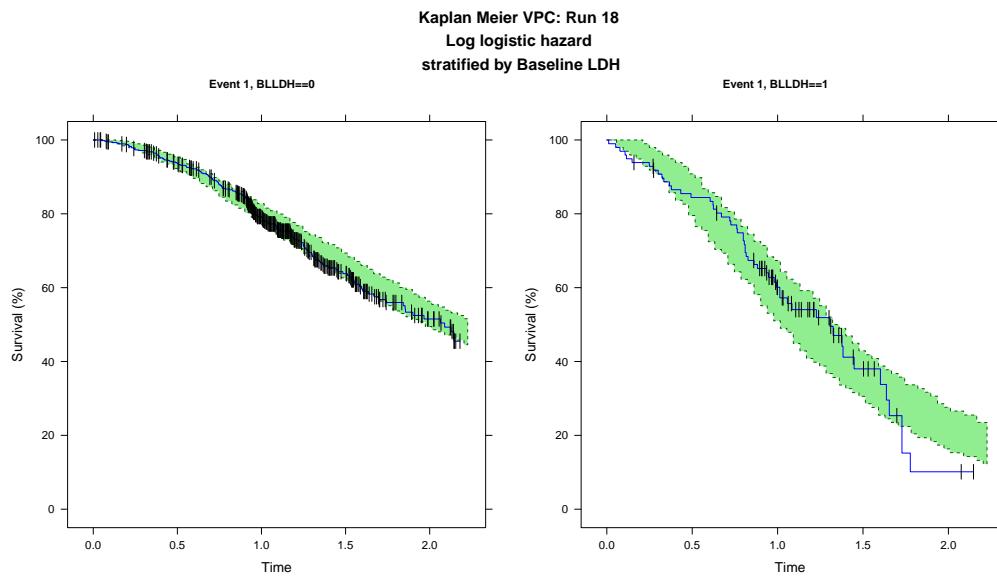


Figure 188: Simulation-based diagnostic - stratified by baseline LDH

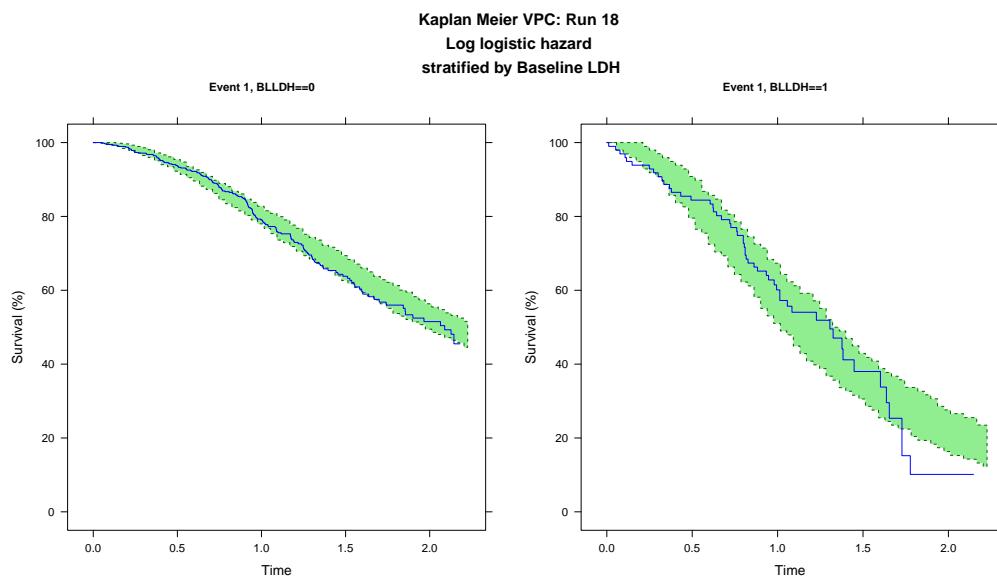


Figure 189: Simulation-based diagnostic - stratified by baseline LDH

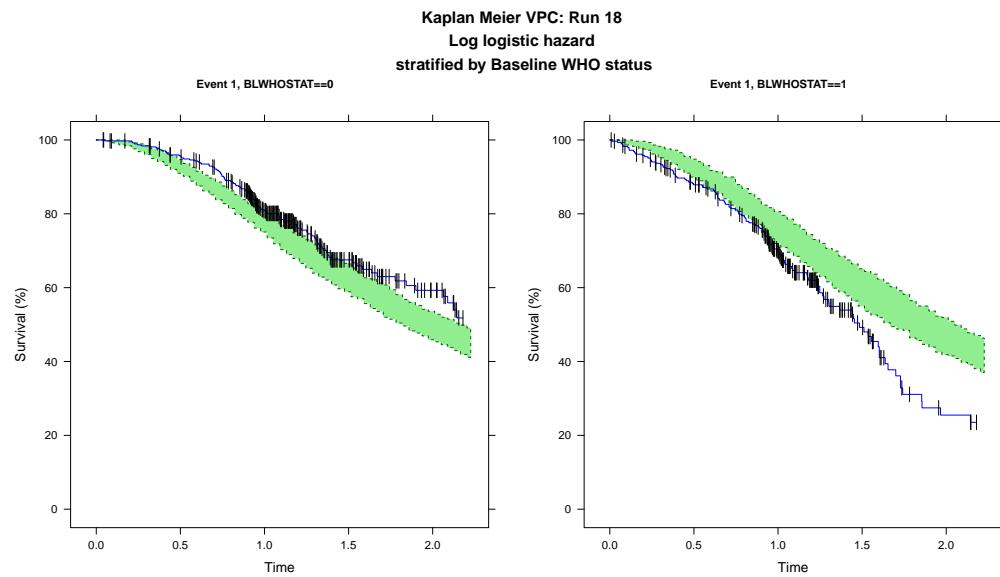


Figure 190: Simulation-based diagnostic - stratified by baseline WHO status

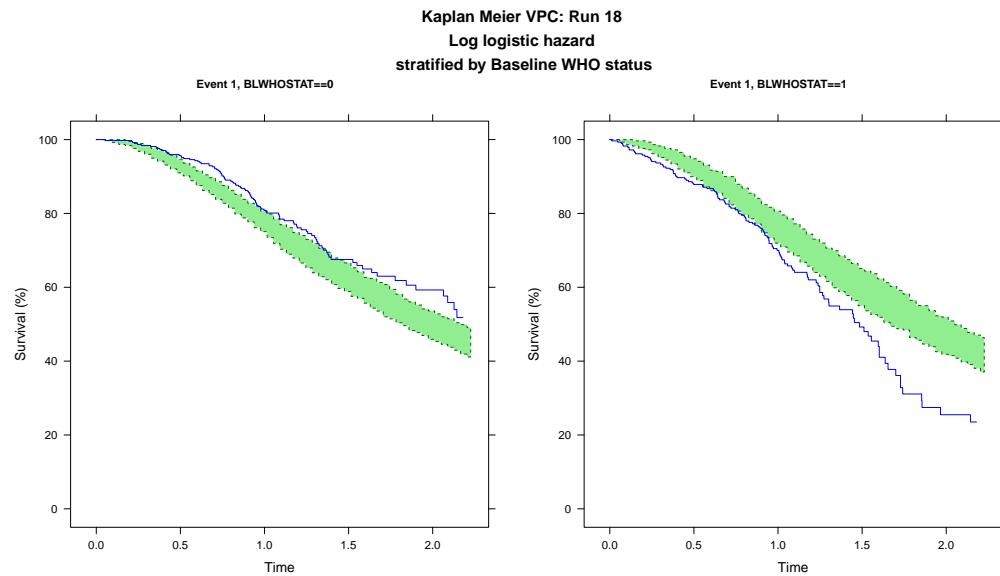


Figure 191: Simulation-based diagnostic - stratified by baseline WHO status

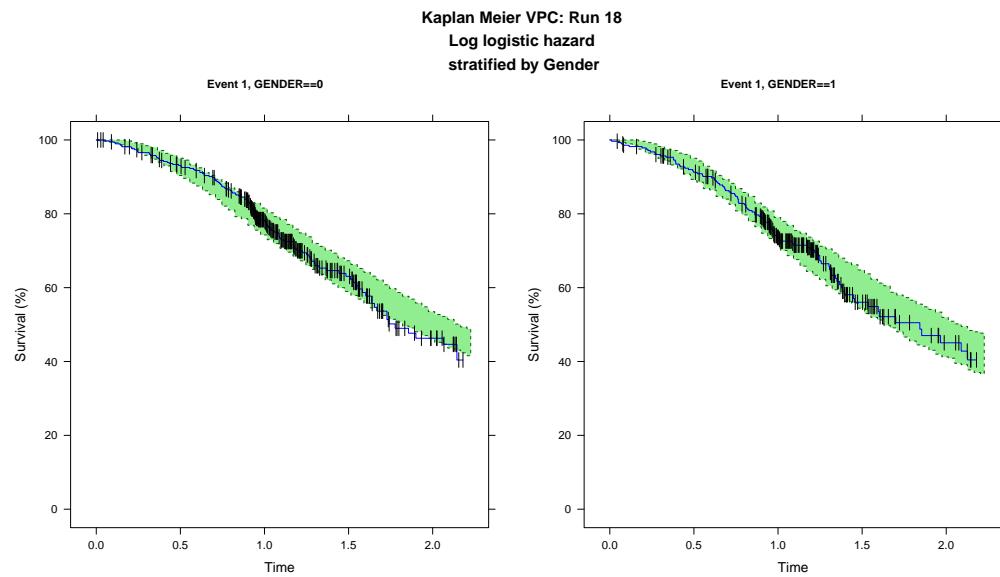


Figure 192: Simulation-based diagnostic - stratified by baseline Gender

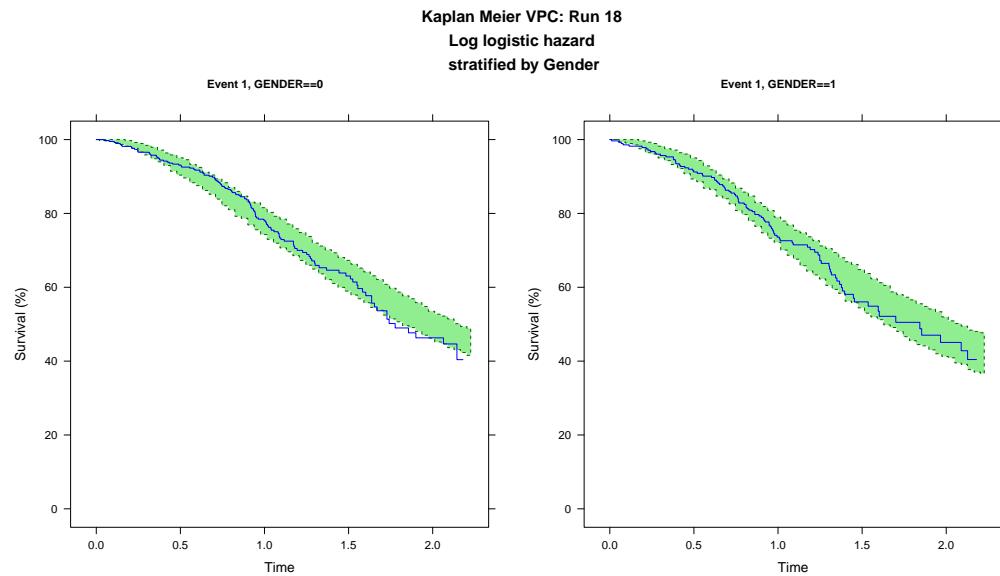


Figure 193: Simulation-based diagnostic - stratified by baseline Gender

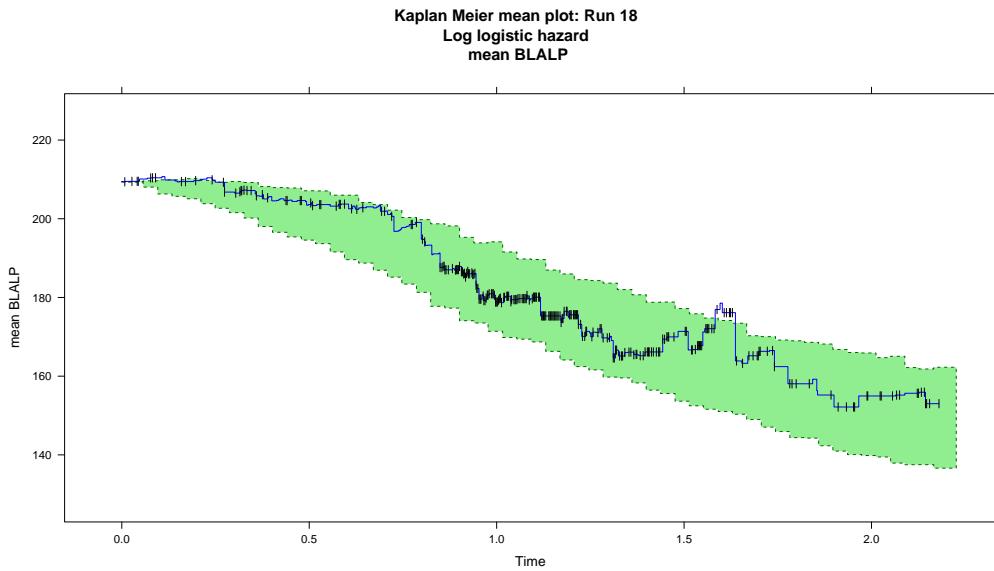


Figure 194: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

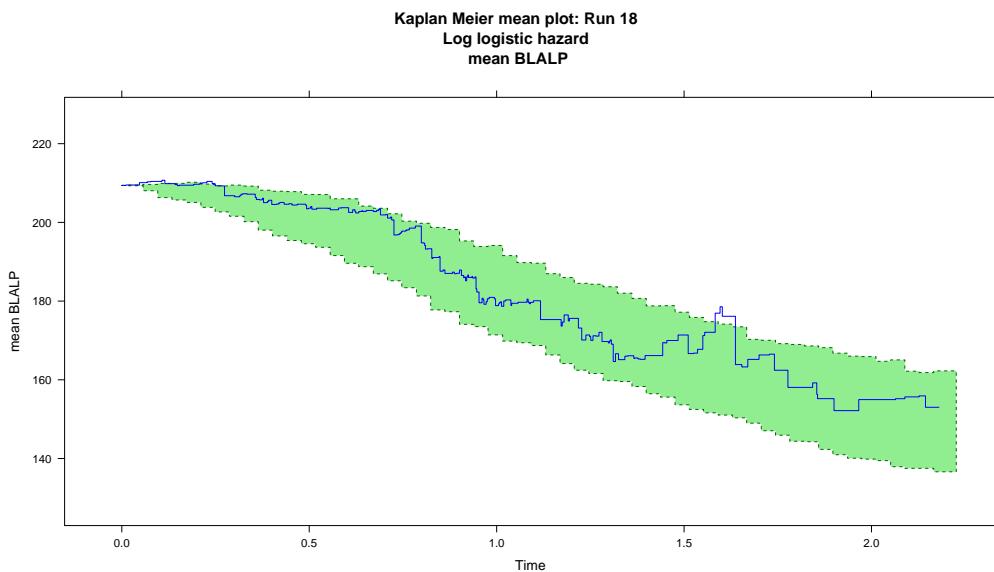


Figure 195: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

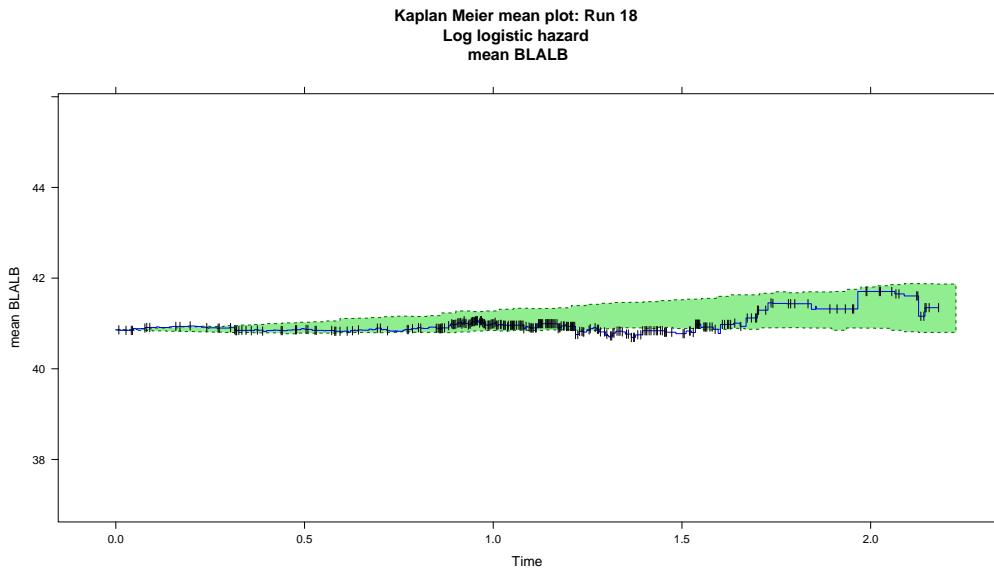


Figure 196: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

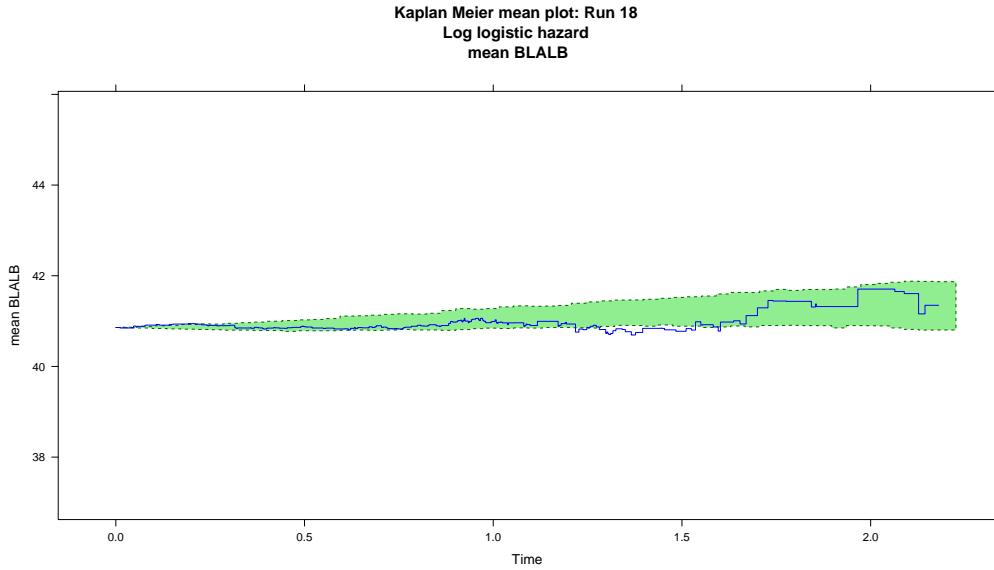


Figure 197: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

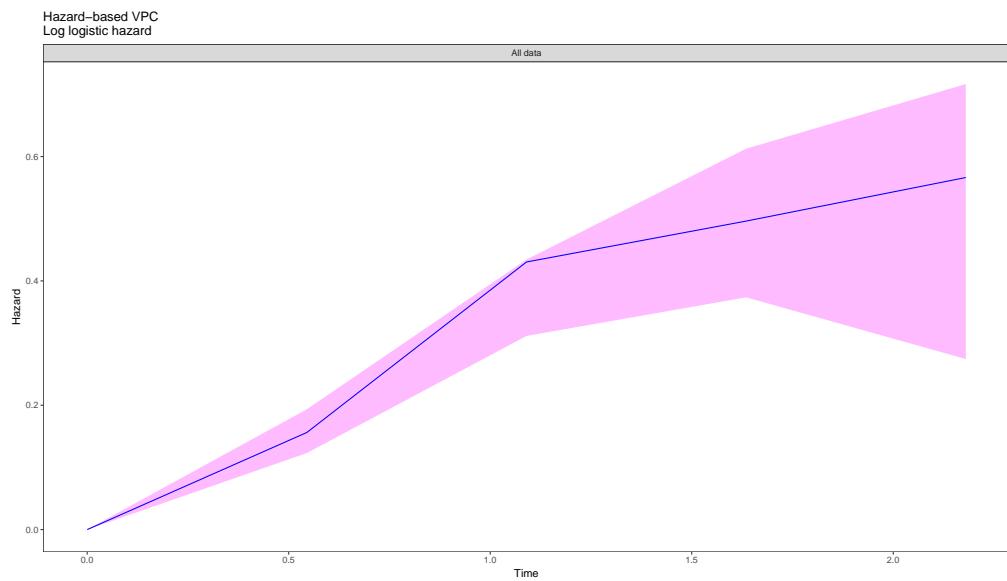


Figure 198: Simulation-based diagnostic: Hazard based VPC

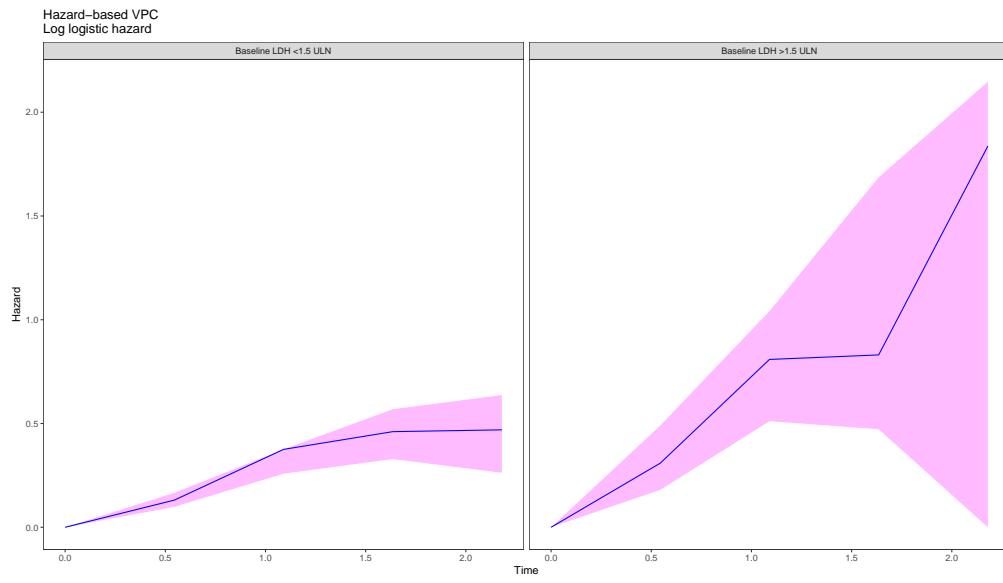


Figure 199: Simulation-based diagnostic: Hazard based VPC

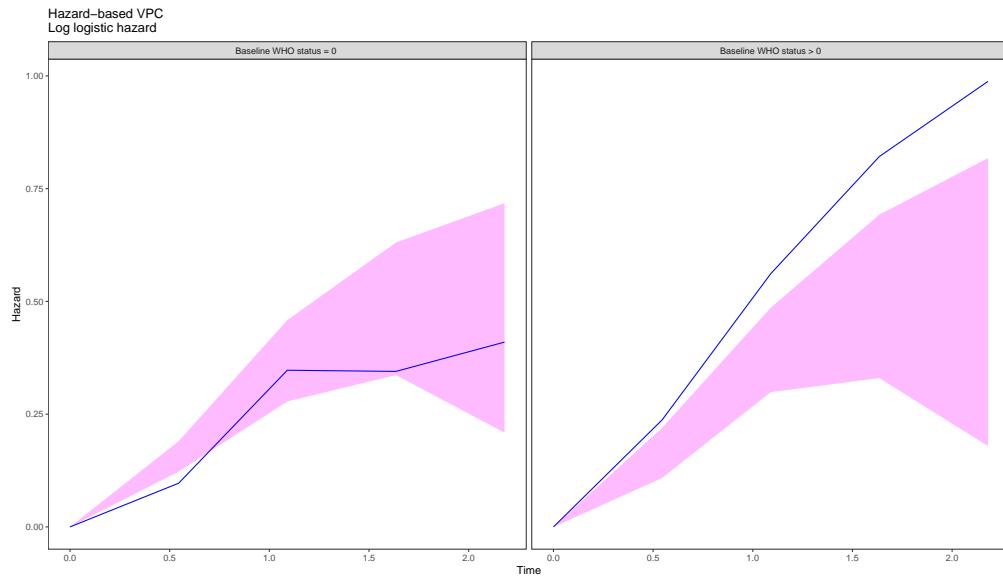


Figure 200: Simulation-based diagnostic: Hazard based VPC

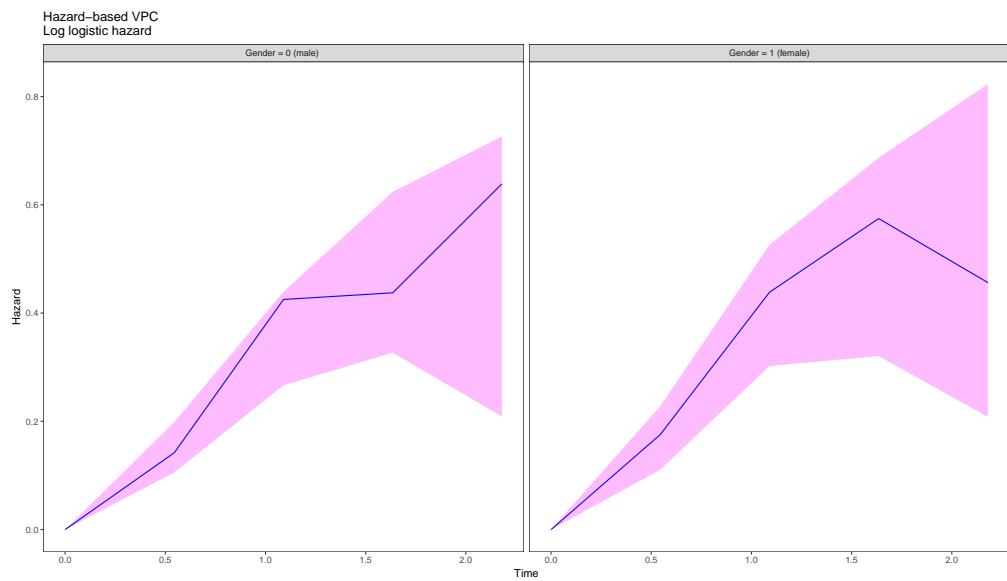


Figure 201: Simulation-based diagnostic: Hazard based VPC

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 occurred 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, binary 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 BLHOSTAT 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

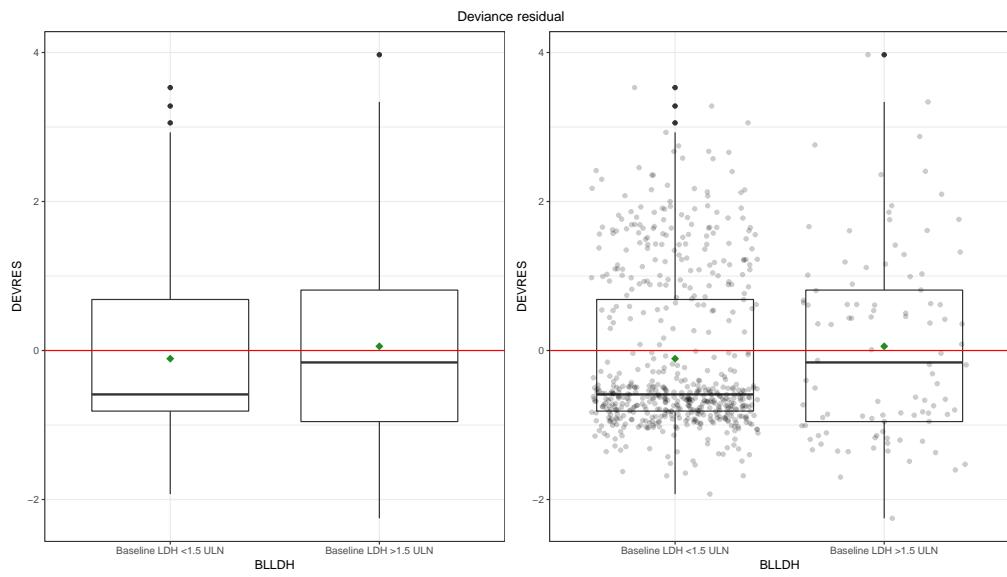


Figure 202: Residual-based diagnostics - Deviance plot

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

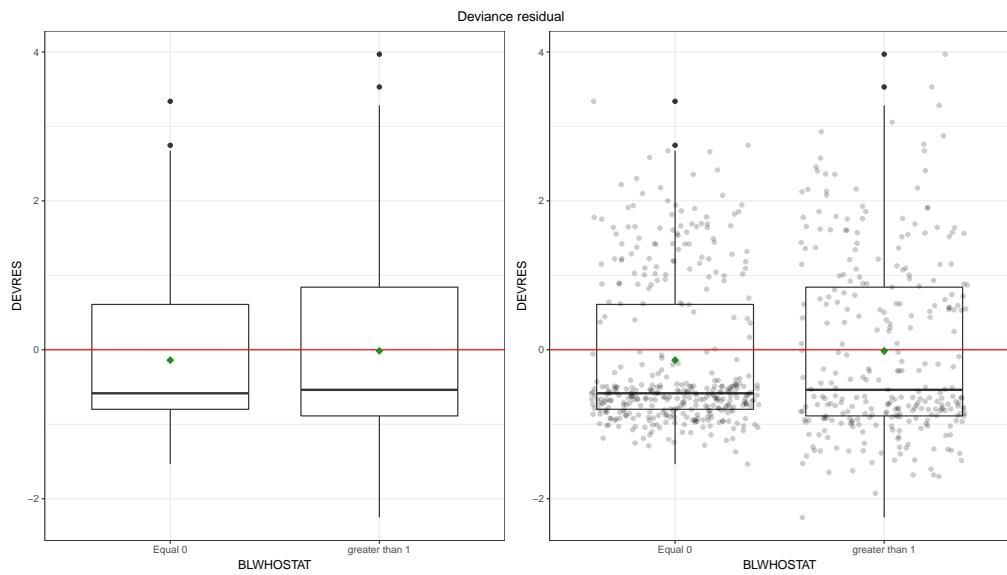


Figure 203: Residual-based diagnostics - Deviance plot

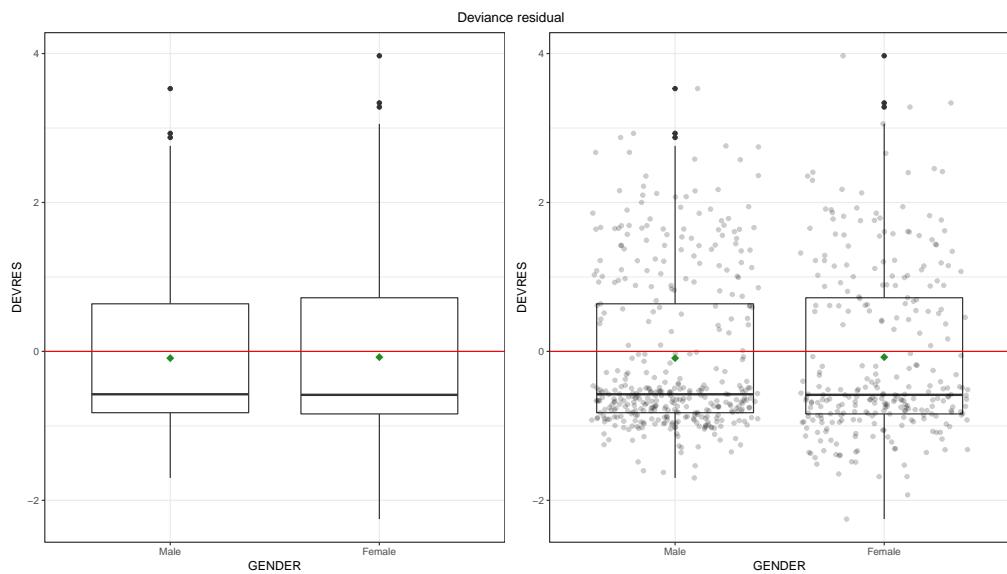


Figure 204: Residual-based diagnostics - Deviance plot

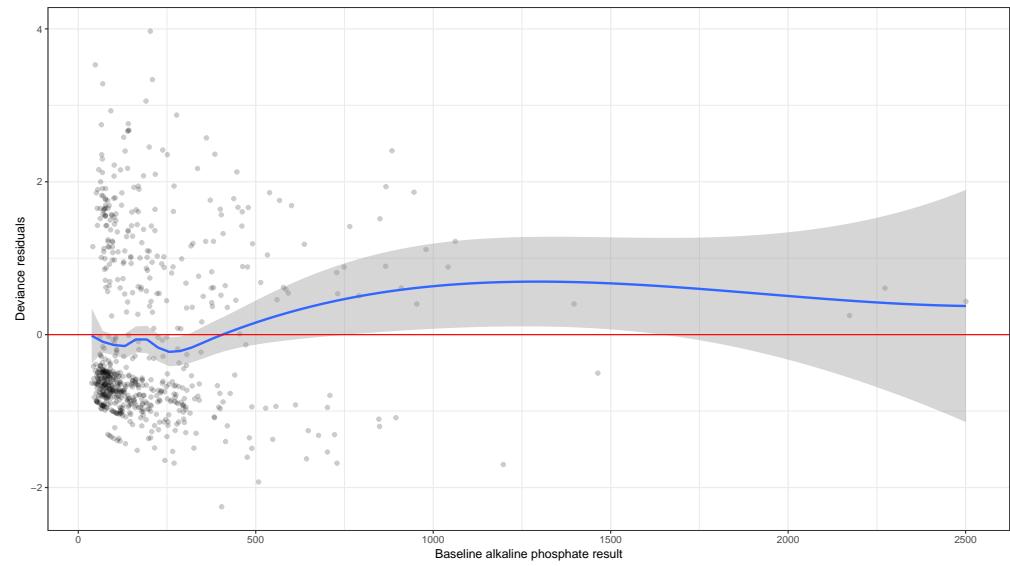


Figure 205: Residual-based diagnostics - Deviance plot

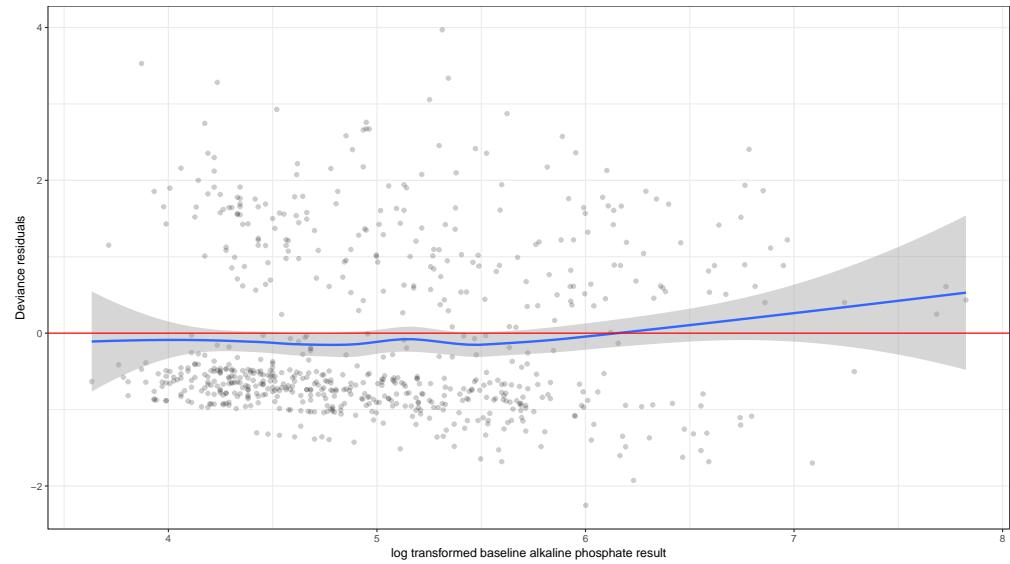


Figure 206: Residual-based diagnostics - Deviance plot

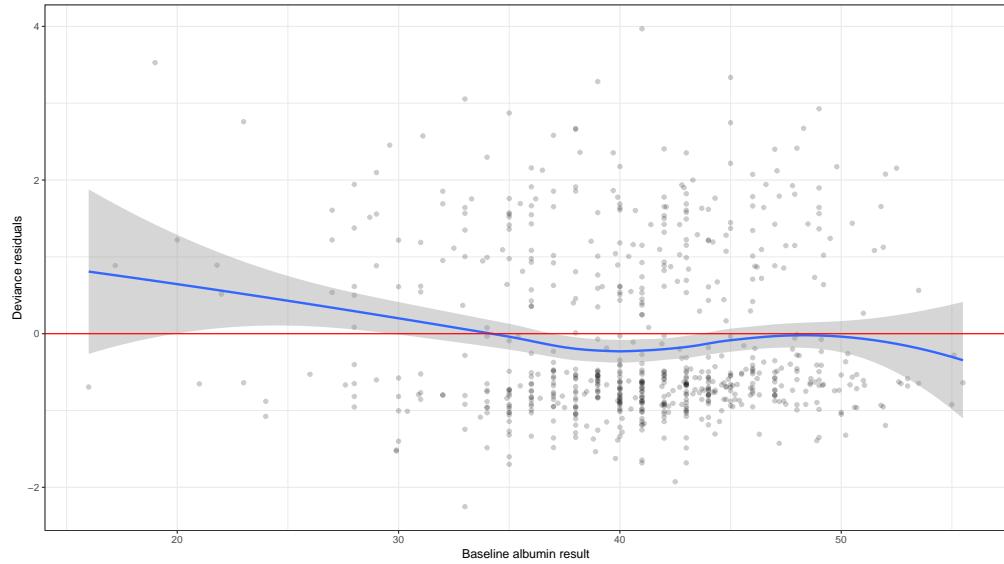


Figure 207: Residual-based diagnostics - Deviance plot

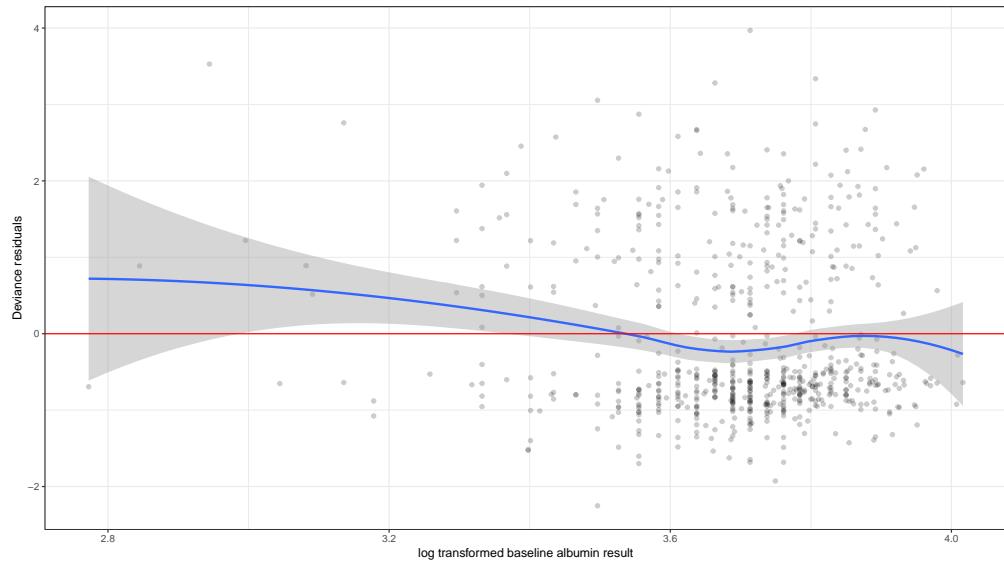


Figure 208: Residual-based diagnostics - Deviance plot

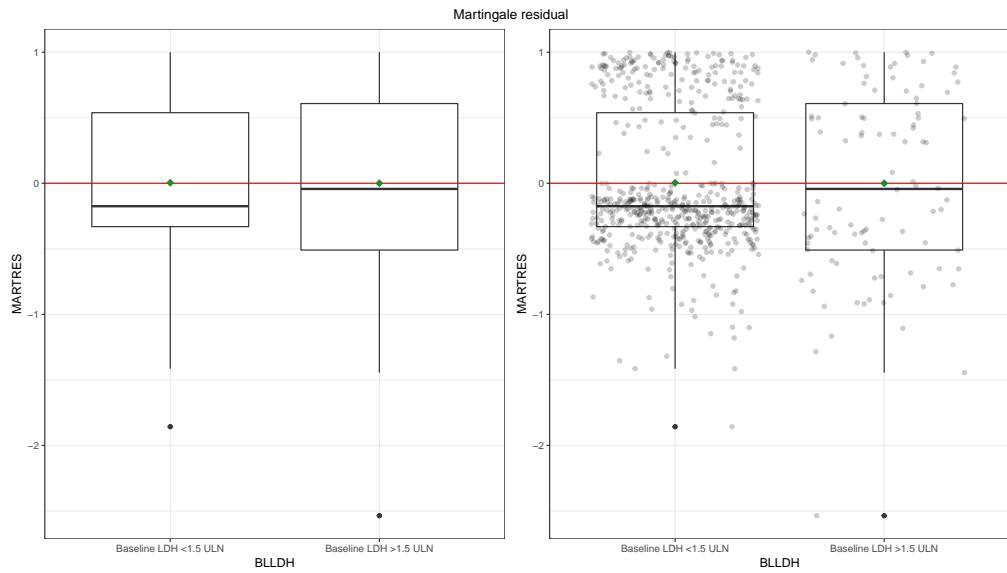


Figure 209: Residual-based diagnostics - Martingale plot

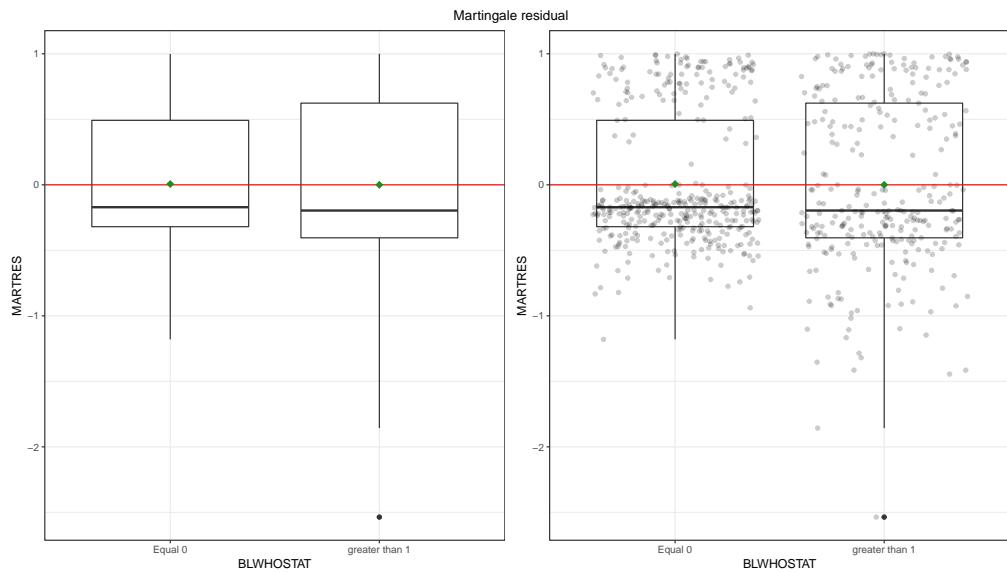


Figure 210: Residual-based diagnostics - Martingale plot

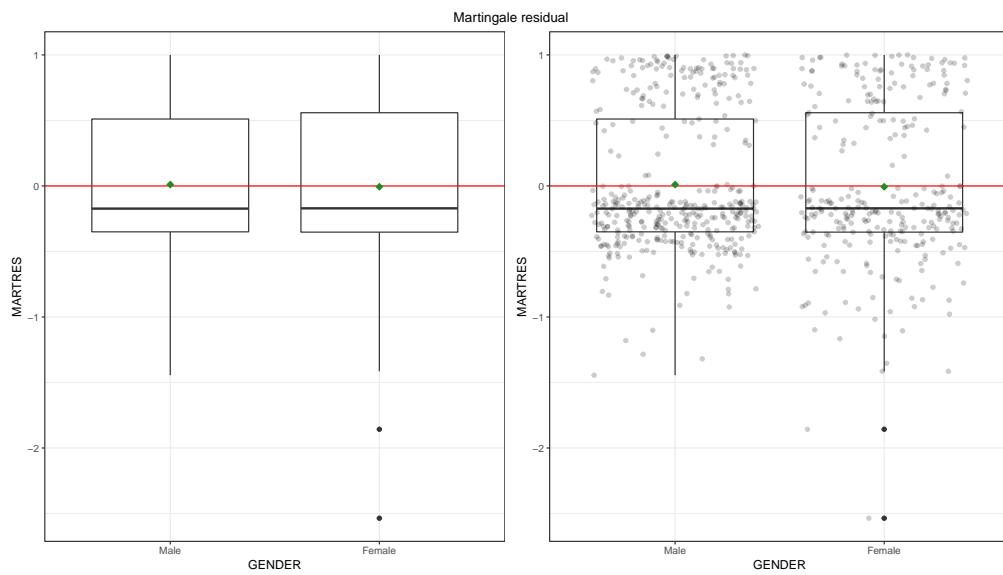


Figure 211: Residual-based diagnostics - Martingale plot

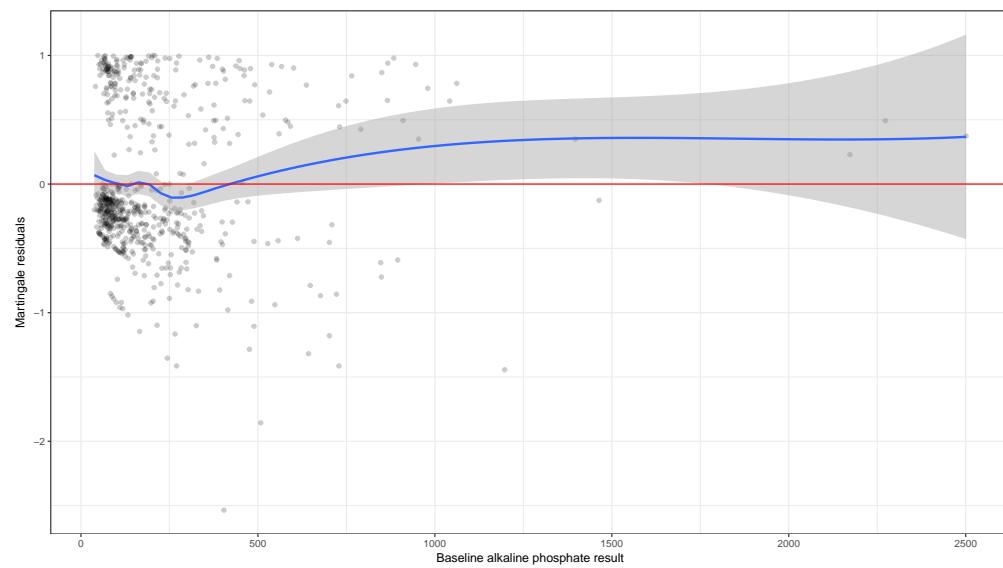
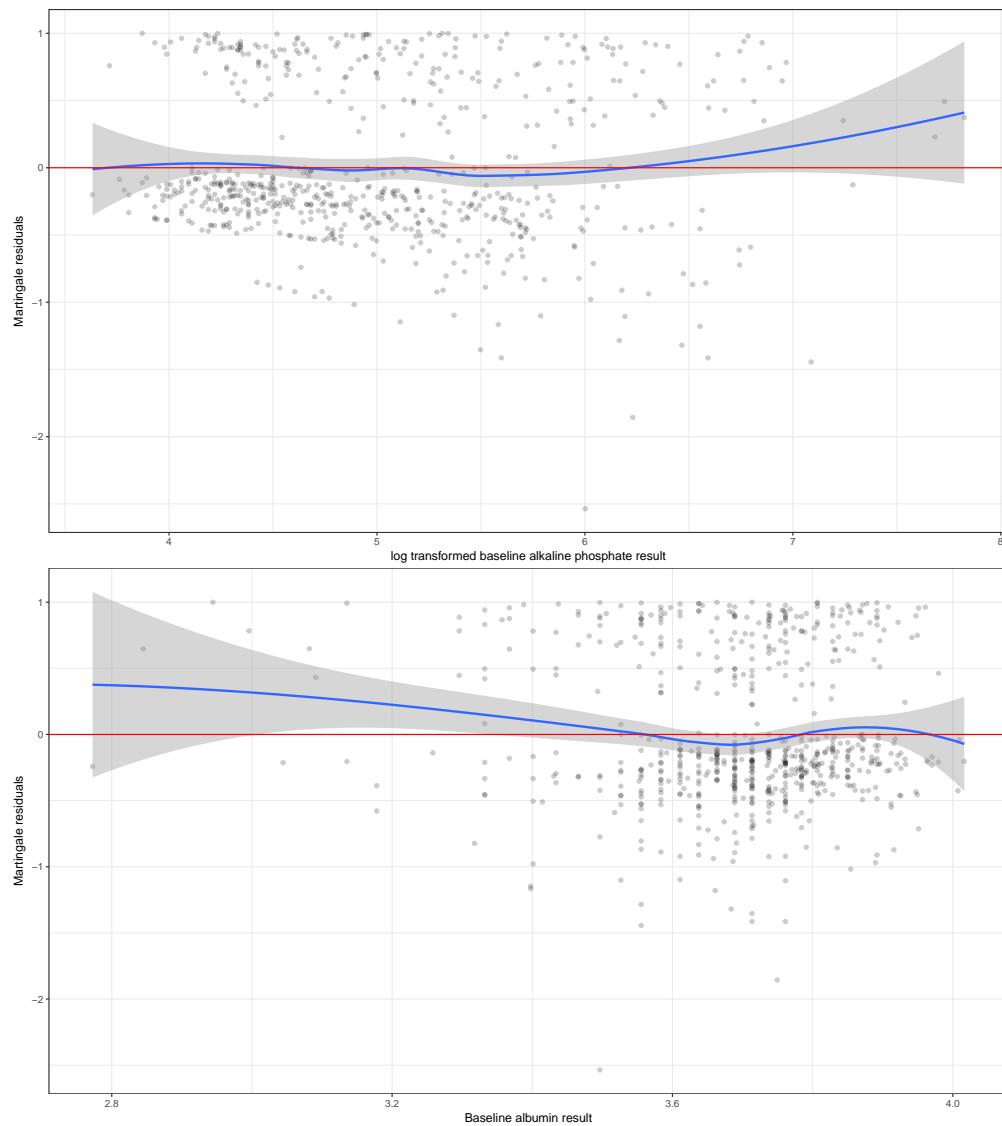


Figure 212: Residual-based diagnostics - Martingale plot



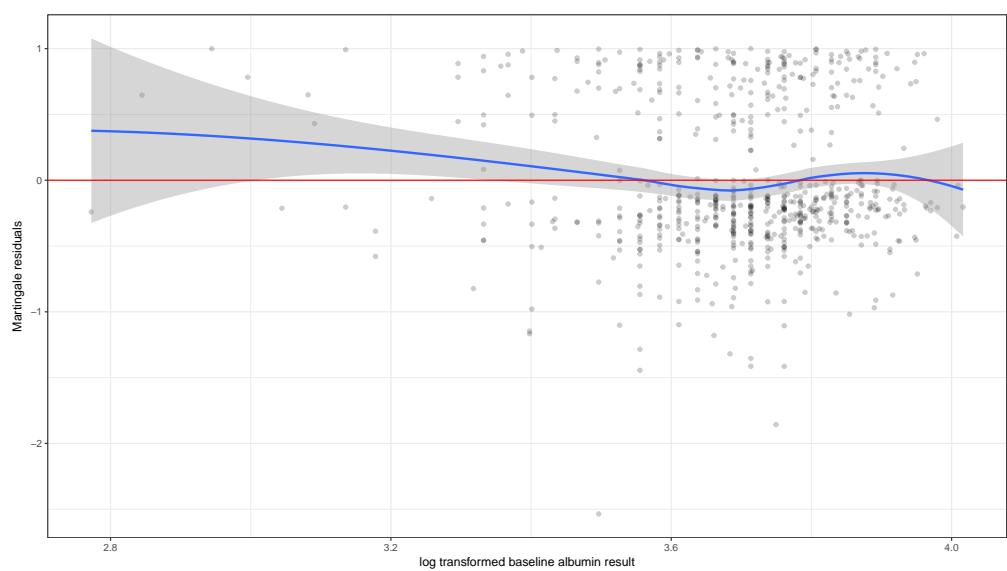


Figure 213: Residual-based diagnostics - Martingale plot

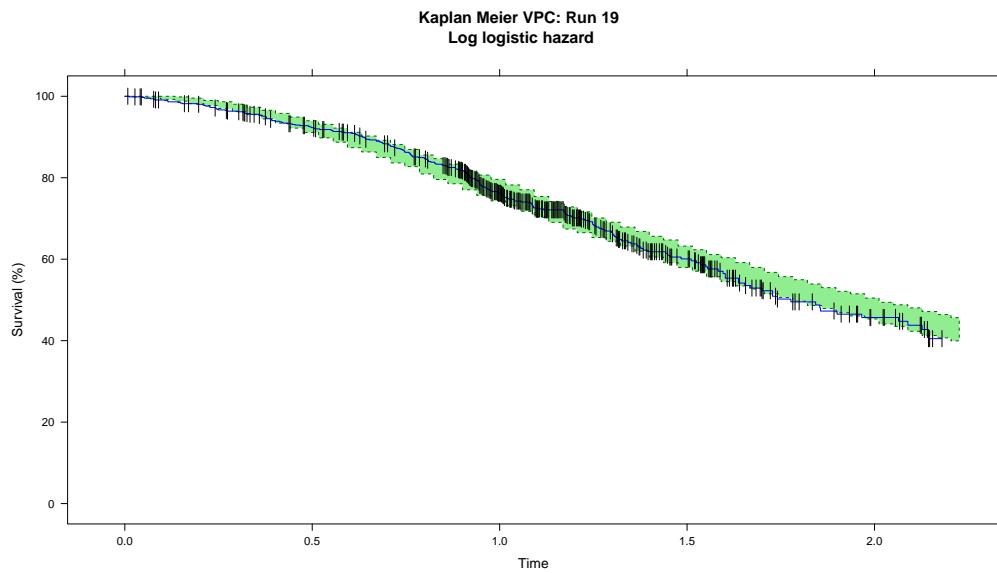


Figure 214: Simulation-based diagnostic

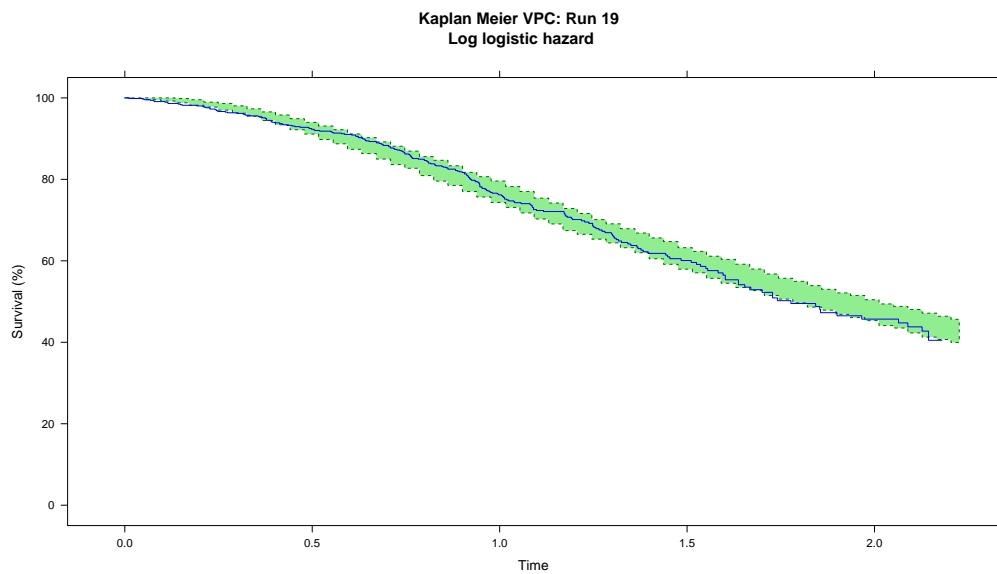


Figure 215: Simulation-based diagnostic

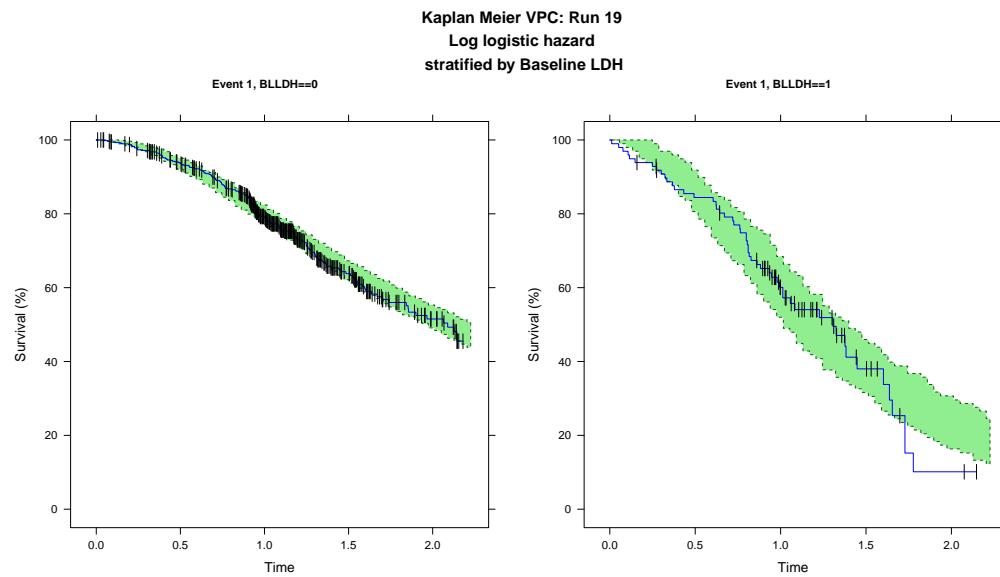


Figure 216: Simulation-based diagnostic - stratified by baseline LDH

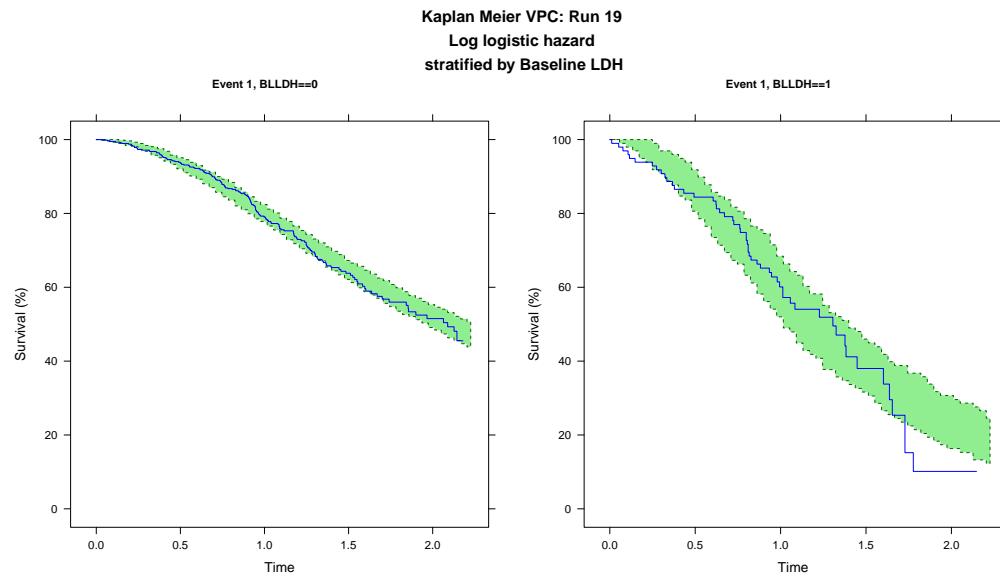


Figure 217: Simulation-based diagnostic - stratified by baseline LDH

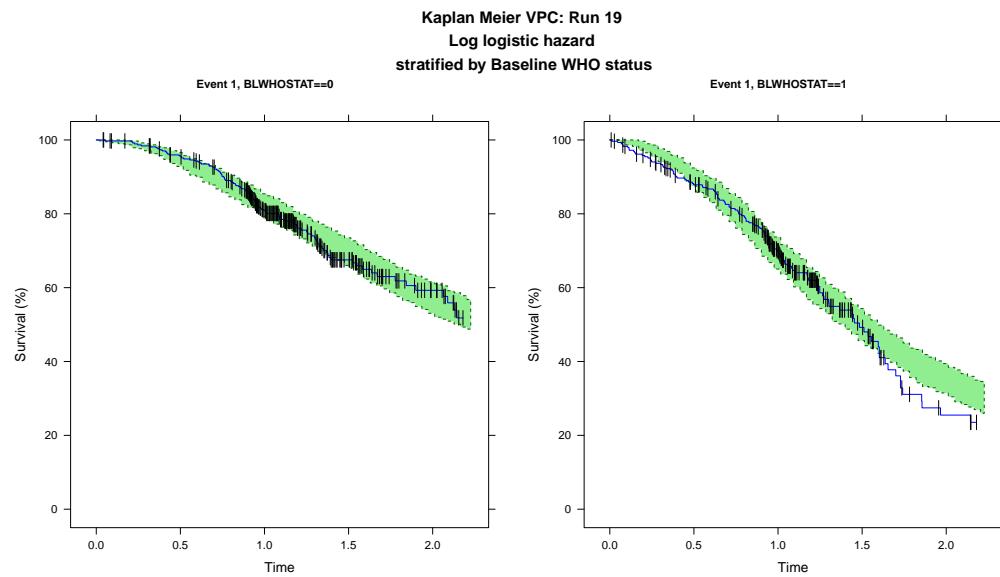


Figure 218: Simulation-based diagnostic - stratified by baseline WHO status

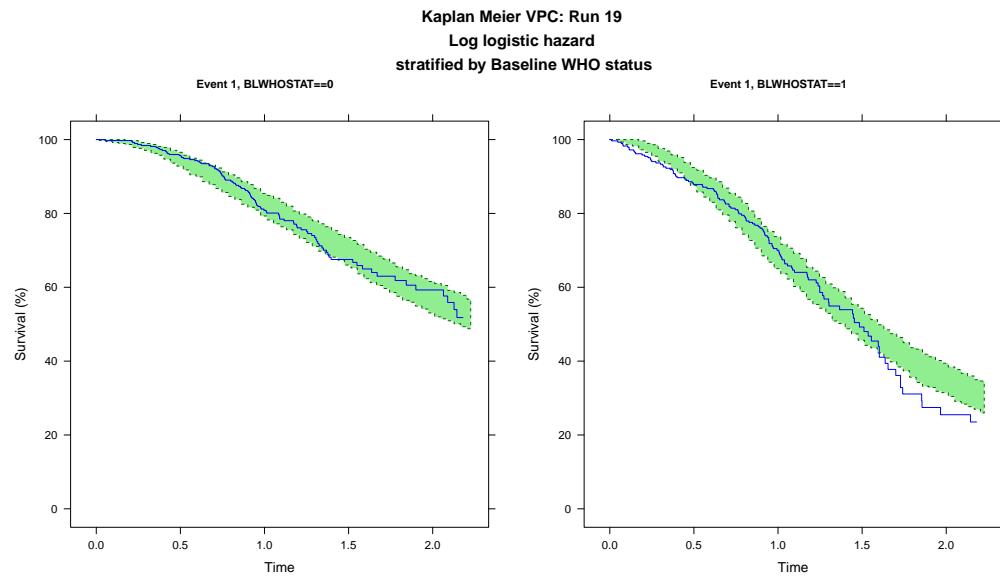


Figure 219: Simulation-based diagnostic - stratified by baseline WHO status

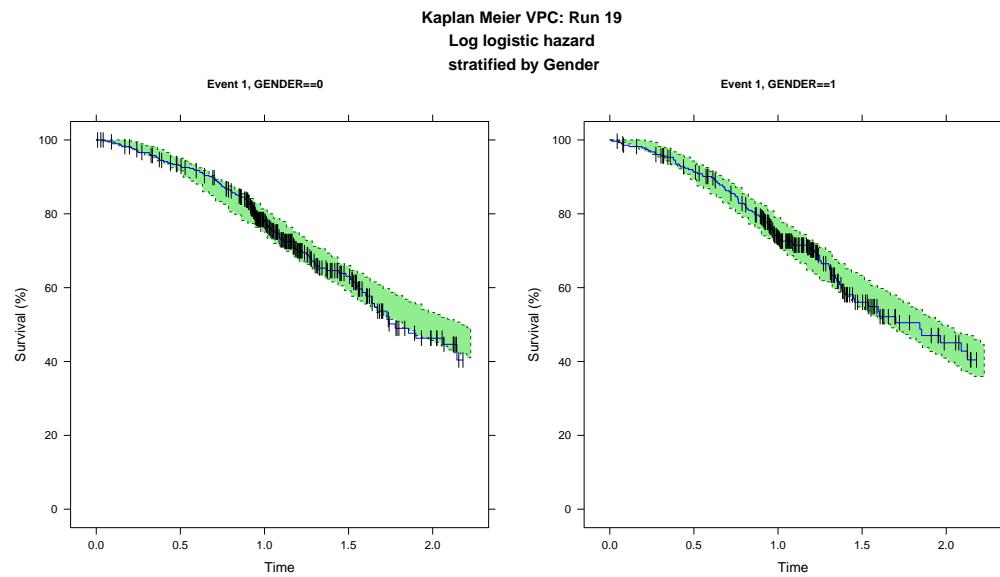


Figure 220: Simulation-based diagnostic - stratified by baseline Gender

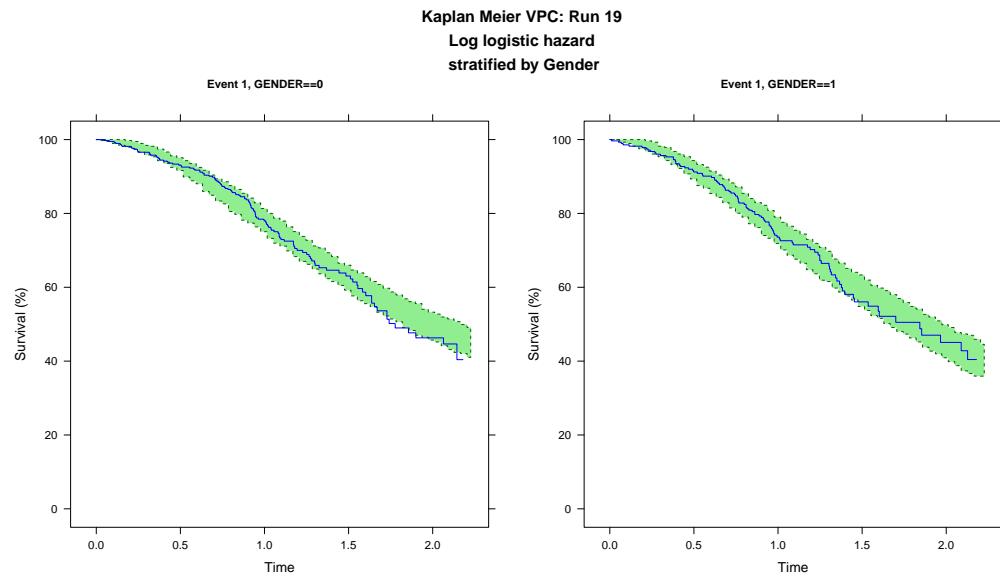


Figure 221: Simulation-based diagnostic - stratified by baseline Gender

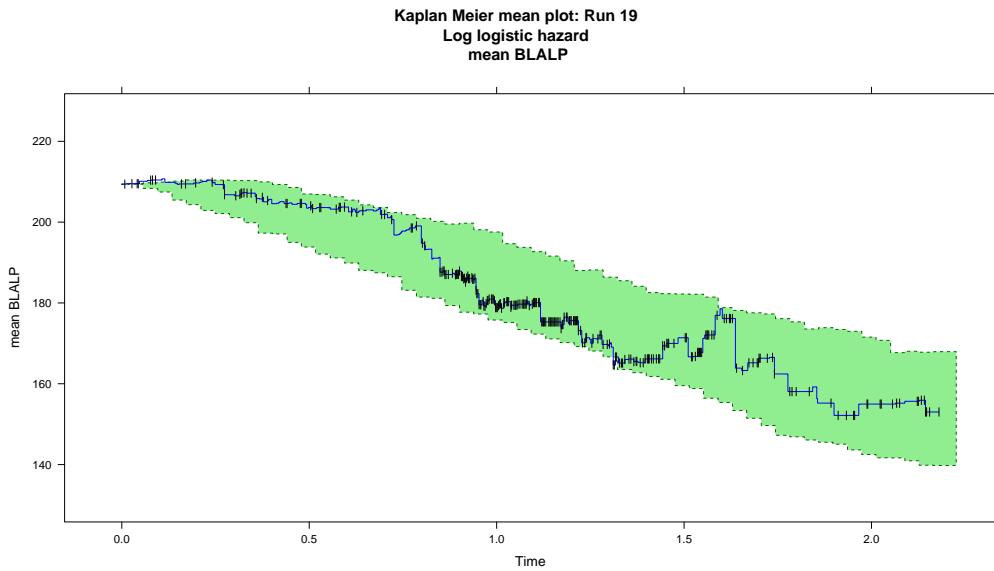


Figure 222: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

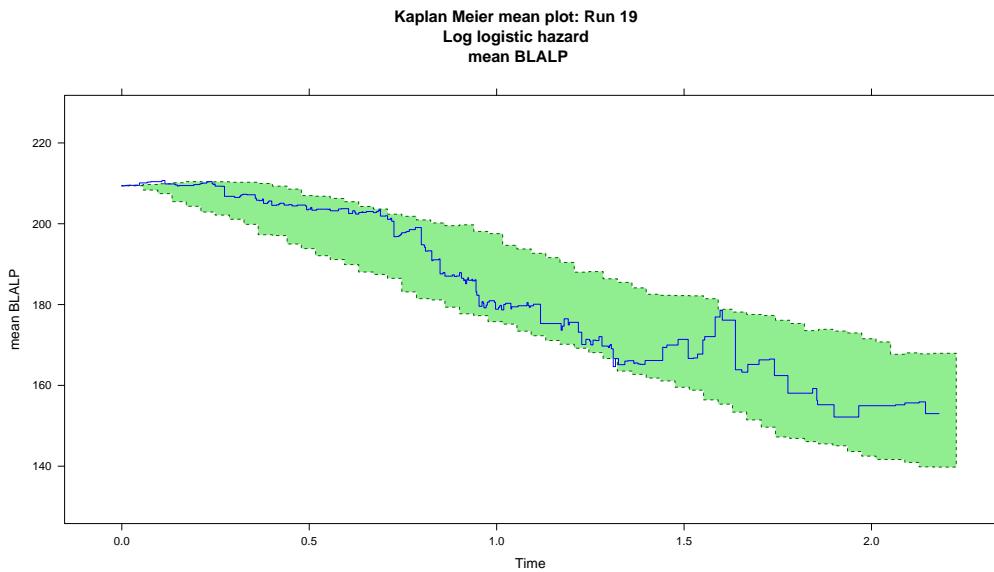


Figure 223: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALP

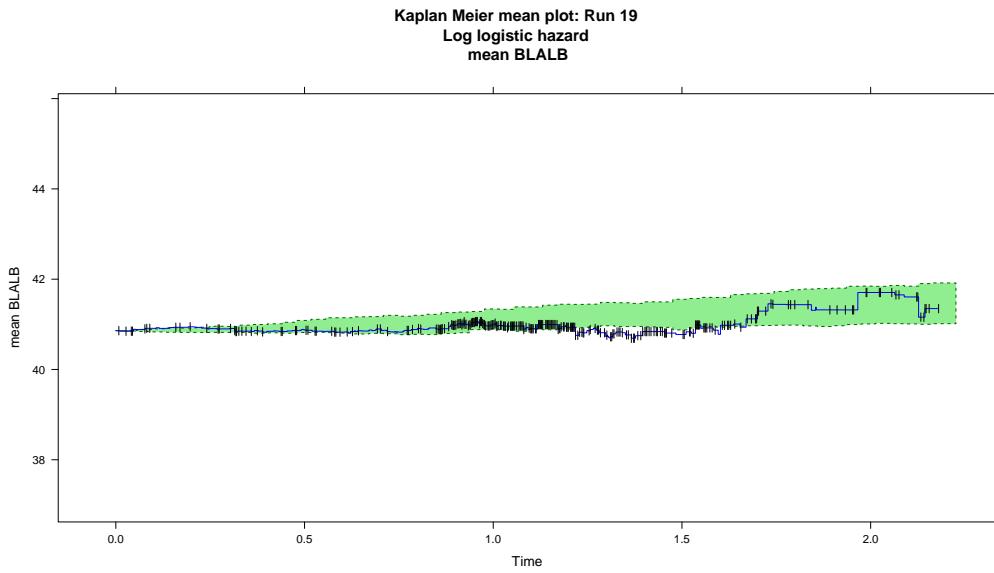


Figure 224: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

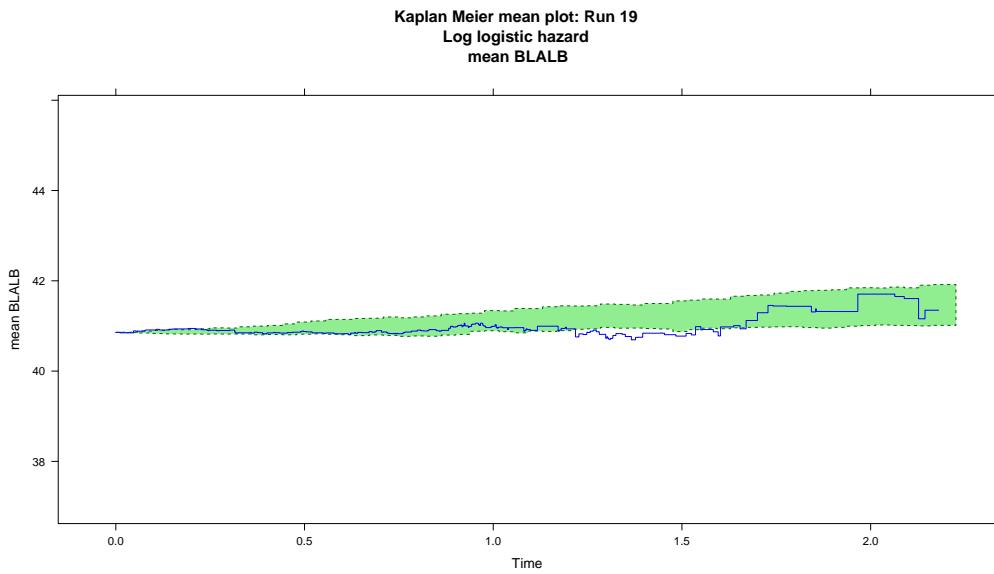


Figure 225: Simulation-based diagnostic - Kaplan-Meier Mean Covariate plot, baseline ALB

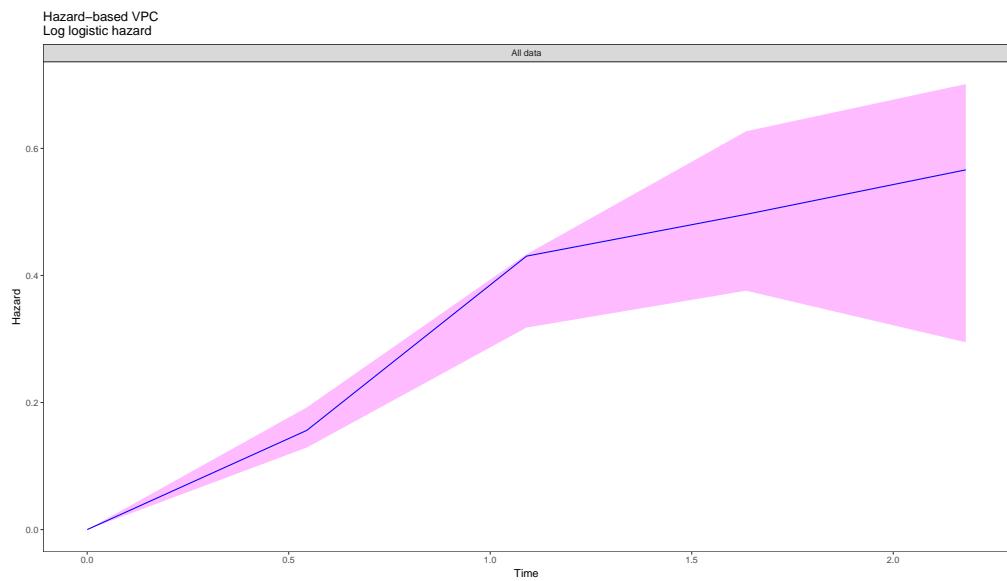


Figure 226: Simulation-based diagnostic: Hazard based VPC

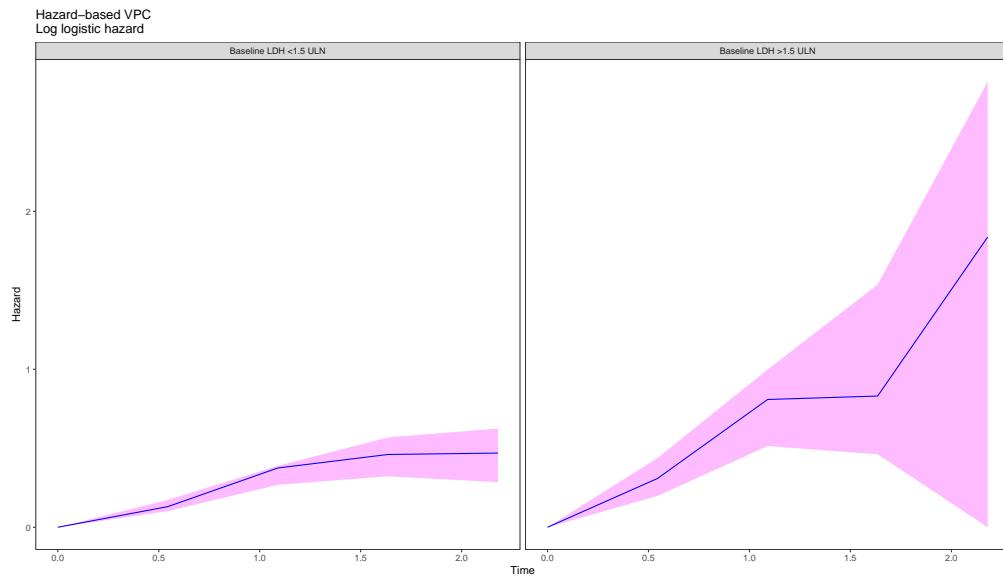


Figure 227: Simulation-based diagnostic: Hazard based VPC

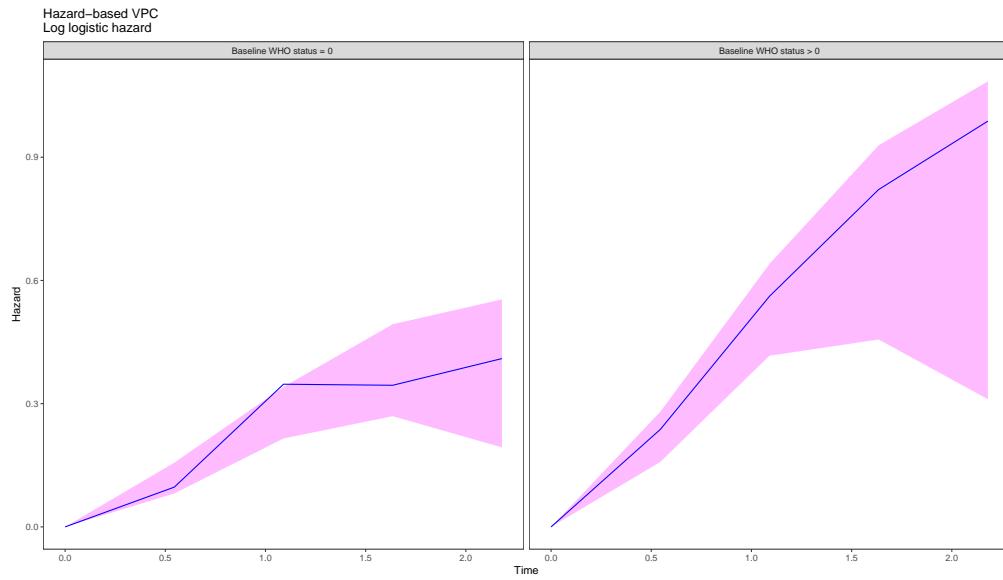


Figure 228: Simulation-based diagnostic: Hazard based VPC

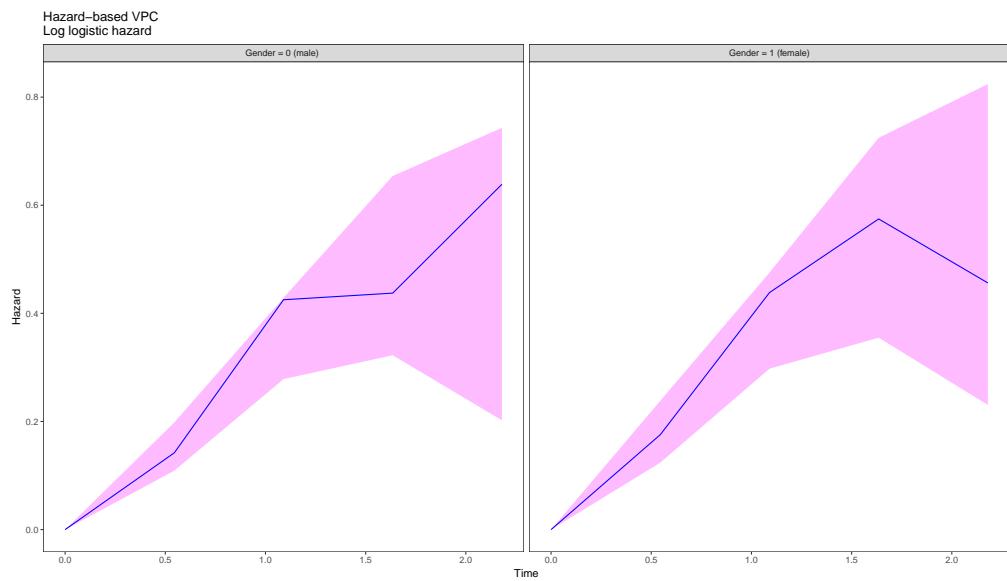


Figure 229: Simulation-based diagnostic: Hazard based VPC

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      tidyrr_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
```