

The impact of the number and the size of clusters on prediction performance of the stratified and the conditional shared gamma frailty Cox proportional hazards models

R code for the illustrative case study

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Overview

We illustrate the analysis of the case study accompanying the simulation study about the impact of the size and the number of clusters on prediction performance of the stratified and the conditional shared gamma frailty Cox proportional hazards models. The case study is the insem data from the R package `parfm` described by the book of Duchateau and Janssen The Frailty Model (2008) (example 1.8)

Some useful notations

Two type of predictions may be possible using frailty:

- Conditional: predictions given the frailty/random effects
For the shared gamma frailty:

$$S_{ij}(t) = \exp[-z_i e^{x_{ij}\beta} H_o(t)] = \exp[-H_0(t)e^{x_{ij}\beta + \mu_j}] = \exp[-z_j H(t)] = \exp[-H(t)e^{\mu_j}]$$

where

$$Z_j \sim \Gamma(\theta, \theta)$$

and

$$\mu_j = \log(Z_j)$$

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where $i = 1, \dots, n_j$ represents the i^{th} subject and $j = 1, \dots, N$ represents the j^{th} cluster.

The measure of within-cluster correlation is Kendall's τ . For the shared gamma frailty model, $\tau = \sigma^2 / (\sigma^2 + 2)$ where σ^2 is the variance of Z_j . The higher is the variance, the higher within-cluster correlation (i.e., homogeneity). Note that $Z_j \sim \Gamma(\theta, \theta)$ then the variance is $\sigma^2 = 1/\theta$ then $\tau = 1/(\theta + 2)$. For details see Hougaard *Analysis of Multivariate Survival Data* (chapter 4) link here, and Collett *Modelling Survival Data in Medical Research*, 4th edition, (chapter 10) link here.

- Marginal: integrating over frailty/random effects

For the shared gamma frailty the marginal predictions may be used when the new individual does not belong to any cluster used to develop the model or to estimate predictions integrating over all frailty. Conditional predictions can be used when the new individual belongs to a cluster used to develop the model.

$$S_i^*(t) = [1 + \theta^{-1} e^{\beta x_{ij}} H_0(t)]^{-\theta}$$

Load packages

The following libraries are needed to achieve the following goals, if you have not them installed, please use `install.packages('')` (e.g. `install.packages('survival')`) or use the user-friendly approach if you are using RStudio.

```
# Use pacman to check whether packages are installed, if not load
if (!require("pacman")) install.packages("pacman")
library(pacman)

pacman::p_load(
  rio,
  stringr,
  knitr,
  kableExtra,
  Hmisc,
  lattice,
  riskRegression,
  polspline,
  gtsummary,
  tidyverse,
  grid,
  gridExtra,
  webshot,
  plotly,
  ggplot2,
  ggpubr,
  patchwork,
  rms,
  webshot2,
  parfm,
  frailtyHL
)
```

Import useful functions

We import useful functions

```
# Useful functions
source(here::here("Functions/predict.coxph.gammafrail.R"))
```

```

#' @description
#'
#' Function to estimate conditional and marginal
#' survival probabilities at specified time horizons
#' for shared Gamma frailty Cox proportional hazards models
#'
#' @author Daniele Giardiello
#' @param model cox model using survival::coxph including frailty gamma term
#' The event of interest must have the indicator variable equal to 1.
#' The model survival::coxph() must specify y = T survival::coxph(..., y = T)
#' The user must define a reference value
#' for all predictors, especially the continuous predictors
#' Example: age50 = age - 50 or age_c = age - mean(age)
#' Then "the baseline" corresponds to a subject with
#' the specified reference predictors values.
#' Ties/methods must be "breslow".
#' @param newdata newdata (for validation).
#' This should have the same variables of the model.
#' Predictors with levels should be coded
#' with exactly the same way and levels of the predictors
#' with factors used to develop the model
#' @param cluster cluster variable. Only one variable possible
#' @param times prediction horizon time(s)
#' @examples
#' # example code
#' data(lung, package = "survival")
#' lung$age_c <- lung$age - mean(lung$age)
#' cox_frailty_lung <- survival::coxph(Surv(time, status) ~ age_c + frailty(inst,
#' distribution = "gamma"),
#' data = lung,
#' x = TRUE,
#' y = TRUE,
#' model = TRUE,
#' ties = "breslow")
#' predict.coxph.gammafrail(model = cox_frailty_lung,
#' newdata = lung_sel,
#' cluster = "inst",
#' times = c(100, 200, 300))
#' @references Collett D - Modelling Survival data in Medical Research,
#' 4th edition chapter 10 (formula 10.9 and 10.12)

# **Disclaimers**
# 1. The current functions provided the conditional estimated
# predictions using the shared gamma frailty Cox model using
# survival::coxph.
# Left-truncation, non-linear terms and stratification terms
# have not been implemented and tested yet.

# 2. Marginal prediction estimation are still
# experimental. We do not advice to use it yet.
# Your suggestions to improve the function are kindly and warmly welcome.

```

```

predict.coxph.gammafrail <- function(model,
                                      newdata,
                                      cluster,
                                      times) {

  # sanity check message warning
  on.exit(base::message(
    Sanity check warning:
    please center all variables before fitting the model or assign reference values
    for continuous variable.
    For example age50 = age - 50.
    newdata should contain the centered/referenced values"))

  # Stopping messages
  if (!inherits(model, "coxph"))
    stop("`model` must be a survival::coxph fit.
      The model must specify y = T and Breslow method.
      Please center all variables before fitting the model or assign reference values
      for continuous variable. For example age50 = age - 50")

  if (missing(cluster))
    stop("Please supply the name of the cluster variable (character).")

  if (!is.character(cluster) || length(cluster) != 1L)
    stop("`cluster` must be a single character string giving the cluster column name.")

  if (!cluster %in% names(newdata))
    stop("`cluster` not found in `newdata`.")

  # Start function ----
  # Step0:
  # Formula with all terms including cluster as it is a fixed covariate
  frm_allterms <- reformulate(base::all.vars(model$formula[[3]]))

  # Select the complete cases of fixed + frailty terms
  # of the development data
  # (same data used to develop the model)
  # The argument survival::coxph(..., x = T) provides
  # the development data
  # NOTE: the development data is necessary to
  # estimate the "baseline" (cumulative) hazard H0 later

  devdata <- stats::model.frame(frm_allterms,
                                 data = base::eval(model$call$data,
                                                   envir = environment(formula(model))),
                                 # NOTE: data.frame(model$x) did not
                                 # provide the same variable names
                                 # (e.g. frailty(id_cluster) instead of id_cluster)
                                 # Alternative: add devdata as a new argument of the
                                 # function.
                                 # The alternative option is probably the most
                                 # intuitive
}

```

```

    na.action = na.omit) # not sure if necessary but safer

# Select only the complete cases of fixed + frailty terms
# of the newdata

newdata <- stats::model.frame(frm_allterms,
                               data = newdata,
                               na.action = na.omit)

# Step 1: survfit for
# a baseline cumulative hazard / survival

# Survfit of the coxph with frailty
# sf_model <- survival::survfit(model)

# NOTE: the survival::survfit with frailty does not accept newdata
# thus, it is important to center all variables or give them a reference.
# In this setting survfit$cumhaz will directly represent our baseline

# NOTE: [20251029]: survfit() with frailty with no newdata
# seems not to include the frailty terms in the "baseline"
# cumulative hazard estimation for a reference subject

# Step 1: linear predictors of fixed effects

# Estimate linear predictors only
# for fixed-effect effects without frailties
# This will be also useful later when
# marginal predictions are estimated

# Since with clusters size < vs >= 5
# frailty terms are treated as coefficients or not,
# I prefer calculate lp for the only fixed terms only manually

# lp calculation for marginal
# save all model coefficients
# for cluster < 5, frailty terms are included in coefficients (not practical)
coefs <- model$coefficients

# Remove frailty named "gamma"
# NOTE/WARNING:
# if a variables called gamma it must be a problem
# to be adjusted
coefs_fixed <- coefs[!base::grepl("gamma", names(coefs))]

# create formula of fixed terms only
terms_vec <- attr(terms(model$formula),
                   "term.labels")

# Remove specials using grep/grep
# NOTE: working in progress

```

```

specials <- c("frailty", "strata", "cluster", "offset", "tt")
fixed_terms <- terms_vec[!grepl(paste(specials, collapse = "|"), terms_vec)]


formula_fixed <- stats::reformulate(fixed_terms,
                                      response = NULL)

# create design matrix of fixed term only
# of the new data
X_fixed <- model.matrix(formula_fixed,
                         newdata)

X_fixed <- X_fixed[, colnames(X_fixed) != "(Intercept)"]

# estimate linear predictor X*beta fixed term only
lp_fixed <- X_fixed %*% cbind(coefs_fixed)

# this should be equivalent to this (when cluster > 5)
# lp_nofrail <- cbind(predict(model,
#
#                               newdata = newdata,
#
#                               type = "lp"))

# create design matrix of fixed term only
# of the development data
# (data used to develop the model)
# useful to estimate the "baseline" cumulative hazard
X_fixed_dev <- model.matrix(formula_fixed,
                             devdata)

X_fixed_dev <- X_fixed_dev[, colnames(X_fixed_dev) != "(Intercept)"]

# estimate linear predictor X*beta fixed term only
lp_fixed_dev <- X_fixed_dev %*% cbind(coefs_fixed)

# Step 2: linear predictors for frailty terms

# NOTE/WARNING:
# for cluster < 5 predict.coxph(model, newdata) includes also frailty
# and frailty terms must not be included for marginal predictions.
# This leads to wrong estimations of marginal predictions
# and the corresponding performance metrics in riskRegression::Score()

# For frailty with not model$frail (where clusters < 5)
# add the model$frail and keep only fixed-effect coefficients
if(is.null(model$frail)) {
  coefs_model <- model$coefficients
  model$frail <- unname(coefs_model[base::grep("gamma", names(coefs_model))])
}

# Force cluster as a factor in the newdata
# number of clusters in the newdata

```

```

# otherwise a factor
# NOTE: for newdata with one cluster, factor does not work
# newdata[[cluster]] <- base::as.character(newdata[[cluster]])

# newdata
newdata[[cluster]] <- base::factor(newdata[[cluster]],
                                     levels = unique(newdata[[cluster]]))

# development data
devdata[[cluster]] <- base::factor(devdata[[cluster]],
                                     levels = unique(devdata[[cluster]]))

# newdata[[cluster]] <- base::factor(newdata[[cluster]],
#                                     levels = 1:length(model$frail))

# Create the design matrix for frailty terms
all_terms <- base::all.vars(model$formula[[3]])
frailty_terms <- c(-1, all_terms[all_terms == cluster])

# design matrix for the frailty terms
# of the new data
X_frail <- stats::model.matrix(stats::reformulate(frailty_terms),
                                 response = NULL,
                                 data = newdata)

# design matrix for the frailty terms
# of the development data (data used to develop the model)
# useful to estimate the "baseline" cumulative hazard H0
X_frail_dev <- stats::model.matrix(stats::reformulate(frailty_terms),
                                      response = NULL,
                                      data = devdata)

# Frailty terms linear predictors
# new data
lp_frail <- X_frail %*% cbind(model$frail)

# Frailty terms linear predictors
# development data
lp_frail_dev <- X_frail_dev %*% cbind(model$frail)

# Total linear predictor
# new data
lp_total <- lp_fixed + lp_frail

# Total linear predictor
# development data
lp_total_dev <- lp_fixed_dev + lp_frail_dev

# Step 3:
# estimate the "baseline" cumulative hazard
# for a reference subject
# NOTE: we use the development data
# NOTE: recalibration might be possible using

```

```

# the linear predictors (lp) of the development data
# but the risk setting of the newdata (i.e., validation)
# It might be considered as future developments

risk_dev <- exp(lp_total_dev) # exp(lp + frailty)

# Unique event times of the
# model fitted using the development data

model_times <- model$y[, "time"] # event time for development data
model_status <- model$y[, "status"] # event indicator for development data

# NOTE: the object model must specify y = T
# Example: survival::coxph(..., y = T)
# NOTE: status == 1 must be the event of reference

# Extract the unique event time
# from the development data
# used to develop the model
unique_event_times <- sort(unique(model_times[model_status == 1]))
n_times <- length(unique_event_times)

# Initialize vectors
h0 <- numeric(n_times)      # incremental baseline hazard
d_i <- numeric(n_times)     # number of events at each time

for (i in seq_along(unique_event_times)) {
  t <- unique_event_times[i]
  d_i[i] <- sum(model_status[model_times == t])

  # Risk set: all individuals still at risk at time t
  risk_set <- which(model_times >= t)

  # Breslow baseline hazard
  h0[i] <- d_i[i] / sum(risk_dev[risk_set])
}

# Cumulative "baseline" hazard
# Create the sf model
H0 <- cumsum(h0)

# Cumulative hazards
# at fixed time horizons
# H_0(t)
cumhaz0_thor <- stats::approx(
  x = unique_event_times,
  y = H0,
  yleft = 0, # y values below min(x). Cumulative hazard zero if below min(time)
  yright = NA, # y values above max(x). Cumulative hazard NA if above max(time)
  xout = times,
  method = "constant",
  f = 0,
  rule = 1)$y

```

```

# NOTE:
# stats::approx should work fine since
# all values from survival::survfit are unique
# for the event time of development data

#  $H(t)$  using the newdata (i.e., validation data)
cumhaz_thor <- exp(lp_total) %*% cumhaz0_thor

# conditional  $S(t)$ 
S_cond_t <- exp(-cumhaz_thor)

# marginal  $S(t)$ 
# NOTE: marginal predictions needs
# to be further investigated
# to check if they are corrected
#
# NOTE/QUESTION
# does the marginal use the baseline hazard including the frailty terms?

theta_hat <- model$history[[1]]$theta
S_marg_t <- (1 + theta_hat * (exp(lp_fixed) %*% cumhaz0_thor))^{(-1/theta_hat)}

# Output
# NOTE: to be better defined
res <- list("conditional" = S_cond_t,
            "marginal" = S_marg_t)

return(res)
# Report only conditional predictions
# return(S_cond_t)

}

# smoothed calibration function

calhaz_map <- function(time,
                        status,
                        covariates,
                        t_hors,
                        predictions) {

tryCatch(
{

# Hazard regression
calhaz_mod <- polspline::hare(data = time,
                                 delta = status,
                                 cov = covariates)

# estimated cumulative probability
pred_calhaz <- polspline::phare(t_hors,
                                  cov = covariates,

```

```

            fit = calhaz_mod)

# ICI/E50/E90
ICI <- mean(abs(pred_calhaz - predictions),
na.rm = T)

E50 <- median(abs(pred_calhaz - predictions),
na.rm = T)

E90 <- quantile(abs(pred_calhaz - predictions),
probs = .90,
na.rm = T)

res <- c(ICI, E50, E90)
res},

error = function(msg) {
  message(paste("Calibration not possible"))
  rep(NA, 3)})

}

```

Import data

Insem data can be imported using the `parfm` R package. We also saved insem data in our repository in the `.rds` format.

```

# Import from the repository
# insem <- readRDS(here::here("Data/insem.rds"))

# Import from parf package
data(insem,
     package = "parfm")

```

1. Descriptive statistics

We provide some descriptive statistics of the case study

```
insem_tab_01 <-
  insem %>%
  dplyr::select(Urem,
    Protein,
    Parity,
    Heifer,
    Status)

label(insem_tab_01$Urem) <- "Milk urem concentration (%) at the start of the
lactation period"
label(insem_tab_01$Protein) <- "Protein concentration (%) at the start of the
lactation period"
label(insem_tab_01$Parity) <- "The number of calvings"
label(insem_tab_01$Heifer) <- "Primiparous cow"
label(insem_tab_01$Status) <- "Inseminated cow"

units(insem_tab_01$Urem) <- "%"
units(insem_tab_01$Protein) <- "%"

gtsummary_table1 <-
  gtsummary::tbl_summary(
    data = insem_tab_01 ,
    label = list(Parity ~ "Number of calvings",
                Heifer ~ "Primiparous cow",
                Urem ~ "Milk urem concentration (%) ",
                Protein ~ "Protein concentration (%)",
                Status ~ "Inseminated cows"),
    type = all_continuous() ~ "continuous2",
    statistic = all_continuous() ~ c(
      "{mean} ({sd})",
      "{median} ({min}, {max})"
    ),
  )
)

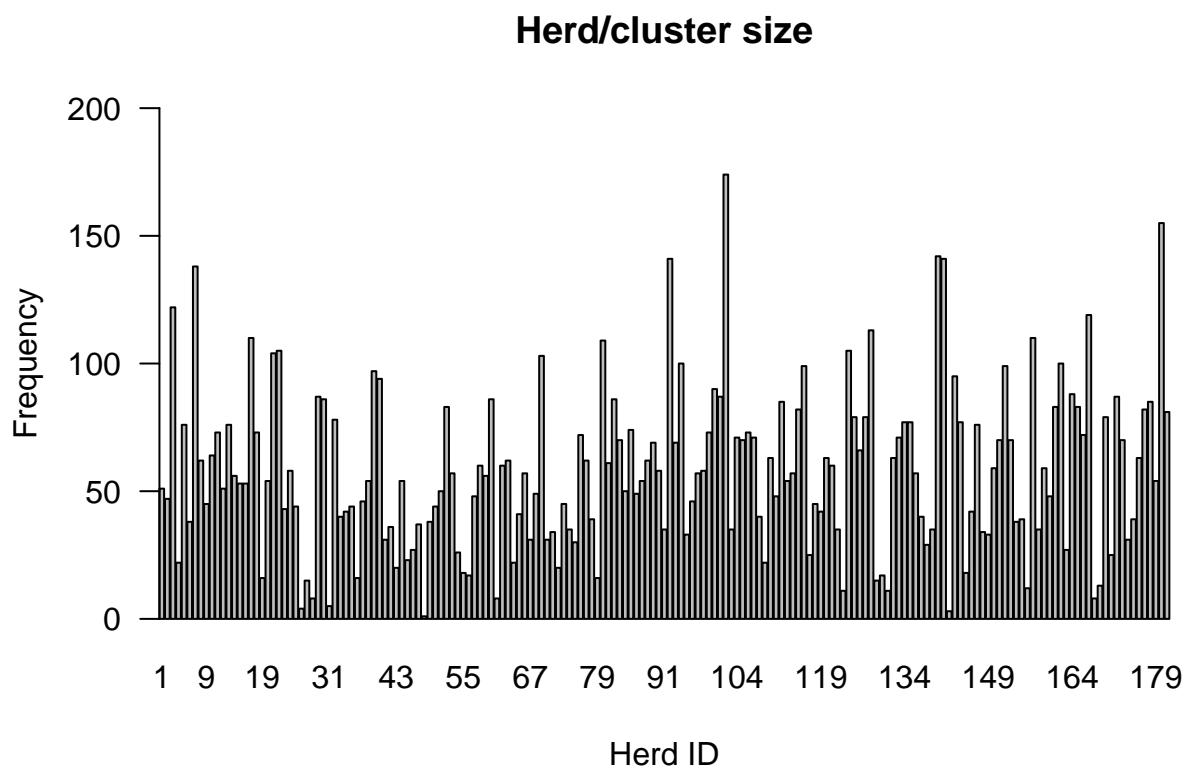
gtsummary_table1 %>%
  gtsummary::as_gt()
```

```
# Cluster size distribution
table_cluster <-
  insem %>%
  dplyr::group_by(Herd) %>%
  dplyr::summarise(n = n()) %>%
  dplyr::arrange(n)

par(xaxs = "i",
  yaxs = "i",
  las = 1)
barplot(table(insem$Herd),
  ylab = "Frequency",
  xlab = "Herd ID",
  ylim = c(0, 200),
```

Characteristic	N = 10,513 ¹
Milk urem concentration (%)	
Mean (SD)	2.58 (0.74)
Median (Range)	2.55 (0.54, 8.24)
Protein concentration (%)	
Mean (SD)	3.25 (0.34)
Median (Range)	3.21 (2.25, 6.48)
Number of calvings	
Mean (SD)	2 (2)
Median (Range)	2 (1, 14)
Primiparous cow	4,200 (40%)
Inseminated cows	9,939 (95%)
¹ n (%)	

```
main = "Herd/cluster size")
```



```
# kable(table_cluster) %>%
#   kableExtra::kable_styling("striped",
#                           position = "center") %>%
#   kableExtra::add_header_above(
#     c("Cluster size distribution" = 2))
```

```

# Summary cluster size
summary_cluster <-
  table_cluster %>%
  dplyr::summarise(min = min(n),
                    q25 = quantile(n, probs = .25),
                    mean = mean(n),
                    sd = sd(n),
                    median = median(n),
                    q75 = quantile(n, probs = .75),
                    max = max(n)) %>%
  round(., 1)

kable(summary_cluster) %>%
  kableExtra::kable_styling("striped") %>%
  kableExtra::add_header_above(
    c("Cluster size statistics" = 7))

```

Cluster size statistics						
min	q25	mean	sd	median	q75	max
1	35	58.1	31.8	56	77	174

```

# Event distribution per cluster
# kable(
#   addmargins(
#     table(insem$Herd,
#           insem$status,
#           useNA = "ifany",
#           dnn = c("Cluster",
#                  "Status")))) %>%
#   kableExtra::kable_styling("striped") %>%
#   kableExtra::add_header_above(
#     c("Cluster" = 1,
#       "Status" = 2,
#       "Sum" = 1))

# survfit
sf_overall <- survival::survfit(Surv(Time,
                                         Status) ~ 1,
                                         data = insem)

sf_cluster <- survival::survfit(Surv(Time,
                                         Status) ~ Herd,
                                         data = insem)

par(xaxs = "i",
     yaxs = "i",
     las = 1)
plot(sf_cluster,
      col = "gray",
      fun = "event",

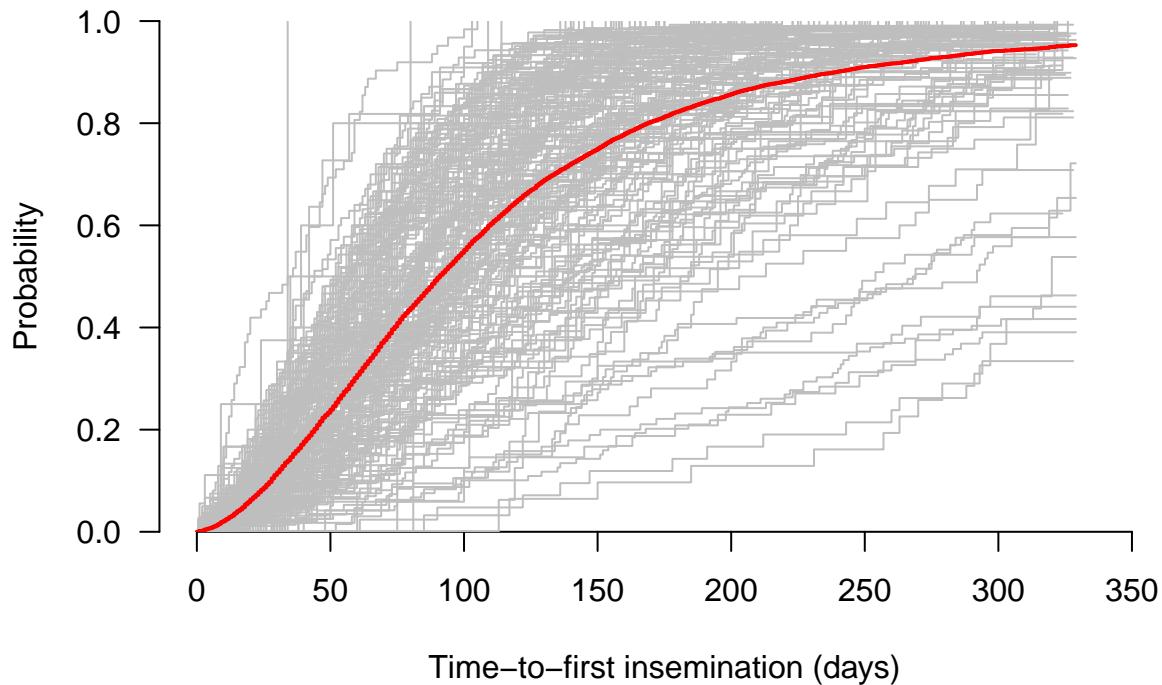
```

```

xlim = c(0, 350),
ylim = c(0, 1),
bty = "n",
xlab = "Time-to-first insemination (days)",
ylab = "Probability",
main = "Overall and by herds inverted Kaplan-Meier curves")
lines(sf_overall,
      fun = "event",
      lwd = 2,
      col = "red",
      conf.int = FALSE)

```

Overall and by herds inverted Kaplan–Meier curves



```

# Time quantiles
q_overall <- quantile(sf_overall,
                      probs = c(.25, .50, .75))$quantile
q_cluster <-
  quantile(sf_cluster,
           probs = c(.25, .50, .75))$quantile

q_surv <- rbind.data.frame("Overall" = q_overall,
                           q_cluster)

kable(q_surv[1, ]) %>%
  kableExtra::kable_styling("striped",
                           position = "center") %>%
  kableExtra::add_header_above(

```

```
c(" " = 1,
  "Time quantile" = 3))
```

	Time quantile		
	25	50	75
Overall	52	91	150

2. Analysis

We provide the accuracy of predictions from the stratified and the shared gamma frailty Cox proportional hazards models in two scenarios

- Small cluster scenario: it includes herds with less than 50 cows
- Large cluster scenario: it includes herds with at least 50 cows

The accuracy of predictions are evaluated in terms of:

- Discrimination using time-varying AUC
- Calibration using O/E ratio, integrated calibration index (ICI), E50 and E90
- Overall performance using time-varying Index of Prediction Accuracy (IPA)

We use the Monte Carlo cross-validation procedure to assess prediction performances of the stratified and frailty Cox model.

- The sample was split into two parts to define derivation (70%) and validation samples (30%)
- The 70/30% random splits are repeated 100 times
- The repeated random splits are stratified by herds(i.e., the cluster) to obtain the same herds in both the derivation and validation samples

We excluded herds with less than 10 cows since it was not possible to obtain sufficient cows in both derivation and validation sample.

The mean of the performances metrics across the 100 random validation samples with the corresponding standard deviation are reported for each scenario and at each prediction time horizon to assess the prediction performances of the stratified and the frailty Cox models.

The fixed time horizons are defined based on the 25th, 50th and 75th quantile fo event time overall distribution using the Kaplan-Meier distribution which corresponds to 51, 91, 150 days, respectively.

```

# time horizons
time_hors <- c(52, 91, 150)

# reference values for continuous
# predictors
insem_ref <-
  insem %>%
  dplyr::mutate(
    Ureum_ref = Ureum - 2.5,
    Protein_ref = Protein - 2.5,
    Parity_ref = Parity - 2.5)

# Herds >= 50 cows
table_insem_small <-
  insem_ref %>%
  dplyr::count(Herd) %>%
  dplyr::filter(n < 50 & n >= 10)

df_insem_small <-
  insem_ref %>%
  dplyr::filter(Herd %in% table_insem_small$Herd)

# Repeat B times
B <- 110
df_tbl_insem_ext <- do.call(rbind,
  lapply(seq(1:B),
    function(k) {
      cbind(id = k, df_insem_small)}))

# Nested tibble
set.seed(20250924)
df_tbl_insem <-
  df_tbl_insem_ext %>%
  dplyr::group_nest(id) %>%
  dplyr::mutate(
    # Splitting
    split = purrr::map(.x = data,
      ~ rsample::initial_split(.x,
        strata = Herd,
        prop = 0.7,
        pool = 0.001)),
    # Development
    development = purrr::map(.x = split,
      ~ rsample::training(.x)),
    # Validation
    validation = purrr::map(.x = split,
      ~ rsample::testing(.x)),
    # Check
    unique_cluster_dev = purrr::map(.x = development,
      ~ unique(.x$Herd)),
```

```

unique_cluster_val = purrr::map(.x = validation,
~ unique(.x$Herd)),

check = purrr::map2(.x = unique_cluster_dev,
.y = unique_cluster_val,
~ all.equal(.x, .y))

# table(do.call(rbind, df_tbl_insem$check))
rm(df_tbl_insem_ext)
# gc()
# check
# table(do.call(rbind, df_tbl_insem$check))
# all TRUE

# Rewrite B
B <- 100

# Models + predictions + performances
# tictoc::tic()
df_tbl_insem <-
df_tbl_insem %>%
dplyr::filter(check == TRUE) %>%
dplyr::select(data,
development,
validation) %>%

dplyr::mutate(
cox_strat = purrr::map(.x = development,
~ survival::coxph(Surv(Time, Status) ~
Heifer +
Parity_ref +
Ureum_ref +
Protein_ref +
strata(Herd),
data = .x,
x = T,
y = T,
ties = "breslow")),

cox_frail = purrr::map(.x = development,
~ survival::coxph(Surv(Time, Status) ~
Heifer +
Parity_ref +
Ureum_ref +
Protein_ref +
frailty(Herd),
data = .x,
x = T,
y = T,
ties = "breslow")),

# predictions at t25/t50/t75

```

```

# stratified cox
pred_strat = purrr::map2(.x = cox_strat,
                         .y = validation,
                         ~ 1 - pec::predictSurvProb(.x,
                                                     newdata = .y,
                                                     times = time_hors)),
# Extremes to make calibration suitable
pred_strat = purrr::map(pred_strat,
                        function(x) {
                          x <- ifelse(x == 0, 0.000001, x)
                          x <- ifelse(x == 1, 0.999999, x)
                        x}),

# separate prediction by time horizons
# due to possible missing values
pred_strat_t25 = purrr::map(.x = pred_strat,
                            ~ .x[, 1]),

pred_strat_t50 = purrr::map(.x = pred_strat,
                            ~ .x[, 2]),

pred_strat_t75 = purrr::map(.x = pred_strat,
                            ~ .x[, 3]),

pred_frail = purrr::map2(.x = cox_frail,
                         .y = validation,
                         ~ 1 - predict.coxph.gammafrail.dev(model = .x,
                                                     newdata = .y,
                                                     cluster = "Herd",
                                                     times = time_hors)$conditional),
# Extremes to make calibration suitable
pred_frail = purrr::map(pred_frail,
                        function(x) {
                          x <- ifelse(x == 0, 0.000001, x)
                          x <- ifelse(x == 1, 0.999999, x)
                        x}),

# Score at t25/t50/t75 - frail
score_frail = purrr::map2(.x = pred_frail,
                           .y = validation,
                           ~ riskRegression::Score(
                             list("frail" = .x),
                             data = .y,
                             formula = Surv(Time, Status) ~ 1,
                             metrics = "auc",
                             summary = "ipa",
                             times = time_hors)),

# save results score - frail
score_frail_res = purrr::map(score_frail,
                              function(x) {

                                res_AUC <-

```

```

x$AUC$score %>%
  dplyr::select(model, times, AUC)

res_IPA <-
  x$Brier$score %>%
  dplyr::select(model, times, IPA) %>%
  dplyr::filter(model %in% c("Null model"))

res <- cbind(res_AUC,
              "IPA" = res_IPA$IPA)

return(res)
}),

# Score at t25 - strata
score_strat_t25 = purrr::pmap(
  list(predictions = pred_strat_t25,
        df = validation,
        frm = list(as.formula(Surv(Time, Status) ~ 1)),
        t_hors = list(time_hors[1])),
  Score_tryCatch),

# Score at t50 - strata
score_strat_t50 = purrr::pmap(
  list(predictions = pred_strat_t50,
        df = validation,
        frm = list(as.formula(Surv(Time, Status) ~ 1)),
        t_hors = list(time_hors[2])),
  Score_tryCatch),

# Score at t75 - strata
score_strat_t75 = purrr::pmap(
  list(predictions = pred_strat_t75,
        df = validation,
        frm = list(as.formula(Surv(Time, Status) ~ 1)),
        t_hors = list(time_hors[3])),
  Score_tryCatch),

# cloglog
# cloglog - strat
cloglog_pred_strat = purrr::map(pred_strat,
  function(x) {
    apply(x, 2, function(y) {
      log(-log(1 - y))
    })
  }),
}

# cloglog - strat t25/t50/t75
cloglog_pred_strat_t25 = purrr::map(.x = cloglog_pred_strat,
                                     ~ .x[, 1]),

```

```

cloglog_pred_strat_t50 = purrr::map(.x = cloglog_pred_strat,
~ .x[, 2]),

cloglog_pred_strat_t75 = purrr::map(.x = cloglog_pred_strat,
~ .x[, 3]),

# cloglog
# cloglog - frail
cloglog_pred_frail = purrr::map(pred_frail,
  function(x) {
    apply(x, 2, function(y) {
      log(-log(1 - y))
    })
  }),
# cloglog - frail t25/t50/t75
cloglog_pred_frail_t25 = purrr::map(.x = cloglog_pred_frail,
~ .x[, 1]),

cloglog_pred_frail_t50 = purrr::map(.x = cloglog_pred_frail,
~ .x[, 2]),

cloglog_pred_frail_t75 = purrr::map(.x = cloglog_pred_frail,
~ .x[, 3]),

# average expected risk
pred_avg_strat = purrr::map(pred_strat,
  function(x){
    apply(x, 2, mean)
  }),

pred_avg_frail = purrr::map(pred_frail,
  function(x) {
    apply(x, 2, mean)
  }),

# estimated actual risk (estimated obs proportion, observed)
sf_obs = purrr::map(validation,
  function(x) {
    sf_sum <-
      summary(survival::survfit(Surv(Time, Status) ~ 1,
        data = x),
        extend = TRUE,
        times = time_hors)

    sf_sum$surv[sf_sum$n.risk == 0] <- NA
    sf_obs_event <- 1 - sf_sum$surv}),
  }

# calibration

# OE ratio - strat
OE_strat = purrr::map2(.x = sf_obs,
.y = pred_avg_strat,

```

```

~ .x / .y) ,

# OE ratio - frail
OE_frail = purrr::map2(.x = sf_obs,
                        .y = pred_avg_frail,
                        ~ .x / .y) ,

# ICI/E50/E90 - frail t25
cal_meas_frail_t25 = purrr::pmap(
  list(time = purrr::map(validation, ~ .x$Time),
       status = purrr::map(validation, ~ .x$status),
       covariates = cloglog_pred_frail_t25,
       t_hors = list(time_hors[1]),
       predictions = purrr::map(pred_frail, ~ .x[, 1])),
  calhaz_map) ,

# ICI/E50/E90 - frail t50
cal_meas_frail_t50 = purrr::pmap(
  list(time = purrr::map(validation, ~ .x$Time),
       status = purrr::map(validation, ~ .x$status),
       covariates = cloglog_pred_frail_t50,
       t_hors = list(time_hors[2]),
       predictions = purrr::map(pred_frail, ~ .x[, 2])),
  calhaz_map) ,

# ICI/E50/E90 - frail t75
cal_meas_frail_t75 = purrr::pmap(
  list(time = purrr::map(validation, ~ .x$Time),
       status = purrr::map(validation, ~ .x$status),
       covariates = cloglog_pred_frail_t75,
       t_hors = list(time_hors[3]),
       predictions = purrr::map(pred_frail, ~ .x[, 3])),
  calhaz_map) ,

# stratify
# ICI/E50/E90 - strat t25
cal_meas_strat_t25 = purrr::pmap(
  list(time = purrr::map(validation, ~ .x$Time),
       status = purrr::map(validation, ~ .x$status),
       covariates = cloglog_pred_strat_t25,
       t_hors = list(time_hors[1]),
       predictions = purrr::map(pred_strat, ~ .x[, 1])),
  calhaz_map) ,

# ICI/E50/E90 - strat t50
cal_meas_strat_t50 = purrr::pmap(
  list(time = purrr::map(validation, ~ .x$Time),
       status = purrr::map(validation, ~ .x$status),
       covariates = cloglog_pred_strat_t50,
       t_hors = list(time_hors[2]),
       predictions = purrr::map(pred_strat, ~ .x[, 2])),
  calhaz_map) ,

```

```

# ICI/E50/E90 - strat t75
cal_meas_strat_t75 = purrr::pmap(
  list(time = purrr::map(validation, ~ .x$Time),
       status = purrr::map(validation, ~ .x>Status),
       covariates = cloglog_pred_strat_t75,
       t_hors = list(time_hors[3]),
       predictions = purrr::map(pred_strat, ~ .x[, 3])),
  calhaz_map)

# tictoc::toc()

```

2.1 Small cluster size

Small cluster scenario							
model	times	pct_comp	AUC		IPA		
			AUC_mean	AUC_sd	IPA_mean	IPA_sd	
frail	52	100	0.688	0.015	0.075	0.016	
strat	52	95	0.658	0.015	0.039	0.021	
frail	91	100	0.730	0.016	0.161	0.024	
strat	91	78	0.723	0.016	0.146	0.026	
frail	150	100	0.813	0.016	0.262	0.033	

Small cluster scenario				
O-E ratio				
model	times	pct_comp	OE_ratio	
			OE_ratio_mean	OE_ratio_sd
frail	52	100	0.994	0.055
strat	52	95	1.024	0.087
frail	91	100	0.999	0.059
strat	91	78	1.023	0.045
frail	150	100	0.987	0.056

Small cluster scenario								
model	times	pct_comp	ICI		E50		E90	
			ICI_mean	ICI_sd	E50_mean	E50_sd	E90_mean	E90_sd
frail	52	100	0.025	0.013	0.023	0.013	0.046	0.013
strat	52	95	0.037	0.011	0.032	0.013	0.071	0.013
frail	91	100	0.022	0.011	0.021	0.011	0.038	0.011
strat	91	78	0.037	0.014	0.033	0.014	0.064	0.014
frail	150	100	0.022	0.011	0.020	0.011	0.039	0.011

```

# time horizons
time_hors <- c(52, 91, 150)

# reference values for continuous
# predictors
insem_ref <-
  insem %>%
  dplyr::mutate(
    Ureum_ref = Ureum - 2.5,
    Protein_ref = Protein - 2.5,
    Parity_ref = Parity - 2.5)

# Herds >= 50 cows
table_insem_large <-
  insem_ref %>%
  dplyr::count(Herd) %>%
  dplyr::filter(n >= 50)

df_insem_large <-
  insem_ref %>%
  dplyr::filter(Herd %in% table_insem_large$Herd)

# Repeat B times
B <- 100
df_tbl_insem_ext <- do.call(rbind,
  lapply(seq(1:B),
    function(k) {
      cbind(id = k, df_insem_large)}))

# Nested tibble
set.seed(20250924)
df_tbl_insem <-
  df_tbl_insem_ext %>%
  dplyr::group_nest(id) %>%
  dplyr::mutate(
    # Splitting
    split = purrr::map(.x = data,
      ~ rsample::initial_split(.x,
        strata = Herd,
        prop = 0.7)),
    # Development
    development = purrr::map(.x = split,
      ~ rsample::training(.x)),
    # Validation
    validation = purrr::map(.x = split,
      ~ rsample::testing(.x)),
    # Check
    unique_cluster_dev = purrr::map(.x = development,
      ~ unique(.x$Herd)),
```

```

unique_cluster_val = purrr::map(.x = validation,
                                ~ unique(.x$Herd)),

check = purrr::map2(.x = unique_cluster_dev,
                    .y = unique_cluster_val,
                    ~ all.equal(.x, .y))

rm(df_tbl_insem_ext)
# gc()
# check
# table(do.call(rbind, df_tbl_insem$check))
# all TRUE

# Models + predictions + performances
# tictoc::tic()
df_tbl_insem <-
  df_tbl_insem %>%
  dplyr::select(data,
                development,
                validation) %>%

dplyr::mutate(
  cox_strat = purrr::map(.x = development,
                         ~ survival::coxph(Surv(Time, Status) ~
                                         Heifer +
                                         Parity_ref +
                                         Ureum_ref +
                                         Protein_ref +
                                         strata(Herd),
                                         data = .x,
                                         x = T,
                                         y = T,
                                         ties = "breslow")),,

cox_frail = purrr::map(.x = development,
                      ~ survival::coxph(Surv(Time, Status) ~
                                         Heifer +
                                         Parity_ref +
                                         Ureum_ref +
                                         Protein_ref +
                                         frailty(Herd),
                                         data = .x,
                                         x = T,
                                         y = T,
                                         ties = "breslow")),,

# predictions at t25/t50/t75
# stratified cox
pred_strat = purrr::map2(.x = cox_strat,
                        .y = validation,
                        ~ 1 - pec::predictSurvProb(.x,

```

```

newdata = .y,
times = time_hors)),

# Extremes to make calibration suitable
pred_strat = purrr::map(pred_strat,
  function(x) {
    x <- ifelse(x == 0, 0.000001, x)
    x <- ifelse(x == 1, 0.999999, x)
    x}),
  }

# separate prediction by time horizons
# due to possible missing values
pred_strat_t25 = purrr::map(.x = pred_strat,
  ~ .x[, 1]),

pred_strat_t50 = purrr::map(.x = pred_strat,
  ~ .x[, 2]),

pred_strat_t75 = purrr::map(.x = pred_strat,
  ~ .x[, 3]),

pred_frail = purrr::map2(.x = cox_frail,
  .y = validation,
  ~ 1 - predict.coxph.gammafrail.dev(model = .x,
  newdata = .y,
  cluster = "Herd",
  times = time_hors)$conditional),

# Extremes to make calibration suitable
pred_frail = purrr::map(pred_frail,
  function(x) {
    x <- ifelse(x == 0, 0.000001, x)
    x <- ifelse(x == 1, 0.999999, x)
    x}),
  }

# Score at t25/t50/t75 - frail
score_frail = purrr::map2(.x = pred_frail,
  .y = validation,
  ~ riskRegression::Score(
  list("frail" = .x),
  data = .y,
  formula = Surv(Time, Status) ~ 1,
  metrics = "auc",
  summary = "ipa",
  times = time_hors)),

# save results score - frail
score_frail_res = purrr::map(score_frail,
  function(x) {

    res_AUC <-
      x$AUC$score %>%
      dplyr::select(model, times, AUC)

    res_IPA <-
  })

```

```

x$Brier$score %>%
  dplyr::select(model, times, IPA) %>%
  dplyr::filter(model %in% c("Null model"))

res <- cbind(res_AUC,
             "IPA" = res_IPA$IPA)

return(res)
}),

# Score at t25 - strata
score_strat_t25 = purrr::pmap(
  list(predictions = pred_strat_t25,
       df = validation,
       frm = list(as.formula(Surv(Time, Status) ~ 1)),
       t_hors = list(time_hors[1])),
  Score_tryCatch),

# Score at t50 - strata
score_strat_t50 = purrr::pmap(
  list(predictions = pred_strat_t50,
       df = validation,
       frm = list(as.formula(Surv(Time, Status) ~ 1)),
       t_hors = list(time_hors[2])),
  Score_tryCatch),

# Score at t75 - strata
score_strat_t75 = purrr::pmap(
  list(predictions = pred_strat_t75,
       df = validation,
       frm = list(as.formula(Surv(Time, Status) ~ 1)),
       t_hors = list(time_hors[3])),
  Score_tryCatch),

# cloglog
# cloglog - strat
cloglog_pred_strat = purrr::map(pred_strat,
  function(x) {
    apply(x, 2, function(y) {
      log(-log(1 - y))
    })
  }),
}

# cloglog - strat t25/t50/t75
cloglog_pred_strat_t25 = purrr::map(.x = cloglog_pred_strat,
                                     ~ .x[, 1]),

cloglog_pred_strat_t50 = purrr::map(.x = cloglog_pred_strat,
                                     ~ .x[, 2]),

cloglog_pred_strat_t75 = purrr::map(.x = cloglog_pred_strat,
                                     ~ .x[, 3]),

```

```

~ .x[, 3]),

# cloglog
# cloglog - frail
cloglog_pred_frail = purrr::map(pred_frail,
  function(x) {
    apply(x, 2, function(y) {
      log(-log(1 - y))
    })
  }),
# cloglog - frail t25/t50/t75
cloglog_pred_frail_t25 = purrr::map(.x = cloglog_pred_frail,
~ .x[, 1]),

cloglog_pred_frail_t50 = purrr::map(.x = cloglog_pred_frail,
~ .x[, 2]),

cloglog_pred_frail_t75 = purrr::map(.x = cloglog_pred_frail,
~ .x[, 3]),

# average expected risk
pred_avg_strat = purrr::map(pred_strat,
  function(x){
    apply(x, 2, mean)
  }),

pred_avg_frail = purrr::map(pred_frail,
  function(x) {
    apply(x, 2, mean)
  }),

# estimated actual risk (estimated obs proportion, observed)
sf_obs = purrr::map(validation,
  function(x) {
    sf_sum <-
      summary(survival::survfit(Surv(Time, Status) ~ 1,
        data = x),
      extend = TRUE,
      times = time_hors)

    sf_sum$surv[sf_sum$n.risk == 0] <- NA
    sf_obs_event <- 1 - sf_sum$surv}),
  })

# calibration

# OE ratio - strat
OE_strat = purrr::map2(.x = sf_obs,
  .y = pred_avg_strat,
~ .x / .y),

# OE ratio - frail
OE_frail = purrr::map2(.x = sf_obs,

```

```

.y = pred_avg_frail,
~ .x / .y),

# ICI/E50/E90 - frail t25
cal_meas_frail_t25 = purrr::pmap(
  list(time = purrr::map(validation, ~ .x$Time),
       status = purrr::map(validation, ~ .x>Status),
       covariates = cloglog_pred_frail_t25,
       t_hors = list(time_hors[1]),
       predictions = purrr::map(pred_frail, ~ .x[, 1])),
  calhaz_map),

# ICI/E50/E90 - frail t50
cal_meas_frail_t50 = purrr::pmap(
  list(time = purrr::map(validation, ~ .x$Time),
       status = purrr::map(validation, ~ .x>Status),
       covariates = cloglog_pred_frail_t50,
       t_hors = list(time_hors[2]),
       predictions = purrr::map(pred_frail, ~ .x[, 2])),
  calhaz_map),

# ICI/E50/E90 - frail t75
cal_meas_frail_t75 = purrr::pmap(
  list(time = purrr::map(validation, ~ .x$Time),
       status = purrr::map(validation, ~ .x>Status),
       covariates = cloglog_pred_frail_t75,
       t_hors = list(time_hors[3]),
       predictions = purrr::map(pred_frail, ~ .x[, 3])),
  calhaz_map),

# stratify
# ICI/E50/E90 - strat t25
cal_meas_strat_t25 = purrr::pmap(
  list(time = purrr::map(validation, ~ .x$Time),
       status = purrr::map(validation, ~ .x>Status),
       covariates = cloglog_pred_strat_t25,
       t_hors = list(time_hors[1]),
       predictions = purrr::map(pred_strat, ~ .x[, 1])),
  calhaz_map),

# ICI/E50/E90 - strat t50
cal_meas_strat_t50 = purrr::pmap(
  list(time = purrr::map(validation, ~ .x$Time),
       status = purrr::map(validation, ~ .x>Status),
       covariates = cloglog_pred_strat_t50,
       t_hors = list(time_hors[2]),
       predictions = purrr::map(pred_strat, ~ .x[, 2])),
  calhaz_map),

# ICI/E50/E90 - strat t75
cal_meas_strat_t75 = purrr::pmap(
  list(time = purrr::map(validation, ~ .x$Time),
       status = purrr::map(validation, ~ .x>Status),

```

```

covariates = cloglog_pred_strat_t75,
t_hors = list(time_hors[3]),
predictions = purrr::map(pred_strat, ~ .x[, 3])),
calhaz_map))

# tictoc::toc()

```

2.2 Large cluster size

Large cluster scenario						
model	times	pct_comp	AUC		IPA	
			AUC_mean	AUC_sd	IPA_mean	IPA_sd
frail	52	100	0.670	0.010	0.068	0.009
strat	52	100	0.656	0.009	0.055	0.009
frail	91	100	0.706	0.008	0.130	0.011
strat	91	97	0.701	0.008	0.124	0.011
frail	150	100	0.776	0.010	0.201	0.017

Large cluster scenario				
O-E ratio				
model	times	pct_comp	OE_ratio_mean	OE_ratio_sd
frail	52	100	1.005	0.028
strat	52	100	1.015	0.045
frail	91	100	1.001	0.029
strat	91	97	1.011	0.024
frail	150	100	0.998	0.030

Large cluster scenario									
model	times	pct_comp	ICI		E50		E90		
			ICI_mean	ICI_sd	E50_mean	E50_sd	E90_mean	E90_sd	
frail	52	100	0.013	0.014	0.012	0.008	0.023	0.021	
strat	52	100	0.026	0.047	0.023	0.039	0.048	0.087	
frail	91	100	0.013	0.018	0.011	0.006	0.024	0.041	
strat	91	97	0.020	0.009	0.019	0.010	0.036	0.018	
frail	150	100	0.015	0.023	0.012	0.007	0.028	0.069	

3. Additional investigations

We additionally estimate predictions from the stratified and the shared gamma frailty Cox model using all data without splitting among clusters in which predictions were possible in both models.

We provide the corresponding plots of predictions at different time horizons from the stratified versus the shared gamma frailty model in the small and large cluster scenario.

```

# Herds < 50 (herds >= 10)
table_insem_small <-
  insem %>%
  dplyr::count(Herd) %>%

```

```

dplyr::filter(n < 50 & n >= 10)

# Herds >= 50 cows
table_insem_large <-
  insem %>%
  dplyr::count(Herd) %>%
  dplyr::filter(n >= 50)

df_insem <-
  insem %>%
  # dplyr::filter(Herd %in% table_insem_50$Herd) %>%
  # reference values for all continuous variable
  # to estimate predictions from frailty correctly
  dplyr::mutate(
    Ureum_ref = Ureum - 2.5,
    Protein_ref = Protein - 2.5,
    Parity_ref = Parity - 2.5)

# Small scenario overall data
df_insem_small <-
  df_insem %>%
  dplyr::filter(Herd %in% table_insem_small$Herd)

# Large scenario overall data
df_insem_large <-
  df_insem %>%
  dplyr::filter(Herd %in% table_insem_large$Herd)

# Stratified Cox - small
cox_strat_small <-
  survival::coxph(Surv(Time, Status) ~
    Heifer +
    Parity_ref +
    Ureum_ref +
    Protein_ref +
    strata(Herd),
    data = df_insem_small,
    x = T,
    y = T,
    ties = "breslow")

# Frailty Cox - small
cox_frail_small <-
  survival::coxph(Surv(Time, Status) ~
    Heifer +
    Parity_ref +
    Ureum_ref +
    Protein_ref +
    frailty(Herd),
    data = df_insem_small,
    x = T,
    y = T,
    ties = "breslow")

```

```

# Stratified Cox - large
cox_strat_large <-
  survival::coxph(Surv(Time, Status) ~
    Heifer +
    Parity_ref +
    Ureum_ref +
    Protein_ref +
    strata(Herd),
  data = df_insem_large,
  x = T,
  y = T,
  ties = "breslow")

# Frailty Cox - small
cox_frail_small <-
  survival::coxph(Surv(Time, Status) ~
    Heifer +
    Parity_ref +
    Ureum_ref +
    Protein_ref +
    frailty(Herd),
  data = df_insem_small,
  x = T,
  y = T,
  ties = "breslow")

## Predictions
# at 25th, 50th, 75th overall percentiles
time_hors <- c(52, 91, 150)
# time_hors <- q_surv[1, ]

# Predictions
# Stratified small
pred_strat_small <- 1 - pec::predictSurvProb(cox_strat_small,
                                               newdata = df_insem_small,
                                               times = time_hors)

# Frailty small
pred_frail_small <- 1 - predict.coxph.gammafrail.dev(model = cox_frail_small,
                                                       newdata = df_insem_small,
                                                       cluster = "Herd",
                                                       times = time_hors)$conditional

# Predictions
# Stratified large
pred_strat_large <- 1 - pec::predictSurvProb(cox_strat_large,
                                               newdata = df_insem_large,
                                               times = time_hors)

# Frailty large
pred_frail_large <- 1 - predict.coxph.gammafrail.dev(model = cox_frail_large,
                                                       newdata = df_insem_large,
                                                       cluster = "Herd",

```

```

times = time_hors)$conditional

# Plot predictions
# from stratify and frailty model

# Small scenario at T25, T50 and T75
oldpar <-
  par(
    mfrow = c(2, 3),
    xaxs = "i",
    yaxs = "i",
    las = 1)
plot(pred_strat_small[, 1],
      pred_frail_small[, 1],
      xlim = c(0, 1.2),
      xlab = expression("Predictions from stratified Cox at T"[25]),
      ylim = c(0, 1.2),
      ylab = expression("Predictions from frailty Cox at T"[25]),
      main = expression("Small case scenario at T"[25]),
      bty = "n")
abline(a = 0,
       b = 1,
       lwd = 2,
       col = "red")

par(xaxs = "i",
     yaxs = "i",
     las = 1)
plot(pred_strat_small[, 2],
      pred_frail_small[, 2],
      xlim = c(0, 1.2),
      xlab = expression("Predictions from stratified Cox at T"[50]),
      ylim = c(0, 1.2),
      ylab = expression("Predictions from frailty Cox at T"[50]),
      main = expression("Small case scenario at T"[50]),
      bty = "n")
abline(a = 0,
       b = 1,
       lwd = 2,
       col = "red")

par(xaxs = "i",
     yaxs = "i",
     las = 1)
plot(pred_strat_small[, 3],
      pred_frail_small[, 3],
      xlim = c(0, 1.2),
      xlab = expression("Predictions from stratified Cox at T"[75]),
      ylim = c(0, 1.2),
      ylab = expression("Predictions from frailty Cox at T"[75]),
      main = expression("Small case scenario at T"[75]),
      bty = "n")
abline(a = 0,

```

```

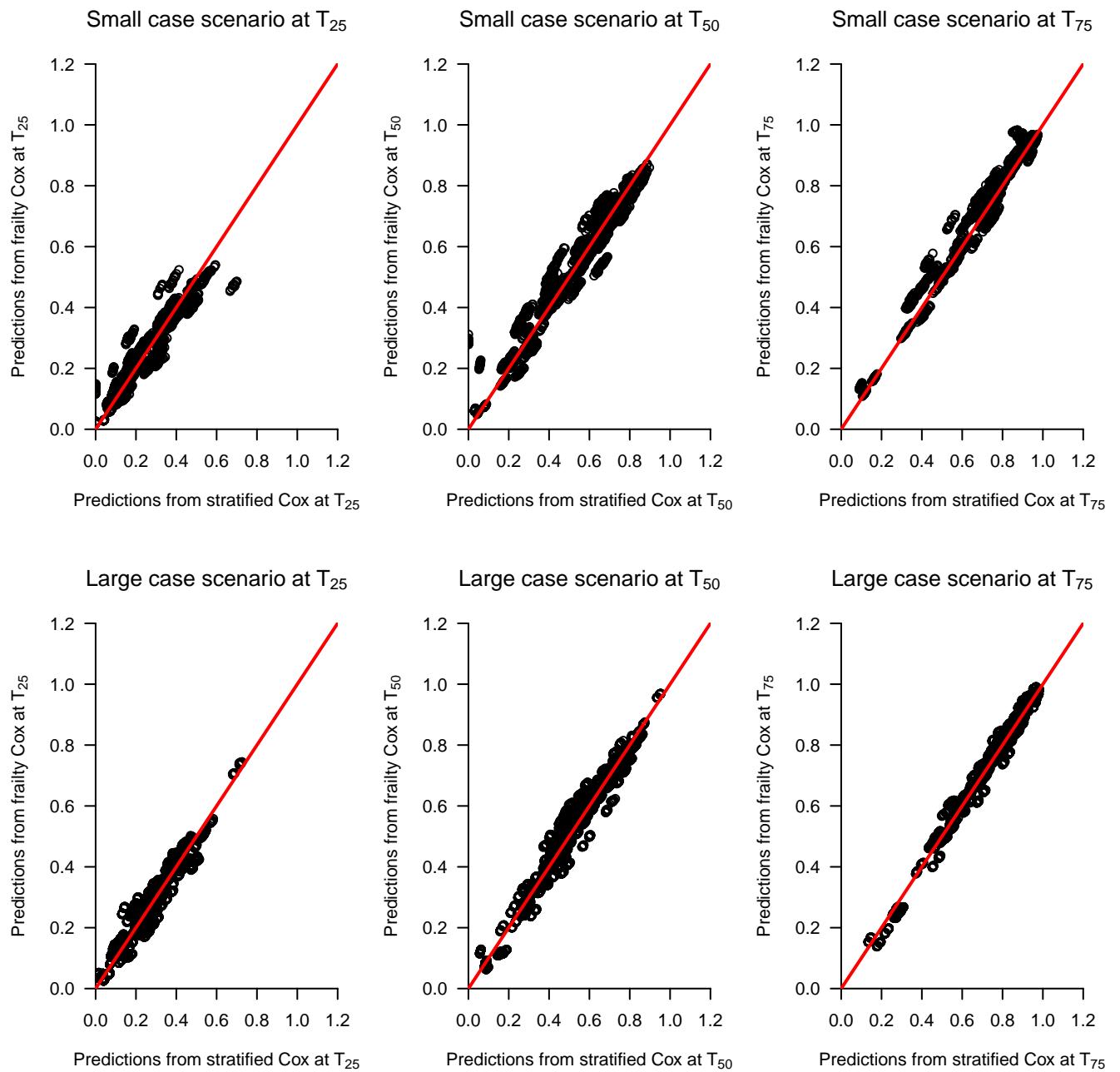
    b = 1,
    lwd = 2,
    col = "red")

# Large scenario at T25, T50 and T75
par(xaxs = "i",
     yaxs = "i",
     las = 1)
plot(pred_strat_large[, 1],
      pred_frail_large[, 1],
      xlim = c(0, 1.2),
      xlab = expression("Predictions from stratified Cox at T"[25]),
      ylim = c(0, 1.2),
      ylab = expression("Predictions from frailty Cox at T"[25]),
      main = expression("Large case scenario at T"[25]),
      bty = "n")
abline(a = 0,
       b = 1,
       lwd = 2,
       col = "red")

par(xaxs = "i",
     yaxs = "i",
     las = 1)
plot(pred_strat_large[, 2],
      pred_frail_large[, 2],
      xlim = c(0, 1.2),
      xlab = expression("Predictions from stratified Cox at T"[50]),
      ylim = c(0, 1.2),
      ylab = expression("Predictions from frailty Cox at T"[50]),
      main = expression("Large case scenario at T"[50]),
      bty = "n")
abline(a = 0,
       b = 1,
       lwd = 2,
       col = "red")

par(xaxs = "i",
     yaxs = "i",
     las = 1)
plot(pred_strat_large[, 3],
      pred_frail_large[, 3],
      xlim = c(0, 1.2),
      xlab = expression("Predictions from stratified Cox at T"[75]),
      ylim = c(0, 1.2),
      ylab = expression("Predictions from frailty Cox at T"[75]),
      main = expression("Large case scenario at T"[75]),
      bty = "n")
abline(a = 0,
       b = 1,
       lwd = 2,
       col = "red")

```



NOTE: comparisons only among clusters where predictions were possible for both models

Reproducibility ticket

```
sessionInfo()
```

```
## R version 4.3.3 (2024-02-29 ucrt)
## Platform: x86_64-w64-mingw32/x64 (64-bit)
## Running under: Windows 10 x64 (build 19045)
##
## Matrix products: default
```

```

## 
## 
## locale:
## [1] LC_COLLATE=English_United Kingdom.utf8
## [2] LC_CTYPE=English_United Kingdom.utf8
## [3] LC_MONETARY=English_United Kingdom.utf8
## [4] LC_NUMERIC=C
## [5] LC_TIME=English_United Kingdom.utf8
##
## time zone: Europe/Rome
## tzcode source: internal
##
## attached base packages:
## [1] grid      stats     graphics grDevices utils     datasets  methods
## [8] base
##
## other attached packages:
## [1] frailtyHL_2.3           cmprsk_2.2-12
## [3] Matrix_1.6-5            parfm_2.7.8
## [5] optimx_2025-4.9         survival_3.8-3
## [7] webshot2_0.1.2          rms_6.8-0
## [9] patchwork_1.2.0          ggpubr_0.6.0
## [11] plotly_4.10.4           webshot_0.5.5
## [13] gridExtra_2.3            lubridate_1.9.4
## [15] forcats_1.0.0            dplyr_1.1.4
## [17] purrr_1.0.2              readr_2.1.5
## [19] tidyverse_1.3.1           tibble_3.2.1
## [21] ggplot2_3.5.2            tidyverse_2.0.0
## [23] gtsummary_1.7.2           polspline_1.1.25
## [25] riskRegression_2025.05.20 lattice_0.22-5
## [27] Hmisc_5.2-3               kableExtra_1.4.0
## [29] knitr_1.50                stringr_1.5.1
## [31] rio_1.2.3                 pacman_0.5.1
##
## loaded via a namespace (and not attached):
## [1] RColorBrewer_1.1-3    rstudioapi_0.17.1   jsonlite_1.8.9
## [4] shape_1.4.6.1          magrittr_2.0.3       TH.data_1.1-3
## [7] farver_2.1.2           nloptr_2.2.1        rmarkdown_2.29
## [10] vctrs_0.6.5             base64enc_0.1-3     rstatix_0.7.2
## [13] htmltools_0.5.8.1     broom_1.0.9         Formula_1.2-5
## [16] parallelly_1.45.1     pracma_2.4.4        htmlwidgets_1.6.4
## [19] sandwich_3.1-1         zoo_1.8-14          gt_1.0.0
## [22] commonmark_2.0.0       lifecycle_1.0.4     iterators_1.0.14
## [25] pkgconfig_2.0.3         R6_2.6.1            fastmap_1.2.0
## [28] future_1.67.0           digest_0.6.35      numDeriv_2016.8-1.1
## [31] colorspace_2.1-1        ps_1.9.1            rprojroot_2.1.0
## [34] timechange_0.3.0        httr_1.4.7          abind_1.4-8
## [37] compiler_4.3.3          here_1.0.1          withr_3.0.2
## [40] htmlTable_2.4.3         backports_1.5.0     carData_3.0-5
## [43] ggsignif_0.6.4          MASS_7.3-60.0.1     lava_1.8.1
## [46] quantreg_6.1             tools_4.3.3          chromote_0.5.1
## [49] foreign_0.8-90          future.apply_1.20.0  nnet_7.3-20
## [52] glue_1.7.0                mets_1.3.5          nlme_3.1-164
## [55] promises_1.3.2           checkmate_2.3.2     cluster_2.1.8.1

```

```
## [58] generics_0.1.4          gtable_0.3.6           tzdb_0.5.0
## [61] sn_2.1.1                 websocket_1.4.2       data.table_1.16.2
## [64] hms_1.1.3                xml2_1.3.6            car_3.1-3
## [67] markdown_2.0              foreach_1.5.2         pillar_1.11.0
## [70] later_1.4.2              splines_4.3.3         SparseM_1.84-2
## [73] tidyselect_1.2.1          litedown_0.7          svglite_2.1.3
## [76] stats4_4.3.3             xfun_0.52             expm_1.0-0
## [79] stringi_1.8.4            lazyeval_0.2.2        yaml_2.3.10
## [82] pec_2025.06.24            evaluate_1.0.4        codetools_0.2-20
## [85] msm_1.8.2                 cli_3.6.2             rpart_4.1.24
## [88] systemfonts_1.2.3         processx_3.8.6        Rcpp_1.1.0
## [91] globals_0.18.0            parallel_4.3.3        MatrixModels_0.5-4
## [94] listenv_0.9.1             glmnet_4.1-10         viridisLite_0.4.2
## [97] broom.helpers_1.15.0       mvtnorm_1.3-3          timereg_2.0.6
## [100] scales_1.4.0              prodlim_2025.04.28    rlang_1.1.6
## [103] multcomp_1.4-28           mnormt_2.1.1
```