

Supplementary Digital Content - The Performance of Hypotension Prediction Index May Be Overestimated Due to Selection Bias

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Setup

```
library(pROC)
library(tidyverse)
# install.packages("faux") # used to simulate data

# A few extra packages are used to create the simulation figure. We load these in
# the relevant section.

theme_set(theme_minimal(base_size = 12))
```

Simulation of the selection problem

OBS: The simulation is not an attempt to produce realistic data. It only serves to illustrate how the selection problem results in a “skewed” ROC curve with very high specificity.

We simulate 1000 paired MAP values, to show what the data selection described in the model-development paper does to the performance of a model that uses MAP as a predictor. Since prediction may not be relevant if the patient is already hypotensive, we exclude data where `map_predictor` is < 65 mmHg.

The specific parameters of the simulation are simply chosen to place most data in a relevant interval: between 55 and 95 mmHg. The correlation coefficient ($r = 0.55$) is chosen to give MAP a modest

predictive ability, similar to what is presented by Davies *et al* (<http://doi.org/10.1213/ANE.00000000000004121>) However, any reasonable distribution of data, and any correlation coefficient between 0 and ~0.9, will convey the intended message.

```
set.seed(12345)
# To get 1000 samples for the "full analysis", we generate too many samples,
# remove samples where map_predictor is < 65 and then select 1000 of the
# remaining samples.
correlated_map <- faux::rnorm_multi(
  n = 2000,
  mu = c(75, 75),
  sd = c(13, 13),
  r = 0.55,
  # "map_predictor" represents the current map value
  # "map_outcome" represents what map is 5 minutes from now.
  varnames = list("map_predictor", "map_outcome")
) |>
  filter(map_predictor >= 65) |>
  head(1000)
```

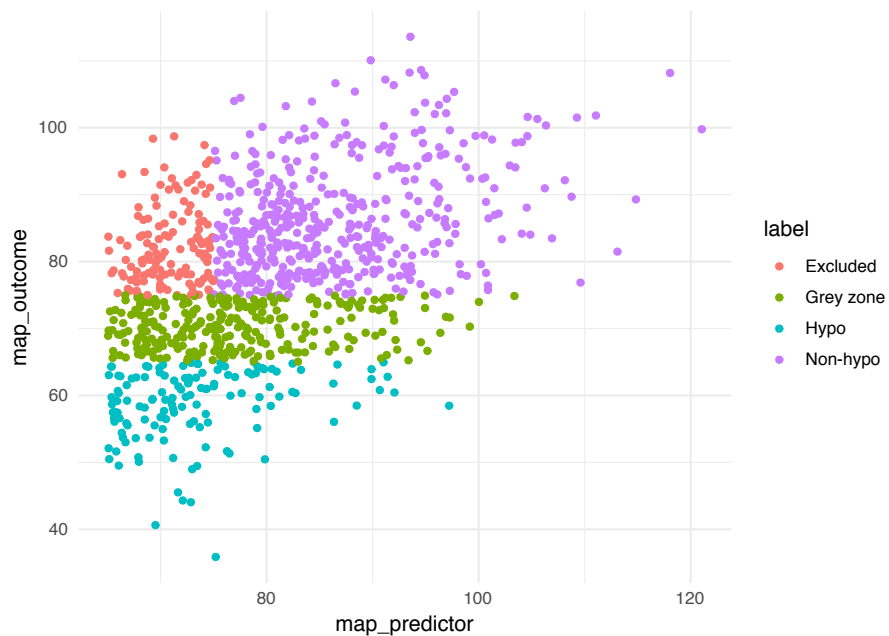
After removing samples with `map_predictor < 65` mmHg, we get a correlation of $r = 0.47$.

We label the relevant zones of the data. Each row is the combination of an event (`hypo == TRUE` or `hypo == FALSE`) and the sample used to predict the event (`map_predictor`).

```
d <- mutate(correlated_map,
  # If map_outcome is < than 65, this is represented as a hypotensive event
  hypo = map_outcome < 65,
  # If map_outcome is between 65 and 75, this is a greyzone event.
  grey = map_outcome >= 65 & map_outcome < 75,
  # If map_outcome and map_predictor is >= 75, this is a nonevent.
  nonhypo = map_outcome >= 75 & map_predictor >= 75,
)
```

Here is a plot to show the applied labels.

```
ggplot(d, aes(map_predictor, map_outcome, color = case_when(hypo ~ "Hypo",
  grey ~ "Grey zone",
  nonhypo ~ "Non-hypo",
  TRUE ~ "Excluded")))) +
  geom_point() +
  labs(color = "label")
```



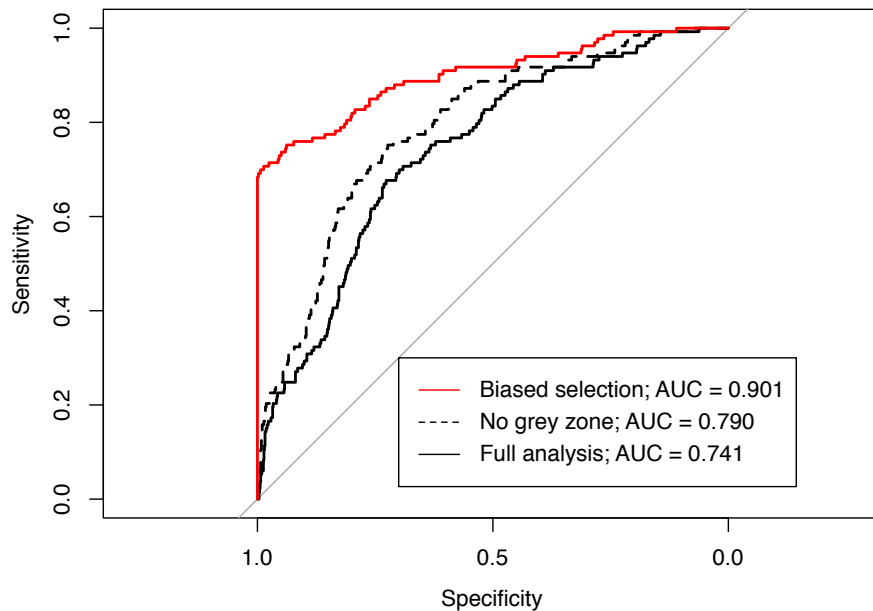
Now we can make the ROC analyses.

```
# With all data
roc_analysis_full <- roc(hypo~map_predictor, data = d)

# Excluding grey zone
roc_analysis_grey <- roc(hypo~map_predictor, data = filter(d, !grey))

# Include only data that is either event or non-event per model-development definition
roc_analysis_biased <- roc(hypo~map_predictor, data = filter(d, hypo | nonhypo))

plot(roc_analysis_full)
plot(roc_analysis_grey, lty = 2, add = TRUE)
plot(roc_analysis_biased, col = "red", add = TRUE)
legend(
  x = 0.7, y = 0.3,
  legend = c(
    sprintf("Biased selection; AUC = %.3f", auc(roc_analysis_biased)),
    sprintf("No grey zone; AUC = %.3f", auc(roc_analysis_grey)),
    sprintf("Full analysis; AUC = %.3f", auc(roc_analysis_full))
  ),
  lty = c(1, 2, 1),
  col = c("red", "black", "black")
)
```



The ROC curve from the biased data selection shows a sharp drop in specificity (when MAPnow is > 75 mmHg) compared to that in the model-development paper (fig. 1). This difference can be explained by a combination of two effects. First, in the model development, all MAP values in a 30-minute period had to be > 75 mmHg; due to the variation in MAP over 30 minutes, any specific measurement (here, the midpoint) is unlikely to be very close to 75 mmHg. Second, although HPI may be driven predominantly by MAP, other predictors influence HPI as well.

Create figure 3

The remaining code combines the scatters and the ROC analyses into figure 3.

```
library(ggrepel)
library(patchwork)

# Set plot theme
# Plot theme
# Theme for plot
theme_set(
  theme_minimal(base_size = 11) +
  theme(
    plot.title = ggtext::element_textbox_simple(
      size = 10,
      vjust = 0,
      minheight = unit(3, "lines"), width = unit(2.5, "inches")
    ),
  ),
  axis.title = element_text(size = 9.5),
  axis.text = ggplot2::element_text(size = ggplot2::rel(0.9),
    color = "#333333"),
```

```

    panel.grid.major = ggplot2::element_line(
      color = "#454545",
      size = 0.3,
      linetype = "dotted"
    ),
    panel.grid.minor = ggplot2::element_blank()
  ))

plot_colors <- c("#2A6EBB", "#bb612a")

# First we extract all combinations of sensitivity, specificity and thresholds for
# all ROC analyses
roc_data_full <- as.data.frame(roc_analysis_full[c("sensitivities",
                                                  "specificities",
                                                  "thresholds")]) |>
  arrange(desc(specificities), sensitivities)

roc_data_grey <- as.data.frame(roc_analysis_grey[c("sensitivities",
                                                  "specificities",
                                                  "thresholds")]) |>
  arrange(desc(specificities), sensitivities)

roc_data_biased <- as.data.frame(roc_analysis_biased[c("sensitivities",
                                                      "specificities",
                                                      "thresholds")]) |>
  arrange(desc(specificities), sensitivities)

# We extract the rows with thresholds closest to 70, 75 and 80
# This is used for labeling the ROC curves.
roc_label_filter <- function(roc_data) {
  roc_data |>
    filter(
      row_number() == which.min(abs(thresholds - 70)) |
      row_number() == which.min(abs(thresholds - 75)) |
      row_number() == which.min(abs(thresholds - 80))
    )
}

roc_labels_full <- roc_label_filter(roc_data_full)
roc_labels_grey <- roc_label_filter(roc_data_grey)
roc_labels_biased <- roc_label_filter(roc_data_biased)

# Make the 3 ROC panels
roc_plot_full <- ggplot(roc_data_full, aes(1-specificities, sensitivities)) +
  geom_step() +
  geom_abline(slope = 1, intercept = 0, linetype = 2, color = "grey") +
  geom_label_repel(aes(label = glue::glue("MAP[now] < {round(thresholds, 0)}")),

```

```

        parse = TRUE,
        size = 3,
        box.padding = 0.1,
        point.size = 0.1,
        segment.color = "#555555",
        position = position_nudge_repel(y = -0.25, x=0.2),
        ylim = c(0.15, 1),
        xlim = c(0, 1.1), # extend to outside plotting area
        direction = "y",
        label.size = NA,
        hjust = 0,
        family = "Helvetica",
        data = roc_labels_full
    ) +
    annotate("label",
            x = 1, y = 0,
            label = sprintf("AUC = %.2f", auc(roc_analysis_full)),
            hjust = 1, vjust = -0,
            label.size = NA,
            family = "Helvetica",
            size = 3.5) +
    labs(x = "1 - specificity", y = "Sensitivity") +
    coord_equal()

roc_plot_grey <- ggplot(roc_data_grey, aes(1-specificities, sensitivities)) +
  geom_step() +
  geom_abline(slope = 1, intercept = 0, linetype = 2, color = "grey") +
  geom_label_repel(aes(label = glue::glue("MAP[now] < {round(thresholds, 0)}")),
        parse = TRUE,
        size = 3,
        box.padding = 0.1,
        point.size = 0.1,
        segment.color = "#555555",
        direction = "y",
        position = position_nudge_repel(y = -0.3, x=0.2),
        ylim = c(0.15, 1),
        xlim = c(0, 1.1), # extend to outside plotting area
        label.size = NA,
        hjust = 0,
        family = "Helvetica",
        data = roc_labels_grey
    ) +
    annotate("label",
            x = 1, y = 0,
            label = sprintf("AUC = %.2f", auc(roc_analysis_grey)),
            hjust = 1, vjust = -0,
            label.size = NA,

```

```

    family = "Helvetica",
    #label.size = NA,
    size = 3.5) +
labs(x = "1 - specificity", y = "Sensitivity") +
coord_equal()

roc_plot_biased <- ggplot(roc_data_biased, aes(1-specificities, sensitivities)) +
  geom_step() +
  geom_abline(slope = 1, intercept = 0, linetype = 2, color = "grey") +
  geom_label_repel(aes(label = glue::glue("MAP[now] < {round(thresholds, 0)}")),
    parse = TRUE,
    size = 3,
    box.padding = 0.1,
    point.size = 0.3,
    segment.color = "#555555",
    position = position_nudge_repel(y = -0.3, x=0.2),
    ylim = c(0.15, 1),
    xlim = c(0, 1.1), # extend to outside plotting area
    direction = "y",
    label.size = NA,
    hjust = 0,
    family = "Helvetica",
    data = roc_labels_biased
  ) +
  annotate("label",
    x = 1, y = 0,
    label = sprintf("AUC = %.2f", auc(roc_analysis_biased)),
    hjust = 1, vjust = -0,
    label.size = NA,
    family = "Helvetica",
    size = 3.5) +
  labs(x = "1 - specificity", y = "Sensitivity") +
  coord_equal()

# Make the 3 scatter plots
color_scale <- scale_color_manual(values = plot_colors,
  labels = c("Non-hypotensive events", "Hypotensive events"))

fill_scale <- scale_fill_manual(values = plot_colors,
  labels = c("Non-hypotensive events", "Hypotensive events"))

x_limits <- round(range(d$map_predictor) + c(-5, 1), 0)

x_scale <- scale_x_continuous(breaks = seq(45, 105, by = 10),
  limits = x_limits,
  expand = c(0,0),
  name = "MAP<sub>now</sub> (predictor) [mmHg]")

```

```

scatter_plot_full <- ggplot(d, aes(map_predictor, map_outcome, color = hypo)) +
  geom_point(size = 0.7, show.legend = FALSE) +
  geom_hline(yintercept = 65, color = "#555555") +
  scale_y_continuous(breaks = seq(45, 105, by = 10), expand = expansion(add = c(2,10))) +
  x_scale +

  labs(y = "MAP 5 minutes later (outcome) [mmHg]", color = "") +
  ggtitle(sprintf("***A** Full analysis (n=%d)", nrow(d))) +
  color_scale +
  coord_equal() +
  theme(axis.title.x = ggtext::element_markdown())

labels <- tribble(
  ~label, ~hypo, ~x, ~y,
  "Hypotensive events", TRUE, Inf, -Inf,
  "Non-hypotensive events", FALSE, -Inf, Inf
)

event_labels <- geom_label(aes(x, y, label = label),
  size = 3.5,
  #label.size = NA,
  fill = alpha("white", 0.5),
  vjust = "inward",
  hjust = "inward",
  family = "Helvetica",
  data = labels,
  show.legend = FALSE
)

scatter_plot_full_w_labs <- scatter_plot_full + event_labels

scatter_plot_grey <- scatter_plot_full %>% filter(d, !grey) +
  geom_hline(yintercept = 75, color = "#555555") +
  event_labels +
  ggtitle(sprintf("***B** Events where MAP (outcome) is between 65 and 75 mmHg (‘gray zone’) are excluded (n=%d)", nrow(d)))

scatter_plot_biased <- scatter_plot_grey %>% filter(d, hypo | nonhypo) +
  annotate("segment",
    x = 75, xend = 75,
    y = 75, yend = max(d$map_outcome),
    color = "#555555"
  ) +
  event_labels +
  ggtitle(sprintf("***C** Samples corresponding to non-hypotensive events must have a MAP (predictor) ≥ 75 mmHg (n=%d)", nrow(d)))

# Density plots
get_density <- function(data, from = from) {

```



```

dens <- density(data$map_predictor, adjust = 2, n = 100, from = from)
data.frame(map_predictor = dens$x, density = dens$y)
}

get_grouped_density <- function(data, from_hypo, from_nonhypo) {
  bind_rows(
    "TRUE" = get_density(data[data$hypo == TRUE,], from = from_hypo),
    "FALSE" = get_density(data[data$hypo == FALSE,], from = from_nonhypo),
    .id = "hypo"
  ) |> mutate(hypo = as.logical(hypo))
}

density_full <- get_grouped_density(d, from_hypo = 65, from_nonhypo = 65) |>
  ggplot(aes(map_predictor, y = density, fill = hypo, group = hypo)) +
  geom_area(alpha = 0.7, position = "identity", show.legend = FALSE) +
  geom_vline(xintercept = c(70, 75, 80), color = "#555555", linetype = 2) +
  color_scale +
  fill_scale +
  labs(y = "Density") +
  x_scale +
  theme(axis.title.x = ggtext::element_markdown())

density_grey <- density_full %>%
  get_grouped_density(filter(d, !grey),
    from_hypo = 65, from_nonhypo = 65)

density_biased <- density_full %>%
  get_grouped_density(filter(d, hypo | nonhypo),
    from_hypo = 65, from_nonhypo = 75)

# Combine plots
simulation_figure <- scatter_plot_full_w_labs + scatter_plot_grey + scatter_plot_biased +
  #density_full + density_grey + density_biased +
  roc_plot_full + roc_plot_grey + roc_plot_biased +
  plot_layout(ncol = 3, byrow = TRUE, heights = c(2.5, 1, NA))

ggsave("figure3_simulation_alt.pdf", simulation_figure, device = cairo_pdf,
  width = 18, height = 18, units = "cm", scale = 1.15)
ggsave("figure3_simulation_alt.png", simulation_figure, device = ragg::agg_png, bg = "white",
  width = 18, height = 18, units = "cm", scale = 1.15)

simulation_figure

```

