STA490: Statistical Practice in Clinical Research

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Tissue Bridges Cut-Off Value in Spinal Cord Injury Patients

Analysis for Patrick Freund, Lynn Farner

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1   Abstract

We investigated the predictive value of preserved tissue bridges for recovery after a cervical spinal cord injury. This analysis was based on the Nogo-A study, a randomized, placebo-controlled, multicentre, phase 2b clinical trial with 78 patients in the NG101 (intervention) group and 48 patients in the placebo group. The relationship of baseline tissue bridges with recovery, measured by upper extremity motor score (UEMS), was modelled with a generalized additive model (GAM). The analysis showed that the amount of preserved mid-sagittal tissue bridges had a linear positive relationship with the 6-month recovery (Δ-UEMS) in both treatment groups. The parasagittal tissue bridges showed also a positive relationship with recovery. However, in the treatment group the recovery reached a plateau for values of preserved parasagittal tissue bridges higher than (approximately) 2 mm.

(Remark: append the abstract for cut-off value if we decide to include it) A total amount of XX in preserved tissue was determined as cut-off value, separating the patients into subgroups of prognosed recovery based on the baseline tissue bridge value. Such a cut-off value can be used in clinical practice to better forecast the probability for recovery and as a selection criterion for clinical trials.

2   Introduction

Traumatic spinal cord injury (SCI) is a severe condition resulting for example from falls and road traffic injuries. Bundles of nerves and nerve fibers are damaged and transmission of nerve signals with the brain are suppressed (NINDS, 2024). SCI can lead to a loss of motor and/or sensory function below the injury site and decrease quality of life (WHO, 2024). The prognosis of recovery is crucial for the patient and the treating physician.

Biomarkers that serve for prognosis are needed. Studies have shown that the amount of preserved tissue bridges around the lesion are an important factor to characterizing and predicting the recovery after a spinal

cord injury. Tissue bridges function as preserved neuronal pathways that restore connection between the brain and the body. It has been observed that the amount of tissue bridges is positively correlated with the recovery (Huber et al., 2017), (Pfyffer et al., 2019) and that certain cut-off values are prognostic for an improved recovery after 3 months and 12 months (Pfyffer et al., 2024).

Another biomarker that showed some prognostic power is the lesion area. It can be seen as the counterpart to the tissue bridges since it represents the damaged tissue. The lesion area is negatively correlated with the recovery (Huber et al., 2017).

The aim of this analysis was to further investigate the relationship between clinical biomarkers such as preserved midsagittal/parasagittal tissue bridges and lesion volume with the recovery after a spinal cord injury. Depending on the form of this relationship, cut-off values could be determined that help to separate patients into likely and unlikely recovery. Assigning patients to subgroups depending on their predicted outcomes is crucial. It helps improving the planning, individualisation and evaluation of therapies. By segmenting patients in clinical studies into more homegeneous subgroups according to their distinct predicted recovery profile, allows to separately assess the treatment sucess in the respective subgroups. Finally, a cut-off value could also be used as inclusion criterion in a clinical trial.

3   Research Questions

1. What is the relationship between preserved tissue bridges after a spinal cord injury with the recovery over time measured by the upper extremity motor score?

2. Can a cut-off value in tissue bridges be determined that helps to separate patients into poor and good expected recovery?

3. Which biomarker (midsagittal tissue bridges, parasagittal tissue bridges or lesion volume) can be used best to determine a cut-off value?

4   Methods

Study Design

Type of study

This is an exploratory post-hoc analysis based on the study "NoGo-A antibody treatment in acute cervical spinal cord injury". The Nogo-A study was a randomized, placebo-controlled, multicentre phase 2b clinical trial. Therefore, we will only briefly explain the methods used in the Nogo-A study, but emphasise those that are relevant to answering the research questions stated in Section 3. The methods of the Nogo-A study are described in detail in the main study report. (Remark: cite as soon as published)

Anti Nogo-A Study

The "NoGo-A antibody treatment in acute cervical spinal cord injury" was a randomised, placebo-controlled, multicentre, phase 2b, clinical trial where the effects of the treatment with an antibody was investigated. The antibody is called NG101 and it binds to the protein Nogo-A. Nogo-A is a protein that inhibits the growth of nerve fibers. The idea is that by targeting Nogo-A, the nerve fibers can regrow better and the recovery is improved.
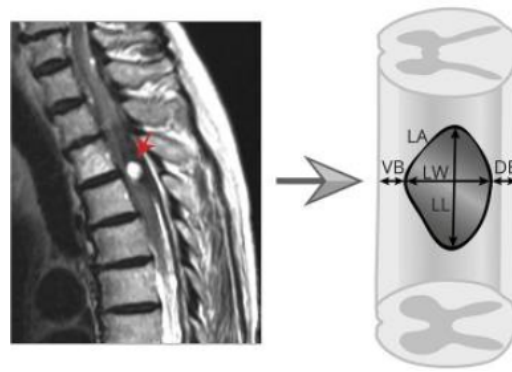
Figure 1: Typical T2W midsagittal slice (left) and schematic lesion segmentation (right) with the quantitative MRI measures analyzed (lesion area [LA], lesion length [LL], lesion width [LW], ventral midsagittal tissue bridges [VB], and dorsal midsagittal tissue bridges [DB]) (Pfyffer et al., 2019).

The study was conducted in specialized SCI centres in Germany, Switzerland, Spain and the Czech Republic. Between 2019 and 2022, 126 patients with acute traumatic cervical spinal cord injury (neurological level of injury C1-C8) were recruited and randomized to treatment (NG101) and placebo in a ratio 2:1.

The primary outcome was the change in upper extremity motor score (UEMS, according to ISNCSCI) in 6 months. The UEMS is a measure that assesses the motor function in multiple muscle groups in the arms and it can take values between 0 and 50. It was measured at baseline and after approximately 1, 3 and 6 months. The statistical analysis was mainly conducted with linear mixed-effect models. The overall primary outcome was not significant, but some subgroups showed promising results.

Tissue Bridges and Lesion Volume

Patients underwent MRI scanning at screening. The protocol included T1-weighted, sagittal T2-weighted, and axial T2-weighted anatomic scans of the cervical spinal cord, centered at lesion level. From the scans, the midsagittal tissue bridges, parasagittal tissue bridges and the lesion volume were determined.

The amount of preserved midsagittal tissue bridges (measured in mm) were calculated as the sum of the ventral and dorsal bridges that were visible on the midsagittal MRI slice. Figure 1 illustrates the schematic lesion segmentation.

Parasagittal tissue bridges were calculated similarly to midsagittal bridges. In this case, however, tissue bridges were also measured in the parasagittal MRI slices. The measurements from all slices where the lesion was visible were added together. To adjust for differences in cord size, this total was divided by the number of slices showing tissue bridges, giving the average amount of preserved tissue bridges in millimeters.

The lesion volume was also calculated by MRI screening. (Remark: add more details?)

Study population

Describe the composition including inclusion/exclusion criteria

Data collection

The primary outcome upper extremity motor score was measured at screening, baseline and 30, 84 and 168 days post baseline. The time variable in the analysis indicates the measurement timepoint of UEMS in days after start of medication. For example if the UEMS was measured at time=1, this means that it was measured

1 day after first dose. The UEMS, assessed using ISNCSCI, ranges from 0 to 50 in increments of 1. A higher UEMS indicates better motor functions.

Statistical Analysis

Data Preparation

Most data preparation was already done for the Nogo-A study. The primary dataset contained all variables except the midsagittal tissue bridges and the lesion volume. Those measures were provided in two separate excel files. We joined the baseline measures of the biomarkers with the patient id and added them to the primary dataset. The dataset with the lesion volume contained 0 where the slice thickness was missing. In this case, the volume should not be 0 but NA instead. This was corrected. (Remark: according to Lynn Farner)

Imputation Methods

There are two types of missing values that are relevant in the analysis of the relationship between baseline biomarkers and the recovery. First, the UEMS was not measured 4 times (baseline and 3 follow up) for all patients. Second, baseline biomarker values are missing for some patients. The reasons for the missing values will be provided in Section 5. In both cases missing values are not imputed. The primary aim of this exploratory analysis is to investigate the relationship between tissue bridges and recovery. No significance testing will be performed. We do not want to introduce additional uncertainty by imputing. The missing biomarker values are handled by excluding the respective patients from the analysis, hence a complete case analysis is performed.

Descriptive Statistics and Simple Methods

The following analysis is conducted for each biomarker individually. Patients are divided into four subgroups according to the quartile of the biomarker. Then, the UEMS over time is plotted with by treatment group and quartile of the biomarker. This should give a first impression of the recovery profiles conditional on the treatment group and different ranges of the biomarker value.

The distributions of the biomarkers against the baseline UEMS are visualized by scatter plots. This should uncover potential surprising baseline distributions in the treatment groups.

Next, a generalized additive model (GAM), as described in the next Section 4, is fitted on both treatmet groups separately. The resulting smooth functions of the predictors are be presented, providing a visual guide on how the relationships are modelled. By using different values of the range of the respective biomarker, predictions for the recovery over time are made with the GAM and added to a plot with the raw patient data. Each line in the plot represents a hypothetical patient with a different baseline value for the biomarker. This should give an impression of how the recovery changes over time depending on the value of the biomarker. For each predicted recovery trajectory, the difference between the UEMS score at 6-month follow-up and baseline is calculated (Δ-UEMS). This difference is then plotted against the baseline value of the biomarker and should give an idea of how the predicted recovery changes depending on the value of the biomarker. If the relationship between the biomarker value at baseline and the 6-month recovery is non-linear, the Δ-UEMS should be represented as a straight line.

The research question of finding a cut-off value depends on this relationship of Δ-UEMS and biomarker. Only if there was a non-linear relationship where the Δ-UEMS is higher or lower over a certain range of the biomarker, a cut-off value would be meaningful.

Description of advanced statistical methods

Before we consider whether a cut-off value can be determined, we need to investigate the relationship between the tissue bridges and the recovery. Since we want to make as few assumptions as possible, a model is needed that allows for great flexibility. A generalized additive model (GAM) can model complex, non-linear relationships between predictors and response. It extends the generalized linear model (GLM) by replacing the linear combination of the predictors $\sum \beta_j X_j$ by the sum of smooth functions of the predictors $\sum f_j(X_j)$ (Hastie and Tibshirani, 1986).

A simpler model such as a linear mixed-effects model would require to make the assumption that the relationship between each predictor and the response variable is linear. For illustration; assuming we model the problem by a linear mixed-effects model, a single coefficient for the tissue bridges would be estimated. This coefficient would represent the average effect of the tissue bridges on the recovery. But this is not what we want to achieve with this analysis. Instead, we want to investigate whether the relationship of the tissue bridges on the response (UEMS) changes depending on the value of tissue bridges. A GAM models the problem by fitting a smooth function of the tissue bridges. This smooth function can have any shape.

The research question of finding a cut-off value is dependent on the shape of the function that models the relationship between tissue bridges and recovery. If the function is linear, a cut-off value is not meaningful. But, if the function suggests, for example, that there is no effect on recovery for tissue bridge values below 2 mm, but for tissue bridge values above 2 mm the recovery increases, then a cut-off value at 2 mm could be determined.

Hence, in this analysis we use a GAM to model the problem. Equation 1 shows the formula of the model that is applied. The model consists of an overall intercept, the main effects of baseline tissue bridges and time, and then we have an interaction effect for tissue bridges and time. The patient-specific random effects capture correlations between repeated measurements.

$$\text{UEMS}_{ij} = \beta_0 + f_1(\text{tissue}_i) + f_2(\text{time}_{ij}) + f_3(\text{tissue}_i, \text{time}_{ij}) + f_{id}(\text{id}_i) + f_{id:tmstd}(\text{id}_i, \text{time}_{ij}) + \epsilon_{ij} \quad (1)$$

- UEMS_{ij} is the upper extremity motor score of patient i at time j. It can take values between 0 and 50.

- β_0 is the overall intercept.

- $f_1(\text{tissue}_i)$ is the smooth function of the baseline tissue bridges. It shows the effect on UEMS depending on the value of tissue bridges. It is centered at 0.

- $f_2(\text{time}_{ij})$ is the smooth function of time. It shows the effect on the UEMS over time. The time variable is normalized so that time = 0 corresponds to the baseline measurement (day of first medication) and time = 1 corresponds to 6 month follow-up (day 168 after first medication). It is centered at 0.

- $f_3(\text{tissue}_i, \text{time}_{ij})$ is the interaction effect of tissue bridges and time on the UEMS. It shows how the effect of tissue bridges on the UEMS changes over time. This interaction is the effect that is not already included in the main effects of tissue bridges and time. It is also centered at 0.

- $f_{id}(\text{id}_i)$ and $f_{id:tmstd}(\text{id}_i, \text{time}_{ij})$ are the patient-specific random effects. They account for the fact that each patient might have an individual intercept (baseline UEMS value) or trajectory of recovery over time regardless of the value of the predictors used in the model. Without including these random effects, the model would assume that all patients with the same value of the biomarker (e.g. midsagittal tissue bridges) at a given time point would have the same baseline UEMS and identical recovery trajectory over time. This would mean that no patient-specific deviations would be allowed and therefore could lead to a biased estimation of the effect on UEMS.

- ϵ_{ij} is the error term. It is assumed to be normally distributed with mean 0 and variance σ^2. (Remark: is this true in a GAM?)

Restricted maximum likelihood (REML) is used as fitting algorithm due to its resistance to occasional severe over-fitting (Wood, 2006, p. 267). The smooth functions are approximated using penalized regression splines.

In contrast to random effects in linear mixed-effects models, where explicit parameters are estimated for each individual, the random intercepts and slopes in this GAM are specified as special cases of smooths. Same as the other terms, they are approximated using penalized regression splines. Additionally, the patient-specific slopes can be non-linear.

To avoid making assumptions about the treatment effect of NG101 in any way on the relationship between tissue bridges on the recovery, the model is fitted separately for the placebo and NG101 group.

Implementation

All analyses were performed in the R programming language (R Core Team, 2024) using base packages and the following analysis-specific packages: `mgcv` to fit generalized additive models with gam() (Wood, 2011), `lattice` to use xyplot() for plotting (Sarkar, 2008).

5   Results

Table 1: Baseline Characteristics by Treatment Group. The measures baseline measurements for UEMS and the three biomarkers are presented as mean (sd).

	Overall	Placebo	NG101
Patients	126	48	78
Time from injury to 1st injectino (days)	22.56 (5.19)	23.81 (4.62)	21.78 (5.40)
UEMS	16.39 (9.21)	17.08 (7.94)	15.96 (9.93)
Midsagittal tissue bridges	1.37 (1.58)	1.40 (1.31)	1.35 (1.75)
Parasagittal tissue bridges	1.73 (1.45)	1.99 (1.38)	1.56 (1.48)
Lesion volume	574.87 (700.82)	394.10 (233.40)	699.76 (872.11)

Anti Nogo-A Study and Neuroimaging Substudy

126 patients with acute traumatic cervical spinal cord injury (neurological level of injury C1-C8) were included in the Nogo-A study. 78 were allocated to the NG101 group and 48 received the placebo. The patients were recruited in 4 countries. The mean age was 46.2 years with a standard deviation of 16.7 years. The percentage of males was 84.9%.

103 out of 126 patients underwent MRI imaging at screening in an exploratory neuroimaging substudy. The screening was carried out on average 17.2 (sd 7.1 Remark: Nogo-A reported 6.9) days after the injury occurred. Some scans were invalid due to metal or motion artifacts and poor image quality. The midsagittal tissue bridges were calculated based on the midsagittal MRI slice and the parasagittal tissue bridges were calculated based on the parasagittal MRI slices. Table 1 shows the baseline measurements in the treatment groups. (Remark: I set the lesion volume to NA if the slice thickness was missing (according to Lynn Farner))

Table 2: Combination of missing values in the three biomarkers under investigation.

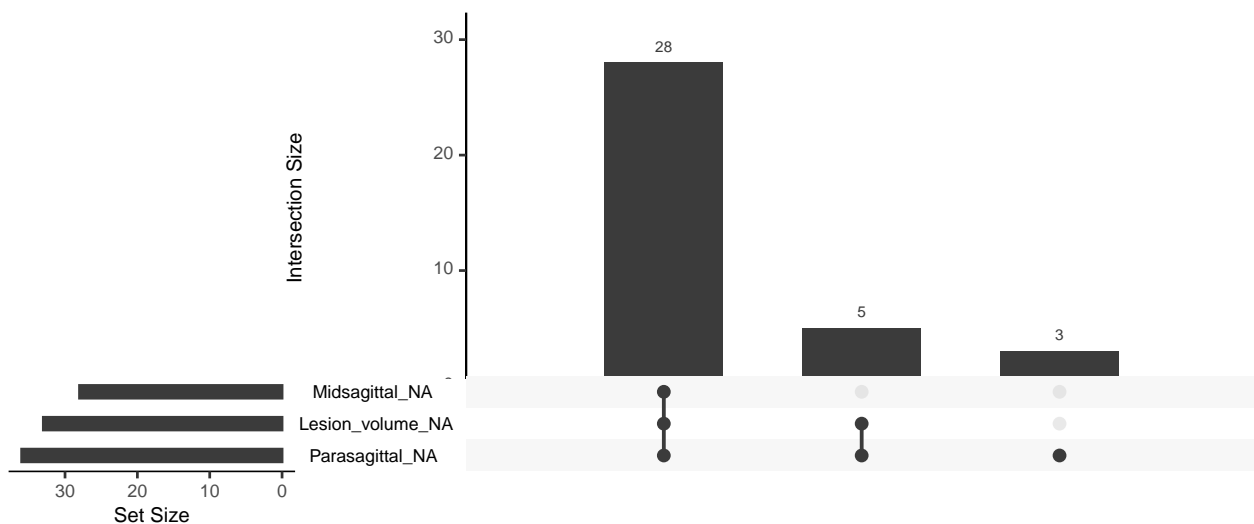| tissue_mid_missing	SR_missing	lesion_volume_missing	patient_count
FALSE	FALSE	FALSE	90
FALSE	TRUE	FALSE	3
FALSE	TRUE	TRUE	5
TRUE	TRUE	TRUE	28

Figure 2: Visualization of Table 2. Pattern of missing variables. The two combinations to the right should not be possible, because having midsagittal bridges but no parasagittal bridges is not plausible.

Table 2 and Figure 2 show the combinations of missing values in the three biomarkers. All 3 biomarker values were recorded for 90 patients. 8 patients have a missing value for the parasagittal tissue bridges, but a value for midsagittal tissue bridges is recorded.

(Remark: This should not be possible, right? Check with clinician. Those patients are shown in Table 3.)

Out of the 126 patients, 111 patients have all 4 measurements for the UEMS recorded. The other patients either discontinued after the first dose or did not receive the full dosing as per protocol. The Upper extremity motor score was first measured on average 1.2 days before receiving the first dose. (Remark: Check with clinicians why some patients discontinued, or appendix of the study when published.)

Figure 3 shows the distributions of the biomarkers at baseline. With regard to the lesion volume, 6 patients are considered outliers and were excluded from the further analysis. All 6 patients were part of the NG101 group. The statistical models would be strongly influenced by these outliers.

(Remark: Make sensitivity analysis also for other biomarkers by removing outliers and redo the analysis? Check whether the model results change significantly. Potentially check with clinicians if the outliers are valid or not.)

Relationship of Biomarkers with Recovery

In this section, the results are shown for each biomarker separately (midsagittal tissue bridges, parasagittal tissue bridges, lesion volume). The results are structured in the following way: First, the raw data is pre-

Table 3: 8 Patients have recorded midsagittal tissue bridge values but no parasagittal tissue bridges. This should not be possible. Check with clinician.

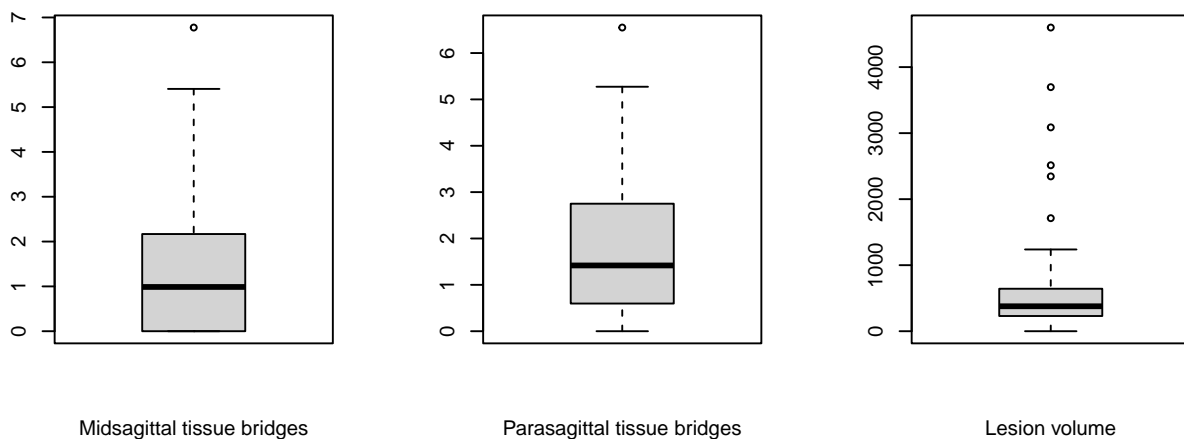| Patient-ID	Tissue midsagittal	Tissue parasagittal	Lesion volume
BSL-001	5.00	Missing	0
BYH-002	1.62	Missing	247.3856
BYH-018	0.00	Missing	Missing
BYH-025	2.81	Missing	202.55664
HLE-013	0.00	Missing	Missing
NTL-002	1.21	Missing	Missing
NTL-005	1.25	Missing	Missing
NTL-007	0.00	Missing	Missing

Figure 3: Boxplots of the midsagittal and parasagittal tissue bridges and the lesion volume at baseline. Concerning the lesion volume, 6 patients are considered outliers and were excluded from the analysis.

sented for each treatment group and corresponding quartile of the biomarker range. Second, the baseline distribution of the biomarker values against the UEMS in the treatment groups is shown. Third, the relationship of the biomarker with the recovery is investigated by the smooth functions that have been fitted by the GAM. Fourth, the fitted models are visualized by adding predictions to the raw data plots. Fifth, the differences in the predicted UEMS scores between baseline and 6-month follow-up (Δ-UEMS) are calculated for different values of the biomarker.
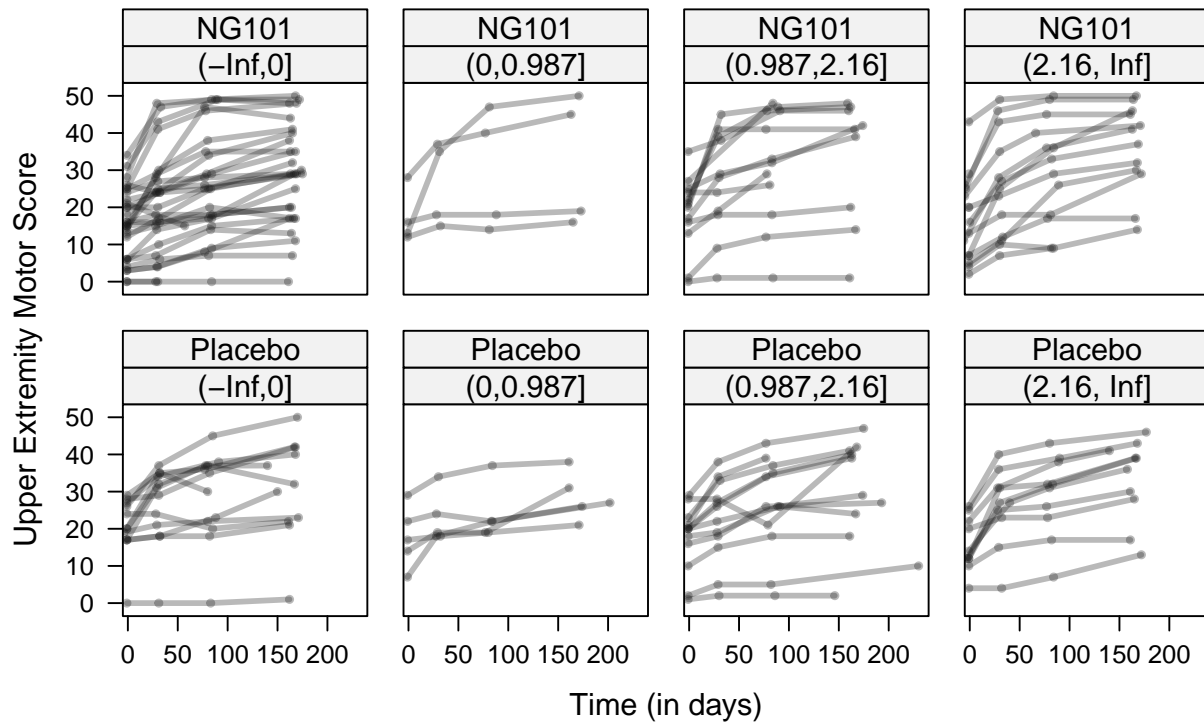
Midsagittal Tissue Bridges

Figure 4: Patient data per treatment group separated in the four quartiles for the amount of midsagittal tissue bridges The quantiles are based on the overall distribution of midsagittal tissue bridges.
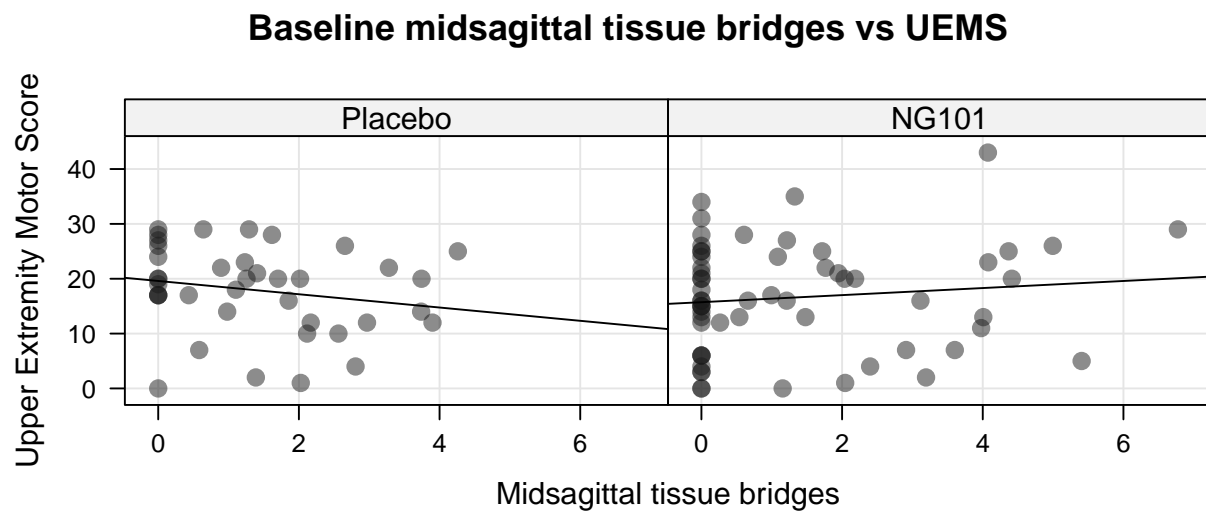
Baseline midsagittal tissue bridges vs UEMS

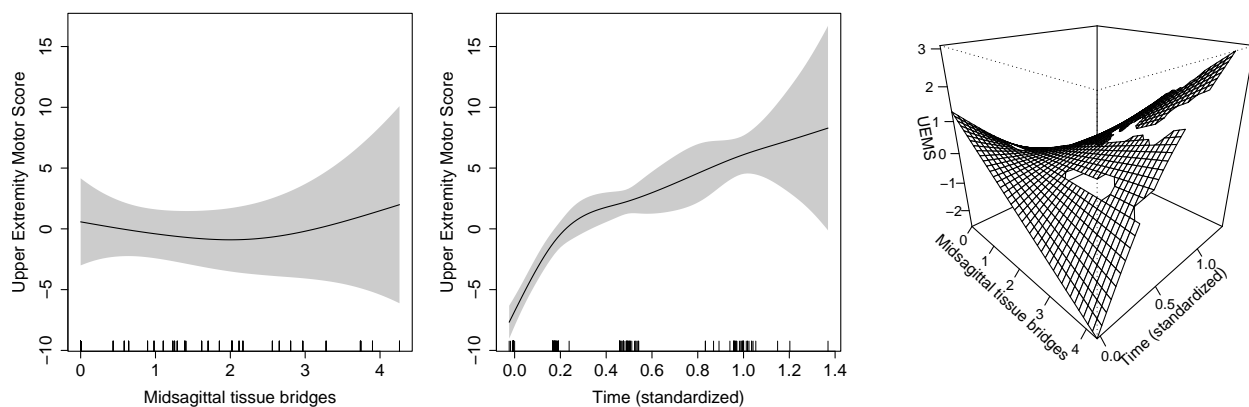Figure 5: Scatterplot of the baseline midsagittal tissue bridges against Upper Extremity Motor Score in the two treatment groups.

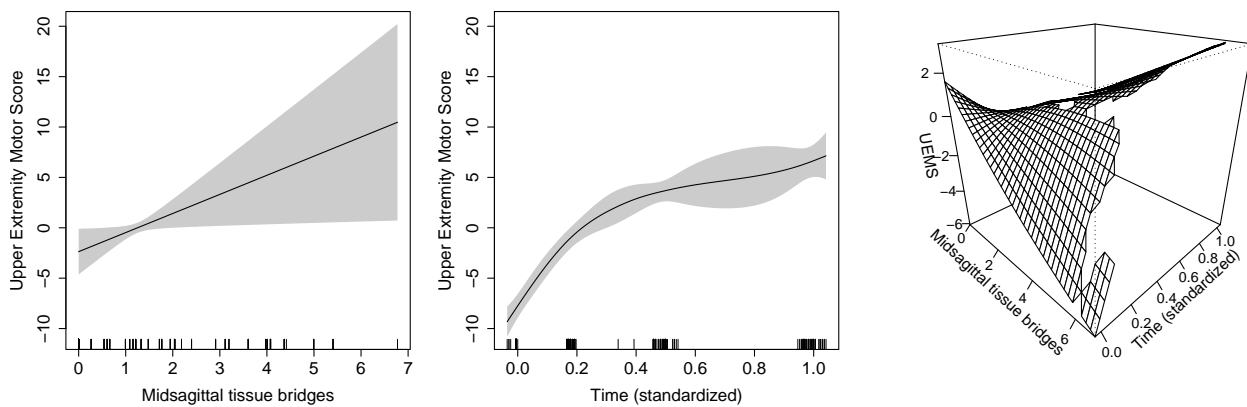Figure 6: Smooth functions fitted by the GAM for the placebo group.

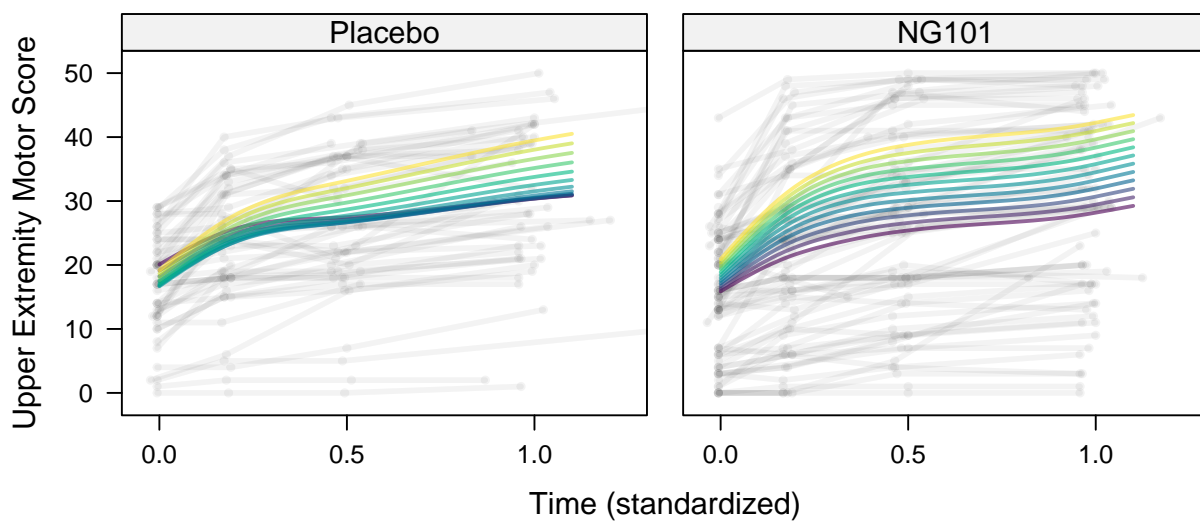Figure 7: Smooth functions fitted by the GAM for the NG101 group.

Figure 8: Predictions made with different values for midsagittal tissue bridges. For each treatment group the respective GAM was fitted separately. The only parameter that changes for the different predictions is the amount of midsagittal tissue bridges.
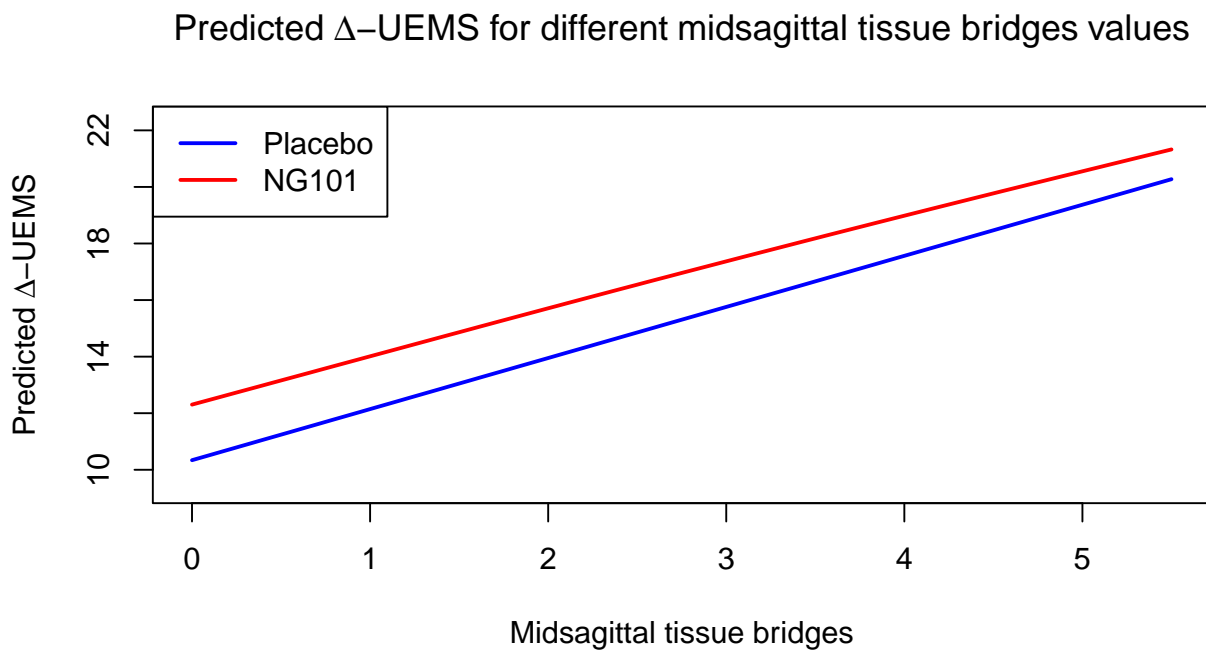
Predicted Δ−UEMS for different midsagittal tissue bridges values

Figure 9: Differences of the predicted 6-month follow-up UEMS scores and the predicted baseline scores for different values of misagittal tissue bridges.
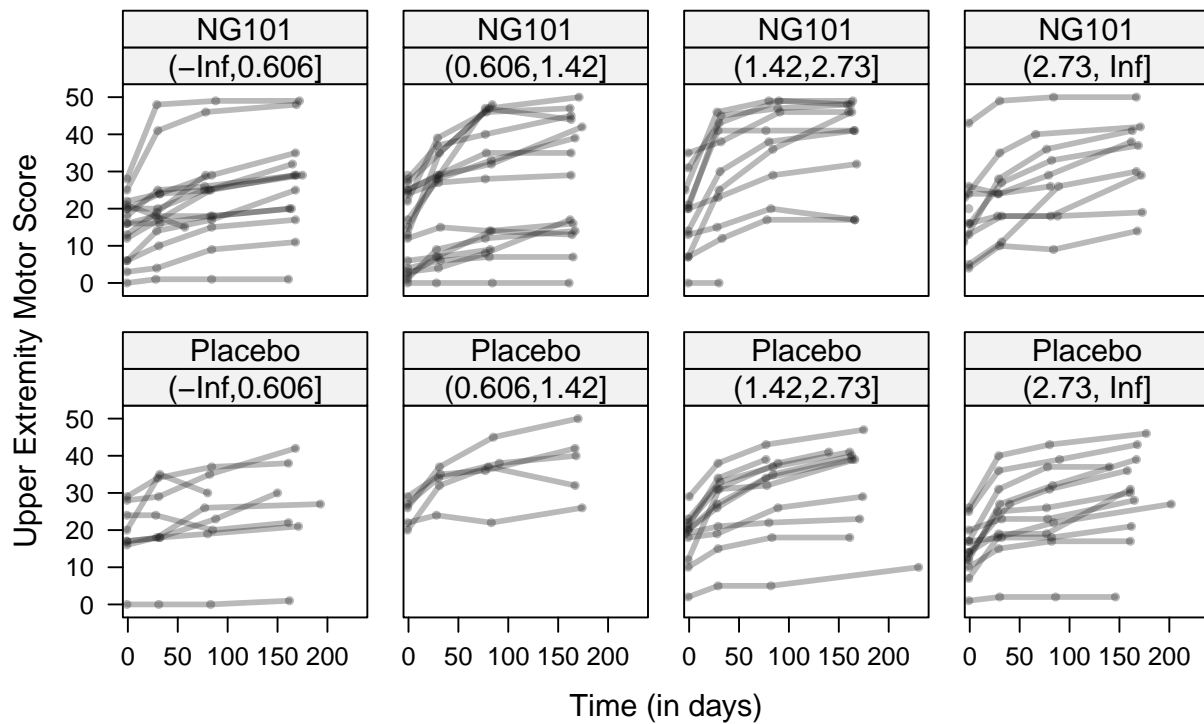
Parasagittal Tissue Bridges

Figure 10: Patient data per treatment group separated in the four quartiles for the amount of parasagittal tissue bridges The quantiles are based on the overall distribution of parasagittal tissue bridges.

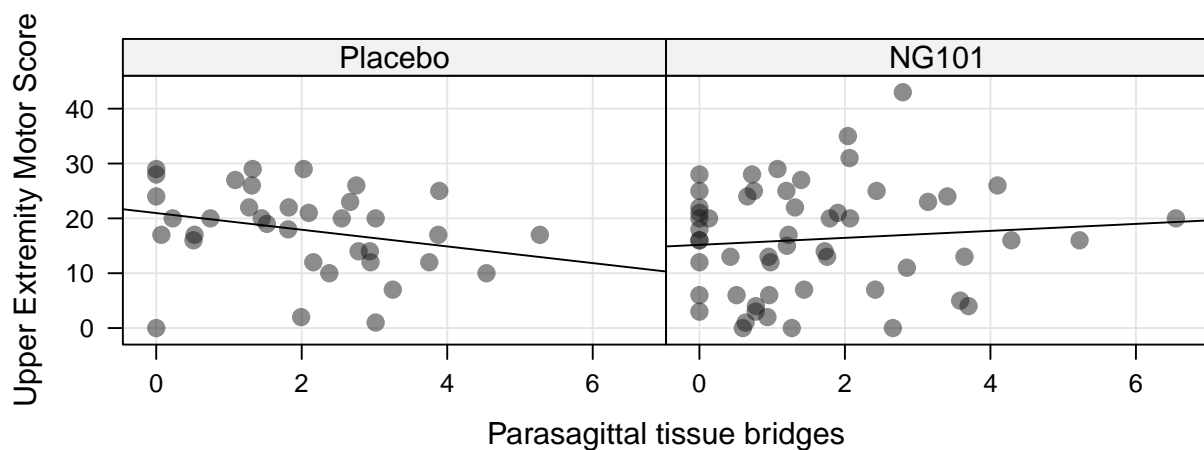## Baseline parasagittal tissue bridges vs UEMS

Figure 11: Scatterplot of the baseline parasagittal tissue bridges against Upper Extremity Motor Score in the two treatment groups.
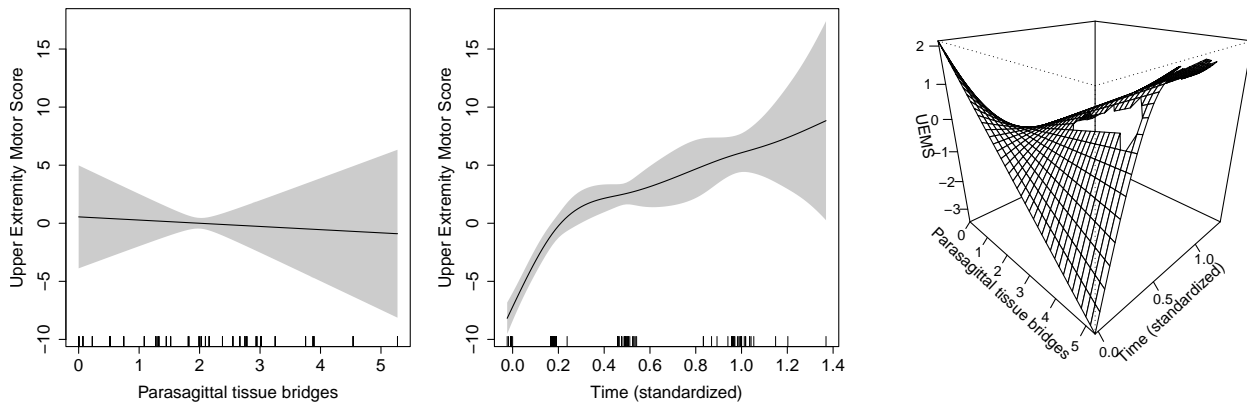
Figure 12: Smooth functions fitted by the GAM for the placebo group.

Figure 13: Smooth functions fitted by the GAM for the NG101 group.

Predictions for different parasagittal tissue bridges values
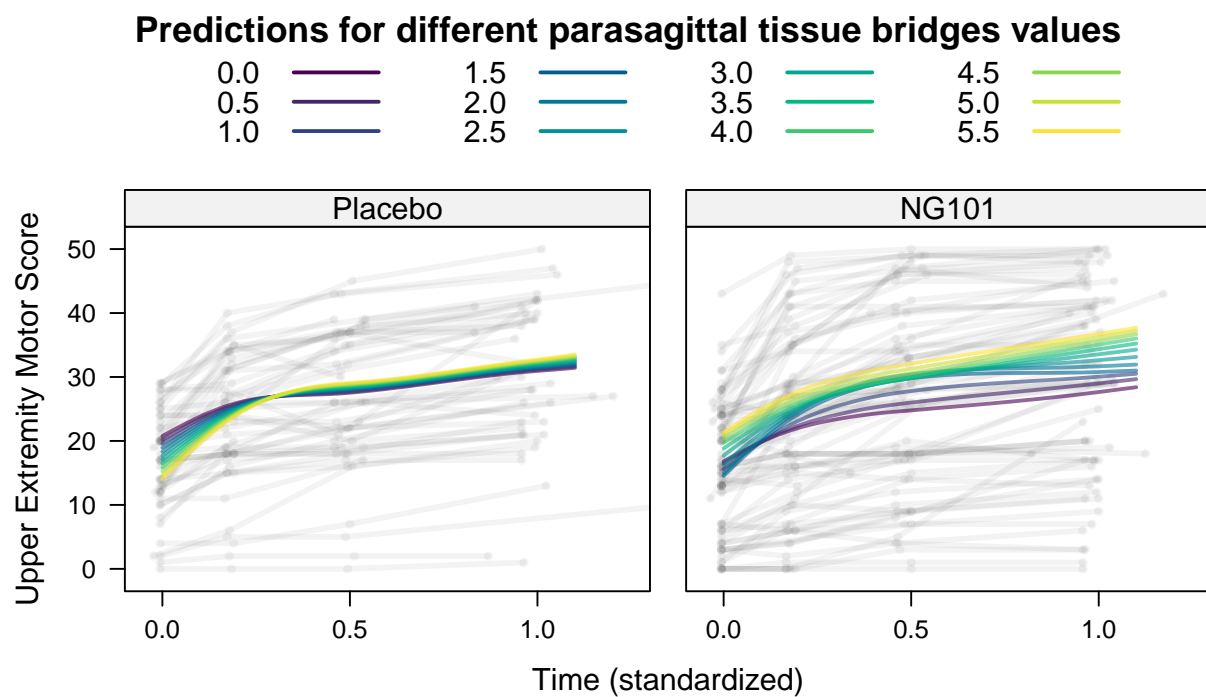
Figure 14: Predictions made with different values for parasagittal tissue bridges. For each treatment group the respective GAM was fitted separately. The only parameter that changes for the different predictions is the amount of parasagittal tissue bridges.

Figure 15: Differences of the predicted 6-month follow-up UEMS scores and the predicted baseline scores for different values of parasagittal tissue bridges.

Lesion Volume

Important: 6 patients with lesion volume > 1200 were excluded and set to NA. They are considered as outliers. Check with the study team!
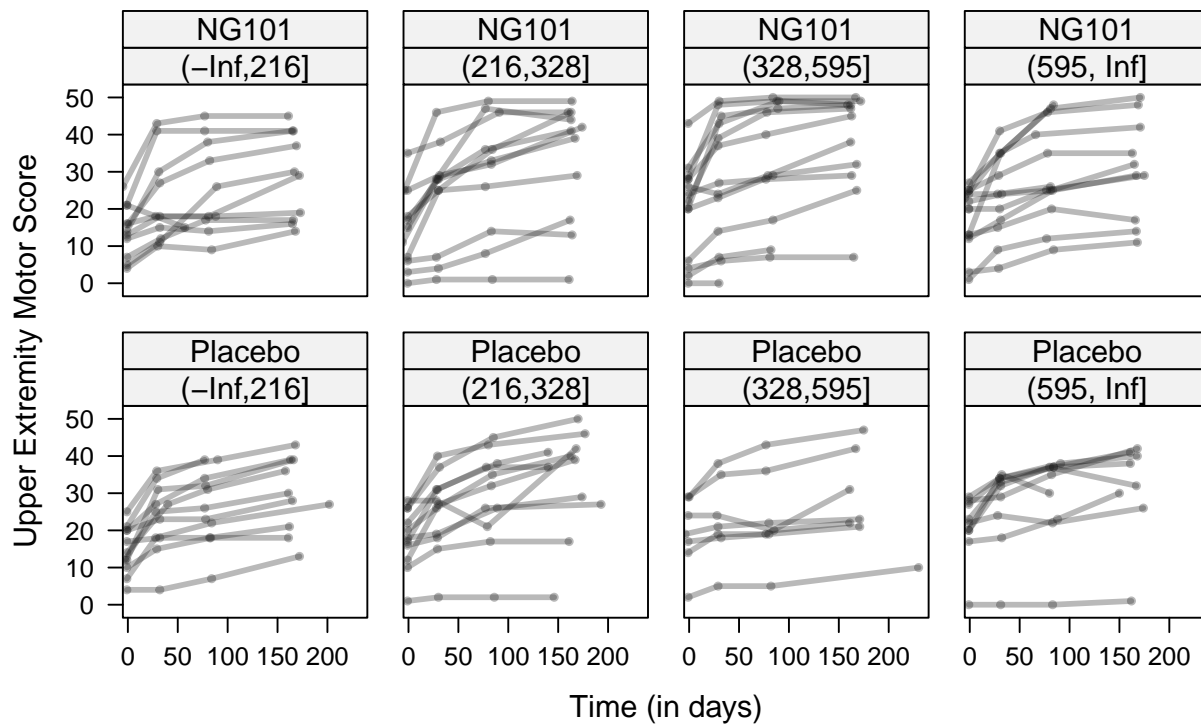
Figure 16: Patient data per treatment group separated in the four quartiles for the lesion volume. The quantiles are based on the overall distribution of lesion volume.

Baseline lesion volume vs UEMS
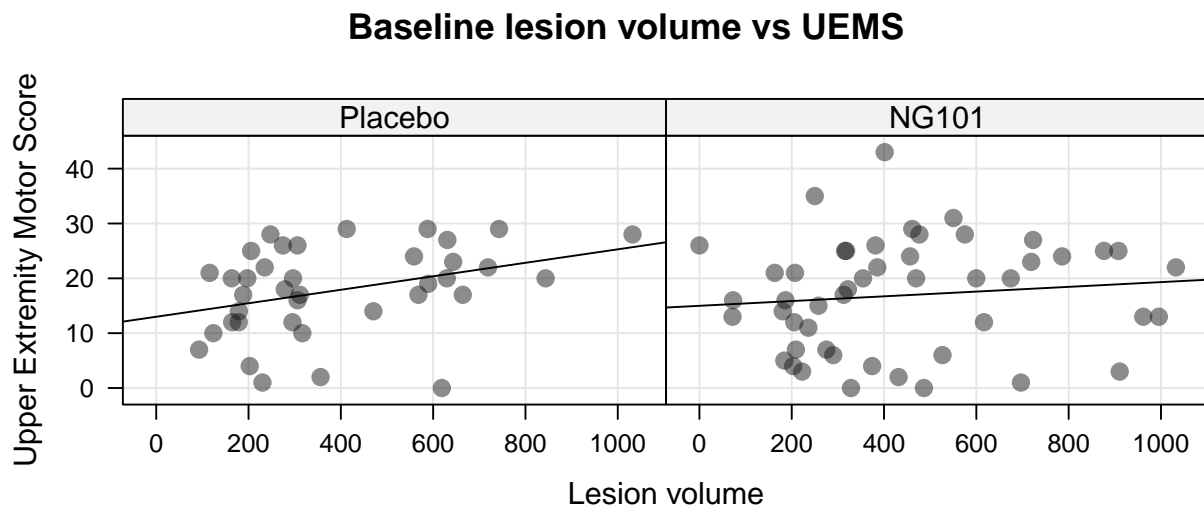
Figure 17: Scatterplot of the baseline lesion volume against Upper Extremity Motor Score in the two treatment groups.
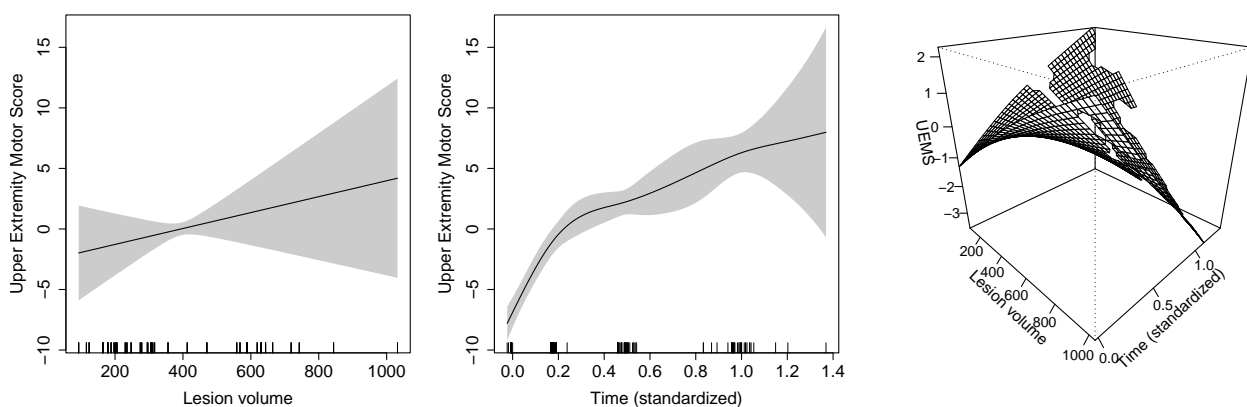
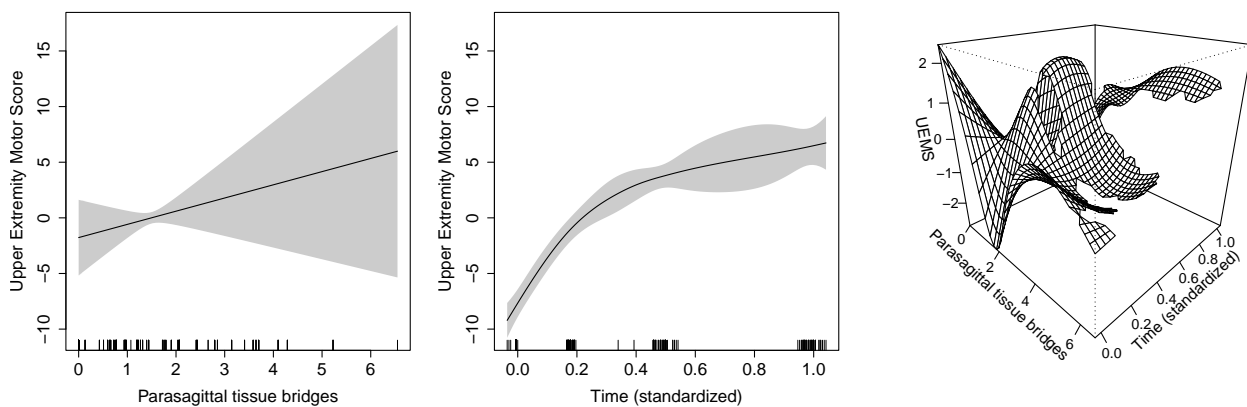Figure 18: Smooth functions fitted by the GAM for the placebo group.
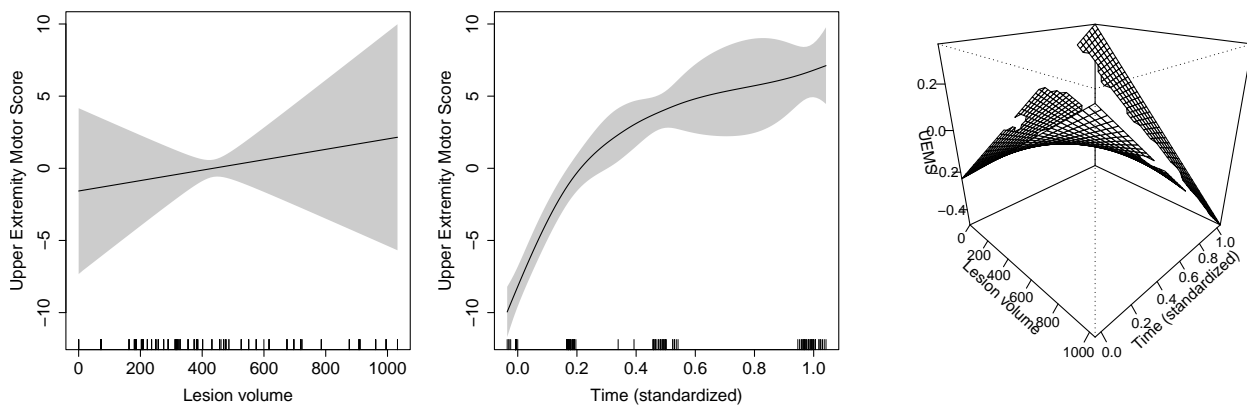
Figure 19: Smooth functions fitted by the GAM for the NG101 group.

Predictions for different lesion volume values

0.0	—	400.0	—	800.0	—	1200.0	—
100.0	—	500.0	—	900.0	—		
200.0	—	600.0	—	1000.0	—		
300.0	—	700.0	—	1100.0	—		

Figure 20: Predictions made with different values for lesion volume. For each treatment group the respective GAM was fitted separately. The only parameter that changes for the different predictions is the amount of lesion volume.
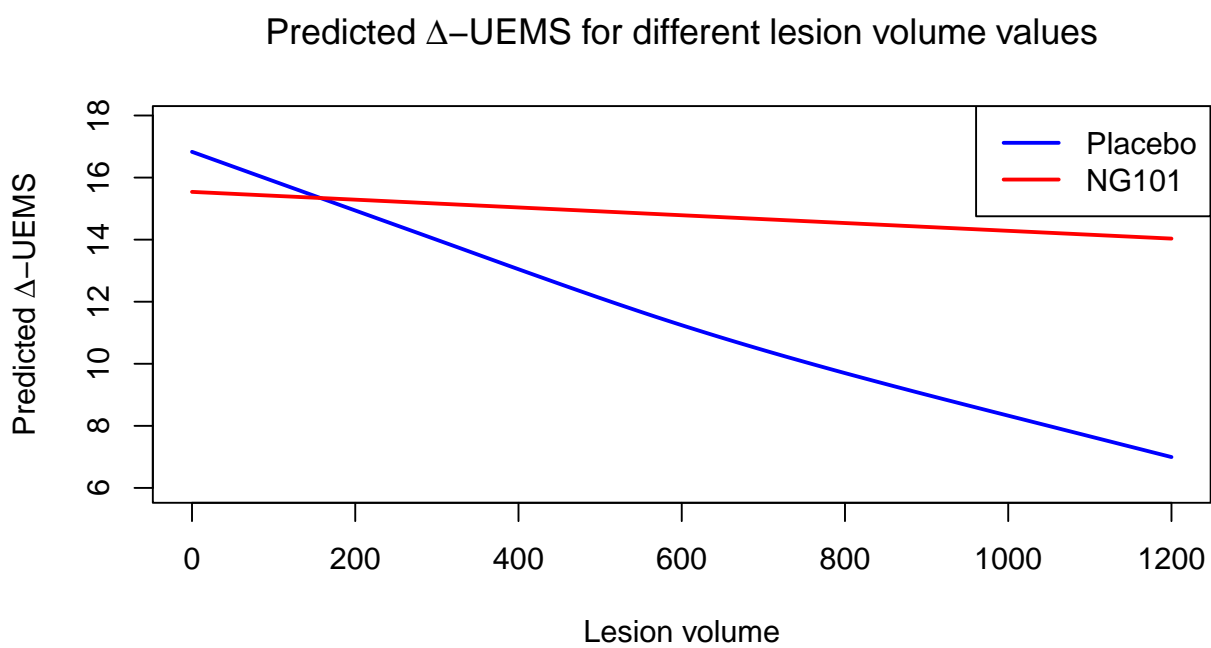
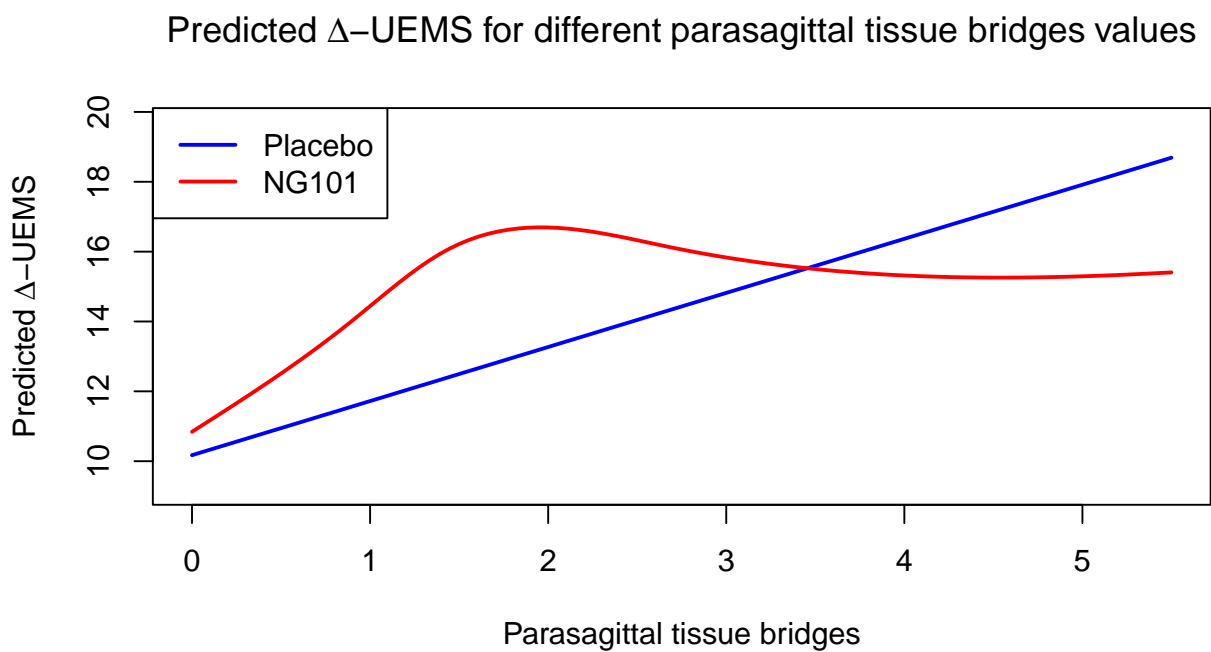Figure 21: Differences of the predicted 6-month follow-up UEMS scores and the predicted baseline scores for different values of lesion volume.

6   Conclusion

Summarize your conclusions regarding each research question. Each question listed in Section 3 should be addressed. Hard numbers belong in Section 5. Your conclusions should provide interpretations of your results in words.

The median survival time found in this study supports the growing literature on disease prognosis for patients with Disease A. Our results suggest that Therapy B is just as effective as Therapy A at fighting Disease A, but with less side effects. Similar to other studies, we found that Factor Y is an important predictor of long-term mortality. We also found Factor Z to be predictive of long-term mortality. This may be due to Reason X. Possible interactions between Factor Z and Therapy B require further research.

Limitations of this study include Q, R, and S.
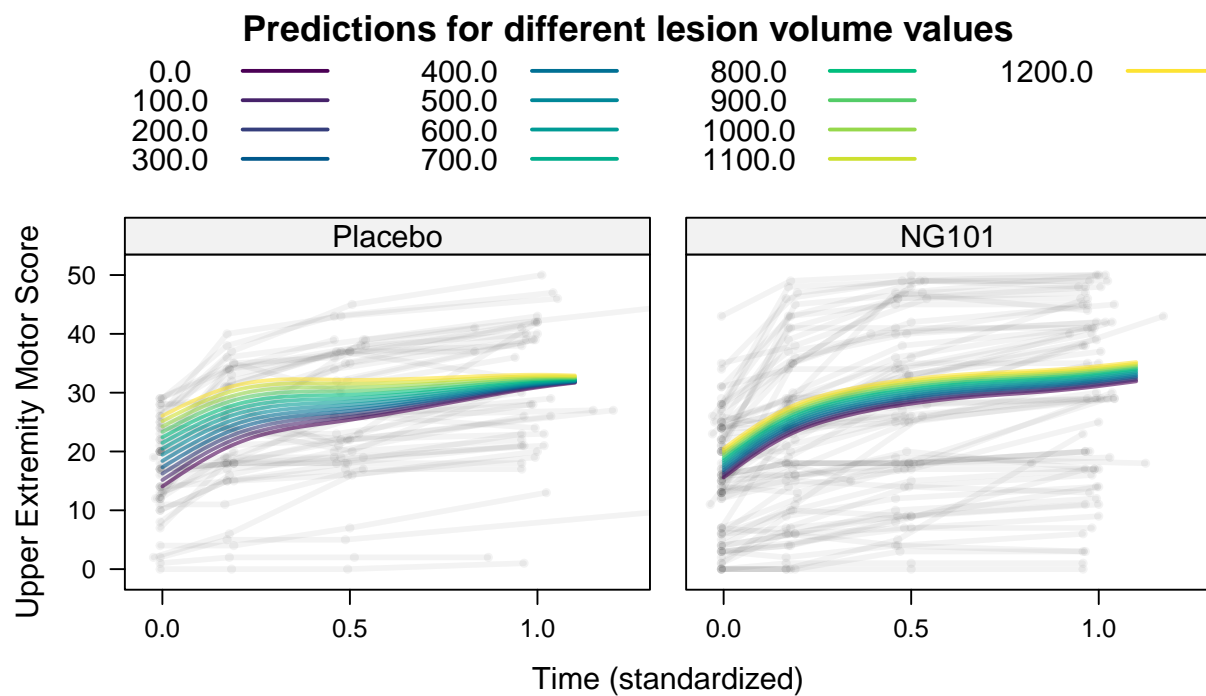
7   Generative AI declaration

Declaration During the preparation of this report, I used Github Copilot and ChatGPT in order to be more efficient with coding. After using this tool/service, I reviewed and edited the content as needed and I take full responsibility for the content of the report.

References

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8   Appendix

8.1   Computational Details

This document was generated on November 21, 2024 at 20:47. R version and packages used to generate this report:

```
## R version 4.4.1 (2024-06-14 ucrt)
## Platform: x86_64-w64-mingw32/x64
## Running under: Windows 11 x64 (build 22631)
##
## Matrix products: default
##
##
## locale:
## [1] LC_COLLATE=German_Germany.utf8  LC_CTYPE=German_Germany.utf8
## [3] LC_MONETARY=German_Germany.utf8 LC_NUMERIC=C
## [5] LC_TIME=German_Germany.utf8
##
## time zone: Europe/Zurich
## tzcode source: internal
##
## attached base packages:
## [1] stats     graphics  grDevices utils     datasets  methods   base
##
## other attached packages:
##  [1] naniar_1.1.0       dplyr_1.1.4        colorspace_2.1-1  mgcv_1.9-1
##  [5] nlme_3.1-164       lattice_0.22-6     readxl_1.4.3       stringr_1.5.1
##  [9] ggplot2_3.5.1      biostatUZH_2.2.7   MASS_7.3-60.2      survival_3.6-4
## [13] xtable_1.8-4       tableone_0.13.2    RColorBrewer_1.1-3 knitr_1.48
##
## loaded via a namespace (and not attached):
##  [1] gtable_0.3.5              xfun_0.47                visdat_0.6.0
##  [4] psy_1.2                   vctrs_0.6.5              tools_4.4.1
##  [7] generics_0.1.3            parallel_4.4.1           tibble_3.2.1
## [10] proxy_0.4-27              fansi_1.0.6              highr_0.11
## [13] pkgconfig_2.0.3           ReplicationSuccess_1.3.3 Matrix_1.7-0
## [16] data.table_1.16.2         lifecycle_1.0.4          farver_2.1.2
## [19] compiler_4.4.1            munsell_0.5.1            mitools_2.4
## [22] codetools_0.2-20          survey_4.4-2             class_7.3-22
## [25] prodlim_2024.06.25        pillar_1.9.0             nloptr_2.1.1
## [28] cmprsk_2.2-12             boot_1.3-30              parallelly_1.38.0
## [31] lava_1.8.0                tidyselect_1.2.1         digest_0.6.37
## [34] stringi_1.8.4             future_1.34.0            listenv_0.9.1
## [37] labeling_0.4.3            forcats_1.0.0            splines_4.4.1
## [40] labelled_2.13.0           grid_4.4.1               cli_3.6.3
## [43] magrittr_2.0.3            utf8_1.2.4               future.apply_1.11.2
## [46] e1071_1.7-16              withr_3.0.1              scales_1.3.0
## [49] globals_0.16.3            lme4_1.1-35.5            gridExtra_2.3
## [52] cellranger_1.1.0          zoo_1.8-12               hms_1.1.3
## [55] evaluate_1.0.0            UpSetR_1.4.0             haven_2.5.4
## [58] rlang_1.1.4               Rcpp_1.0.13              glue_1.7.0
## [61] DBI_1.2.3                 rstudioapi_0.17.1        minqa_1.2.8
## [64] plyr_1.8.9                R6_2.5.1
```

8.2   Code

Please provide ALL code with which you produced this report by code chunk reuse, i.e. name all your chunks and display them here by typing «chunkname». You can also display code from external scripts, see the example for data preparation below. Try to

format your code such that it fits in the lines. include comments to indicate which section the chunks were used in.

```r
################################################################################
# code for packages, settings
################################################################################
## Import external functions
## ---------------------------------------------------------------------------

## Packages
## ---------------------------------------------------------------------------
library(RColorBrewer) # colors for plots
library(tableone) # for Table 1 functions
library(xtable) # formatting tables and generating the tex code
library(biostatUZH) # EBPI-written package, if not installed, uncomment code below
#devtools::install\_github(repo = "felix-hof/biostatUZH")
library(ggplot2) # customizable plots
library(stringr) # to prettify tables
library(readxl) # to import data
library(lattice) # for xyplot
library(mgcv) # for GAMs
library(colorspace) # sequential colors
library(dplyr)
library(naniar) # for missing data visualization (gg_miss_upset)
# library(gtsummary) # for table creation
### include project-specific packages here as well (e.g., lme4 for linear mixed effects models)
### if possible do not load libraries in chunks further below or in scripts that you source

#############################################
### only load libraries that you really use!####
#############################################

## Additional settings
## ---------------------------------------------------------------------------
cols <- brewer.pal(3, "Set1")
options(width = 85, digits = 4, show.signif.stars = FALSE)


################################################################################
# code for data preparation from external script
################################################################################
dat.raw <- read.csv("../data/iris_data_20121206.csv")

## Final Dataset
## ---------------------------------------------------------------------------
dat <- dat.raw


## Data Preparation
## ---------------------------------------------------------------------------

# for teaching purposes, a few numbers are set to missing
obs.to.missing <- sample(x=length(iris$Sepal.Length), size=2)
dat$Sepal.Length[obs.to.missing] <- NA

# to include a categorical variable, we create one here
dat$Sepal.Length.Cat <- cut(dat$Sepal.Length, breaks=c(0, 5, 8),
                            labels=c("length <=5 cm", "length >5 cm"))
```

```r
###########################################################################
# code for results: descriptive results
###########################################################################


###########################################################################
# code for results: first research question
###########################################################################
mod.lm <- lm(Sepal.Length ~ Sepal.Width, data = dat)
mod.lm1 <- lm(Sepal.Length ~ ., data = dat)



## choosing columns
tableRegression(mod.lm1, stats = c("estimate", "ci.95", "p.value"),
                col.nam = c("Coefficient", "95\\% confidence interval", "$p$-value"),
                caption = "Linear regression model choosing some columns.",
                caption.placement = "top",
                label = "tab:regmod1", booktabs = TRUE)

## adapt row names
tableRegression(mod.lm, row.nam = c("Intercept", "Width Sepal"),
                stats = c("estimate", "ci.95", "p.value"),
                col.nam = c("Coefficient", "95\\%-confidence interval", "$p$-value"),
                caption = "Linear regression model with adapted row names.",
                caption.placement = "top",
                label = "tab:regmod2", booktabs = TRUE)

###########################################################################
# code for results: second research question
###########################################################################
## important for tables: set 'results = "asis"' in the knitr chunk options

## single header
## -----------------------------------------------------------------------
mat <- head(dat)

mat.xtab <- xtable(mat, align = "lrcccccc",
                   caption = "First six records of the iris dataset.", label = "tbl:head")
print(mat.xtab, size = "footnotesize", table.placement = "!ht",
      caption.placement = "top", include.rownames = FALSE,
      hline = c(-1,0, nrow(mat.xtab)), sanitize.text.function = function(x){x},
      booktabs = TRUE)


## with additional header
## -----------------------------------------------------------------------
mat <- table(dat$Species, dat$Petal.Width < 1.5)


addtorow <- list()
addtorow$pos <- list()
addtorow$pos[[1]] <- -1
addtorow$command <- c('\\hline Species & \\multicolumn{2}{c}{Petal.Width $<$ 1.5} \\\\')

mat.xtab <- xtable(mat, align = "r|cc",
                   caption = "Contingency table for iris data.",
                   caption.placement = "top", label = "tbl:cont")
print(mat.xtab, size = "footnotesize", table.placement = "!ht",
```

```
        caption.placement = "top", include.rownames = TRUE,
        hline = c(0,nrow(mat.xtab)), add.to.row = addtorow,
        sanitize.text.function = function(x){x})
```