Vedolizumab Deep Dive Overall Report

Bill Prucka, Klaus Gottlieb, Bohdana Raditch*

*No longer with Lilly

This document provides an overall summary of the work and insights gather from the deep dive on Vedolizumab. The focus of this effort is on the Gemini 1 study (Feagan 2013), NCT00783718. This trial enrolled patients with moderate to severe ulcerative colitis.

Reference:

Feagan BG et al. Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med 2013;369(8):699-710

Vedolizumab Deep Dive Overall Report

Table of Contents

Goals of the Project

This goals of this project have shifted, but the initial approach was to:

1) Use Unsupervised Learning of Laboratory Values Based on Change from Baseline to look for clusters
2) Use Feature Selection methods to Identify the Features that are Predictive of Endoscopic and Disease outcomes
3) Create a predictive model using these features

Unsupervised Learning of Laboratory Values Based on Change from Baseline

To summarize (previous work by Dana), there were no strong findings indicating that clusters of laboratory values would improve prediction. The code was developed in R and derived laboratory values and changes that were associated with endoscopy score timeing.

Initial clustering assessment using PCA and Kmeans did not reveal strong clustering in the data. Other clustering approaches such as TSNE and Support vector clustering don't have the required packages in R. Other approaches using Python were considered but did not result in a strong finding.

Additionally we looked at correlation among lab features:

Pairs of variables with Spearman correlation >0.5

Var 1	Var 2	Spearman's correlation
ALB_T6_CHG	CA_T6_CHG	0.591199815273285
ALB_T6_CHG	PROT_T6_CHG	0.745216369628906
ALT_T6_CHG	AST_T6_CHG	0.596681892871857
CA_T6_CHG	PROT_T6_CHG	0.651567757129669
CL_T6_CHG	SODIUM_T6_CHG	0.568026423454285
HCT_T6_CHG	HGB_T6_CHG	0.848601341247559
HCT_T6_CHG	RBC_T6_CHG	0.845066785812378
HGB_T6_CHG	RBC_T6_CHG	0.862924873828888
LYMP_T6_CHG	NEUTP_T6_CHG	-0.933720469474792
MONOP_T6_CHG	NEUTP_T6_CHG	-0.557900428771973

Feature Selection of Laboratory Tests with High Predictive Power for Endoscopic and Disease Specific

To evaluate feature importance, a random forest (RF) approach using conditional inference trees was used. The features selected for inclusion were change scores for lab values and various demographic variables. Feature importance was determine via the surrogate minimum depth (SMD) which is a measure of how deep into a tree the variable is included as a split. The SMD approach includes cases where either the variable is used directly, or is a surrogate for the split (i.e. then next best split to use). This approach better accounts for correlation among the potential predictors.

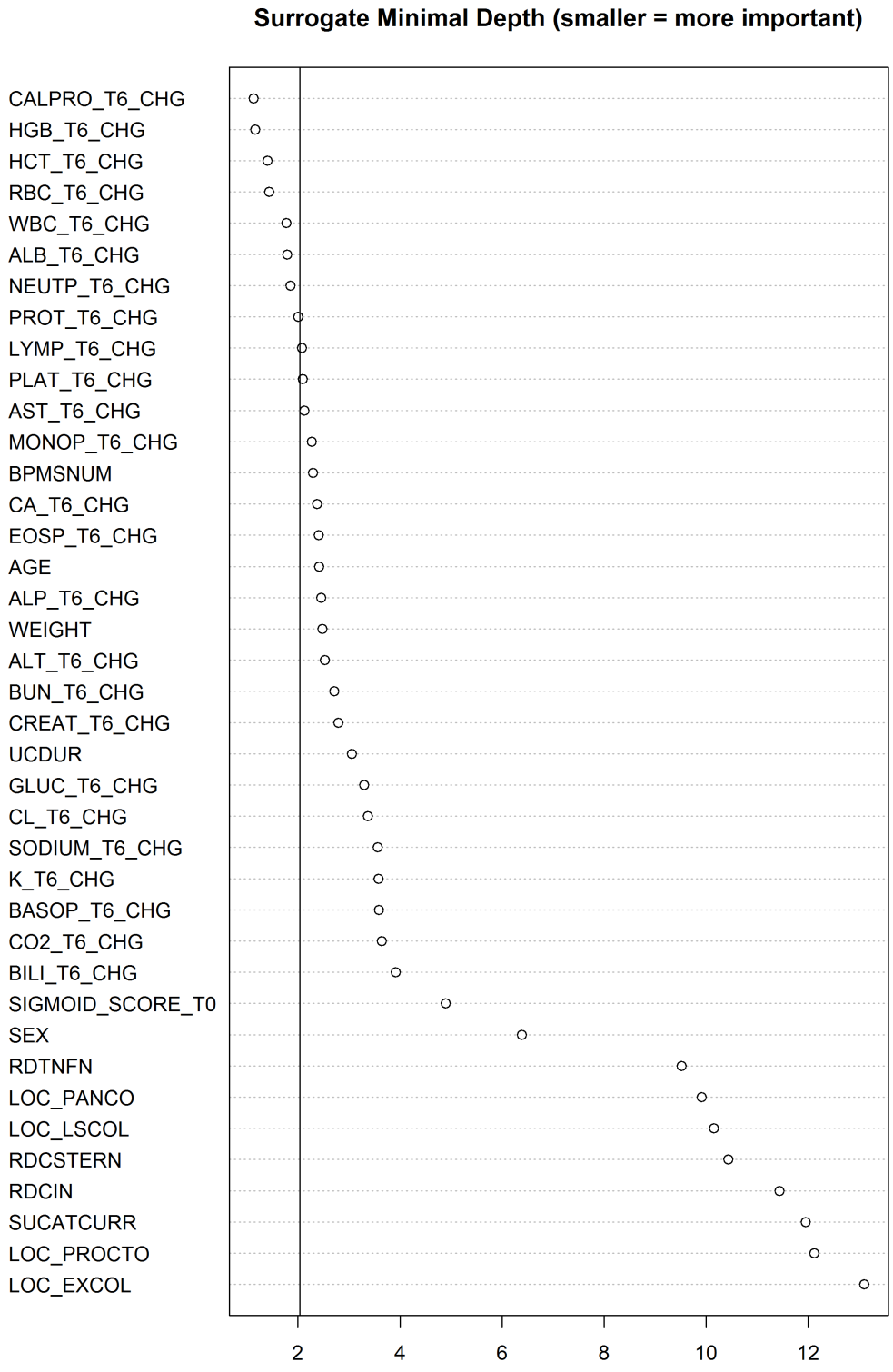
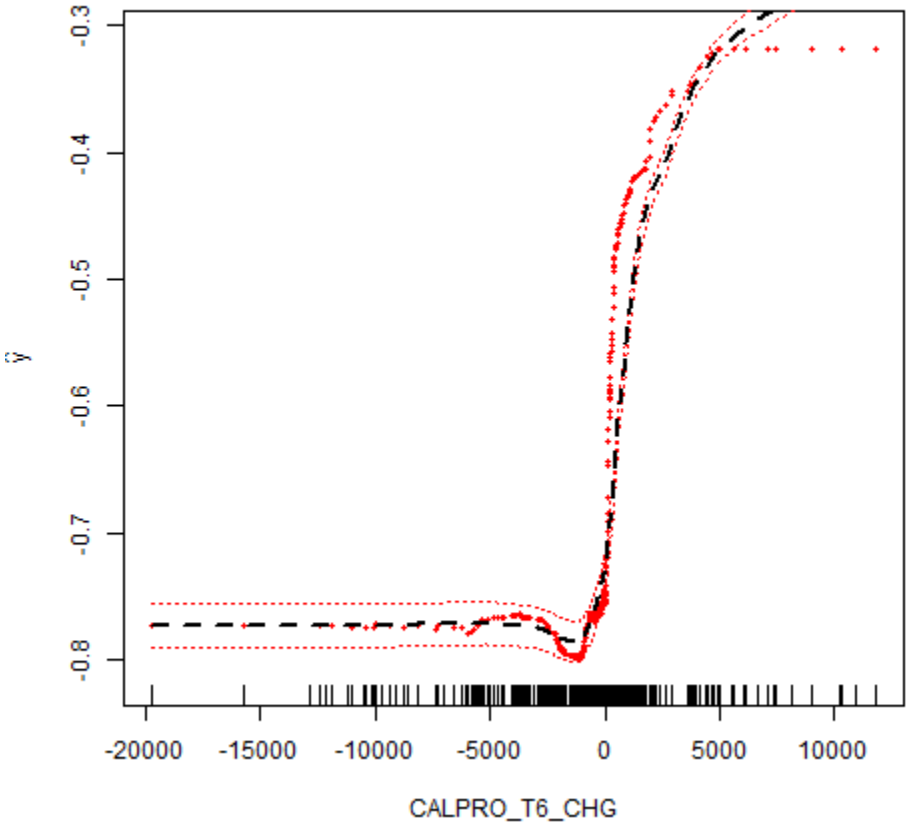
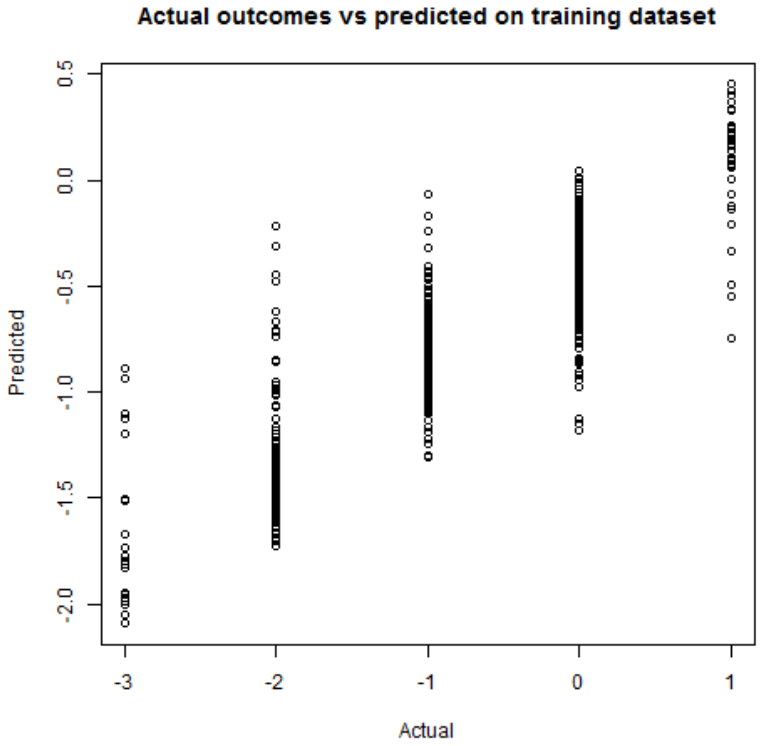

Surrogate Minimal Depth (smaller = more important)
CALPRO_T6_CHG
HGB_T6_CHG
HCT_T6_CHG
RBC_T6_CHG
WBC_T6_CHG
ALB_T6_CHG
NEUTP_T6_CHG
PROT_T6_CHG
LYMP_T6_CHG
PLAT_T6_CHG
AST_T6_CHG
MONOP_T6_CHG
BPMSNUM
CA_T6_CHG
EOSP_T6_CHG
AGE
ALP_T6_CHG
WEIGHT
ALT_T6_CHG
BUN_T6_CHG
CREAT_T6_CHG
UCDUR
GLUC_T6_CHG
CL_T6_CHG
SODIUM_T6_CHG
K_T6_CHG
BASOP_T6_CHG
CO2_T6_CHG
BILI_T6_CHG
SIGMOID_SCORE_T0
SEX
RDTNFN
LOC_PANCO
LOC_LSCOL
RDCSTERN
RDCIN
SUCATCURR
LOC_PROCTO
LOC_EXCOL
2
4
6
8
10
12

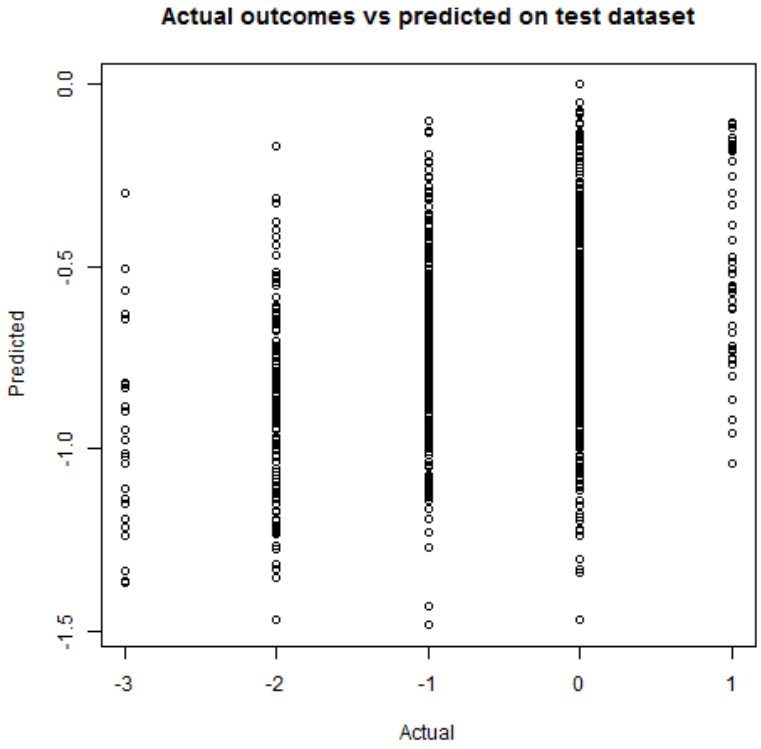
Figure: Sigmoid score variable Importance



Modeling of sigmoid score change from baseline to week 6

Random Forest Model





A bit of overtraining is evident. The error on the test set is quite a bit larger than the train set.

For total Mayo score a similar approach was used. Below are plots for the RF analyses. Again, CALPRO appears as a predictive features, with the strongest finding for Albumin.

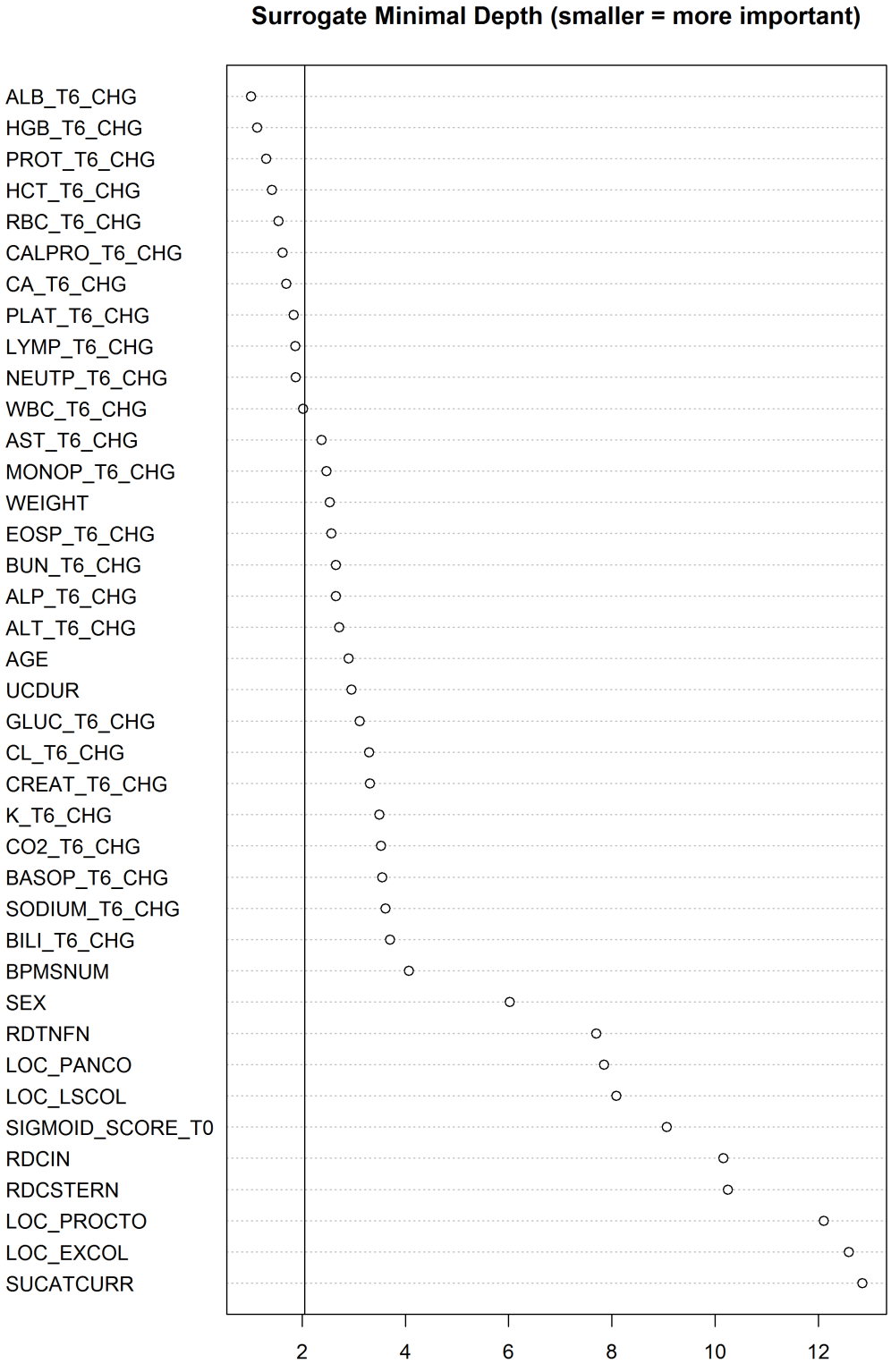
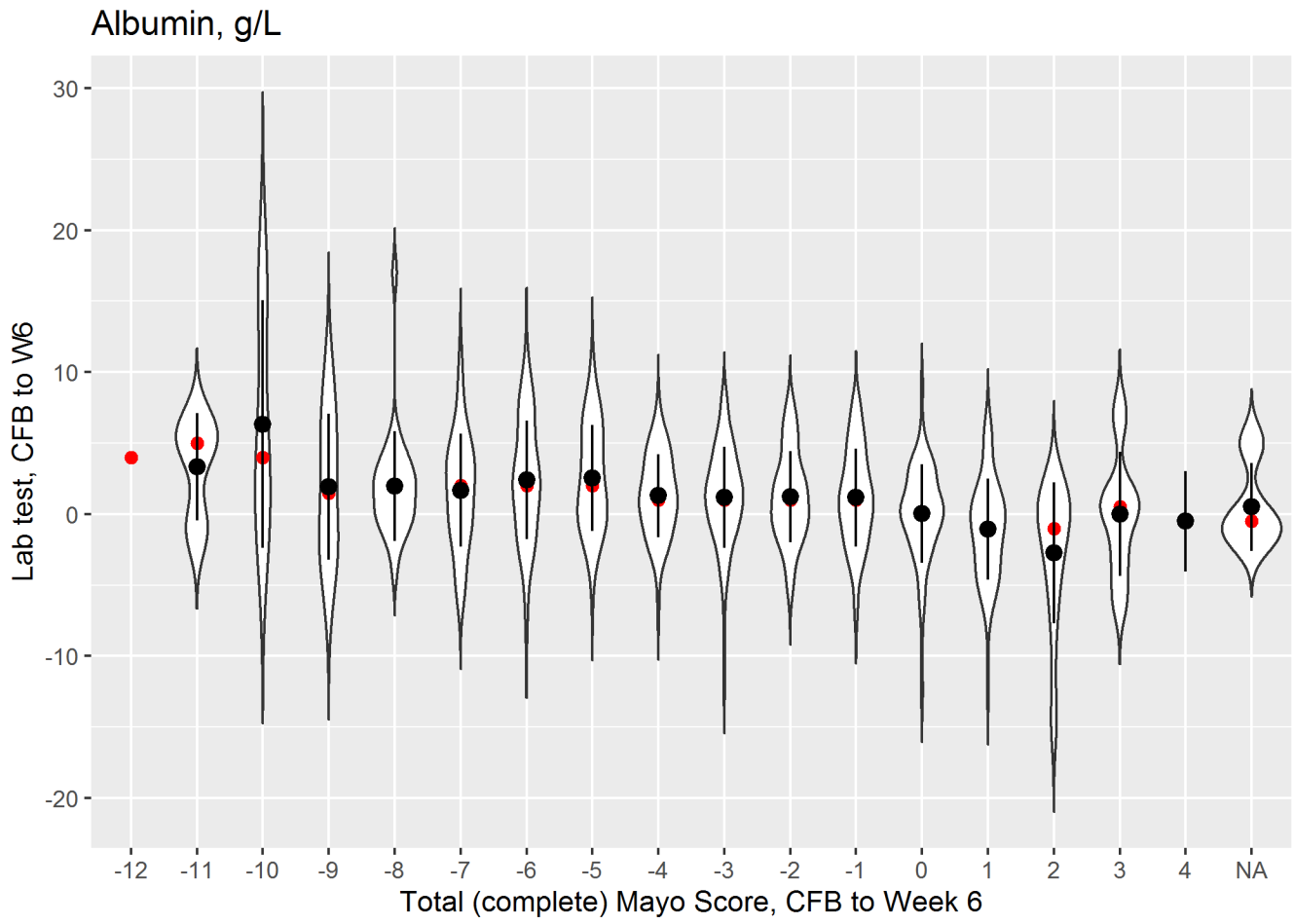
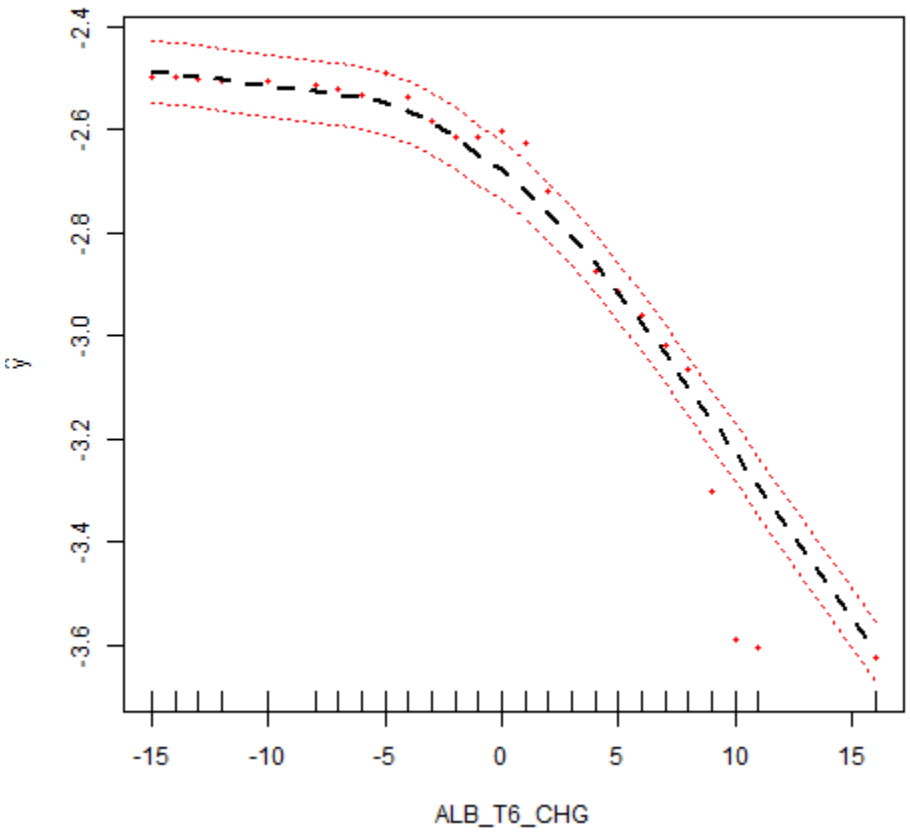

Surrogate Minimal Depth (smaller = more important)
ALB_T6_CHG
HGB_T6_CHG
PROT_T6_CHG
HCT_T6_CHG
RBC_T6_CHG
CALPRO_T6_CHG
CA_T6_CHG
PLAT_T6_CHG
LYMP_T6_CHG
NEUTP_T6_CHG
WBC_T6_CHG
AST_T6_CHG
MONOP_T6_CHG
WEIGHT
EOSP_T6_CHG
BUN_T6_CHG
ALP_T6_CHG
ALT_T6_CHG
AGE
UCDUR
GLUC_T6_CHG
CL_T6_CHG
CREAT_T6_CHG
K_T6_CHG
CO2_T6_CHG
BASOP_T6_CHG
SODIUM_T6_CHG
BILI_T6_CHG
BPMSNUM
SEX
RDTNFN
LOC_PANCO
LOC_LSCOL
SIGMOID_SCORE_T0
RDCIN
RDCSTERN
LOC_PROCTO
LOC_EXCOL
SUCATCURR
2
4
6
8
10
12

Figure: Total Mayo variable Importance

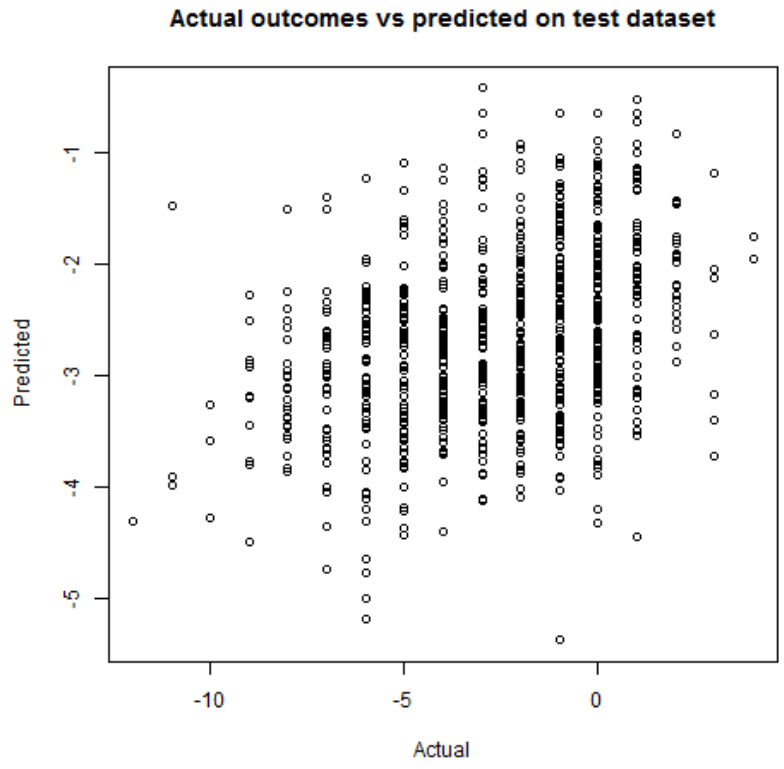
Violin Plot for Albumin, g/L
: change from baseline lab vs outcome

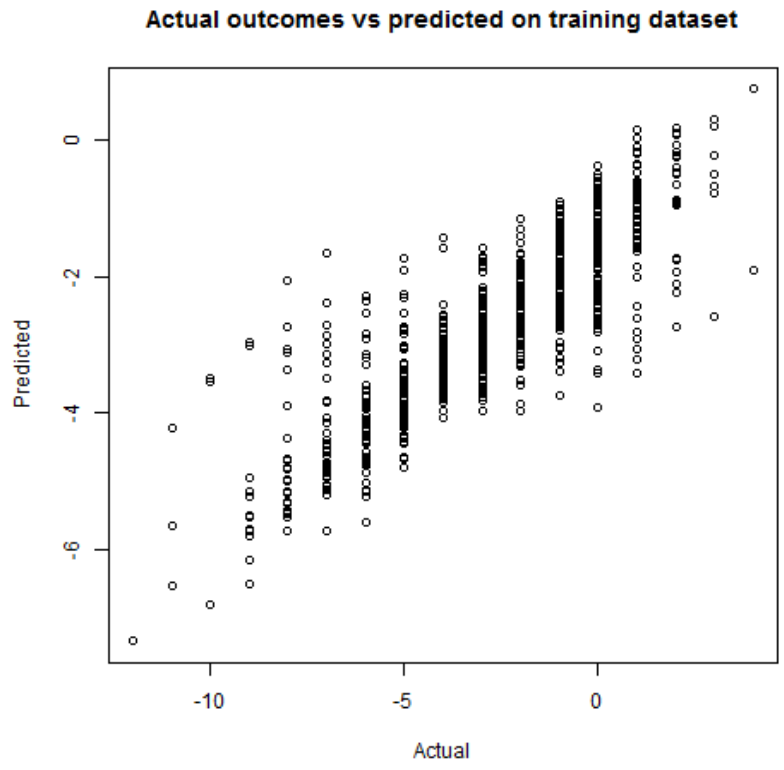


This plot shows the relationship between Albumin and total mayo change score. While there is some trend evident, it does not strongly predict the Mayo score.



Random Forest Model


Actual outcomes vs predicted on test dataset
Predicted
-1
-2
-3
-4
-5
-10
-5
0
Actual


Actual outcomes vs predicted on training dataset
Predicted
0
-2
-4
-6
-10
-5
0
Actual

Overall, the predictive modeling of laboratory scores with mayo score did not find strong associations sufficient to monitory in place of the score. This work did point to the importance of fecal calprotectin as a key measure of disease severity.

Summary of Fecal Calprotectin Dispersion over Time

The goal is to evaluate the temporal relationship between the log of fecal calprotectin and the Mayo scores over time. The assessment considers the correlation among scores (which grows over time).

Time Course of Correlation of Log Fecal Calprotectin and Mayo Scores

At baseline there is low correlation between log fecal calprotectin and the mayo scores (~0.10). As the study progresses, the correlation grows.

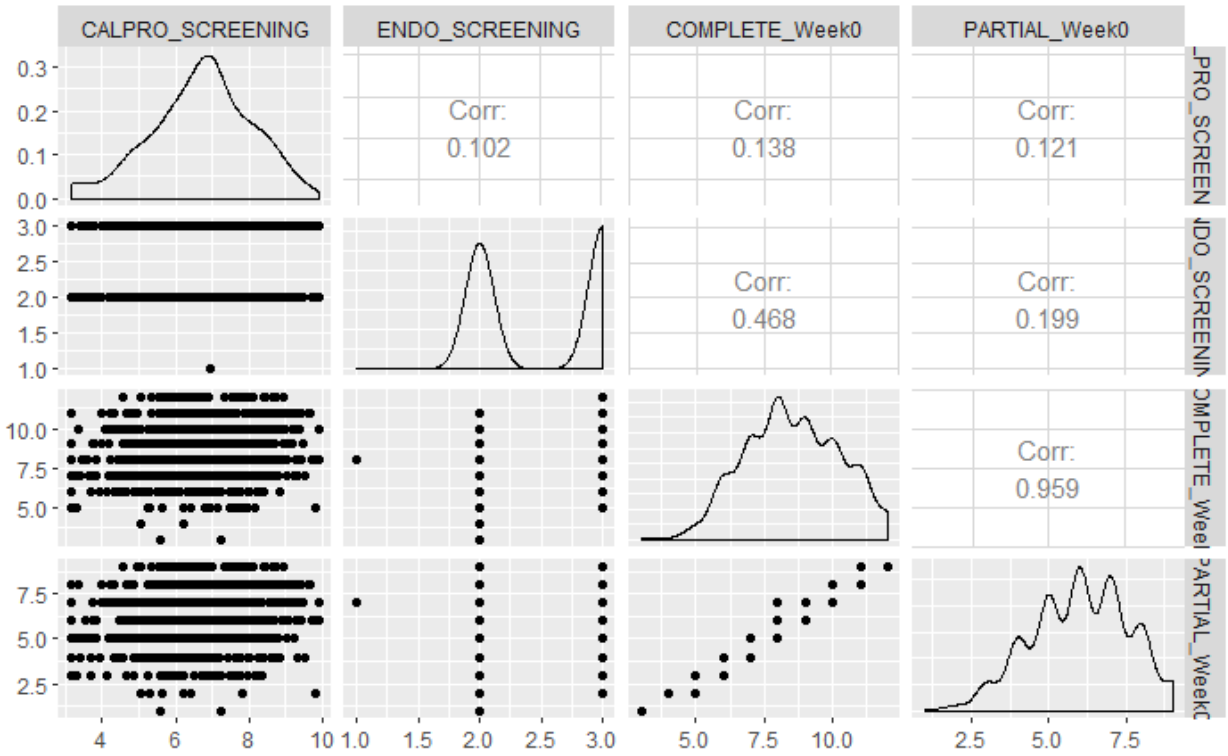


Figure : Baseline (or Week 0) Correlation for the Log Fecal Calprotectin and Mayo Scores (Endoscopic, Partial, Complete)

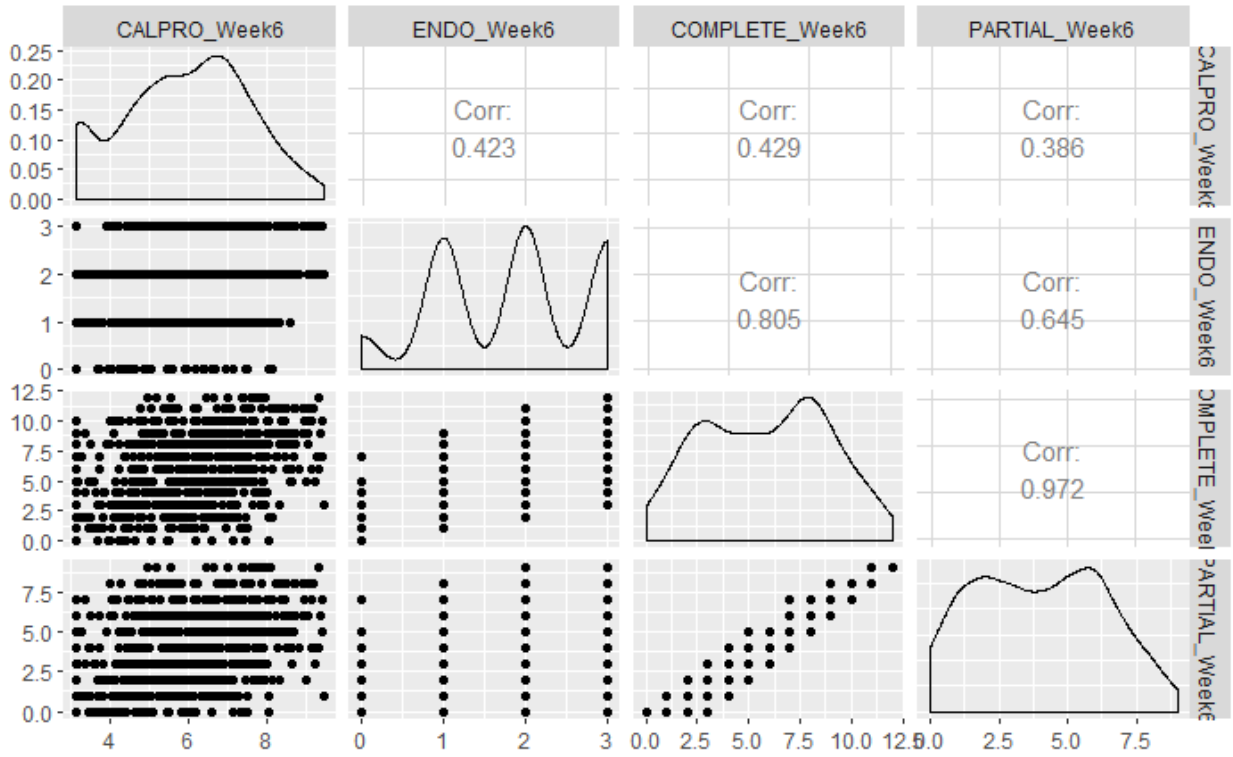


Figure : Week 6 Correlation for the Log Fecal Calprotectin and Mayo Scores (Endoscopic, Partial, Complete)

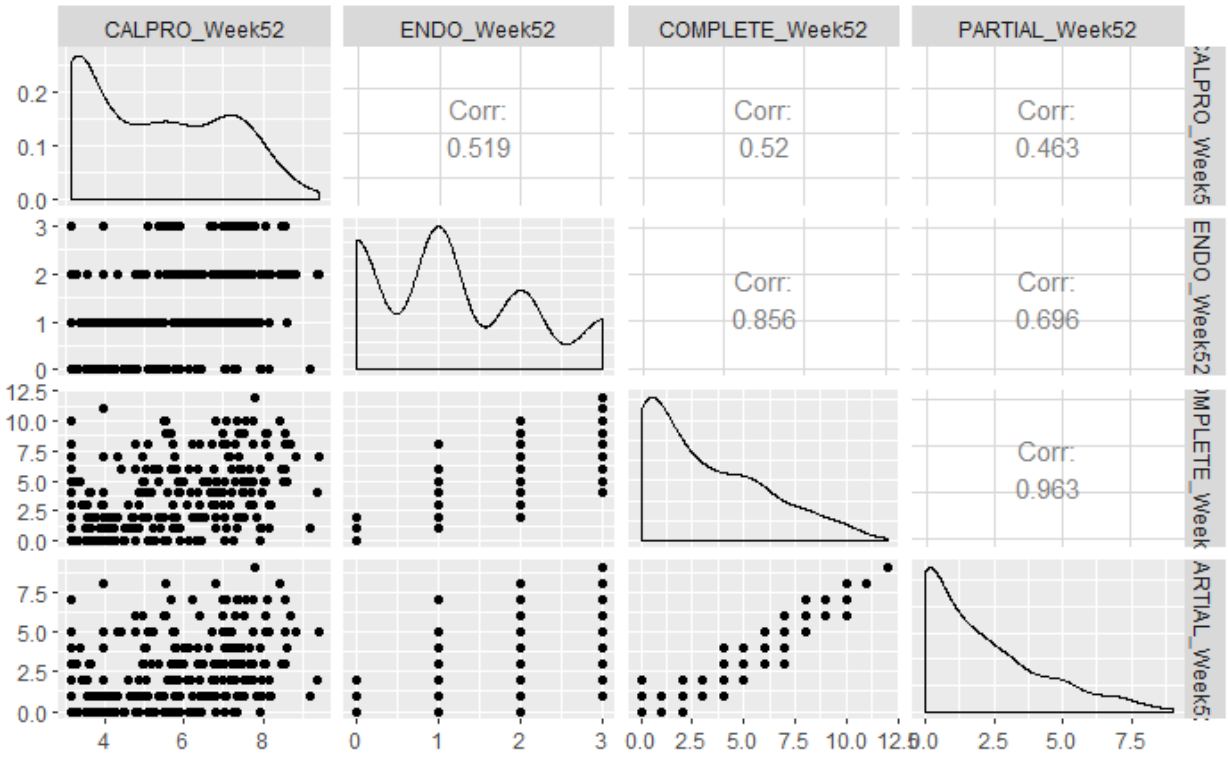


Figure : Week 52 Correlation for the Log Fecal Calprotectin and Mayo Scores (Endoscopic, Partial, Complete)

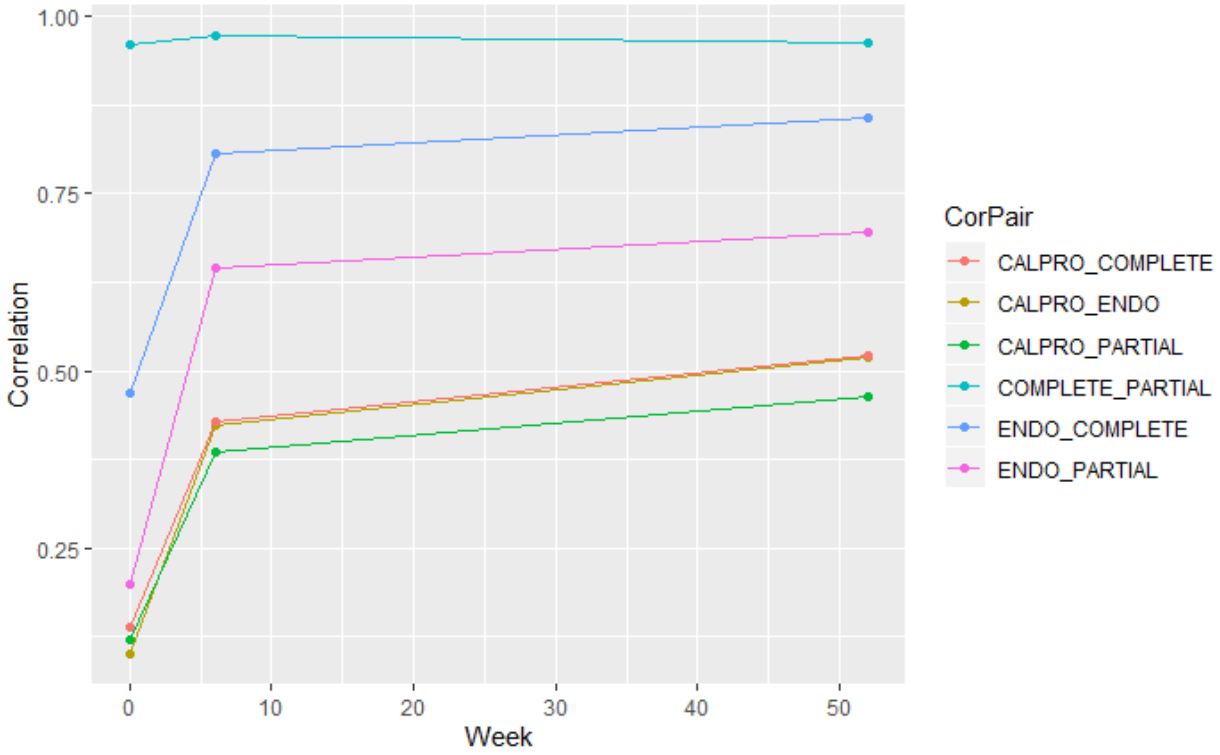


Figure: Plot of Correlation Pairs over Time for the Log Fecal Calprotectin and Mayo Scores (Endoscopic, Partial, Complete)

Distributional Assessment over Time of Fecal Calprotectin and Mayo Scores

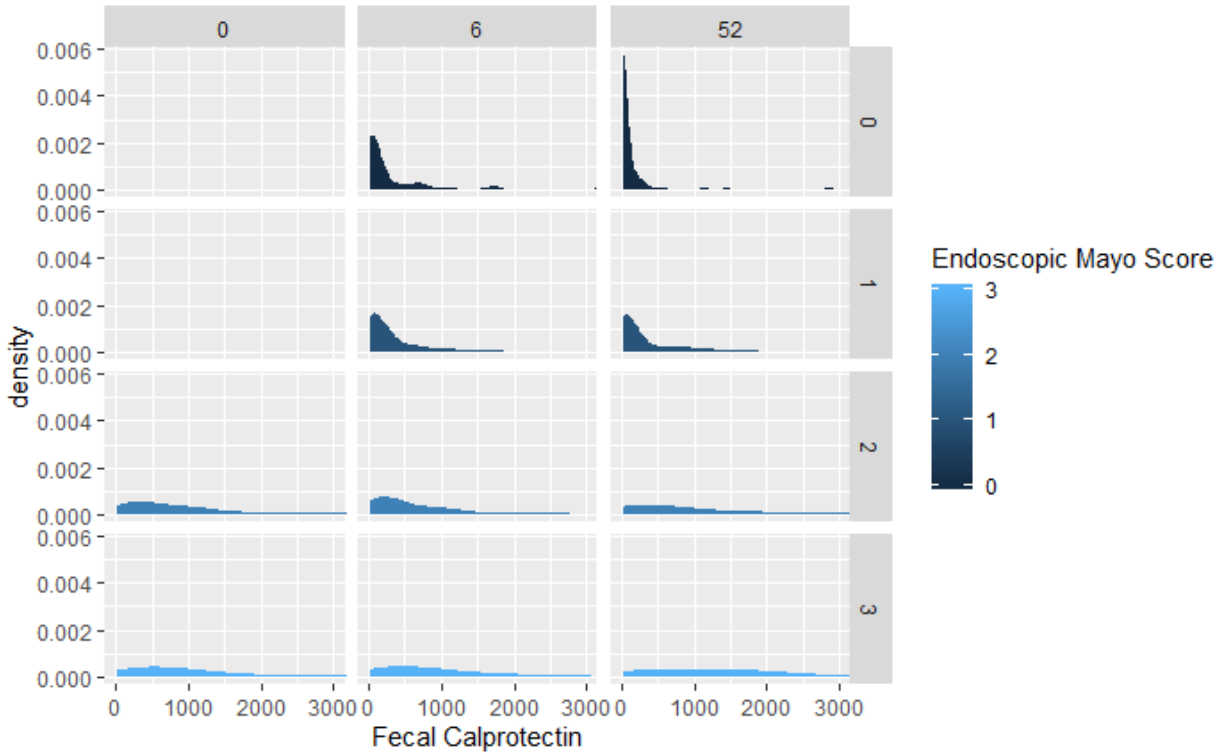


Figure: Distribution of Fecal Calprotectin by Endoscopic Mayo and Time

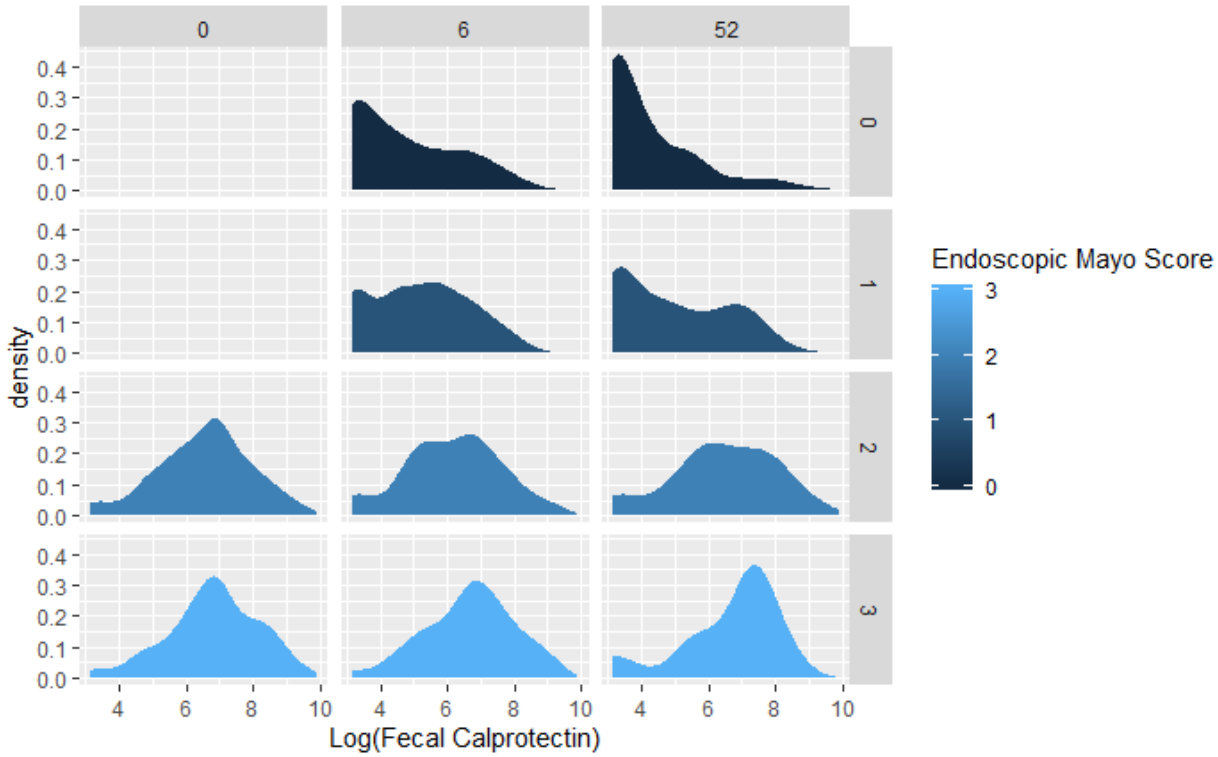


Figure: Distribution of Log(Fecal Calprotectin) by Endoscopic Mayo and Time

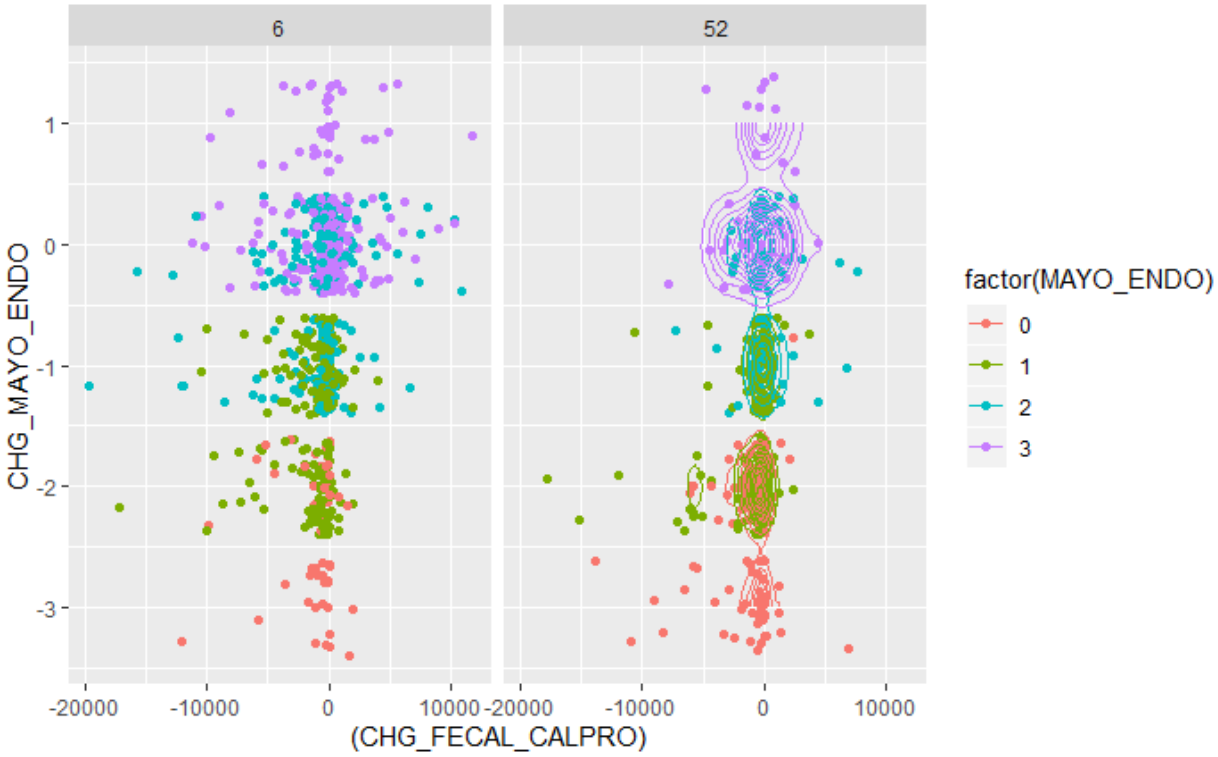


Figure: Distribution of Change Fecal Calprotectin by Change Endoscopic Mayo and Time

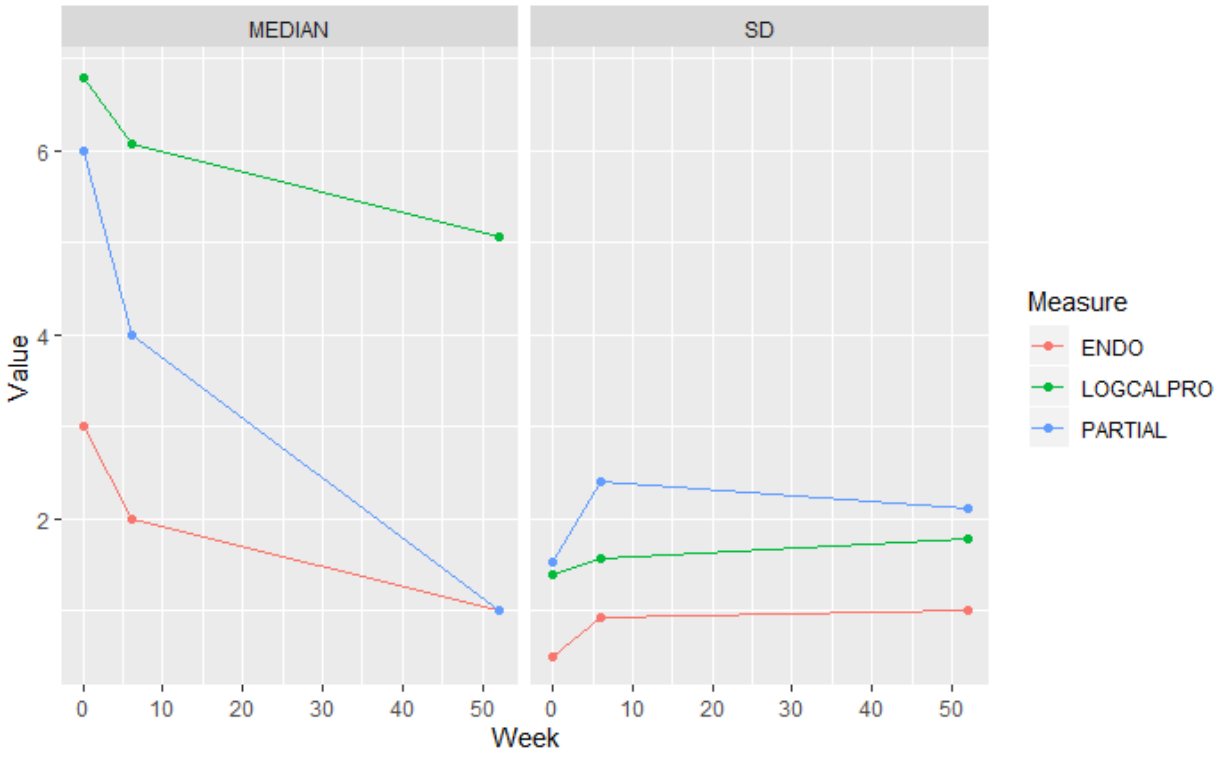


Figure: Median and Standard Deviations of Log(Fecal Calprotectin) and Mayo Scores over Time

Quantiles of Fecal Calprotectin versus Endoscopic Mayo

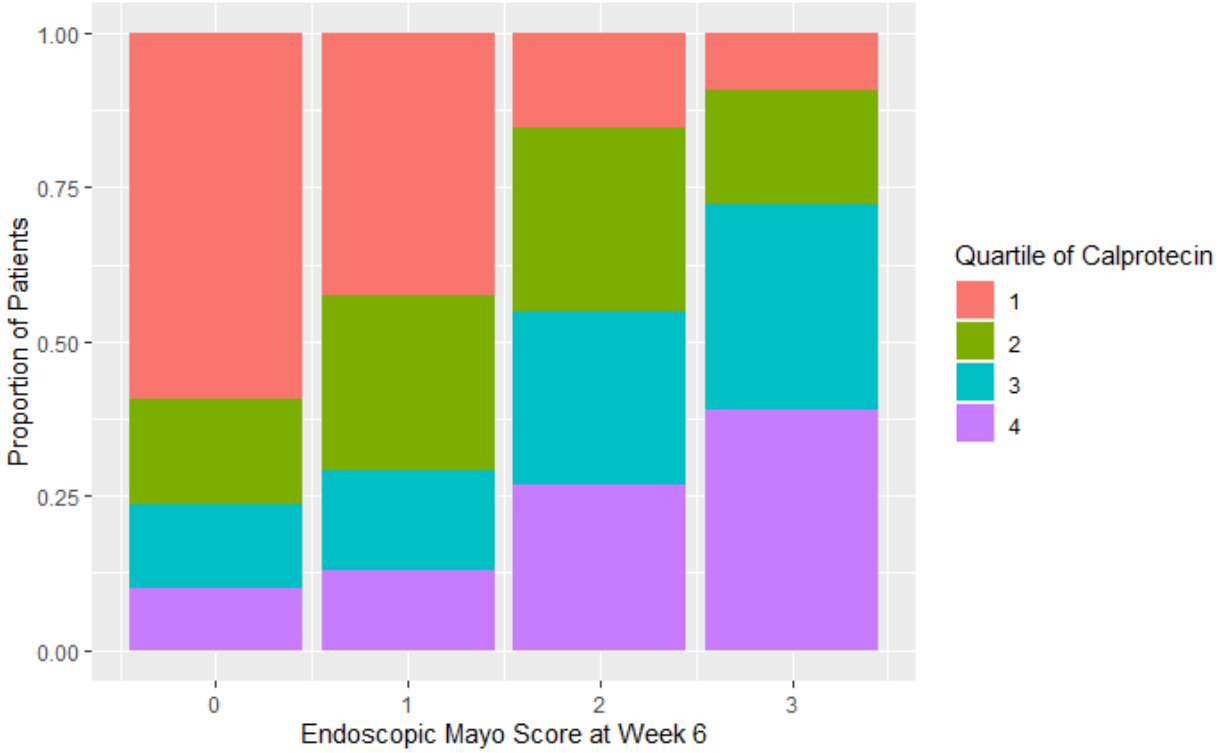


Figure: Quantile of Week 6 Fecal Calprotectin versus Endoscopic Mayo Score at Week 6

As expected, higher endoscopy score is associated with higher calprotectin value.

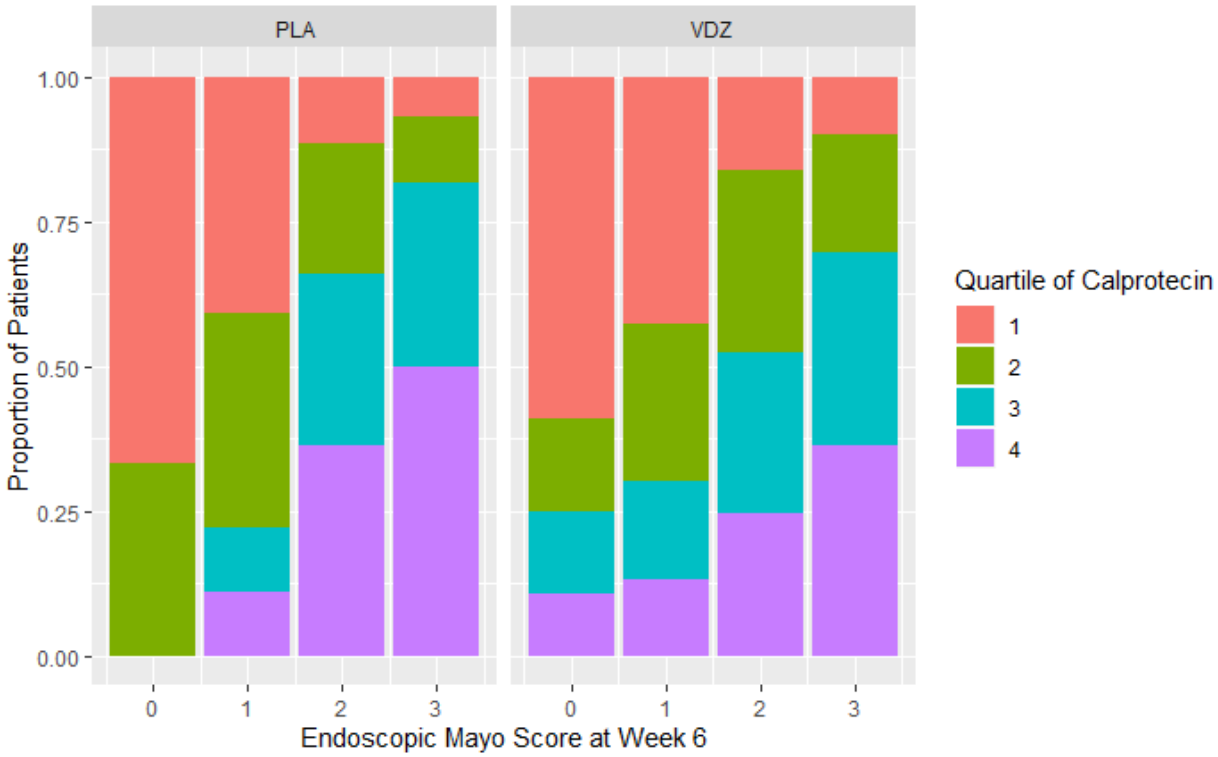


Figure: Quantile of Week 6 Fecal Calprotectin versus Endoscopic Mayo Score at Week 6 by Treatment

Shows that for treated patients a larger proportion of those that have an endoscopic score of 0 have high fecal calprotectin scores at week 6.

Summary

Overall the correlations between fecal calprotectin and the mayo scores grow over time. At baseline patients must have a mayo score with the range of the trial to quality. This could be the reason for low correlation at baseline. As the trial progresses the change in mayo score correlates with the change in fecal calprotectin.