

Statistical Supplementary Material: The Impact of Prepartum Factor XIII Activity on Postpartum Blood Loss

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This dynamic document contains the patient-level data as well as computer source codes for the reproduction of tables and figures presented in the manuscript “The Impact of Prepartum Factor XIII Activity on Postpartum Blood Loss” (Haslinger et al., 2020). This document is described as supplementary in the main publication, unfortunately, the publisher was unable to provide access to this document through their system.

The source file `blood_loss_report.Rnw` can be processed in the R system via

```
library("knitr")
knit("blood_loss_report.Rnw")
library("tools")
texi2pdf("blood_loss_report.tex")
```

1 Maternal Characteristics

The baseline distribution of variables are in Table 1. For measured blood loss, the unconditional distributions stratified by mode of delivery are depicted in Figure 1 (a model-based analysis) and Figure 2 (a non-parametric analysis).

2 Statistical Analysis

2.1 Sample Size Calculation

For sample size calculation, a case-control design was assumed. In a previous study, F. XIII activity prior to delivery was 83 IU/dL (standard deviation 24 IU/dL Sharief et al., 2014). Based on the hypothesis that women with postpartum hemorrhage (PPH) would have a mean F. XIII activity of < 70 IU/dL, 54 patients with PPH were needed to prove this assumption with a statistical power of 80% at a level of significance of 5% (two-sided t -test). Supposing a PPH-rate of 4.9% in our patients, a minimal sample size of 1100 patients was calculated.

During the first months of the study, it was observed that in several patients, the 6mL Vacutainer tube was not adequately filled and analysis would hence have been inaccurate

Variable			Vaginal delivery (677)	Planned Cesarean (409)	Unplanned Cesarean (223)
measured blood loss	ml	Med (IQR)	350.0 (300.0-500.0)	500.0 (400.0-600.0)	500.0 (400.0-700.0)
prepartum F. I	g/l	missing	1	2	2
		Med (IQR)	4.6 (3.9-5.1)	4.3 (3.9-4.8)	4.5 (3.9-5.2)
prepartum F. II	%	missing	3	2	2
		Med (IQR)	128.0 (118.0-140.0)	128.0 (115.0-138.0)	128.0 (115.0-140.0)
prepartum hemoglobin	g/l	Med (IQR)	128.0 (121.0-135.0)	124.0 (118.0-131.0)	127.0 (120.0-134.0)
prepartum F. XIII	%	missing	3	2	1
		Med (IQR)	98.5 (86.0-117.8)	93.0 (82.0-107.0)	93.0 (80.2-111.0)
number of colloids		Med (IQR)	0.0 (0.0-0.0)	1.0 (1.0-1.0)	1.0 (0.0-1.0)
spontaneous delivery		no	111	409	223
		yes	566	0	0
vacuum delivery		no	566	409	223
		yes	111	0	0
elective cesarean delivery		no	677	0	223
		yes	0	409	0
unplanned cesarean delivery		no	677	409	13
		yes	0	0	210
emergency cesarean delivery		no	677	409	210
		yes	0	0	13
gestational age	days	Med (IQR)	280.0 (273.0-285.0)	267.0 (265.0-270.0)	277.0 (267.5-284.0)
maternal age	years	Med (IQR)	32.0 (29.0-35.0)	34.0 (30.0-37.0)	33.0 (30.0-36.0)
multiparity		no	367	155	153
		yes	310	254	70
body mass index	kg/m ²	missing	7	0	1
		Med (IQR)	23.2 (20.5-26.8)	25.1 (21.7-28.8)	23.4 (21.0-26.4)
duration of second stage labor	min	missing	0	409	179
		Med (IQR)	51.0 (18.0-121.0)	NA (NA-NA)	172.5 (119.2-206.8)
multiple fetus pregnancy		no	671	377	210
		yes	6	32	13
induction of labor		no	414	405	138
		yes	263	4	85
induction of labor > 48 hours		no	655	408	205
		yes	22	1	18
chorioamnionitis		no	676	409	214
		yes	1	0	9
neonatal weight	g	Med (IQR)	3370.0 (3090.0-3650.0)	3200.0 (2890.0-3510.0)	3340.0 (2945.0-3690.0)
uterine rupture		no	677	409	220
		yes	0	0	3
uterine atony		no	635	402	219
		yes	42	7	4
retained placenta		no	653	409	223
		yes	24	0	0
retained placental material		no	651	408	223
		yes	26	1	0
morbidly adherent placenta		no	676	406	222
		yes	1	3	1
placenta previa		no	677	400	219
		yes	0	9	4
bleeding from laceration		no	628	409	223
		yes	49	0	0
placental abruption		no	675	407	217
		yes	2	2	6

Table 1: Distribution of feto-maternal and perinatal characteristics, stratified by mode of delivery.

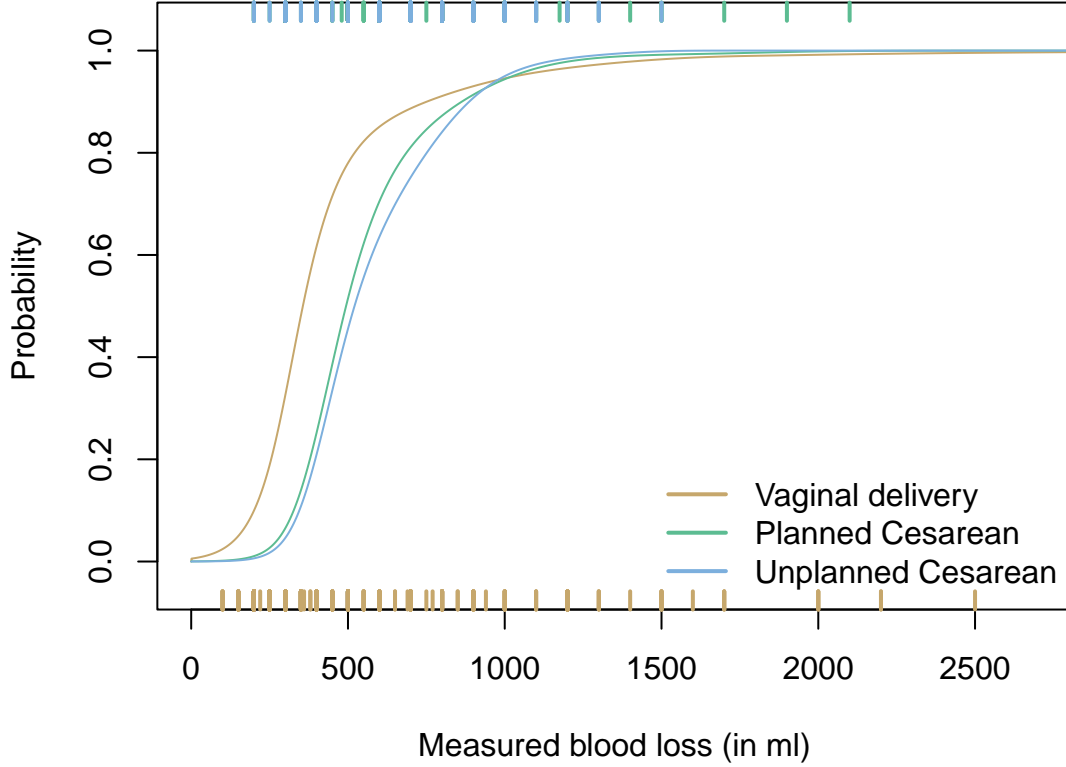


Figure 1: Measured blood loss: Distribution of measured blood loss stratified by mode of delivery. Rugs indicate measured blood loss observations. One vaginal delivery with 5700 ml blood loss not shown.

due to incorrect dilution with the predefined volume of the Na-citrate buffer. Also, the blood draw was not performed in time in several patients. To achieve the required sample size of 1100 evaluable patients, we thus decided to increase the enrollment target to 1500 patients overall, after repeated approval of the IRB. In addition, instructions to the research staff were intensified. Analysis of coagulation factors only began after recruitment to the study was completed; thus, it can be excluded that the increase of the sample size was due to any kind of interim results.

2.2 Methods

The conditional distribution of measured blood loss given prepartal hemoglobin (in g/l), F. I (in g/l), F. II (in %), and F. XIII (in %) was estimated by continuous outcome logistic regression (Lohse et al., 2017; Liu et al., 2017). In a first step, all possible binary logistic regression models for all potential cut-off points measured blood loss were estimated simultaneously while treating the regression coefficients as constants and thus applicable to any cut-off point. The regression coefficients describe the log-odds ratio and assess the change induced by a one-unit increase in one of the four prepartal blood parameters simultaneously for all potential cut-off points. In more detail, the model describes the

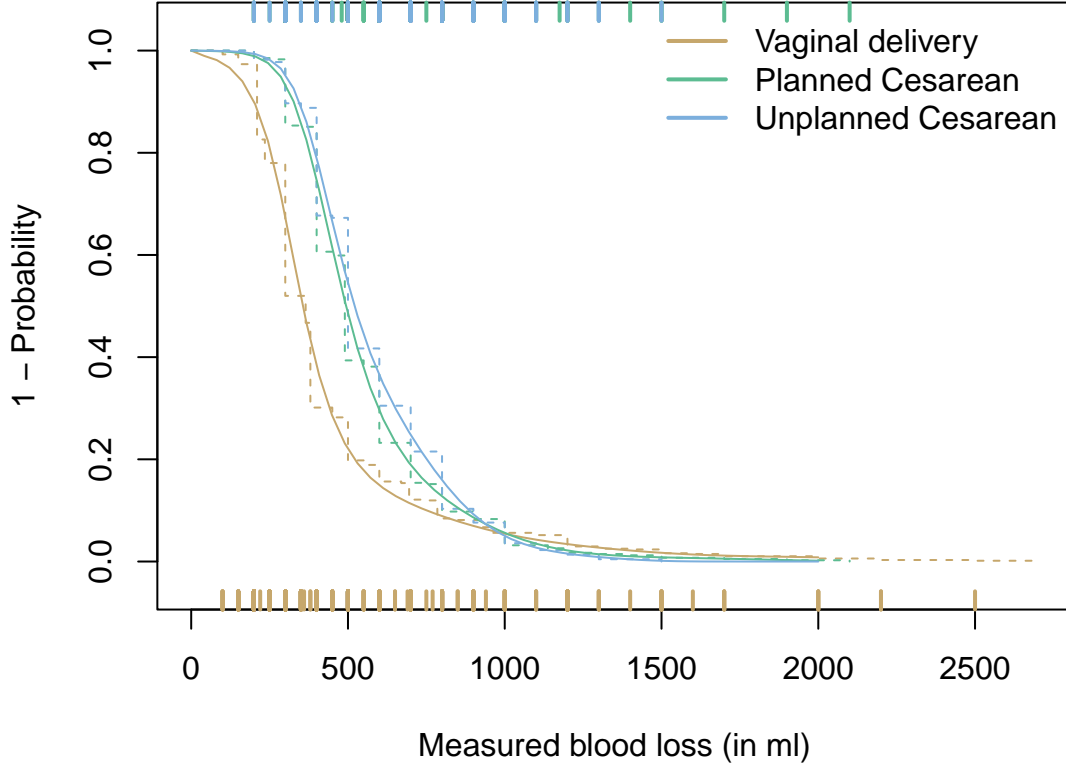


Figure 2: Measured blood loss: Comparison of model-based distribution estimation (solid lines, Fig. 1) and the non-parametric Turnbull estimator (dashed lines) for interval-censored responses; stratified by mode of delivery. One vaginal delivery with 5700 ml blood loss not shown.

conditional distribution of measured blood loss as

$$\text{Prob}(\text{MBL} \leq m \mid x_{\text{Hb}}, x_{\text{F. I}}, x_{\text{F. II}}, x_{\text{F. XIII}}) = \text{logit}^{-1}(\alpha(m) + \beta_{\text{Hb}}x_{\text{Hb}} + \beta_{\text{F. I}}x_{\text{F. I}} + \beta_{\text{F. II}}x_{\text{F. II}} + \beta_{\text{F. XIII}}x_{\text{F. XIII}})$$

where $\alpha(m)$ is a cut-off specific non-decreasing intercept function and $\beta_{\text{Hb}}, \dots, \beta_{\text{F. XIII}}$ are the regression coefficients for prepartal hemoglobin (x_{Hb}), F. I ($x_{\text{F. I}}$), F. II ($x_{\text{F. II}}$), and F. XIII ($x_{\text{F. XIII}}$). These regression coefficients can be interpreted as log-odds ratios comparing the odds of a patient with an F. XIII of $x_{\text{F. XIII}} + a > x_{\text{F. XIII}}$ with the odds of a patient with an F. XIII of $x_{\text{F. XIII}}$:

$$\frac{\text{Prob}(\text{MBL} \leq m \mid x_{\text{Hb}}, x_{\text{F. I}}, x_{\text{F. II}}, x_{\text{F. XIII}} + a)}{1 - \text{Prob}(\text{MBL} \leq m \mid x_{\text{Hb}}, x_{\text{F. I}}, x_{\text{F. II}}, x_{\text{F. XIII}} + a)} \bigg/ \frac{\text{Prob}(\text{MBL} \leq m \mid x_{\text{Hb}}, x_{\text{F. I}}, x_{\text{F. II}}, x_{\text{F. XIII}})}{1 - \text{Prob}(\text{MBL} \leq m \mid x_{\text{Hb}}, x_{\text{F. I}}, x_{\text{F. II}}, x_{\text{F. XIII}})} = \exp(\beta_{\text{F. XIII}})^a.$$

Thus, positive regression coefficients and corresponding odds ratios larger than one increase the odds and, consequently, increasing values of F. XIII increase the probability of suffering from blood loss less than m (a move of the conditional distribution of measured blood loss to the left).

In our analysis, measured blood loss was treated as interval censored (with interval length of 50 ml for blood losses up to 1000 ml and 100 ml for larger blood losses) reflecting the uncertainty in the actual measurements. The null hypothesis of all regression

coefficients being zero was tested by the likelihood ratio test (at nominal level $\alpha = 0.05$); 95% Wald-type confidence intervals for odds ratios are reported without multiplicity adjustment.

In a second step, the impact of potential effect modifiers on the odds ratios of prepartal blood parameters was assessed using model-based recursive partitioning (Zeileis et al., 2008). Subgroups of patients identified by fetomaternal and perinatal characteristics were obtained maximising discrepancies between the regression coefficients of models estimated within the corresponding subgroups. Variable selection was performed under Bonferroni correction. Subgroup-specific odds ratios are reported. All analyses were performed using the add-on packages **partykit** (Hothorn and Zeileis, 2015) and **mlt** (Hothorn, 2018) to the R system for statistical computing (version 4.5.1, R Core Team, 2019).

2.3 Results: Models for Measured Blood Loss

```
mvars <- c("Hb.prae", "F1.prae", "F2.prae", "F13.Akt.prae")
fm <- paste(mvars, collapse = "+")
### continuous outcome logistic regression
m_MBL <- Colr(as.formula(paste("MBLsurv ~ ", fm)), data = blood,
              bounds = c(0, Inf), support = c(250, 2000))
### number of observations
sum(complete.cases(model.frame(m_MBL)))

## [1] 1300

summary(m_MBL)

##
## Continuous Outcome Logistic Regression
##
## Call:
## Colr(formula = as.formula(paste("MBLsurv ~ ", fm)), data = blood,
##       bounds = c(0, Inf), support = c(250, 2000))
##
## Coefficients:
##              Estimate Std. Error z value Pr(>|z|)
## Hb.prae      0.009636   0.004621   2.085  0.03704 *
## F1.prae     -0.060481   0.059033  -1.025  0.30559
## F2.prae      0.007711   0.002927   2.634  0.00843 **
## F13.Akt.prae 0.010854   0.002406   4.511 6.46e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Log-Likelihood:
## -3696.599 (df = 11)
## Likelihood-ratio Test: Chisq = 34.36389 on 4 degrees of freedom; p = 6.275e-07

logLik(m_MBL)

## 'log Lik.' -3696.599 (df=11)
```

The distribution of measured blood loss is affected by prepartal blood parameters ($\chi^2 = 34.364$, $df = 4$, $p < 0.001$). Both increasing prepartal F. II and F. XIII move the conditional distribution of measured blood loss to the left (positive regression coefficients) and thus indicate lower blood loss. For the corresponding odds ratios, the confidence intervals exclude one:

```
(ci_all <- ci(m_MBL))

##                2.5 %   97.5 %
## Hb.prae        1.009682 1.0005795 1.018868
## F1.prae        0.941312 0.8384639 1.056776
## F2.prae        1.007741 1.0019761 1.013538
## F13.Akt.prae 1.010914 1.0061568 1.015693
```

The same model (although not under interval-censoring, we used the raw measurements of blood loss) but with negative log-odds ratios can be estimated as

```
(m_MBL_orm <- orm(as.formula(paste("MBL ~ ", fm)), data = blood))

## Frequencies of Missing Values Due to Each Variable
##           MBL           Hb.prae           F1.prae           F2.prae F13.Akt.prae
##           0             0             5             7             6
##
## Logistic (Proportional Odds) Ordinal Regression Model
##
## orm(formula = as.formula(paste("MBL ~ ", fm)), data = blood)
##
##
##           Model Likelihood           Discrimination           Rank Di
##           Ratio Test           Indexes           I
## Obs           1300   LR chi2           31.17   R2           0.024   rho
## ESS           1275.1   d.f.           4   R2(4,1300)           0.021   Dxy
## Distinct Y           39   Pr(> chi2) <0.0001   R2(4,1275.1)           0.021
## Median Y           400   Score chi2           31.22   |Pr(Y>=median)-0.5| 0.157
## max |deriv|   5e-11   Pr(> chi2) <0.0001
##
##           Coef      S.E.   Wald Z Pr(>|Z|)
## Hb.prae      -0.0067 0.0046  -1.46  0.1442
## F1.prae       0.0608 0.0588   1.03  0.3018
## F2.prae      -0.0066 0.0029  -2.28  0.0229
## F13.Akt.prae -0.0103 0.0024  -4.29  <0.0001

### OR and confidence interval for F. XIII
### (sign of the coefficient is different in rms::orm and tram::Colr)
exp(-coef(m_MBL_orm)["F13.Akt.prae"])

## F13.Akt.prae
##           1.010382
```

```
exp(-rev(confint(m_MBL_orm)["F13.Akt.prae",]))

##      97.5 %      2.5 %
## 1.005629 1.015156
```

The estimated odds ratio for F. XIII and its confidence interval match the results reported on above very closely.

The model was furthermore estimated using mode of delivery as stratum. Thus, two separate models for vaginal delivery and Cesarean section were estimated:

```
m_MBL_C <- Colr(as.formula(paste("MBLsurv | VCmode ~ VCmode:", fm, "))),
                data = blood, bounds = c(0, Inf), support = c(250, 2000))
summary(m_MBL_C)

##
## (Stratified) Continuous Outcome Logistic Regression
##
## Call:
## Colr(formula = as.formula(paste("MBLsurv | VCmode ~ VCmode:",
##      fm, "))), data = blood, bounds = c(0, Inf), support = c(250,
##      2000))
##
## Coefficients:
##
##              Estimate Std. Error z value Pr(>|z|)
## VCmodeVaginal delivery:Hb.prae -0.006172  0.006618  -0.933  0.35104
## VCmodeCesarean Sectio:Hb.prae  0.006273  0.006678   0.939  0.34750
## VCmodeVaginal delivery:F1.prae  0.010094  0.087281   0.116  0.90793
## VCmodeCesarean Sectio:F1.prae -0.146898  0.079988  -1.836  0.06628 .
## VCmodeVaginal delivery:F2.prae  0.002204  0.004099   0.538  0.59085
## VCmodeCesarean Sectio:F2.prae  0.010660  0.004225   2.523  0.01163 *
## VCmodeVaginal delivery:F13.Akt.prae 0.009668  0.003327   2.906  0.00367 **
## VCmodeCesarean Sectio:F13.Akt.prae 0.007560  0.003360   2.250  0.02446 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Log-Likelihood:
## -3566.539 (df = 22)
## Likelihood-ratio Test: Chisq = 27.23993 on 8 degrees of freedom; p = 0.0006426

logLik(m_MBL_C)

## 'log Lik.' -3566.539 (df=22)
```

For F. XIII, the estimated log-odds ratios and the corresponding standard errors are roughly the same for both delivery modes and are very close to the unstratified analysis. The effect for F. II seems only present in Cesarean sections.

The sample size planning was performed under choice-based sampling. The difference in prepartum F. XIII was used as effect measure for comparing two groups of patients

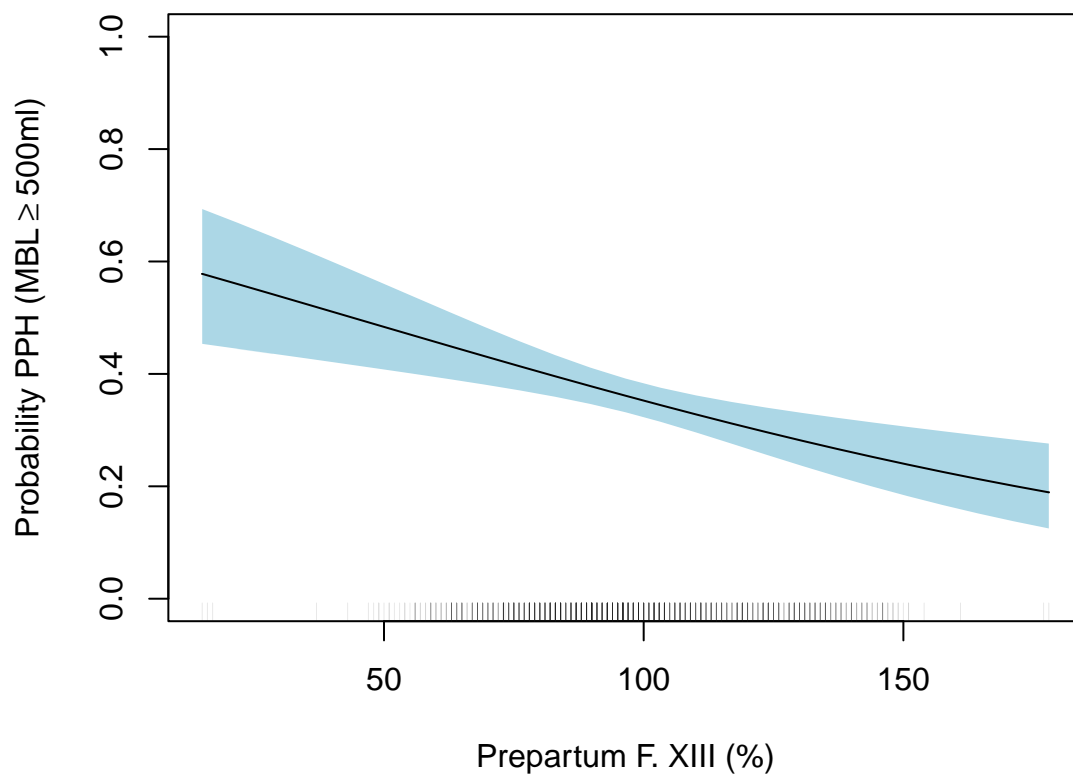


Figure 3: Prevalence curve of PPH (defined as $MBL \geq 500\text{mL}$) as a function of prepartum F. XIII for a hypothetical subject with prepartum hemoglobin 127 g/l, prepartum F. I 4.5 g/l, and prepartum F.II 128%. The blue area represents a 95% confidence band.

(PPH: postpartum hemorrhage, defined as measured blood loss larger than 500 ml). The one-way analysis of variance matching the sample size planning is

```
blood$PPH <- factor(blood$MBL >= 500, levels = c(FALSE, TRUE),
                    labels = c("no", "yes"))
summary(m_PPH <- lm(F13.Akt.prae ~ PPH, data = blood))

##
## Call:
## lm(formula = F13.Akt.prae ~ PPH, data = blood)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -84.981 -14.954  -2.954   15.019   78.019
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)   99.9810     0.8174  122.321  < 2e-16 ***
## PPHyes        -4.0274     1.2230   -3.293  0.00102 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 21.95 on 1301 degrees of freedom
## (6 observations deleted due to missingness)
## Multiple R-squared:  0.008266, Adjusted R-squared:  0.007504
## F-statistic: 10.84 on 1 and 1301 DF, p-value: 0.001018

confint(m_PPH)["PPHyes",]

##      2.5 %      97.5 %
## -6.426666 -1.628115
```

and a corresponding Wilcoxon rank sum test reports

```
wilcox_test(F13.Akt.prae ~ PPH, data = blood,
             distribution = approximate(10000), conf.int = TRUE)

##
## Approximative Wilcoxon-Mann-Whitney Test
##
## data:  F13.Akt.prae by PPH (no, yes)
## Z = 3.4999, p-value = 8e-04
## alternative hypothesis: true mu is not equal to 0
## 95 percent confidence interval:
##  2 7
## sample estimates:
## difference in location
##                               4
```

Patients suffering PPH had, on average, four units less F. XIII compared to patients with normal blood loss. It should be noted that logistic regression allows to estimate odds ratios under choice-based sampling, therefore, the analysis by continuous outcome logistic regression is also appropriate under the design applied for sample size planning.

```
### Tobit model
tll <- logLik(t_MBL <- Lm(as.formula(paste("MBLsurv ~ ", fm)),
                        data = blood))

### distribution regression
drll <- logLik(dr_MBL <- Colr(as.formula(paste("MBLsurv | ", fm, "~ 1")),
                           data = blood, bounds = c(0, Inf),
                           support = c(250, 2000)))
```

Continuous outcome logistic regression for measured blood loss was evaluated by means of comparison against a Tobit model (normal linear regression for interval-censored response), distribution regression (Foresi and Peracchi, 1995; Chernozhukov et al., 2013, simultaneous estimation of all possible binary logistic regression models without constant log-odds ratio regression coefficients) and a selection of binary logistic regression models using the cut-off points 500 ml, 750 ml, and 1000 ml for measured blood loss. The in-sample log-likelihood for the continuous outcome logistic regression model (-3696.599) is much larger than the log-likelihood of the Tobit model (-4068.522) and almost equivalent to the log-likelihood (-3691.321) of the much more flexible distribution regression model. The response-varying effects from this distribution regression model are contrasted with the (response-constant) odds ratios from the continuous outcome logistic regression in Figure 4. In the relevant domain, the response-varying effects are covered by the confidence intervals for the response-constant effects. In summary, continuous outcome logistic regression seems a fair and interpretable compromise between the simpler Tobit model assuming conditional normality for measured blood loss and the distribution regression model allowing non-constant regression coefficients.

The estimated odds ratios for prepartal F. II and F. XIII and also roughly the corresponding confidence intervals can be reproduced by looking at binary logistic regression models for selected cut-off points in measured blood loss. The odds ratios and corresponding confidence intervals for F. XIII are roughly constant across the different cut-off points, as could be expected from the results of distribution regression (Table 2).

Cut-off	Parameter	OR	lower	upper	<i>p</i> -value
All	Hb.prae	1.010	1.001	1.019	0.03704
	F1.prae	0.941	0.838	1.057	0.30559
	F2.prae	1.008	1.002	1.014	0.00843
	F13.Akt.prae	1.011	1.006	1.016	< 0.001
500	Hb.prae	1.007	0.996	1.018	0.19906
	F1.prae	0.921	0.807	1.051	0.22004
	F2.prae	1.009	1.002	1.016	0.01279
	F13.Akt.prae	1.009	1.003	1.014	0.00245
750	Hb.prae	1.003	0.989	1.018	0.65713
	F1.prae	0.867	0.725	1.041	0.12179
	F2.prae	1.016	1.006	1.026	0.00116
	F13.Akt.prae	1.012	1.004	1.020	0.00446
1000	Hb.prae	0.999	0.980	1.019	0.95076
	F1.prae	0.904	0.712	1.159	0.41560
	F2.prae	1.004	0.991	1.016	0.57442
	F13.Akt.prae	1.010	0.999	1.021	0.06605

Table 2: Odds ratios and corresponding confidence intervals for prepartal blood parameters. “All” refers to all cut-off points simultaneously via continuous outcome logistic regression.

Parameter	OR	lower	upper	<i>p</i> -value
VCmodeVaginal delivery:Hb.prae	0.994	0.981	1.007	0.35104
VCmodeCesarean Sectio:Hb.prae	1.006	0.993	1.020	0.34750
VCmodeVaginal delivery:F1.prae	1.010	0.851	1.199	0.90793
VCmodeCesarean Sectio:F1.prae	0.863	0.738	1.010	0.06628
VCmodeVaginal delivery:F2.prae	1.002	0.994	1.010	0.59085
VCmodeCesarean Sectio:F2.prae	1.011	1.002	1.019	0.01163
VCmodeVaginal delivery:F13.Akt.prae	1.010	1.003	1.016	0.00367
VCmodeCesarean Sectio:F13.Akt.prae	1.008	1.001	1.014	0.02446

Table 3: Odds ratios and corresponding confidence intervals for prepartal blood parameters, stratified by mode of delivery.

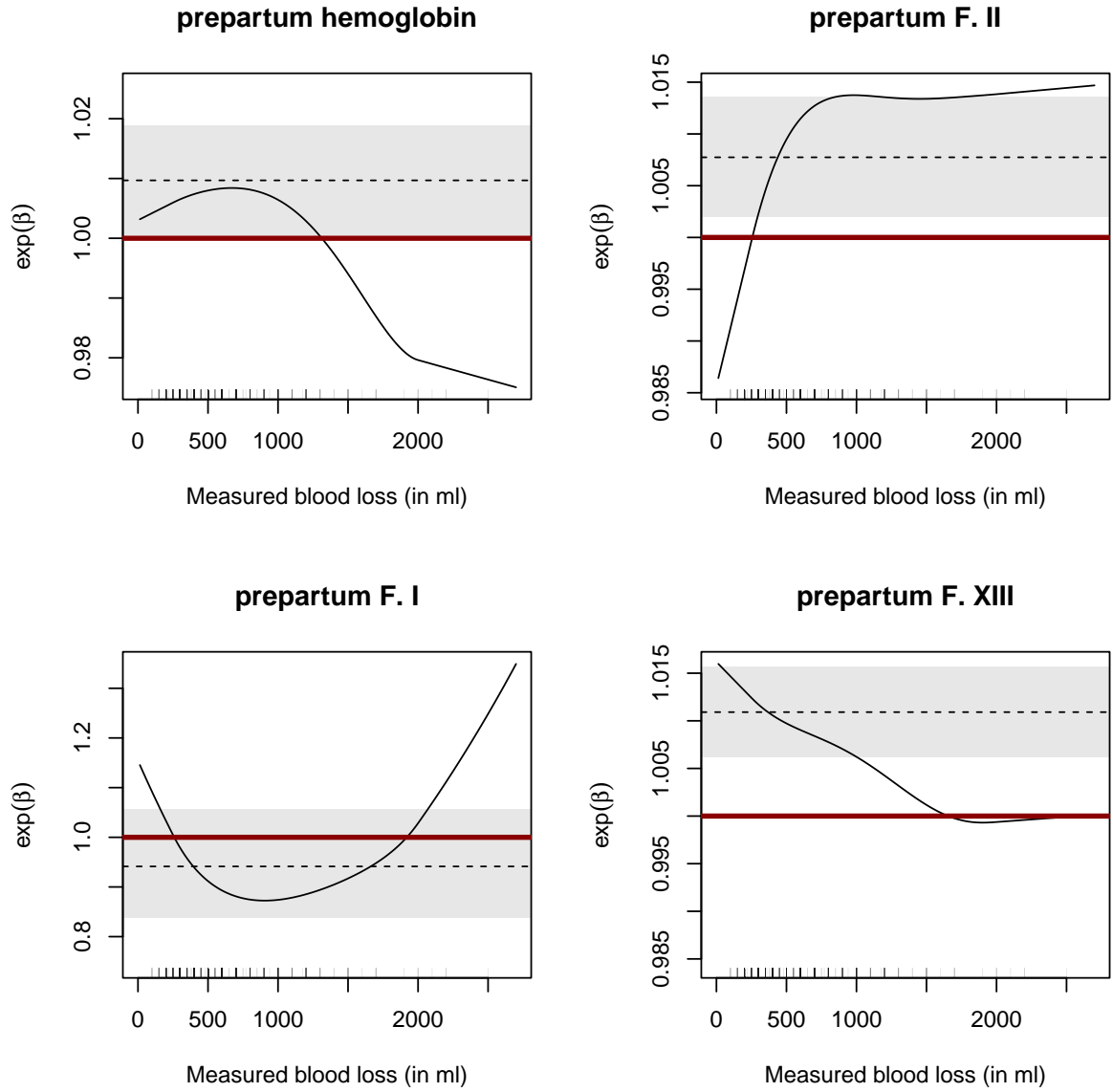


Figure 4: Measured blood loss: Response-varying regression coefficients (solid curves, on the odds ratio scale) in the distribution regression model, separately for each prepartal blood parameter. For a given cut-off value y on the x-axis, the line corresponds to the odds ratio in a binary logistic regression model for the outcome “measured blood loss $\leq y$ ”. The dashed lines represent the response-constant regression coefficients (on the exp-scale) from the continuous outcome logistic regression model, the grey area depicts the corresponding confidence interval. The thick red line corresponds to an absent effect (odds ratio one).

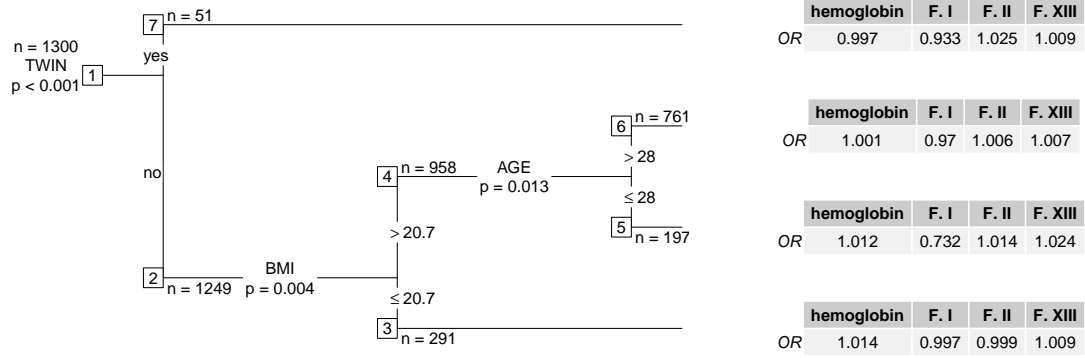


Figure 5: Measured blood loss: Subgroup model for measured blood loss based on prepartal available information.

2.4 Results: Identification of Effect Modifiers

In the second step of the analysis, the dependency of the regression coefficients for prepartal blood parameters on two sets of external variables were analysed and are given in Figures 5 and 7. Figure 5 depicts the model built on 8 prepartal available variables (gestational age, maternal age, multiparity, body mass index, multiple fetus pregnancy, neonatal weight, induction of labor, and chorioamnionitis). The model in Figure 7 uses all 24 prepartal and postpartal available variables (number of colloids, spontaneous delivery, vacuum delivery, elective cesarean delivery, unplanned cesarean delivery, emergency cesarean delivery, gestational age, maternal age, multiparity, body mass index, duration of second stage labor, multiple fetus pregnancy, induction of labor, induction of labor > 48 hours, chorioamnionitis, neonatal weight, uterine rupture, uterine atony, retained placenta, retained placental material, morbidly adherent placenta, placenta previa, bleeding from laceration, and placental abruption). The model in Figure 5 indicates that higher values of F. XIII correspond to lower blood loss (odds ratio > 1 and thus a distribution move to the left) in subgroups 5 and 6. The effect seems lower for twin births (subgroup 7) and mothers with low body mass index (subgroup 3). Using all prepartal and postpartal variables in Figure 7, the effect of F. XIII is most pronounced in subgroup 4 (spontaneous delivery and not colloids).

From the subgroup model presented in Figure 5, the probability of measured blood loss > 500 ml was estimated for each of the four subgroups with a corresponding confidence interval effects.

##	Subgroup	Estimate	upr	lwr
## 1	3	27.64146	23.05628	32.75037
## 2	5	26.20747	20.95941	32.23370
## 3	6	38.55525	35.43838	41.76891
## 4	7	75.43011	62.80021	84.80921

For measured blood loss > 750 ml, the probabilities change to

##	Subgroup	Estimate	upr	lwr
## 1	3	8.348382	5.899628	11.68730
## 2	5	7.546596	4.872566	11.51055
## 3	6	14.475997	12.314150	16.94403
## 4	7	35.656620	24.266648	48.93809

and for measured blood loss > 1000 ml to

##	Subgroup	Estimate	upr	lwr
## 1	3	2.970771	1.691322	5.167223
## 2	5	3.288140	1.683177	6.325033
## 3	6	6.691317	5.236836	8.513474
## 4	7	14.119782	7.548473	24.872682

When a hypothetical increase of F. XIII by 50 was assumed, these probabilities reduced to

##	Subgroup	Estimate	upr	lwr
## 1	3	19.33376	11.83243	29.97393
## 2	5	10.15011	5.19615	18.88625
## 3	6	30.65736	23.99560	38.23812
## 4	7	66.38870	33.11671	88.73787

for measured blood loss > 500 , to

##	Subgroup	Estimate	upr	lwr
## 1	3	5.406037	2.902441	9.850114
## 2	5	2.530678	1.106946	5.680404
## 3	6	10.655282	7.637690	14.675667
## 4	7	26.282838	7.997050	59.389939

for measured blood loss > 750 , and to

##	Subgroup	Estimate	upr	lwr
## 1	3	1.884762	0.8683219	4.042506
## 2	5	1.069892	0.4060172	2.788864
## 3	6	4.809699	3.2452755	7.073140
## 4	7	9.566072	2.3246771	31.979240

for measured blood loss > 1000 . These values can be used as potential treatment effects in the design of a prospective randomised clinical trial. The corresponding conditional distribution functions illustrating this hypothetical treatment effect are given in Figure 6.

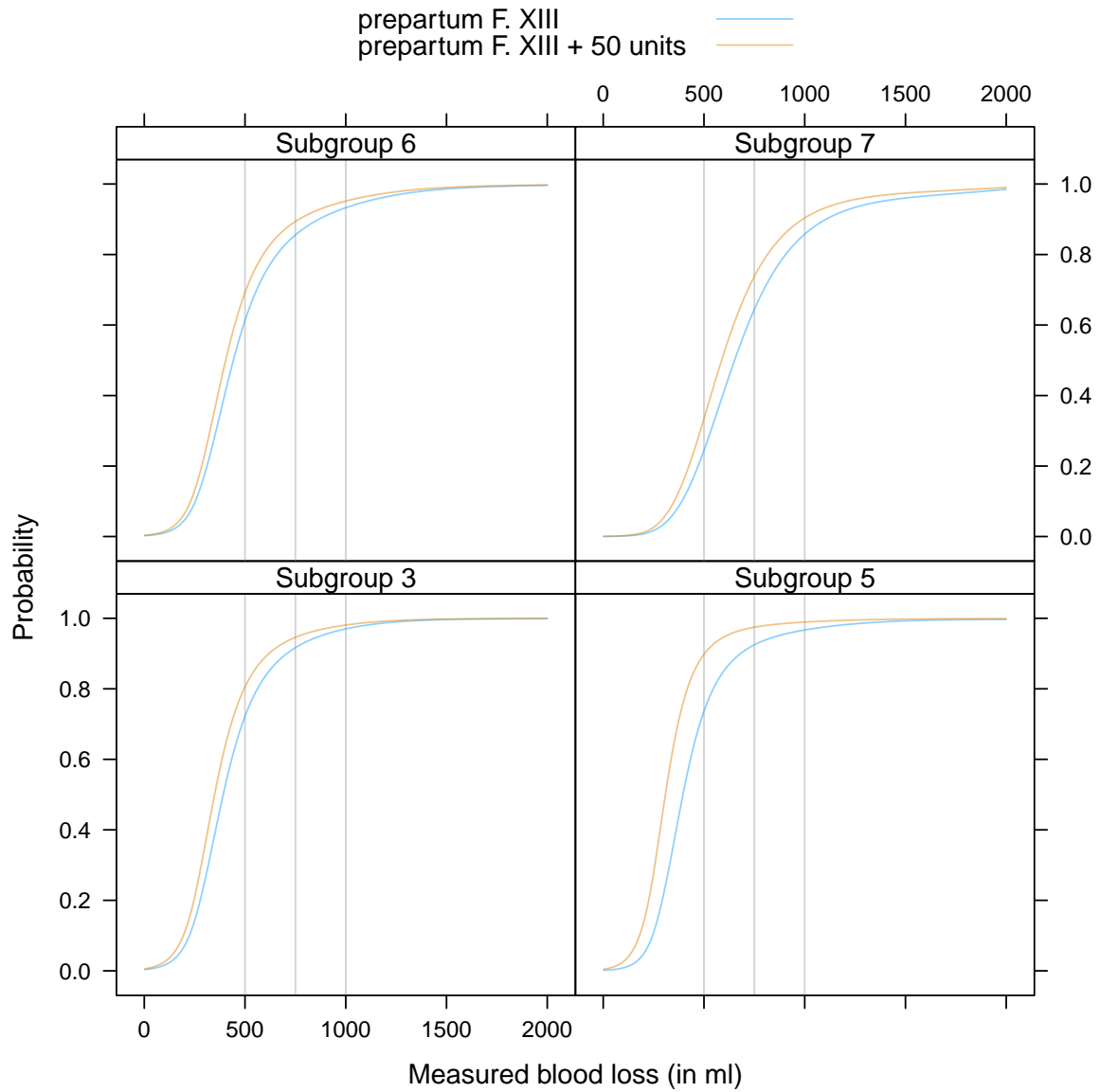


Figure 6: Measured blood loss: Conditional distribution of measured blood loss in the subgroups given in Figure 5 for original F. XIII measurements (blue lines) and under hypothetical treatment (yellow lines). Vertical grey lines indicate 500, 750, and 1000 ml measured blood loss.

```
## Warning in doTest(lev, teststat = teststat, pvalue = pvalue, lower =
TRUE, : cmvnorm: completion with ERROR > EPS
```

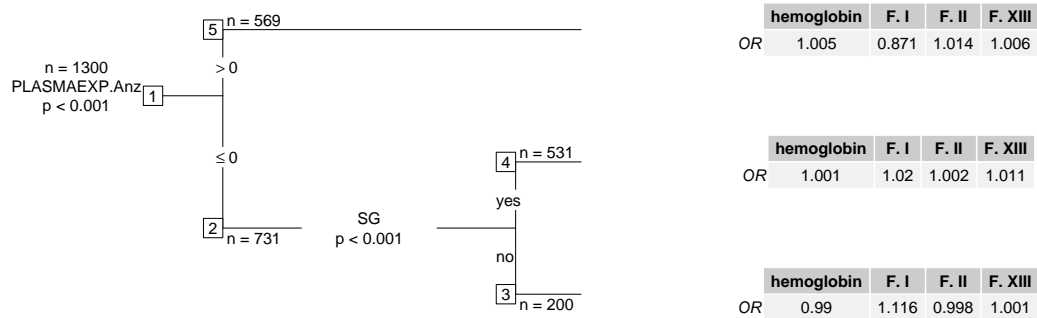


Figure 7: Measured blood loss: Subgroup model for measured blood loss based on prepartal and postpartal available information.

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Reproducibility (Supplementary Material)

The results are reproducible by running the R transcript file `blood_loss_report.R` in the following environment:

```
## R version 4.5.1 (2025-06-13)
## Platform: x86_64-pc-linux-gnu
## Running under: Debian GNU/Linux 12 (bookworm)
##
## Matrix products: default
## BLAS:   /usr/local/lib/R/lib/libRblas.so
## LAPACK: /usr/lib/x86_64-linux-gnu/lapack/liblapack.so.3.11.0  LAPACK version 3.11.0
##
## locale:
##  [1] LC_CTYPE=en_GB.UTF-8      LC_NUMERIC=C
##  [3] LC_TIME=en_GB.UTF-8      LC_COLLATE=C
##  [5] LC_MONETARY=en_GB.UTF-8  LC_MESSAGES=en_GB.UTF-8
##  [7] LC_PAPER=en_GB.UTF-8     LC_NAME=C
##  [9] LC_ADDRESS=C             LC_TELEPHONE=C
## [11] LC_MEASUREMENT=en_GB.UTF-8 LC_IDENTIFICATION=C
##
## time zone: Europe/Berlin
## tzcode source: system (glibc)
##
## attached base packages:
## [1] grid      stats      graphics  grDevices  utils      datasets  methods
## [8] base
##
## other attached packages:
##  [1] lattice_0.22-7  colorspace_2.1-1  vcd_1.4-13      gridExtra_2.3
##  [5] multcomp_1.4-28 TH.data_1.1-4     MASS_7.3-65     ATR_0.1-1
##  [9] coin_1.4-3      survival_3.8-3    rms_8.0-0       Hmisc_5.2-3
## [13] trtf_0.4-3      tram_1.2-4        partykit_1.2-24 mvtnorm_1.3-4
## [17] libcoin_1.0-10  mlt_1.6-7         basefun_1.2-3   variables_1.1-2
##
## loaded via a namespace (and not attached):
##  [1] gtable_0.3.6      xfun_0.52          ggplot2_3.5.2
##  [4] htmlwidgets_1.6.4 numDeriv_2016.8-1.1 quadprog_1.5-8
##  [7] vctr_0.6.5        tools_4.5.1        generics_0.1.4
## [10] stats4_4.5.1      parallel_4.5.1     sandwich_3.1-1
## [13] tibble_3.3.0      highr_0.11         cluster_2.1.8.1
## [16] coneproj_1.20      pkgconfig_2.0.3     Matrix_1.7-3
## [19] data.table_1.17.8 checkmate_2.3.2     RColorBrewer_1.1-3
## [22] alabama_2023.1.0  lifecycle_1.0.4     compiler_4.5.1
## [25] farver_2.1.2      stringr_1.5.1      MatrixModels_0.5-4
## [28] codetools_0.2-20  SparseM_1.84-2      quantreg_6.1
## [31] htmltools_0.5.8.1 htmlTable_2.4.3     Formula_1.2-5
## [34] pillar_1.11.0     nloptr_2.2.1       rpart_4.1.24
## [37] nlme_3.1-168      tidyselect_1.2.1    digest_0.6.37
```

```
## [40] polyspline_1.1.25      inum_1.0-5             stringi_1.8.7
## [43] dplyr_1.1.4            splines_4.5.1          fastmap_1.2.0
## [46] cli_3.6.5              magrittr_2.0.3         base64enc_0.1-3
## [49] orthopolynom_1.0-6.1   foreign_0.8-90         scales_1.4.0
## [52] backports_1.5.0        rmarkdown_2.29         matrixStats_1.5.0
## [55] nnet_7.3-20            BB_2019.10-1           modeltools_0.2-24
## [58] zoo_1.8-14             evaluate_1.0.4          knitr_1.50
## [61] lmtest_0.9-40          rlang_1.1.6            Rcpp_1.1.0
## [64] glue_1.8.0             polynom_1.4-1          rstudioapi_0.17.1
## [67] R6_2.6.1
```