Supplementary Material for analysis of Anti-Xa and APTTr anticoagulation on VV-ECMO patients

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`#refugeeswelcome`

1 VARIABLES and DEFINITIONS

1.1 Outcome variables

1. Bleeding or thrombotic events(BTE)

1a. no BTE - 1b. only haemorrhagic complications 1c. only thrombotic complications 1d. both BTE

2. ECMO circuit changes
3. Heparin Prescription 3a. cumulative dose of heparin 3b. heparin prescription changes
4. Blood products consumption

1.2 Calculated variables

1. Time in Therapeutic Range (Rosendaal Method)
2. Variability in Anticoagulation (Fihn's method)

1.3 Independent Variables

1. Demographics (age, sex, ethnicity, height, weight, BMI etc)
2. Blood variables (Full blood count results, renal function, CRP , etc)
3. Anticoagulation related variables (all the APTTr and anti-Xa results)

1.4 Time related variables

- time to any bleeding or thrombotic event
- time to only bleeding events
- time to only thrombotic event
- time to ECMO circuit change

2 DATA SOURCE

- Electronic health records data extraction from GSTT systems using ECMO pump speed as definition of cases.
- Cases cross-checked with ECMO VV referral system database.
- Complications individually reviewed where relevant.
- Electronic health records accessed through GDPR compliant system and saved in encrypted work spaces.
- All investigation results (CT imagings, blood results) in between ECMO run times are extracted.
- All prescription related data (e.g., heparin infusions are extracted to the nearest hour)

3 GROUND TRUTHS & DEFINITIONS

3.1 Assumptions

3.1.1 Assumption 1 : each patients receive only 1 ECMO run

- verified through discussion with clinicians at regular mortality and morbidity meeting

3.1.2 Assumption 2: all ECMO pump speed run times are accurate with automatic entry to EHR system

- verified through daily clinical use
- Thus, this time period is used as a basis to calculate other times in relation.

3.1.3 Assumption 3: As mandated legally by NHS Blood and Transfusion, all blood products transfusion are documented.

- This was used to verify and cross-check ECMO run times and related complications.
- all blood products prescribed and given are checked and confirmed if there are discrepancies.
- Assumed that the blood product is given in whole – e.g., if 1 unit Packed Red blood cells are prescribed, it is assumed the whole unit is given.

3.2 Definitions

3.2.1 Outcome variables

3.2.2 Bleeding and Thrombotic Complications

Any relevant bleeding and thrombotic complications simultaneously occuring and documented in medical notes are recorded and nearest most accurate time period extracted.

This does not include complications sustained through ECMO cannulation process nor incurred through retrieval process.

In addition, relevant complications identified incidentally through cross sectional imaging are also supplemented.

EOLIA definition of bleeding complications restrict to bleeding events requiring transfusion of blood products.

Our definition of bleeding complication is more broad. This is to allow analysis at granular scale.

We separately analyse blood products transfusion as a proxy marker of complications.

3.2.3 Time to events

Our analysis is to answer the question of the impact of monitoring tool after being established on anticoagulation for VV ECMO.

As a result, our time to "first" BTE is defined as the first BTE after having established on VV ECMO. Thus, the complications at admission associated to pre-ECMO status or associated to cannulation is not counted. The time starts at the time of successful cannulation and arrival to GSTT ECMO unit and ends at the time of first BTE.

Similarly, the ECMO circuit change is counted as the first circuit change after being established on VV ECMO.

3.2.4 ECMO circuit changes

Similarly, documentation of ECMO circuit changes and rationales were extracted.

3.2.5 Heparin administrations

All administration of heparin prescribed under different regimes were extracted and relevant units obtained.

Regimes	Description	Units
1	Heparin	units per hour
2	Heparin ECMO Xa IV Infusion	units per kilogram per hour
3	Heparin IV injection	units
4	Heparin RR INF 20000 IU	units
5	Heparin systemic Inf 20000 Units	units per hour

Table of heparin administration types.

3.2.6 Independent Variables

3.2.7 Height and Weight

Original documentaion of height and weight on ECMO cannulation were used due to likely later variation of patients through out their critical illness.

3.2.8 Time in Therapeutic Range (Rosendaal method)

Time in Therapeutic Range is an intuitive measure for evaluating the quality of anticoagulation. Multiple definitions exist.

Traditional definition is effectively no of tests in range as numerator divided by total no of tests. This does not take into account different durations that patient are anticoagulated for. Thus, Rosendaal et al has calculated a linear interpolation method incorporating duration of measurements.

TTR is a value of range between 0 to 100%.

Each individual time period between each anticoagulation blood test was calculated to the nearest hour.

Then Time in Range for that period was calculated. Finally, for each patient and their ECMO duration, the cumulative TTR was calculated.[1]

$$Time\,in\,Therapeutic\,Range\,_{Rosendaal} = \frac{Time\,in\,range}{Total\,Time}$$

No of anticoagulation blood tests per day was calculated to detect anomalous results. When outlier values were noted and duplicate record with non outlier value was found, this was chosen and randomly verified manually.

3.2.9 Variability of Anticoagulation (Fihn's method of Variance Growth rate)

$$\sigma^2 = \frac{1}{n}\sum_{i=1}^{n}\frac{(value_i - target)^2}{\tau_i}$$

Variance Growth Rate is a derivation of a statistical measure "variance" adjusted for each individual time period.

For each value of anti-coagulation test result, this was subtracted from target and squared, then divided by time period. Summary of all of this for the entire duration of ECMO was then calculated to generate a final value of VGR for each patient.

The benefit of Variance Growth Rate is that this does not assume the patient to be in a target range(which TTR does). VGR calculates how "far" each value is from target range adjusted for time period.

3.2.10 Targets of anticogulation

For aPTTr : target range xxx is thus, target value xxx is chosen as midpoint and

For anti-Xa : target range xxx is , and mid point xxx is chosen as target value ### Blood related variables - All blood related variables are extracted and first 24 hour blood values summarised.

https://onlinelibrary.wiley.com/doi/10.1111/jth.12322

4 DATA CLEANING PROCESS

All relevant variables and time-stamps are verified to be within ECMO run times.

Categorical variables are summarised and visualised. Numeric variables are summarised and visualised to allow for visual inspection of distribtion (e.g., normal distribution or kurtosis).

If data is transformed (e.g., log transformation), post transformation distribution is visualised

Count data is visualised and modeled as poisson / quasi-poisson distribution.

5 DESCRIPTIVE ANALYSIS

Supplementary Table of the first 24-hour admission blood results variables

Blood investigation variables	aPTTr group	anti-Xa group	p Value
	(N=74)	(N=180)	
Haemoglobin (g/L)			
Mean (SD)	101 (15.2)	99.8 (14.8)	0.656
Median [Min, Max]	99.8 [71.0, 139]	98.0 [70.5, 147]	
Platelets (10 ^9/L)			
Mean (SD)	152 (94.9)	231 (102)	<0.001
Median [Min, Max]	141 [17.0, 390]	219 [0, 495]	
Neutrophils (10 ^9/L)			
Mean (SD)	9.26 (7.29)	12.0 (5.44)	<0.001

Blood investigation variables	aPTTr group	anti-Xa group	p Value
Median [Min, Max]	7.48 [0.100, 41.9]	11.0 [0.950, 31.9]	
Fibrinogen (g/L)			
Mean (SD)	4.89 (2.16)	5.49 (2.49)	0.086
Median [Min, Max]	4.70 [0, 9.70]	5.38 [0.500, 11.8]	
Lactate dehydrogenase (U/L)			
Mean (SD)	616 (405)	793 (1130)	0.389
Median [Min, Max]	528 [0, 2390]	558 [0, 9840]	
Ferritin (ug/L)			
Mean (SD)	2200 (5150)	2760 (5320)	<0.001
Median [Min, Max]	70.0 [0, 36200]	1330 [0, 51500]	
Creatinine Kinase (umol/L)			
Mean (SD)	2200 (4380)	2640 (23600)	0.00771
Median [Min, Max]	620 [0, 22600]	327 [0, 317000]	
C-reactive protein (mg/L)			
Mean (SD)	223 (106)	178 (147)	0.00292
Median [Min, Max]	213 [53.5, 515]	151 [0, 622]	
Procalcitonin (ug/L)			
Mean (SD)	16.2 (29.1)	6.90 (15.9)	0.033
Median [Min, Max]	2.79 [0, 100]	0.913 [0, 91.6]	
Bilirubin (umol/L)			
Mean (SD)	21.3 (19.9)	17.2 (30.4)	0.0666
Median [Min, Max]	14.0 [0, 127]	11.0 [0, 389]	
Albumin (g/L)			
Mean (SD)	24.6 (3.86)	26.7 (3.99)	<0.001
Median [Min, Max]	24.0 [15.5, 35.0]	27.0 [18.0, 39.5]	

Blood investigation variables	aPTTr group	anti-Xa group	p Value
Creatinine (umol/L)			
Mean (SD)	170 (117)	120 (106)	<0.001
Median [Min, Max]	146 [34.0, 671]	75.3 [21.0, 626]	
eGFR (needed)			
Mean (SD)	58.0 (45.6)	89.8 (55.2)	<0.001
Median [Min, Max]	38.8 [6.00, 208]	91.3 [0, 330]	
Corrected Calcium (umol/L)			
Mean (SD)	2.34 (0.147)	2.30 (0.283)	0.0851
Median [Min, Max]	2.36 [1.83, 2.64]	2.32 [0, 3.01]	
Bicarbonate (mmol/L)			
Mean (SD)	24.9 (5.51)	28.1 (3.97)	<0.001
Median [Min, Max]	23.4 [10.7, 38.6]	28.2 [15.0, 37.6]	
Lactate (mmol/L)			
Mean (SD)	3.10 (3.34)	1.85 (1.39)	0.342
Median [Min, Max]	1.60 [0.700, 18.2]	1.60 [0.600, 16.8]	
pH			
Mean (SD)	7.37 (0.0604)	7.36 (0.553)	<0.001
Median [Min, Max]	7.37 [7.06, 7.46]	7.40 [0, 7.47]	

6 MULTIVARIATE MODELS

6.1 Outcome 1a : Time-in-Therapeutic-Range (TTR)

Table 3: TTR multivariable analysis

	ttrgf		
Predictors	Estimates	CI	p

	ttrgf		
(Intercept)	0.56	0.20 – 1.54	0.260
age	1.01	1.00 – 1.03	0.141
sex [M]	0.78	0.59 – 1.05	0.100
bmi	1.01	0.99 – 1.03	0.279
apache	0.99	0.95 – 1.03	0.628
group [gaxa]	0.95	0.68 – 1.32	0.742
rrt [yes]	0.60	0.43 – 0.85	**0.004**
ecmod	1.01	1.00 – 1.02	**0.008**
Observations	254		
R^2	0.087		

6.1.1 Interpretation

Membership of anti-Xa group decreases by 0.95 the odds of having a larger TTR. Each additional day on ECMO increases the odds of having a larger TTR by 1.01. Receipt of renal replacement therapy decreases the odds of having a large TTR by 0.6.

https://journals.sagepub.com/doi/10.1177/0962280217690413?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed

6.1.2 Beta regression assumptions

TTR is a value of range between 0 to 100%. Thus, beta-regression is used, using {betareg} package.

TTR includes values including 0 and 100%, whereas strictly beta-regression does not include values 0 or 100%. Thus, data-transformation y1 = y * n-1) + 0.5 / as per Smithson and Vekuilen was carried out.

It was hypothesised that 1. age 2. BMI 3. sex 4. apache II score 5. monitoring group 6. renal replacement therapy 7. duration on ecmo 8. admission period median pH value

are likely to affect “time-in-therapeutic range”

Beta regression model using above 8 variables were fitted. Step-wise variable selection was undertaken using Akaike Information Criteria. Likelihood ratio test {lmtest} using function “lrtest” was used to evaluate final model against a null model.

Likelihood ratio test confirms that p-value of final model is 0.000171 compared to null model.

In this model, variables “sex, renal replacement therapy, and duration of ECMO” are the only variables that have statistical significant. Thus, a reduced model using only this 3 variables were fitted.

Reduced model and full models were compared using likelihood ratio test and there were not statistically significant differences.

Reduced model AIC was lower than full model AIC by 5 points. As a result, we have selected a full variable model for its ability to infer effects of biologically plausible variables such as age, sex.

APACHE 2 score already includes pH value and APACHE 2 score was not known to be predictive of outcome in ECMO patients. Thus, sensitivity analysis was undertaken with both variables - APACHE 2 score and median pH value. Models were evaluated using AIC and likelihood ratio test. Likelihood ratio tests found that model including only APACHE score without pH variable has the lowest chi-square value and is statistically significant ($p<0.0001$).

Thus, this model was selected further.

6.1.3 Variable Dispersion

In the final model, dispersion parameter - phi coefficient- was estimated at 2.27 and was statistically significant. The most likely variable contributing to dispersion was 'duration of ecmo'.

Thus, final model was re-fitted with the same mean equation but now with duration of ECMO as additional regressor for the precision parameter - phi.

https://cran.r-project.org/web/packages/betareg/vignettes/betareg.pdf

The model including of ecmo duration as regressor for the precision parameter was statistically significant and improved a model fit, without significant difference in estimates of other paramters. AIC of this new model was significantly lower than model without precision parameter.

Thus, there was a statistically significant evidence for variable dispersion, and thus was chosen as a final model.

6.1.4 Fit assessment

Maximum likelihood estimation was used to calculate p-values.

Model assumptions were also evaluated using diagnostic plots; and was graphically satisfacotry for normal assumption, homeoskedasticity, and influential observations effects.

Heteroskedasticity was also checked numerically using studentized Bresuch-Pagan test and demonstrated no evidence of heteroskedasticity.

Multicollinearity was assessed using variable inflation factors using {car} package function "vif". All variables have VIF score < 2 demonstrating no evidence of multi collinearity.

Link function of logit is used.

6.2 Outcome 1b : Variability of Anticoagulation as VGR

Table 4: Multivariable analysis of VGR

	sigm 2		
Predictors	Estimates	CI	p
(Intercept)	-0.61	-1.99 – 0.77	0.388
age	0.00	-0.01 – 0.01	0.983
bmi	0.01	-0.01 – 0.03	0.401
apache	0.01	-0.03 – 0.05	0.641
sex [M]	-0.02	-0.31 – 0.27	0.893
group [gaxa]	-2.04	-2.38 – -1.70	**<0.001**
alb median	0.01	-0.03 – 0.05	0.544
lactate median	0.11	0.04 – 0.18	**0.002**
plt median	0.00	-0.00 – 0.00	0.294
rrt [yes]	0.22	-0.14 – 0.58	0.230
ecmod	-0.00	-0.01 – 0.01	0.677
Observations	253		
R^2 / R^2 adjusted	0.504 / 0.484		

6.2.1 Interpretation

Variability of anticoagulation is a measure of quality of anticoagulation, with lower Variability results in better control of anticoagulation. For 1 unit increase in lactate, our variability increases by 10.6% membership in anti Xa decreases variability by 86%.

6.2.2 Choice of model and assumptions

Variability of anticoagulation was significantly right skewed thus, a natural logarithmic transformation was undertaken of dependent variable and then a linear model was fitted against.

It was hypothesised that 1. age 2. BMI 3. sex 4. apache II score 5. monitoring group 6. renal replacement therapy 7. duration on ecmo

were thought to be affecting variability of anticoagulation.

On a multi-variate modelling, as evaluated by AIC and likelihood ratio tests, monitoring group and lactate are the only two statistically significant variables.

Thus,a reduced model using only statistically significant model was evaluated against a full model - there were no improvement of a reduced model. And, due to ability to infer effects of other biologically plausible variables, age, bmi, apache etc are included in a final model.

6.2.3 Fit assessment

Multiple R squared value of fitted model was 0.5 and model was statistically significant, whilst R squared value is not encouraging, it offers a bility to infer the reduction in variability in anti-Xa group whilst adjusting for other varibles.

Model assumptions were checked for normality, heteroskedasticity, effect of outlying values and distribution of residuals.

Numerical check of final model using Breusch-Godfrey test confirmed visual findings that model residuals are homoskedastic.

https://data.library.virginia.edu/interpreting-log-transformations-in-a-linear-model/

6.3 Outcome 2a : Rate of bleeding and thrombotic events

Dependent variable is selected for "any" bleeding and thrombotic events. Each event is considered as seperate event, thus discrete count.

Table 5: Rate of any bleeding or thrombotic events

	abte		
Predictors	Incidence Rate Ratios	CI	p
(Intercept)	0.17	0.06 – 0.46	**0.001**
age	1.01	0.99 – 1.02	0.250
sex [M]	0.72	0.55 – 0.95	**0.021**
bmi	0.99	0.97 – 1.01	0.374
apache	0.98	0.94 – 1.02	0.302
group [gaxa]	1.07	0.77 – 1.50	0.698
ttrg	0.16	0.10 – 0.25	**<0.001**
sigm	0.99	0.96 – 1.01	0.546
rrt [yes]	1.37	0.99 – 1.88	0.054
Observations	254		
R^2 Nagelkerke	0.327		

Given the count nature of "events" data, a dependent variable is visualised and found to conform to poisson distribution. Thus, this is modeled as multivariable poisson regression using a standard "log" link function.

However, it is important to note that there are statistically significant differences and variation of ECMO duration between two different study groups. The longer duration on ECMO, the longer the duration of anticoagulation and the potential risk of any complication is higher.

This is taken into account by using an “offset” of ecmo duration.

As per above, model assumptions checked.

6.4 Outcome 2b : Rate of only bleeding events

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Table 6: Only haemorrhagic complication events

	toth		
Predictors	Incidence Rate Ratios	CI	p
(Intercept)	0.02	0.00 – 0.11	**<0.001**
age	1.03	1.00 – 1.05	**0.023**
sex [M]	0.87	0.56 – 1.37	0.532
bmi	1.01	0.98 – 1.04	0.478
apache	1.00	0.94 – 1.06	0.896
group [gaxa]	0.64	0.37 – 1.12	0.120
ttrg	0.12	0.06 – 0.25	**<0.001**
sigm	0.86	0.70 – 0.99	0.099
rrt [yes]	1.51	0.93 – 2.44	0.093
Observations	254		
R^2 Nagelkerke	0.276		

As per above but restricted to analysis of only “haemorrhagic complications”. Similar treatment was followed.

6.5 Outcome 2c : Rate of only thrombotic events

Table 7: Thrombotic Complications only

	totthr		
Predictors	Incidence Rate Ratios	CI	p
(Intercept)	0.28	0.07 – 1.11	0.073
age	1.00	0.98 – 1.02	0.853
sex [M]	0.57	0.39 – 0.83	**0.003**
bmi	0.98	0.95 – 1.00	0.057
apache	0.95	0.90 – 1.00	0.070
group [gaxa]	1.57	0.96 – 2.64	0.081
ttrg	0.22	0.12 – 0.43	**<0.001**
sigm	1.00	0.98 – 1.01	0.817
rrt [yes]	1.34	0.85 – 2.09	0.205
Observations	254		
R^2 Nagelkerke	0.180		

As per above, but for only thrombotic complications.

6.6 Outcome 2d : Rate of ECMO circuit change

Table 8: ECMO circuit change analysis

	totc		
Predictors	Incidence Rate Ratios	CI	p
(Intercept)	0.04	0.01 – 0.12	**<0.001**
age	1.01	1.00 – 1.02	0.136
sex [M]	1.19	0.89 – 1.60	0.246
bmi	1.01	1.00 – 1.03	0.149
apache	0.97	0.93 – 1.01	0.169
group [gaxa]	0.68	0.48 – 0.95	**0.025**
ttrg	0.92	0.56 – 1.51	0.731
sigm	0.97	0.90 – 1.01	0.319
rrt [yes]	1.30	0.94 – 1.79	0.105
Observations	254		
R^2 Nagelkerke	0.108		

The next or first ECMO circuit change after cannulation on VV ECMO first are modelled against independent variables.

The ECMO circuit change events are modelled as count data - poisson regression- is used again using ecmo duration as an offset.

6.7 Outcome 2e : Cumulative Dose of Heparin

Table 9: Cumulative dose of heparin - log transformed

	cud 2		
Predictors	Estimates	CI	p
(Intercept)	11.38	10.78 – 11.97	**<0.001**
age	-0.00	-0.01 – 0.01	0.714
sex [M]	0.13	-0.04 – 0.29	0.124
bmi	0.01	-0.00 – 0.02	0.124
group [gaxa]	0.10	-0.15 – 0.35	0.441
lactate median	-0.13	-0.17 – -0.09	**<0.001**
ecmod	0.04	0.04 – 0.05	**<0.001**
ttrg	0.78	0.43 – 1.13	**<0.001**
sigm [log]	0.03	-0.05 – 0.10	0.517
Observations	232		
R^2 / R^2 adjusted	0.689 / 0.678		

6.7.1 Model Choice

- log transformed of heparin dose given a significantly skewed distribution of heparin.
- Given the likely interaction of duration of ecmo, interaction between ecmo duration and TTR & ecmo duration and VGR are included in an extended model.
- The model fit is not improved and the interactions are not statistically significant.
- Thus, the reduced model without interaction effects are chosen.

6.7.2 Fit assessment

- Linear regression fit assessment as per AIC, and likelihood ratio tests.

6.7.3 Interpretation

Given log transformation of dependent variable, the effect size is interpreted as a percentage change.

6.8 Outcome 2f : Rate of change of heparin prescriotion

Table 10: Analysis of heparin prescription changes

	runl		
Predictors	Incidence Rate Ratios	CI	p
(Intercept)	0.72	0.37 – 1.35	0.309
age	1.00	0.99 – 1.00	0.247
sex [M]	1.01	0.87 – 1.17	0.925
bmi	1.00	0.99 – 1.01	0.801
group [gaxa]	1.37	0.91 – 2.10	0.136
lactate median	0.94	0.89 – 1.00	**0.043**
ttrg	3.11	1.74 – 5.74	**<0.001**
sigm	1.01	1.00 – 1.01	**0.013**
rrt [yes]	1.12	0.94 – 1.33	0.195
group [gaxa] × ttrg	0.28	0.14 – 0.53	**<0.001**
Observations	254		
R^2 Nagelkerke	0.665		

Rate of change of heparin prescription is modelled as count data, poisson generalised model, with an offset for ecmo duration.

The interaction between TTR and monitoring is found. It is stastically significant with p<0.001 and thus included.

6.9 Outcome 2g : Rate of blood products transfused per ECMO duration

Our definition of BTE is more relaxed than ELSO definition since we count all documented and imaged BTEs. The ELSO definition of bleeding event is defined as that requiring blood product transfusion.

Given the predominance of red blood cell transfusion over other blood products and given we are looking at overall effect on coagulation, we have modelled all blood together summatively.

Table 11: Total blood products transfused

	bldtot		
Predictors	Incidence Rate Ratios	CI	p
(Intercept)	0.36	0.22 – 0.59	**<0.001**
age	1.00	1.00 – 1.01	0.075
sex [M]	1.05	0.94 – 1.18	0.372
bmi	0.99	0.99 – 1.00	**0.038**
apache	1.05	1.03 – 1.06	**<0.001**
rrt [yes]	1.61	1.42 – 1.83	**<0.001**
cudose	1.00	1.00 – 1.00	**0.035**
ttrg	0.24	0.16 – 0.36	**<0.001**
sigm [log]	1.07	1.02 – 1.12	**0.004**
group [gaxa]	0.78	0.60 – 1.01	0.055
ttrg × group [gaxa]	1.57	1.01 – 2.44	**0.046**
Observations	232		
R^2 Nagelkerke	0.943		

Blood products consumption were modelled as a count data using multivariate poisson regression.

The interaction were found between time in therapeutic range and monitoring group and was statistically significant.

6.10 Outcome 2h : Time to any bleeding or thrombotic complication

7 Summary

8 References

9 To Do

1. when reading the manuscript, please consider if we fulfill STROBE guidelines
2. references need sort out
3. update some more of the table
4. answer andy doyles answers
5. Suggest list of reviewers – Nunez, Schmidt, Alain V?

https://www.springer.com/journal/134/submission-guidelines?detailsPage=pltci_1060748#Instructions%20for%20Authors_Authorship%20principles

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