Anticoagulation and Bleeding during Veno-Venous Extracorporeal Membrane Oxygenation: Insights from the PROTECMO Study

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All authors had full access to all the data. G.M., F.T., M.R., A.A., D.B., M.G., M.S., K.T., R.L. take responsibility for the integrity of the data and the accuracy of the data analysis.

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Running head

Anticoagulation and Bleeding during VV ECMO

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At a Glance Commentary

Current scientific knowledge on the subject: Definitive guidelines for the management of anticoagulation during veno-venous extracorporeal membrane oxygenation (VV ECMO) are lacking, while bleeding complications continue to pose major challenges

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What this study adds to the field: The PROTECMO STUDY describe anticoagulation modalities and bleeding events in adults receiving VV ECMO over 28 days of follow up during the ecmo run.

To the best of our knowledge these large cohort longitudinal data are the first able to illustrate the actual daily practice for anticoagulation.

The increased risk of bleeding associated with higher aPTT might provide further rationale for future interventional studies investigating lower anticoagulation targets or at least considering narrowing the aPTT range

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Abstract

Rationale: Definitive guidelines for anticoagulation management during veno-venous extracorporeal membrane oxygenation (VV ECMO) are lacking, while bleeding complications continue to pose major challenges.

Objectives: To describe anticoagulation modalities and bleeding events in adults receiving VV ECMO.

Methods: International prospective observational study in 41 centers, from December 2018 to February 2021. Anticoagulation was recorded daily in terms of type, dosage, and monitoring strategy. Bleeding events were reported according to site, severity, and impact on mortality.

Measurements and Main Results: The study cohort included 652 patients, and 8471 days on ECMO were analyzed. Unfractionated heparin (UFH) was the initial anticoagulant in 77% of patients, and the most used anticoagulant during the ECMO course (6221 days, 73%). Activated partial thromboplastin time (aPTT) was the most common test for monitoring coagulation (86% of days): the median value was 52 seconds (39-61), but dropped by 5.3 seconds after the first bleeding event (95% CI -7.4 to -3.2, $p< 0.01$).

Bleeding occurred on 1202 days (16.5 %). Overall, 342 patients (52.5 %) experienced at least one bleeding event (one episode every 215 hours on ECMO), of which 10 (1.6%) were fatal. In a multiple penalized Cox proportional hazard model, higher aPTT was a potentially modifiable risk factor for the first episode of bleeding (for 20 seconds increase, hazard ratio 1.07).

Conclusions: Anticoagulation during VV ECMO was a dynamic process, with frequent stopping in cases of bleeding, and restart according to the clinical picture. Future studies might explore lower aPTT targets to reduce the risk of bleeding.

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Introduction

Anticoagulation therapy is deemed necessary during extracorporeal membrane oxygenation (ECMO) to prevent thrombus formation in the circuit, pump, and oxygenator because the contact of blood with an extracorporeal surface and shear stress can trigger activation of the coagulation system.(1) However, hemorrhagic and thrombotic complications continue to pose major challenges, despite the number of technological improvements and increasing experience in ECMO care.(2)

Unfractionated heparin (UFH) is currently the most common anticoagulant for adult and pediatric ECMO, but is a known trigger for heparin-induced thrombocytopenia (HIT) and bleeding adverse events.(3–5) Alternative anticoagulants, such as bivalirudin, argatroban and, in some countries, nafamostat mesilate, have been used in a subset of ECMO patients.(6) Avoiding anticoagulation or minimal anticoagulation with low molecular weight heparin (LMWH) has been proposed in cases of veno-venous (VV) ECMO in patients at high risk of bleeding.(7, 8) However, due to the lack of robust comparative data among anticoagulants, current guidelines and recommendations fall short of defining the best practice.(4, 9)

The principal drawback of anticoagulation is bleeding, which still occurs in up to 50% of patients, despite increasingly more biocompatible materials of ECMO circuits and a trend toward lower intensity of anticoagulation.(10) Comprehensive data on the rate of bleeding according to body site and severity are lacking, and there is a paucity of consensus on the definition of severe bleeding.(11)

Moreover, guidelines and position papers, provide suggestions for the initial anticoagulation protocol but, notwithstanding the evidence of frequent episodes of bleeding, no concrete recommendations are available for the dynamic management of anticoagulation since

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longitudinal data on changing approaches during the ECMO stay are substantially missing.(1, 2, 4, 9)

The PRospective Observational study on Transfusion in VV ECMO (PROTECMO) gathered additional information on anticoagulation and bleeding events.(12) The aim of the current analysis was to describe a real-time picture of the type, dosage, monitoring strategies, and targets of anticoagulation drugs, as well as of the site and severity of bleeding events during VV ECMO. In addition, we explored the risk factors associated with the first bleeding episode. Some of the results of these studies have been previously reported in the form of an abstract.(13)

Methods

PROTECMO was an international, multicenter, prospective observational study endorsed by the European Society of Intensive Care Medicine (ESICM) and the International ECMO network (ECMONet), and carried out in 41 ECMO centers, from 19 countries. We followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines in reporting the data in the manuscript.

Study population and data collection

We included all consecutive adults (≥18 years old) receiving VV ECMO for respiratory failure for at least 24 hours, at each center (eFigure 1). The enrollment in each center was planned to last one year. However, given that part of the study was conducted during the COVID-19 pandemic, in some centers the enrollment was stopped earlier due to a lack of resources to dedicate to the project and the aim of maintaining prospective and consecutive data retrieval. The case report form (CRF) consisted of three sets of data: Baseline characteristics of the patients at cannulation, Daily Forms, and Outcome (CRF and definitions

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in the Online Supplement). Longitudinal data were reported for 28 days or fewer if the ECMO-related ICU stay was shorter and the registration was requested for the morning values (between 6 and 10 a.m.). Hemodynamics, fluid balance, biochemistry, transfusions, ECMO data, bleeding, hemolysis, and circuit change were recorded. Clinical outcomes included ECMO weaning, and survival at discharge from the intensive care unit (ICU), from the hospital, and 6 months after ICU discharge.

Daily screening for anticoagulation, coagulation monitoring, and bleeding

Type and dosage of anticoagulant and antiplatelet therapies administered were assessed daily (UFH, direct thrombin inhibitors [DTIs] – bivalirudin and argatroban, LMWH, aspirin, no anticoagulation, and others). Patients were also categorized and described according to the anticoagulant medication administered on ECMO day 1 (group names: UFH, bivalirudin, argatroban, LMWH, nafamostat mesilate, no anticoagulation).

The single or multiple anticoagulation monitoring tests were recorded daily through a predefined multiple-choice variable: activated partial thromboplastin time (aPTT), aPTT ratio, activated clotting time (ACT), reaction time in thromboelastography (r-TEG), anti-factor Xa (anti-Xa), and others (free text space to include other assays). To increase the description of anticoagulation dynamic changes, the dose of anticoagulant drugs, the type of monitoring and the values of monitoring tests were also compared before and after the first bleeding episode.

Bleeding episodes were assessed using a set of predefined sites (cannulation, cerebral, gastric, ear/nose/throat, intestinal, intra-abdominal, intra-thoracic, tracheal/pulmonary, and urinary tract). Severity was standardized using 4 categories according to the following modified version of the Bleeding Academy Research Consortium (BARC) score.(14) Type 1: any overt bleeding that required reduction of heparin infusion rate or packed red blood cell

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(PRBC) transfusion (provided hemoglobin drop was related to bleeding); Type 2: any overt bleeding that required reduction of heparin infusion rate and transfusion of packed red blood cells or non-surgical procedure to stop bleeding (provided hemoglobin drop was related to bleeding); Type 3, any life-threatening bleeding that required PRBC transfusion with or without surgical intervention for control of bleeding or ECMO discontinuation; Type 4: any fatal bleeding. The daily form collected bleeding episodes that occurred in the preceding 24 hours. For this reason, the analysis of the risk factors for the first bleeding during ECMO was based on the information (e.g., anticoagulation level) gathered on the day before the bleeding event. For bleeding that occurred on the first day of ECMO we considered the data from day one since it was assumed that they were the nearest data before the bleeding episode. ECMO day one started at 00:00 after the ECMO cannulation day regardless the hour of cannulation to standardize the follow-up. Further information on the data reporting is provided in the Online Supplement.

To explore the factors among the coagulation/anticoagulation covariates associated with bleeding during ECMO, we considered as outcome the first bleeding episode to reduce confounding. In fact, during ECMO some patients do not experience any episode of bleeding, while the majority experience one or more episodes. These episodes can be in different body sites or in the same site but on different days, raising the question of whether they can be considered separate or exacerbation of a previous episode (they can have the characteristics of recurrent events but usually cannot be considered independent).

Statistical analysis

Missing data amounted to roughly 0.5%, as previously published.(12) Missing data were imputed using stochastic regression imputation for the quantitative variables.(14) Qualitative

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variables were imputed using the last-observation-carried-forward (LOCF) method.(15) A wide description of the process of missing data is provided in the Online Supplement.

Quantitative variables are expressed as median and interquartile range or mean ± standard deviation, and qualitative variables expressed as percentage and frequency distribution. The Chi square test and Fisher's exact test were used to assess the association between categorical variables. A T-test or Wilcoxon Mann-Whiney U model was employed when appropriate.

To analyze the correlation between heparin dose and aPTT we selected days on which heparin was administered and aPTT available on the same day. Then we employed the Spearman correlation coefficient, considering the two variables reported on the same day to give a practical and time-framed picture.

Generalized estimating equations (GEE) models were applied to assess the effect of bleeding (exposure variable of the model) on the ICU mortality (outcome variable of the model). These models were built adjusting the results for two main baseline covariates: age and SAPS 2. GEEs are useful in the presence of a correlation between repeated measures over time for the same patient. Odds ratio (OR) with 95% confidence interval are reported.

Cox proportional hazards regression models for a set of predefined clinically meaningful variables were applied to assess the risk of having the first bleeding within 28 days (eFigure 2). A penalized Cox proportional model with LASSO selection was used in order to evaluate the relevance of the association between the covariates and first bleeding. Further description of the methodology is reported in the Supplement.

P-values < 0.05 were considered statistically significant. Statistical analysis was done using SAS 9.4 (SAS Institute Inc., Cary, North Carolina, U.S.A.) and R 4.0.3 statistical software (R Core Team (2022). R: A language and environment for statistical computing. R Foundation

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for Statistical Computing, Vienna, Austria) with *glmnet* package version 4.1-8 for the LASSO procedure.

Results

From December 1st, 2018 through February 22nd, 2021, 652 adults supported with VV ECMO were enrolled, and data of 8471 days on ECMO were analyzed. 604 patients were affected with acute respiratory distress syndrome (ARDS), 34 received ECMO as a bridge-to-lung-transplantation, and 14 had severe asthma as an indication. Patient characteristics are reported in Table 1.

Type and dosage of anticoagulation

The frequency and dosage of different anticoagulants used during ECMO are reported in Figure 1. UFH was the most used anticoagulant (6221 days, 73.3 %). Aspirin was associated for only 4 days, and the other anticoagulant category was exclusively represented by nafamostat mesilate (available and used solely in Asia).

Even considering the initial anticoagulation strategy, UFH was the most frequent anticoagulant (506 patients, 77.6 %), while 122 patients (18.7 %) started with no anticoagulant, 11 were treated with bivalirudin, 9 with LMWH, and 2 with argatroban or nafamostat mesilate (eTable 1).

A unique anticoagulant strategy was used for the entire ECMO duration in 303 (46%) patients (eTable 2).

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On the other hand, anticoagulation was frequently a dynamic process, as evidenced by the alluvial diagram in Figure 2, with several patients stopping and restarting anticoagulation over the follow-up period. 58 patients subsequently used two anticoagulant drugs (eTable 3).

Patients without anticoagulation at cannulation had a lower BMI, a higher severity profile (RESP score), longer ICU stay pre-ECMO, and lower platelet count (eTable 4). They remained with no anticoagulant during 46% of days. No relevant difference at cannulation was found between patients on bivalirudin or other anticoagulants (eTable 5); bivalirudin was used prevalently in North America, while argatroban mostly in Europe.

HIT was reported in 29 patients (4.9%): it was suspected/known before cannulation in four patients (one used argatroban, three no anticoagulation), while in 25 patients it was diagnosed during the ECMO run. In 14 patients anticoagulation was suspended, in 6 UFH was replaced by argatroban, and in 5 by bivalirudin.

Type of monitoring and average values

The most widely used coagulation monitoring test was aPTT (7297 days, 86%). (Figure 1 C) aPTT was the single monitoring strategy in 51.2% of days, no monitoring was in place in 2.5% of days, and there was a combination of tests in the remaining cases (eFigure 3). In centers using bivalirudin and nafamostat as anticoagulant, aPTT was the main monitoring (eTable 1).

The occurrence of a bleeding event was associated with a change in the monitoring strategy, reducing the use of aPTT as single monitoring from 66% to 58%, $p< 0.01$ (eTable6). Indeed, other methods were used more frequently: TEG R-timer (5% of days with bleeding vs. 2% in

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days without bleeding, p<0.01), and anti-Xa essay (20% of days vs. 13%, p <0.01). Factor VIII activity was investigated in just two cases.

The average value of aPTT was 52 seconds, with a broad interquartile range (39.2-60.9), and the Spearman correlation coefficient between aPTT and UFH was very low in magnitude: 0.24, p<0.01. aPTT dropped after the first episode of bleeding on average by 5.3 seconds (95% CI -7.36; - 3.21) (p< 0.01).

Bleeding sites, severity, and dynamics over the follow-up

Bleeding occurred in 1202 ECMO days (16.5 %). At least one bleeding event was experienced in 342 patients (52.5 % of whom experienced one episode of bleeding every 215 hours on ECMO), while 310 (47.5 %) had none. A single episode was reported in 125 patients (36.6% of those with a bleeding episode), while 217 patients reported 2 or more episodes (eFigure4). Considering the follow-up, the rate of bleeding slightly but consistently increased after follow-up day 7 (eFigures 5 and 6). According to the modified BARC classification, the majority of episodes were Type 1 (n=729, 60.7%) (Figure 3B). The incidence rate of bleeding events according to severity did not significantly change over time during ECMO support (eFigure 7), but the occurrence of Type 1 bleeding was a risk factor for subsequent bleeding Types 2-4: HR 1.97 (95% CI, 1.45-2.68) p<0.01.

The most frequent bleeding was at the cannulation site (281 of 1184 episodes with site available, 23.7%), followed by the tracheal-pulmonary site (n=273, 23.1%) (Figure 3A). Over the follow-up, the incidence rate of bleeding by the site of cannulation reduced, while there was an increase in the risk of bleeding from pulmonary and oro-nasal sites (eFigure 8 and eTable 7).

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On bleeding occasions, patients normally experienced bleeding from a single site. In 130 patients there were 2 or more bleeding sites simultaneously (eFigure 9).

The occurrence of bleeding (excluding the fatal bleedings) was associated with increased ICU mortality, odds ratio 1.68 (95% CI 1.31-2.16) p< 0.01, regardless of the severity of the event (Figure 4).

Risk factors for the first episode of bleeding

Factors associated with bleeding on univariate analysis are reported in eTable 8. Longitudinal data for the overall population and on the day of bleeding are presented in eTable 9. In a multiple penalized Cox proportional hazard model, the most relevant factors associated with increased risk of first bleeding were COVID-19 diagnosis, sepsis diagnosis, higher aPTT, lower platelet count, hemoglobin and fibrinogen levels (Figure 5). In particular, for every standard deviation increase (20 seconds) in the aPTT, the hazard ratio for the first bleeding was 1.07. The test for non-proportional hazard was not statistically significant (p=0.46), indicating that the relation between aPTT increase and bleeding events is fairly linear (eFigure 10, 11).

Considerations for COVID-19 subgroup

COVID-19 patients (n=218, 33%) were a specific portion of the PROTECMO cohort (eTable 10). In terms of pre-ECMO features, they were older, had a higher BMI, had higher severity scores, and were in the hospital or ICU for longer periods before ECMO cannulation compared to patients supported with VV ECMO for other indications. Regarding the anticoagulation strategy, COVID-19 patients received higher doses of UFH and had higher

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aPTT levels: 53 (41.2-65.4) vs. 46.8 seconds (37.5-56.7); p value <0.01. Bleeding events were more frequent in the COVID-19 group: 548 days with bleeding of 3619 ECMO days (15%) vs. 654 days of 5852 (13.5%), p value=0.03; 127 patients with at least one bleeding (58%) vs. 215 patients (50%), p value=0.04. No relevant differences were found in the rate of bleeding according to the bleeding severity classification, and the average days with bleeding per ECMO run among COVID-19 and non-COVID groups.

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Discussion

The key findings of this prospective observational study were, first, that UFH was the most used anticoagulant (approximately 80% of ECMO days), and bivalirudin was the next most common choice; in all cases, anticoagulation management was reported as a dynamic clinical process with frequent stopping of anticoagulant drugs and change in targets and monitoring. Second, aPTT was the principal test used as a daily monitoring strategy, usually maintained in a range between 40 and 60 seconds. Third, bleeding remains a frequent complication (14.3% of ECMO days), and associated with increased mortality. Fourth, higher aPTT, as a likely modifiable factor, was associated with increased risk of bleeding.

Currently, UFH is the main anticoagulant drug used during VV ECMO, and this was confirmed in our study.(4, 16) Though it is well known that UFH exerts its pharmacodynamic effect by binding to antithrombin (AT), the monitoring and administration of AT is not routinely carried out worldwide, as confirmed by a rate of 10% of days with supplementation in our cohort.(17, 18) The principal advantages of UFH are low cost, availability of an antidote, and long standing historical use.(19) However, in an explorative analysis, we found a weak correlation between the dose of UFH and the aPTT values, confirming the need of wide coagulation monitoring since the effect of UFH is not entirely predictable, and offering a further rationale for alternative approaches as proposed in a recent randomized controlled trial (RCT) with low-dose of UFH and adjuvant medications.(20, 21)

In the last decade, the use of DTIs has been increasingly implemented because these medications are purported to have a more predictable dosing regimen. The shift from the use of UFH to DTIs is advocated because during ECMO the occurrence of thrombocytopenia is frequent and multifactorial, and bivalirudin may help in the differential diagnosis of HIT occurrence.(22–24) However, DTIs are more expensive, their monitoring is more difficult,

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there is no antidote, and there is relatively limited experience with their use, with debated ranges of aPTT target.(22) It is worth noting that, in the this study, a trend toward higher bleeding was recorded in the bivalirudin and argatroban groups, where the highest aPTT ranges were registered.(25) Therefore, the only factor associated with the use of bivalirudin was the COVID-19 diagnosis as cause of ARDS, and its use is determined more by the preferences of individual centers. In addition, nafamostat mesilate was reported in centers from Japan, and the promising reduction of bleeding previously reported appeared to be confirmed, though it must be taken into account that there was a lower aPTT target compared to other patients.(26) However, two issues prevent us from drawing any conclusion about the anticoagulation strategies used as an alternative to UFH: the aPTT targets reported were different, as was the prevalence of COVID-19 patients, and the sample of patients using nafamostat mesilate, bivalirudin, and argatroban were imbalanced compared to those treated with UFH.

Regarding the monitoring strategy, according to current guidelines the optimal method for monitoring UFH and DTI is unknown.(4) Plasma-based tests do not provide information on the effect of anticoagulants on the endothelial surface, on the *in vivo* interaction between the artificial surface and blood components, or on the contribution of platelets to clot strength.(27, 28) The majority of centers enrolled in PROTECMO used aPTT as a daily monitoring, but other methods, such as anti-Xa and TEG, were increasingly employed after a bleeding episode occurred.(29) In addition, even the aPTT can be measured with different reagents, showing variability in the results, and the use of aPTT ratio is still uncommon.(30) To date, despite promising efficacy, a personalized approach, including the study of primary hemostasis, is still confined to pilot research.(31–33) The aPTT target is likely the main modifiable risk factor for bleeding, since the reduction of fibrinogen, platelets, and hemoglobin is likely more related to the interaction with the circuit and membrane.(34–36)

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However, the picture is still unclear, and more basic knowledge should be produced since, during ECMO run, the release of platelet factor 4 (a potent heparin inhibitor) is quite relevant and frequently associated with low platelet count.(37) The increased risk of bleeding associated with higher aPTT might provide further rationale for future interventional studies investigating lower anticoagulation targets or at least considering narrowing the aPTT range, also considering that recent retrospective studies and the EOLIA trial targeted lower aPTT (i.e., between 40 and 55 seconds) when using coated circuits.(38–41) This is also implied by the high occurrence of Type 1 bleeding in our cohort, which was associated with a reduction or discontinuation in the administration of UFH. Therefore, recent position papers, even prompting a reduced aPTT target for VV ECMO, still suggest wide ranges that are the same reported in our dataset (between 40 and 60 seconds). However, the explorative results of our multiple model suggest that the risk of bleeding is clearly increased by passing from one extremity of this range to the other.(1, 9)

A relevant number of patients were on VV ECMO for ARDS due to COVID-19, posing further challenges.(42) As reported in large series, we confirm a higher aPTT target based on the pro-thrombotic state in these patients. This approach was associated with a higher number of patients with at least one bleeding, and a higher rate of days with bleeding, and further corroborates the relation between aPTT and bleeding.(43)

Finally, the data from PROTECMO study confirms the trend toward a reduction in fatal bleeding episodes in VV ECMO over recent years.(10) Using a standardized severity classification and a daily screening, bleeding events were relatively frequent, slightly more than reported in the ELSO registry.(2) Minor bleeding events appeared to be relevant because they induced a change in the approach to anticoagulation (reduction in aPTT target and increasing of the coagulation assessment), and were associated with mortality.(12) Finally, the report on the bleeding locations confirmed the cannulation site as the most common

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bleeding site.(2, 44) However, data provided by daily screening highlight the importance of other relevant bleeding sites, such as ear/nose/throat or gastric and intestinal sites, which account for a non-negligible number of complications, and may be difficult to diagnose and manage under the ECMO support.(45–47)

Our multicenter prospective study, despite its observational nature, has several strengths. This is the largest available set of prospective daily data on hematologic issues in VV ECMO patients, and we were able to make a sequential assessment of anticoagulation, ECMO parameters, and bleeding events. The daily assessment forced each center to screen daily for bleeding events, which were systematically reported. The data analysis method was robust regarding missing data, and the proportion of missing data was low. The recorded mortality in the present study was 34% in non-COVID and 50% in COVID-19 patients, which was in line with ELSO data and with recent literature on COVID-19 patients, confirming the validity of our findings as real-world data.(48, 49) However, our study also has several limitations. First, the observational nature of the study prevents us from directly inferring causality, though the thorough description of events and patients was aimed at exploring associations and developing a solid data base for further studies comparing different strategies. Second, our daily analysis, for reasons of feasibility, lasted a maximum of 28 days after ECMO initiation; as a result, we cannot exclude that for longer ECMO runs (> 28 days) there may be differences and factors that we were unable to assess. Third, the risk factors associated with the first bleeding may be confounded by other clinical factors unreported in the study, and the report of complications such as bleeding was made by the investigators that were aware of the coagulation status so the complication reporting was not blinded considering likely causal factors (but this would be impossible to realize in real-life studies). Fourth, the occurrence of thrombosis (apart from the circuit change and cannulation site) was not screened thoroughly, and the true incidence of thromboembolic events might be underestimated. However, the

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change of the circuit might also be determined by the existence of coagulopathy, without evidence of thrombosis.(50)

Conclusions

In a large international cohort of patients supported by VV ECMO, UFH was the main anticoagulant used, and was targeted on aPTT usually between 40 and 60 seconds. Bleeding events occurred in about 50% of patients during VV ECMO, but they were fatal in only about 1% of cases. Higher aPTT was the major determinant for the first bleeding episode during VV ECMO. Our results suggest that reducing the anticoagulation targets may be effective in minimizing the risk of bleeding in VV ECMO patients, though this should be confirmed in RCTs with comparable populations.

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Availability of data and material

Individual patient data reported in this study will be shared after de-identification, beginning 6 months and ending 2 years after publication, with researchers who provide a

methodologically sound proposal, and after approval by the Study Steering Committee. Proposals should be addressed to the corresponding author.

Declarations

Conflict of interest

None reported related to the present manuscript.

Daniel Brodie receives research support from and consults for LivaNova. He has been on the medical advisory boards for Abiomed, Xenios, Medtronic, Inspira and Cellenkos. He is the President-elect of the Extracorporeal Life Support Organization (ELSO) and the Chair of the Executive Committee of the International ECMO Network (ECMONet), and he writes for UpToDate.

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Ethics approval

The study was approved by the Institutional Ethics Committee at ISMETT (Palermo, Italy, IRRB/15/17). All participating intensive care units (ICUs) obtained ethics committee approval as per their local regulation. Giving the observational nature of the study, written informed consent from each participant or representative was requested according to the rules valid in each center.

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AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

Table 1. Characteristics of patients at cannulation, and outcomes.

Continuous variables are presented as median and 25%-75% percentiles; qualitative variables are expressed as frequency distribution and percentage.

BMI: body mass index; SAPS 2: Simplified Acute Physiology Score 2; SOFA score: Sequential Organ Failure Assessment score; PRESERVE score: PRedicting dEath for SEvere ARDS on VV-ECMO score; RESP score: Respiratory ECMO Survival Prediction score; P/F ratio: ratio of arterial oxygen tension to inspiratory oxygen fraction; ECMO: extracorporeal membrane oxygenation; COVID-19: coronavirus disease 2019; ICU: intensive care unit.

Patient characteristics at cannulation, n=652	
Age, years	52 (40-60)
Male gender, n (%)	463 (71)
Height, cm	170 (165-178)
BMI, Kg/m^2	28.4 (24.9-33.7)
SAPS 2	40 (30-54.5)
SOFA score at cannulation	9 (7-12)
PRESERVE score	3 (2-5)
RESP score	2 (0-4)
P/F ratio	72 (60-95)
Pre-ECMO hospital stay, days	5.4 (1.9-10.9)
Pre-ECMO ICU stay, days	3 (1-7)
Pre-ECMO mech. vent., days	2.2 (0.6-5.5)
Hemoglobin, g/dL	10.8 (9.3-12.3)
Platelet count, x10^3/µL	207 (140-291)
Cause of ARDS, n (%)	
Bacterial pneumonia	103 (15.8)
Viral pneumonia	115 (17.6)
COVID-19	218 (33.4)
Aspiration pneumonia	27 (4.1)
Trauma/burns	25 (3.8)
Asthma	14 (2.2)
Pancreatitis	8 (1.2)
Graft failure after lung transplant	31 (4.8)
Other acute respiratory diagnosis	61 (9.4)
Non-respiratory and chronic respiratory	50 (7.7)
Surgical procedure in the last 7 days	86 (13.2)
Pregnancy or puerperium, n (%) Female n=189	8 (4.2)
Configuration, n (%)	
Femoro-jugular	416 (63.8)
Femoro-femoral	164 (25.2)
Double-lumen cannula	43 (6.6)
Jugular-femoral	23 (3.5)
Femoro-jugular-femoral	5 (0.8)
Subclavian-femoral	1 (0.2)
Cannulation by surgeon, n (%)	302 (46.3)
Cannulation by ICU physician or interventional cardiologist, n (%)	350 (53.7)

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Outcomes	
Heparin-induced thrombocytopenia, n (%)	29 (4.5)
Cannulation site thrombosis, n (%)	95 (14.6)
Change of the circuit, n. patients/total patients (%)	153/652 (23.5)
ECMO days	19.8 (11.5-32)
ECMO weaning, n (%)	445 (68.3)
ICU discharge alive, n (%)	396 (60.7)
Hospital discharge, n (%)	387 (59.4)
6-month survival, n (%)	372 (56.9)

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Figures

Figure 1. Type and dosage of anticoagulant drugs and type and values of coagulation tests used during all ECMO days.

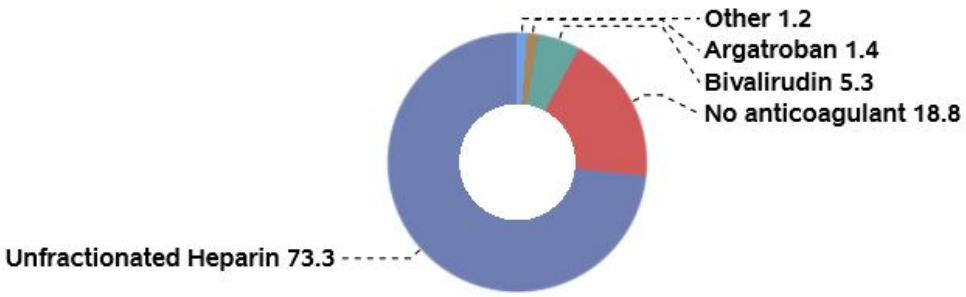
A. Donut chart for the frequency of the use of the different anticoagulants.

B. Use and median dosages for anticoagulant medications.

C: Use of different coagulation tests and average values.

ACT: activated clotting time; aPTT: activated partial thromboplastin time; LMWH: low-molecular weight heparin; TEG: thromboelastography; UFH: unfractionated heparin

A - Type of anticoagulant



B - Doses of anticoagulant medications

Type of anticoagulant	Frequency of use days (%)	Median dose	25%-75%
UFH, IU/Kg/h	6211 (73.3)	13.3	9.4-18
Bivalirudin, mg /kg/h	446 (5.3)	0.09	0.05-15
Argatroban, µg/kg/min	120 (1.4)	0.67	0.47-1.6
LMWH, IU/day	78 (0.9)	5000	1500-5000
Nafamostat, mg /kg/h	20 (0.3)	0.1	0.1-0.29
No Anticoagulation	1592 (18.8)	/	/

C - Type and values of coagualtion monitoring

Coagulation Monitoring			
Coagulation test	**Frequency of use days (%)**	**Median value**	**25%-75%**
aPTT, sec	7297 (86.1)	52	39.2-60.9
aPTT ratio	2796 (33)	1.6	1.2-1.9
ACT, sec	1982 (23.4)	174	157-188
Reaction time – TEG, mm	221 (2.6)	29.8	9.4-41
Anti-Xa, IU/mL	1188 (14)	0.32	0.13-0.42

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Figure 2. Flow diagram to represent changes in type of anticoagulation type over time. The follow up was divided into four weeks.

UFH: unfractionated heparin; LMWH: low-molecular weight heparin

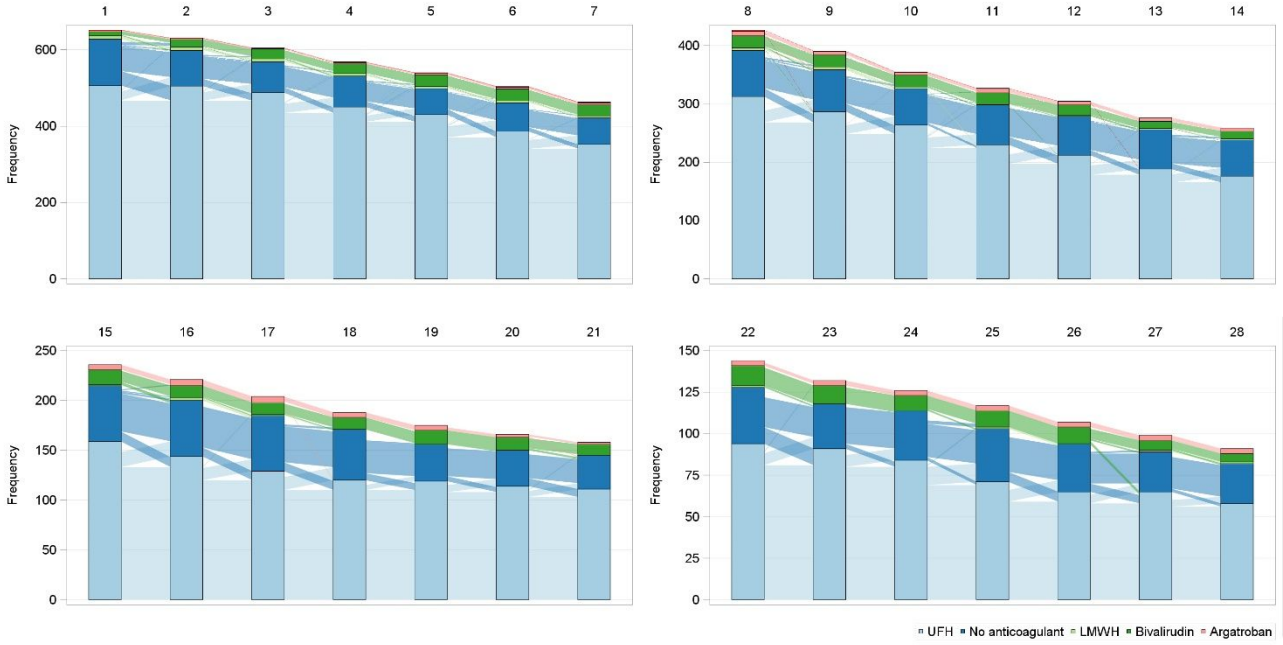

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Figure 3. Infographic of bleeding episodes during VV ECMO.

A. Frequency of bleeding sites.

B. Rate of bleeding severity according to the modified Bleeding Academy Research Consortium score.

Type 1: any overt bleeding that required reduction of heparin infusion rate or packed red blood cell (PRBC) transfusion (provided hemoglobin drop was related to bleeding); Type 2: any overt bleeding that required reduction of heparin infusion rate and transfusion of packed red blood cells or non-surgical procedure to stop bleeding (provided hemoglobin drop was related to bleeding); Type 3, any life-threatening bleeding that required PRBC transfusion with or without surgical intervention for control of bleeding or ECMO discontinuation; Type 4: any fatal bleeding.

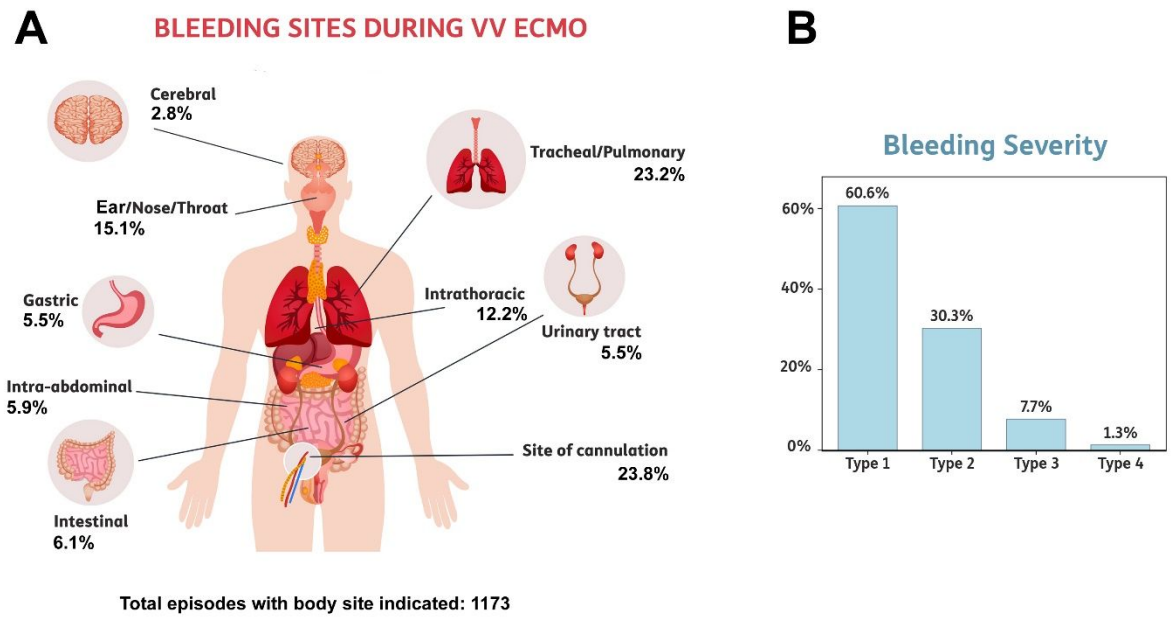

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Figure 4. Visual representation of the effect of bleeding on ICU mortality, excluding the fatal bleeding episodes.

A: Association with ICU mortality comparing no bleeding to bleeding Types 1,2 and 3.

Odds ratio for ICU mortality in cases of any bleeding 1-3 versus no bleeding: 1.68 (95% CI 1.31-2.16) p< 0.01

B: Comparison between no bleeding with bleeding Type 1 and Types 2 and 3.

Odds ratio for ICU mortality in cases of any bleeding Type 1 versus no bleeding: 1.71 (95% CI 1.31-2.22) p< 0.01.

Odds ratio for ICU mortality in cases of bleeding Types 2 and 3 versus no bleeding: 1.64 (95% CI 1.16-2.32) p=0.05.

Odds ratio for ICU mortality in cases of bleeding Types 2 and 3 versus Type 1: 1.04 (95% CI 0.74-1.45) p=0.82.

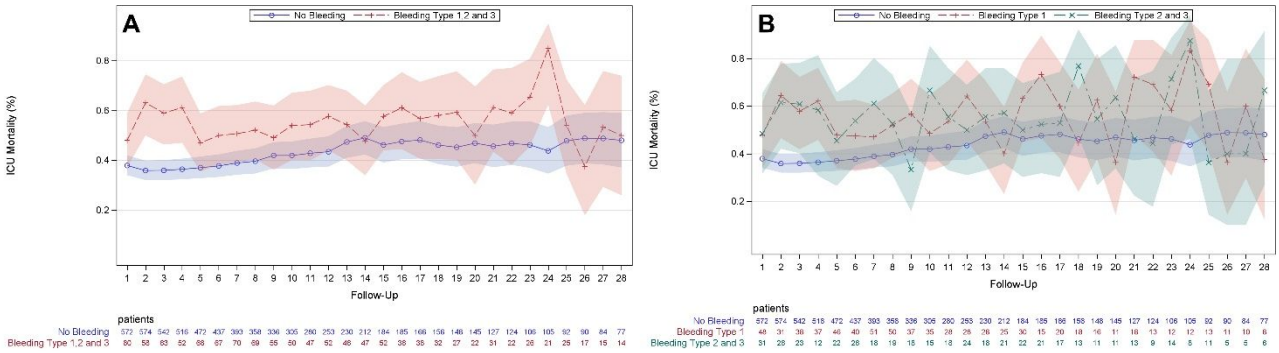

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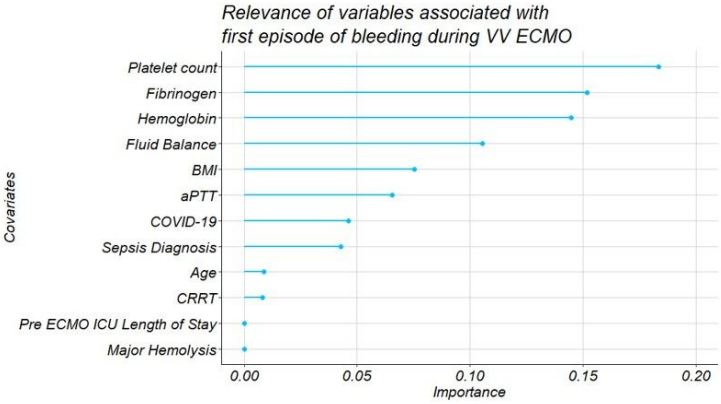
Figure 5. Lasso procedure and hazard ratio for multiple penalized Cox proportional hazard model

aPTT: activated partial thromboplastin time; BMI: body mass index; CRRT: continuous renal replacement therapy; ICU: intensive care unit



Variables	Hazard Ratio
Platelet, 100000 microL	0.83
Fibrinogen, 250 mg/dL	0.86
Hemoglobin, 2 g/dL	0.87
Fluid balance, 1800 ml	1.11
BMI, 8 k/m^2	1.08
aPTT, 20 seconds	1.07
COVID-19 vs other ARF causes	0.95
Sepsis Diagnosis vs No Sepsis	1.04
Age, 10 years	0.99
CRRT use vs No CRRT	0.99
Pre ECMO ICU length of stay, 5 days	1
Major Hemolysis vs no hemolysis	1

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ONLINE DATA SUPPLEMENT

Anticoagulation and Bleeding during Veno-Venous Extracorporeal Membrane Oxygenation: Insights from the PROTECMO Study

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Flow chart of patients included

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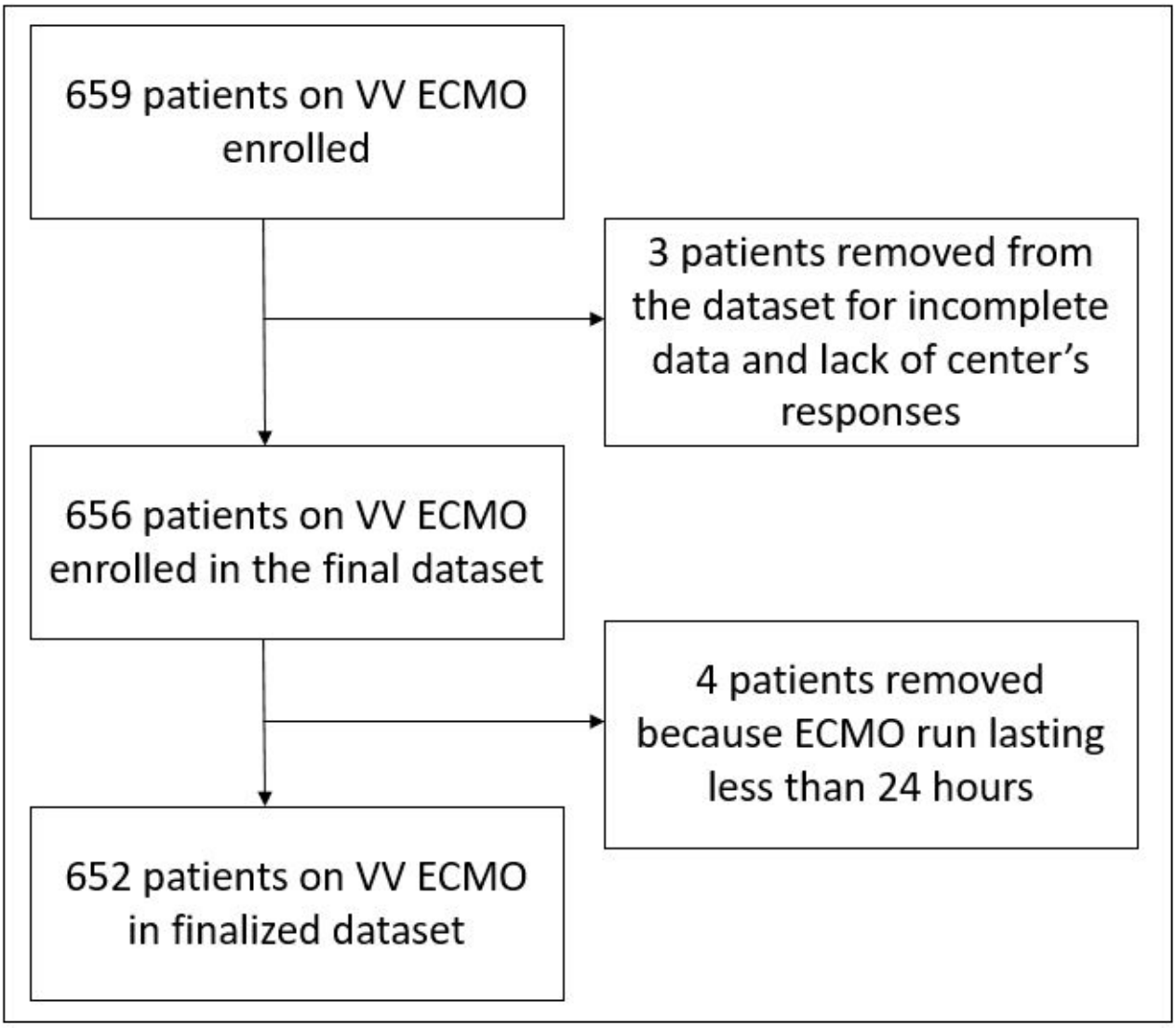
eFigure 1. Flow chart of included patients.



Statistical Analysis

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Site investigators were responsible for ensuring data integrity and validity. Data were verified for missing data monthly and, ultimately, for erroneous data or outliers, and then checked and corrected by site investigators.

One ICU from each center was involved. Centers unable to complete baseline or outcome data for all their patients enrolled were eliminated from the cohort (3 centers).

Data were collected through an online platform customized for the purpose of the study on a REDCap server. The site investigators were required to answer all the queries raised by the case report form with the aim of having no missing data in the baseline and outcome forms. For daily data, investigators were asked to fill in only data available in their daily practice. After this procedure the actual total missing data level was 0.5%.

For longitudinal studies, missing data are frequent, and can be traced to several reasons. In our dataset, the few missing data were found in the daily set. (1) Since data were verified for missing items monthly, there was no evidence of the missing not at random (MNAR) mechanism. In particular, the discussion with the local principal investigators confirmed that the data missing was due to random external factors (e.g., unavailability of the reagents during pandemic) and not due to the patients' status, or did not depend on previous responses, so the process that governs this lack of data was assumed as a missing at random (MAR) mechanism. Moreover, the rate of these few missing data was only of 0.5%. (2) This was extensively discussed with each investigator from the various centers whenever missing data were evidenced. In consideration of the previous observations, missing data imputation of quantitative variables was carried out using the stochastic regression imputation. (3) This approach first estimates a trend of the data under a cubic model, then calculates the predicted value for each missing value, and adds a random draw from a residual model to the prediction. In this case, a normal distribution residual model was considered. (4) The only missing data in the outcome form was not imputed since it was one date of mechanical ventilation weaning, and this was used only for a descriptive purpose.

To focus on the aim of the study, description of blood management, coagulation and bleeding during VV ECMO, all the analyses were done only on the days the patients were supported by ECMO. The dataset also provided the first day after ECMO weaning, but these data were not included in the present analyses. Consequently, all the subsequent analyses should be considered the image of the practice during ECMO, and not generally as the practice during the entire stay in the ICU or the hospital for patients undergoing VV ECMO support.

Quantitative variables are summarized as mean and standard deviation or median and interquartile range when appropriate, while qualitative variables are summarized as percentage and frequency distribution. Differences between continuous variables were analyzed by 2-sample T-test, Wilcoxon-Mann-Whitney test or median test, when appropriate. In particular, normal distribution was assessed with a graphical approach (Q-Q Plot, histogram, box plot), and test of homoscedasticity was done as assumption of the F-test. When normality distributions were violated, the Wilcoxon-Mann-Whitney test or median tests were adopted. Chi-square test and Fisher's exact test were used to assess the association between categorical variables. Fisher's exact test was adopted when the expected values in any of the cells of a contingency table were below 5.

Generalized estimating equations (GEE) models were applied to assess the effect of bleeding on the ICU mortality. GEE models were applied in order to estimate the effect of variables on the outcome while considering the correlated data of the repeated measures over time of the same subjects. The correlated data is the main characteristic of the data sets that arise from longitudinal studies in

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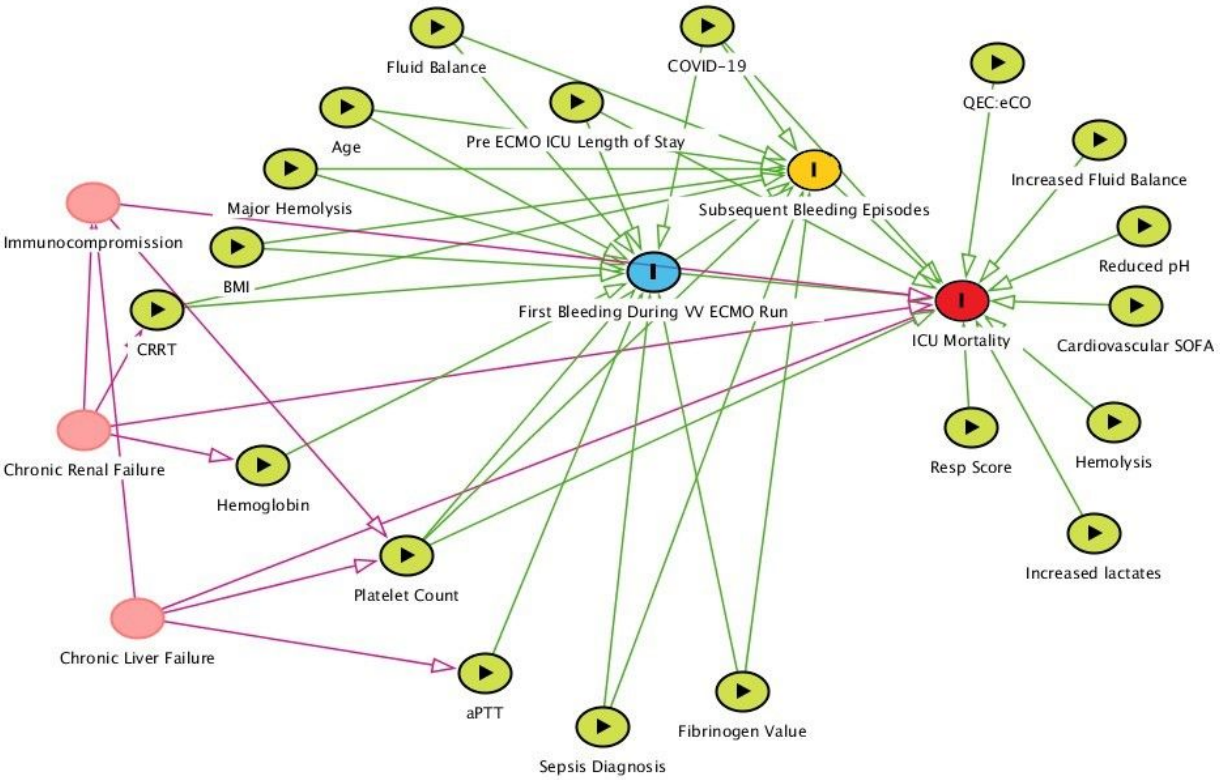
which subjects are measured at different points in time. The distribution of the outcome variable (ICU mortality) was binomial, and the link function was defined as logit. The QIC (Quasi-likelihood under the Independence model Criterion) statistic was used to provide the most appropriate working correlation matrix of the repeated measures. The QIC statistic was also used for comparing models fit with likelihood-based methods. In order to consider a nonlinear relationship between time and the outcome variable, the time variable was added in the model both as linear and as quadratic terms.

Cox proportional hazards regression models for a set of predefined clinically meaningful variables were applied to assess the risk of having the first bleeding within 28 days.



eFigure 2. Directed acyclic graph (DAG) illustrating the potential actions of confounding covariates on the occurrence of the first episode of bleeding. The graph also illustrates the logic relation with two other related outcomes: the occurrence of possible further episodes of bleeding and the ICU mortality. The DAG was modeled with the online application at www.dagitty.net

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A penalized Cox proportional model with LASSO selection was used in order to evaluate the relevance of the association between the covariates and first bleeding event.

In order to check the proportional hazards assumption of the Cox proportional hazard models we had to make the diagnostics based on the weighted Schoenfeld residuals. For each predictor of the univariate Cox Model we explored the plot of the time-varying coefficients in addition to a correlation test between the weighted residuals and failure times. In particular, the tests for non-proportional hazards with the Rank method was applied.

The method used for variable selection and shrinkage in Cox's proportional hazards model is penalized likelihood, known as Lasso regression. This is a variation of Lasso build for regression model. In this case, our response variable is a survival data, with data in counting process form. The effect of using Lasso is to shrink the coefficients of explanatory variables in a model towards zero, and in so doing, some estimates are set automatically to exactly zero. Before using the Lasso procedure the matrix of explanatory variables will be standardized to have 0 mean and unit variance.

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eTable 1. Description of anticoagulation, monitoring, and bleeding according to the initial anticoagulation strategy.

	Patients according to Initial Anticoagulation Strategy	

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	UFH	Bivalirudin	Argatroban	LMWH	Nafamostat	No Anticoagulation
N	506	11	2	9	2	122
Days	6829	176	47	79	42	1298
Dose*	13.0 (9.6 – 17.2)	0.06 (0.05-0.11)	0.39 (0.22-0.56)	5000 (1500-5000)	0.1 (0.1-0.21)	/
Monitoring days (%)						
aPTT, sec	87.5	99.6	56.7	83.3	100	79.2
aPTT ratio	34.4	13.5	79.2	43.6	0	29.7
ACT, sec	25.9	0	43.3	14.1	0	19.2
r-TEG, mm	2.7	0.22	12.5	1.3	0	2.3
Anti-Xa, IU/mL	16.7	1.6	12.5	7.7	0	7.9
Monitoring values						
aPTT, sec	49.2 (40-60.5)	61.6 (49.4-67.5)	50.4 (33-56.7)	46.4 (31.5-56.7)	41.35 (38.4-45.8)	42.2 (33.9-55.3)
aPTT ratio	1.57 (1.25-1.88)	/	1.82 (1.62-1.89)	1.71 (1.55-1.97)	/	1.2 (1-1.57)
ACT, sec	170 (157-188)	/	229 (202-266)	155 (148-159)	/	169 (156-183)
r-TEG, mm	22 (10-44.2)	/	8 (4.2-11)	5.7 (5.7-5.7)	/	13.7 (3.8-34)
Anti-Xa, IU/mL	0.28 (0.14-0.42)	1.01 (1.01-1.01)	/	/	/	0.2 (0.1-0.32)
Platelet count, $x10^3/\mu L$	154 (107-203)	149 (95-251)	167 (166-168)	167 (97-229)	118 (106-130)	106 (73-172)
Antithrombin monitoring, days (%)	2729 (40)	0	6 (13)	39 (50)	42 (100)	367 (28)
Antithrombin level, % of activity	84 (68-101)	/	88 (67-116)	97 (89-102)	87 (68-123)	81 (67-102)
Antithrombin administration, days (%)	711 (10.4)	0	1 (2.1)	9 (11.4)	0	48 (3.7)
Antithrombin dosage, units	1800 (1000-2000)	/	1000 (1000-1000)	1000 (1000-2000)	/	2000 (1500-2000)
No anticoagulation days, % of days (25%-75%)	18 (10-36)	23 (13-50)	57 (57-57)	35 (16-50)	0	50 (22-100)†
Bleeding, days/total days (%)	925/6829 (13.6)	42/176 (23.9)	16/47 (34.1)	11/79 (13.9)	1/42 (2.4)	207/1298 (16)
Patients without bleeding (%)	252 (49.8)	3 (27.3)	/	2 (22.2)	1 (50)	52 (42.6)
Circuit change, N (% of total days)	183 (2.7)	5 (2.8)	2 (4.3)	3 (3.8)	1 (2.4)	26 (2)
Patients with at least one PRBC transfusion, n/total patients (%)	414/506 (82)	9/11 (82)	2/2 (100)	9/9 (100)	2/2 (100)	105/122 (86)
Average PRBC transfused, ml	411 (349-525)	539 (500-600)	479 (429-529)	530 (486-738)	327 (280-373)	500 (350-617)
Patients with at least one Plasma transfusion, n/total patients (%)	124/506 (24)	3/11 (27)	1/2 (50)	2/9 (22)	1/2 (50)	40/122 (33)
Average Plasma transfused, ml	632 (424-981)	691 (484-918)	863	975 (950-1000)	480	700 (500-1000)
Patients with at least one Platelets transfusion, n/total patients (%)	145/506 (29)	4/11 (36)	0/2	3/9 (33)	1/2 (50)	57/122 (47)
Average Platelets transfused, ml	346 (280-465)	396 (267-548)	/	246 (150-250)	200	375 (300-500)
Patients with at least one Fibrinogen administration, n/total patients (%)	38/506 (8)	0/11	0/2	1/9 (11)	0/2	22/122 (18)
Average fibrinogen dose, mg	1600 (1000-2500)	/	/	4000	/	2000 (2000-2000)
Patients with at least one Tranexamic Acid administration, n/total patients (%)	25/506 (5)	0/11	0/2	2/9 (22)	0/2	10/122 (8)
Average Tranexamic Acid dose, mg	1000 (1000-2000)	/	/	1000 (1000-1000)	/	1000 (1000-1500)
ECMO duration, days	20 (11.8-32.7)	25.4 (16.7-31.3)	27.7 (18.9-27.7)	21 (7.1-24.7)	93.6 (13.9-93.6)	15.9 (8.7-25.6)

ACT: activated clotting time; aPTT: activated partial thromboplastin time; ECMO: extracorporeal membrane oxygenation; LMWH: low-molecular weight heparin; PRBC: packed red blood cells; TEG: thromboelastography; UFH: unfractionated heparin.

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

*: Unit of measure for different anticoagulants. Unfractionated heparin: IU/Kg/h; bivalirudin: mg /kg/h; argatroban: µg/kg/min; low molecular weight heparin: IU; nafamostat: mg /kg/h.

†: An anticoagulant was introduced in the remaining days, and these were principally UFH (526 days (40.5%)) and bivalirudin (151 days (11.6%)).

eTable 2. Patients with a single type of daily anticoagulation strategy during the ECMO run.

Patients with single daily strategy for anticoagulation		
Type of anticoagulation	**Number of patients**	**Length of stay** Days (25%-75%)

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UFH	258	8 (5-13)
No anticoagulation	40	4.5 (2-8.5)
LMWH	3	4 (2-7)
Bivalirudin	1	3 (/)
Argatroban	1	19 (/)

eTable 3. Type of anticoagulation strategies in patients with more than one anticoagulant during the ECMO run.

N Patients	Type of anticoagulant during the ECMO run
12	UFH, LMWH, no anticoagulation
12	UFH, Bivalirudin, no anticoagulation
12	UFH, Bivalirudin
6	UFH, LMWH
5	UFH, Argatroban, no anticoagulation
4	UFH, Argatroban
3	UFH, No anticoagulation, aspirin
2	UFH, Nafamostat
1	LMWH, Bivalirudin, no anticoagulation
1	LMWH, Bivalirudin

eTable 4. Baseline characteristics of patients with no anticoagulation at the beginning of the ECMO support compared with those who started with an anticoagulant.

Patient characteristics at cannulation	**NO**	**All**	**P value**

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	ANTICOAGULATION n=122	**anticoagulants n=530**	
Age, years	47 ± 15	50 ± 13	0.0731
Male gender, n (%)	74 (61)	389 (73)	0.0052
Height, cm	169 ± 10	171 ± 10	0.1808
BMI, Kg/m^2	28.6 ± 7.8	30.6 ± 8.2	0.0136
SAPS 2	45 ± 18	42 ± 15	0.1756
SOFA score at cannulation	10 ± 3.7	9.2 ± 3.5	0.0164
PRESERVE score	4 ± 3	3 ± 2	0.0616
RESP score	1 ± 4	2 ± 3	0.0052
P/F ratio	89 ± 66	87 ± 50	0.6980
Pre-ECMO hospital stay, days	7.5 ± 12.8	7.8 ± 8.2	0.7926
Pre-ECMO ICU stay, days	3.7 ± 4.3	5.2 ± 6.2	0.0015
Pre-ECMO mech. vent., days	2.9 ± 3.5	4.2 ± 5.4	0.0007
Hemoglobin, g/dL	10.4 ± 2.4	11.1 ± 2.4	0.0031
Platelets, x10^3/μL	175 ± 103	239 ± 127	<0.0001
Chronic renal failure, n (%)	4 (3.3)	24 (4.5)	0.5393
Chronic liver failure	5 (4.1)	11 (2.1)	0.1929
Cause of ARDS, n (%)			<0.0001
Bacterial pneumonia	18 (15)	85 (16)	
Viral pneumonia	16 (13)	99 (19)	
COVID-19	14 (12)	204 (38)	
Aspiration pneumonia	6 (5)	21 (4)	
Asthma	0	14 (3)	
Trauma/burns	16 (13)	9 (2)	
Pancreatitis	0	8 (2)	
Graft failure after lung transplant	18 (15)	13 (2.4)	
Other acute respiratory diagnosis	23 (19)	38 (7)	
Non-respiratory and chronic respiratory	11 (9)	39 (7)	
Surgical procedure in the previous 7 days	43 (35.3)	43 (8.1)	<0.0001

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

Pregnancy or puerperium Female n=189	2/48 (4.2%)	6/141 (4.3)	0.9790
Cannulation by surgeon, n (%) Cannulation by ICU physician and interventional cardiologist, n (%)	50 (41) 72 (59)	252 (48) 278 (52)	0.1356

eTable 5. Baseline characteristics of patients treated with bivalirudin at the beginning of the ECMO support compared with those who started with other anticoagulant.

Patient characteristics at cannulation	**Bivalirudin n=11**	**Other anticoagulants**	**P value**

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		n=519	
Age, years	43 ± 16	50 ± 13	0.0715
Male gender, n (%)	9 (82)	380 (73)	0.5230
Height, cm	173 ± 11	171 ± 10	0.5539
BMI, Kg/m^2	34 ± 7	31 ± 8	0.1405
SAPS 2	42 ± 15	42 ± 15	0.9204
SOFA score at cannulation	10.8 ± 3.2	9.2 ± 3.5	0.1205
PRESERVE score	3.5 ± 2.7	3.5 ± 2.3	0.9383
RESP score	1.9 ± 4.1	2.1 ± 3.4	0.8997
P/F ratio	63 ± 21	87 ± 50	0.0293
Pre-ECMO hospital stay, days	10.3 ± 17.3	7.8 ± 7.1	0.6436
Pre-ECMO ICU stay, days	6.1 ± 7.8	5.2 ± 6.2	0.6612
Pre-ECMO mech. vent., days	4.4 ± 7.1	4.2 ± 5.4	0.9113
Hemoglobin, g/dL	11.8 ± 3.3	11.1 ± 2.3	0.3073
Platelets, x10^3/μL	233 ± 103	240 ± 128	0.8673
Chronic renal failure, n (%)	1 (9)	23 (4)	0.6232
Chronic liver failure	0	11 (2)	0.3872
Cause of ARDS, n (%)			<0.0001
Bacterial pneumonia	1 (9)	84 (16)	
Viral pneumonia	2 (18)	97 (17)	
COVID-19	5 (45)	199 (38)	
Aspiration pneumonia	1 (9)	20 (4)	
Asthma	0	14 (2.7)	
Trauma/burns	0	9 (2)	
Pancreatitis	0	8 (2)	
Graft failure after lung transplant	0	13 (2.5)	
Other acute respiratory diagnosis	2 (18)	36 (7)	
Non-respiratory and chronic respiratory	0	39 (8)	
Surgical procedure in the previous 7 days	1 (9)	42 (8)	0.9045
Pregnancy or puerperium, n (%)	0	6 (4)	0.9554

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Female n=189			

eFigure 3. Type of coagulation tests used to monitor coagulation during ECMO, with proportion of days with combined exams.

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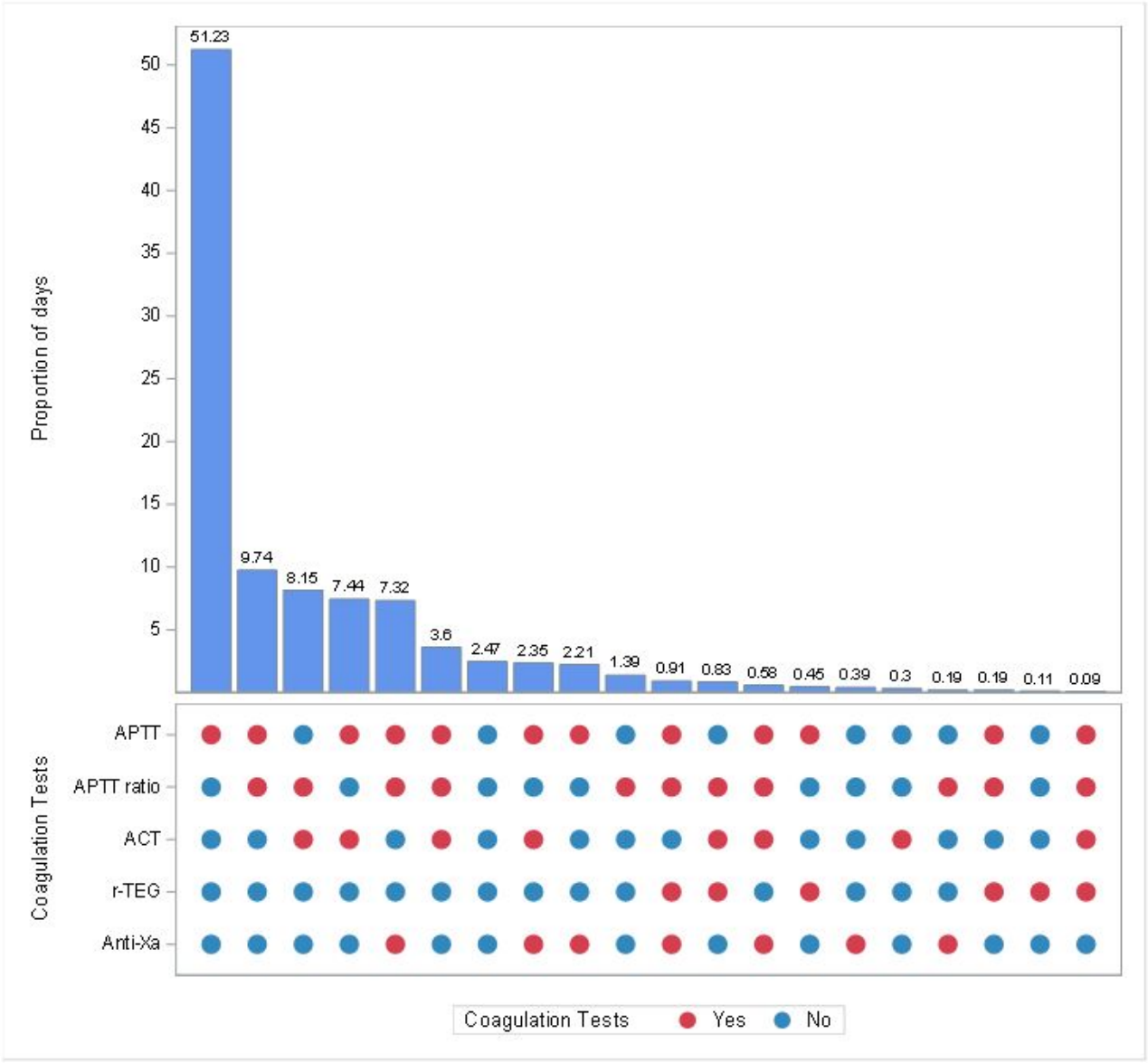

eTable 6. Different types of coagulation monitoring before and after the first bleeding. Number of measurements and percentage.

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	aPTT	aPTT ACT	aPTT Anti-Xa	aPTT ACT Anti-Xa	No Exam	APTT All ACT r-TEG	APTT All r-TEG Anti-Xa	APTT All r-TEG	Anti-Xa	ACT	r-TEG	r-TEG Anti-Xa	All Exams	Total
Before First Bleeding	3010 66.17	843 18.53	393 8.64	85 1.87	82 1.80	51 1.12	37 0.81	20 0.44	14 0.31	8 0.18	0 0.00	4 0.09	2 0.04	4549 53.70
After First Bleeding	2273 57.96	782 19.94	430 10.96	163 4.16	127 3.24	27 0.69	41 1.05	34 0.87	19 0.48	17 0.43	9 0.23	0 0.00	0 0.00	3922 46.30
Total	5283 62.37	1625 19.18	823 9.72	248 2.93	209 2.47	78 0.92	78 0.92	54 0.64	33 0.39	25 0.30	9 0.11	4 0.05	2 0.02	8471 100.0

eFigure 4. Descriptive table for multiple bleeding and number of patients.

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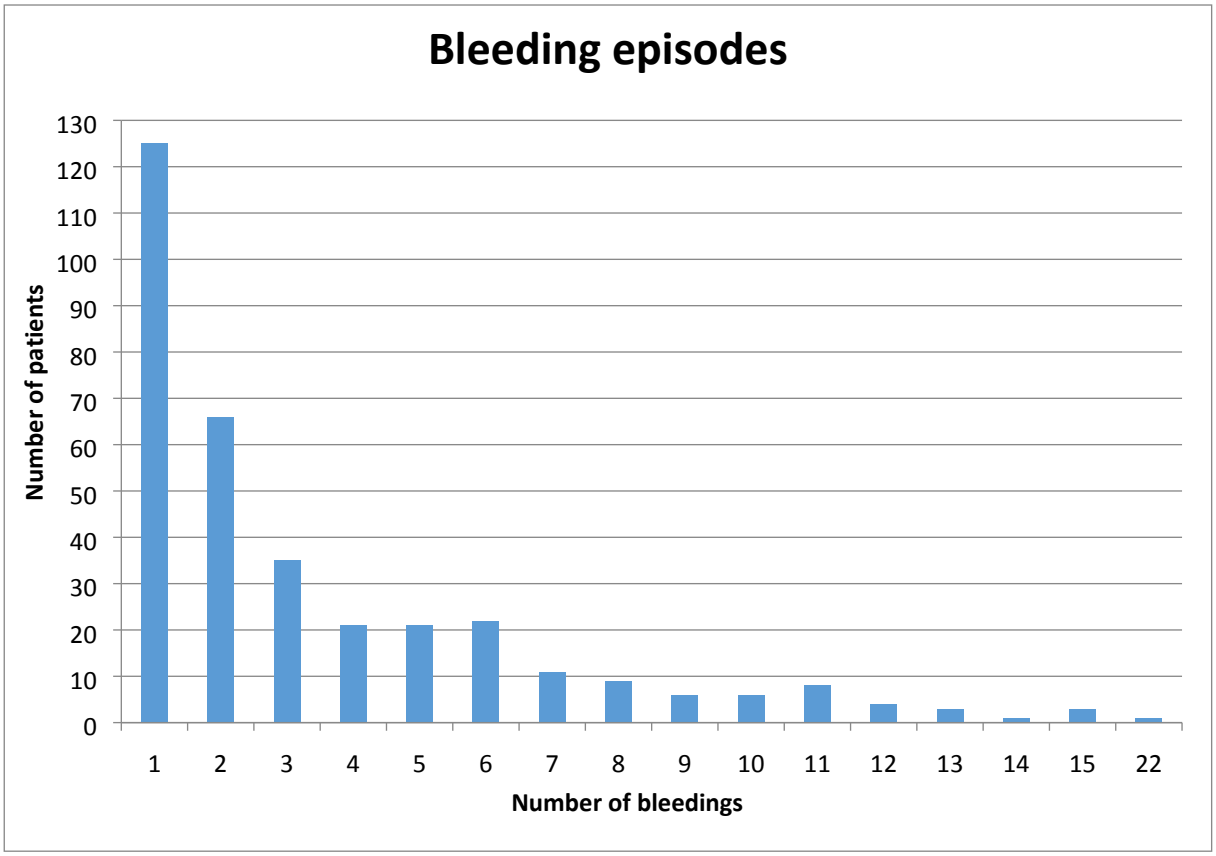

eFigure 5 and 6. Incidence rate of overall bleeding over the 28-day follow-up.

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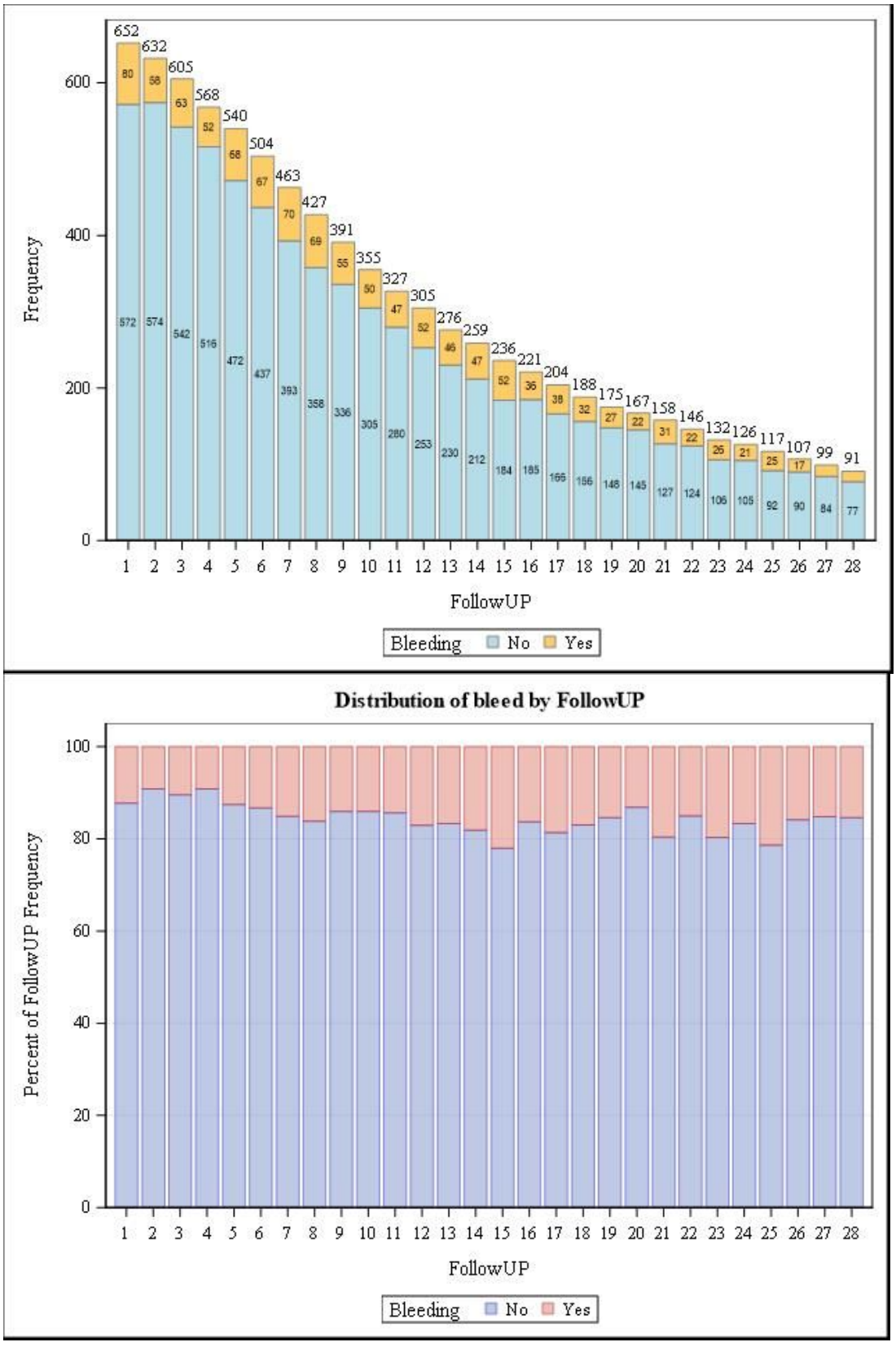
Increased risk of bleeding over time according to daily follow-up: 0.03 (CI 95% limit 0.01-0.04), p value <0.01.



eFigure 7. Dynamics of bleeding severity over the 28-day follow-up.

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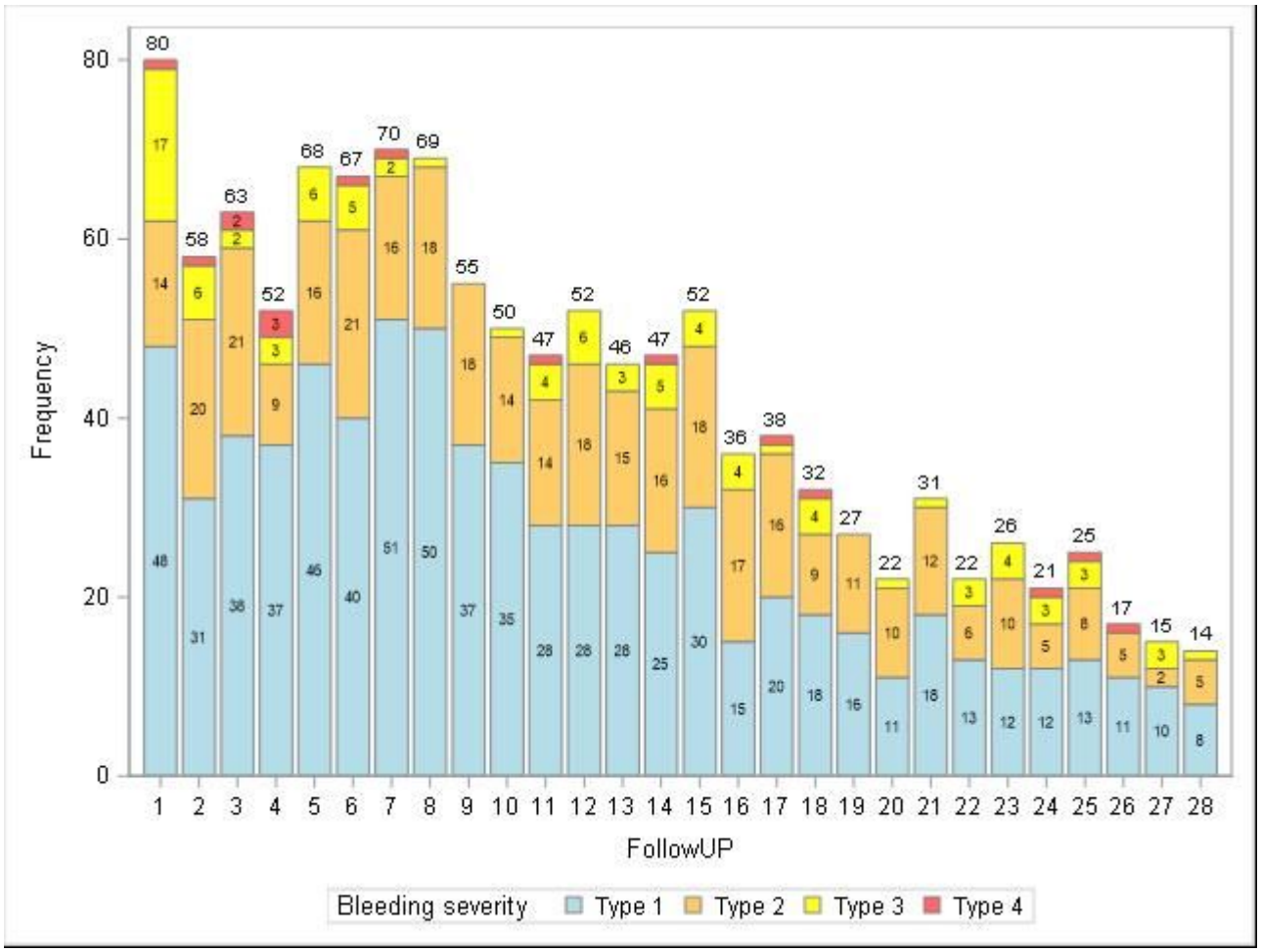
Risk of different incidence of various severe bleeding over time: -0.02 (CI 95% limit -0.04; 0.01), p value=0.15.



eFigure 8. Dynamics of bleeding sites over the 28-day follow-up.

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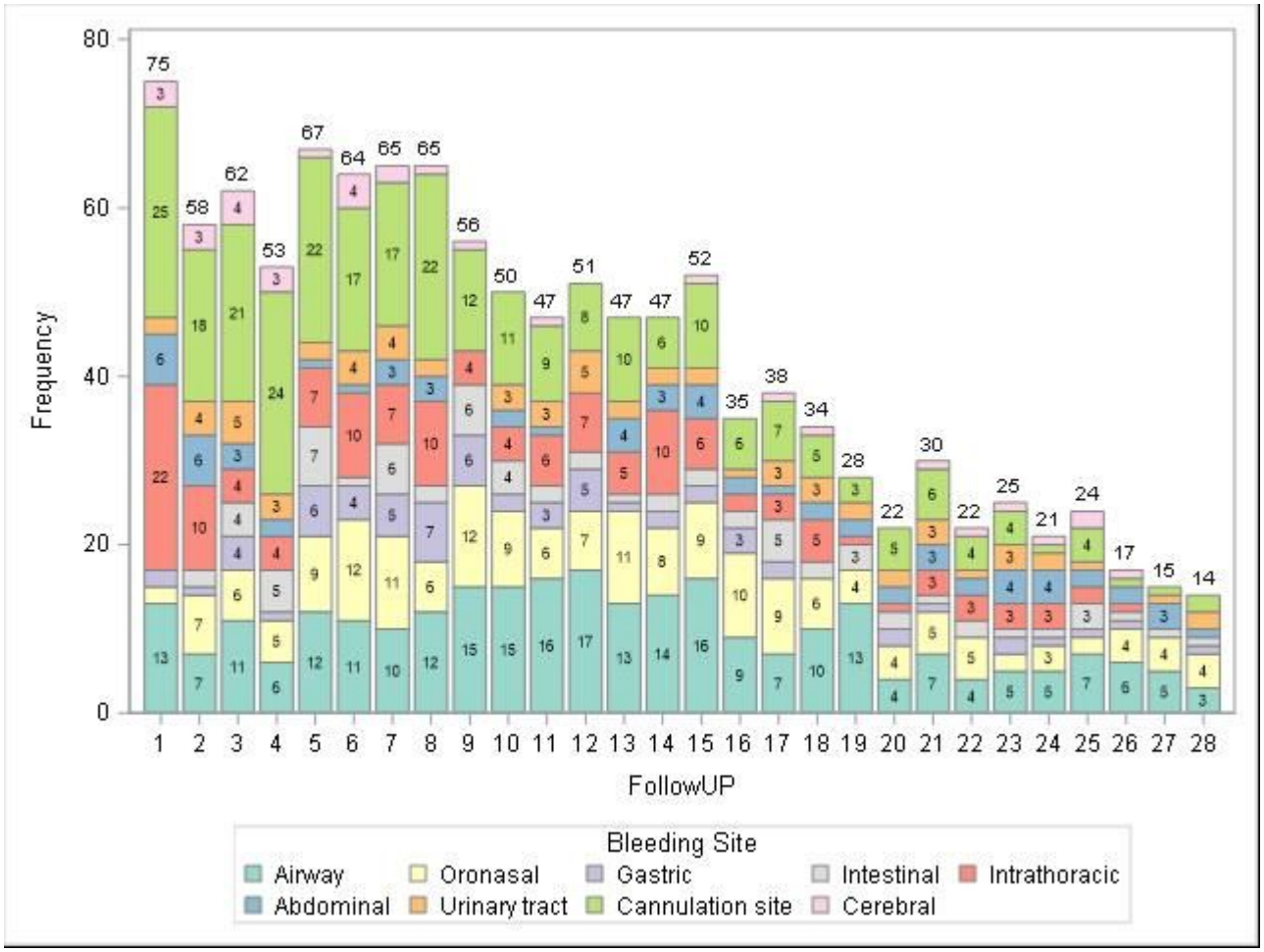

eTable 7. Table for the risk of different bleeding sites over the 28-day follow-up.

Bleeding site	Estimate	CI 95% limit	P value
Tracheal/Pulmonary	0.03	0.01; 0.06	0.03
Ear/Nose/Throat	0.03	0.01; 0.06	0.04
Gastric	-0.01	-0.05; 0.03	0.62
Intestinal	0.02	-0.04; 0.08	0.57
Intrathoracic	-0.03	-0.07; 0.01	0.07
Intra-abdominal	0.05	-0.02; 0.11	0.17
Urinary tract	0.02	-0.02; 0.07	0.28
Cannulation site	-0.06	-0.09; -0.03	<0.01

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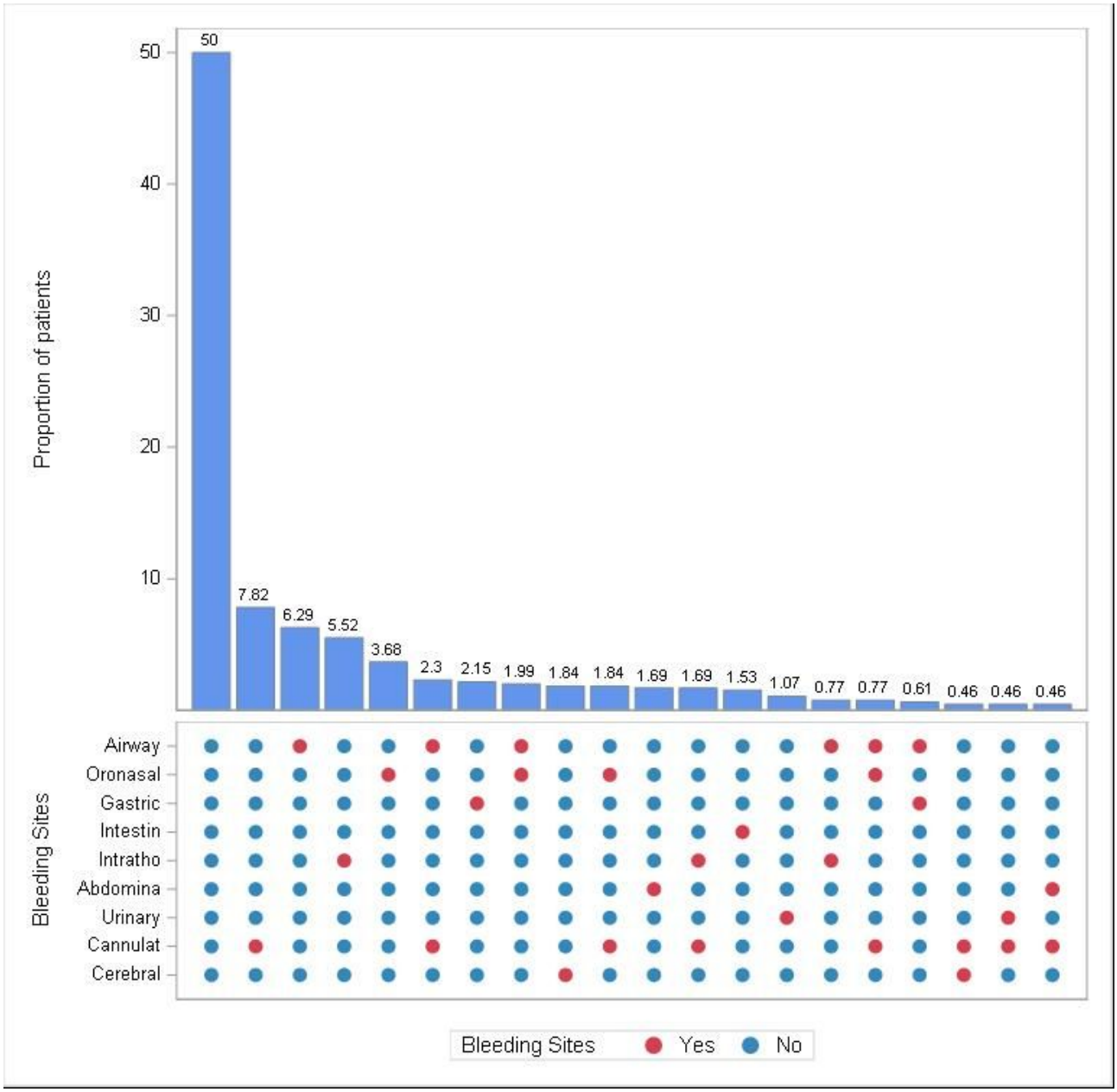
eFigure 9. Bleeding sites and combined bleeding sites in the same patient.



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eTable 8. Univariate Cox model with time-fixed and time-dependent covariates for first bleeding episode.

Parameter	Hazard Ratio	95% Lower Confidence	95% Upper Confidence	P-value
Time independent variables				
Age	**1.001**	**0.993**	**1.009**	**0.7377**
Male gender	**0.887**	**0.703**	**1.118**	**0.3106**
Body mass index	**0.996**	**0.983**	**1.009**	**0.5222**
Pre-ECMO ICU stay	**1.014**	**0.998**	**1.031**	**0.0873**
Chronic renal failure	**1.808**	**1.091**	**2.997**	**0.0215**
Ischemic heart disease	**1.355**	**0.937**	**1.961**	**0.1068**
Chronic liver failure	**2.077**	**1.137**	**3.791**	**0.0174**
Surgical procedure in the previous 7 days	**1.26**	**0.911**	**1.743**	**0.163**
Pregnancy or peripartum	**0.89**	**0.279**	**2.843**	**0.8443**
SAPS 2	**1.0**	**0.993**	**1.007**	**0.9776**
Immunocompromised	**1.272**	**0.974**	**1.662**	**0.0768**
Heparin-induced thrombocytopenia	**1.238**	**0.788**	**1.946**	**0.3541**
Cause of Acute Respiratory failure COVID-19 vs. No-COVID	**1.006**	**0.786**	**1.288**	**0.9637**
Time-dependent variables				
Fluid balance x 1000 mL increase	**1.084**	**1.030**	**1.140**	**0.0020**
Urine output x 500 mL increase	**1.000**	**0.969**	**1.033**	**0.9815**

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CRRT	**1.049**	**0.822**	**1.339**	**0.6985**
Septic shock	**1.080**	**0.833**	**1.400**	**0.5599**
Hemoglobin	**0.838**	**0.776**	**0.906**	**0.0001**
Platelets	**0.998**	**0.996**	**0.999**	**0.0001**
Creatinine	**1.074**	**0.986**	**1.169**	**0.1009**
APTT x 5 sec. increase	**1.028**	**1.007**	**1.048**	**0.0077**
pH	**0.867**	**0.195**	**3.851**	**0.8512**
Type of anticoagulation Heparin IV vs. Argatroban	**1.343**	**0.429**	**4.204**	**0.6121**
Type of anticoagulation Heparin IV vs. Bivalirudin	**1.111**	**0.658**	**1.877**	**0.6931**
Type of anticoagulation Heparin IV vs. Heparin SC	**2.117**	**0.941**	**4.764**	**0.0699**
Heparin dose x 1 IU increase	**1.016**	**0.999**	**1.034**	**0.0658**
Bivalirudin dose x 1 IU increase	**0.964**	**0.808**	**1.151**	**0.688**
Antithrombin x 10% increase	**1.000**	**1.000**	**1.001**	**0.2878**
Fibrinogen x 50 mg/dL increase	**0.954**	**0.932**	**0.977**	**0.0001**
Major hemolysis	**0.750**	**0.279**	**2.012**	**0.5671**
Platelet transfusion in the last 24 h	**1.000**	**0.999**	**1.002**	**0.5288**
Plasma transfusion in the last 24 h	**1.065**	**1.006**	**1.126**	**0.029**

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eTable 9. Longitudinal data for the overall population and on the day of the first bleeding.

CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; Q_{EC}: extracorporeal blood flow; Q_{EC}/eCO: extracorporeal blood flow rate to estimated cardiac output ratio; SOFA: Sequential Organ Failure Assessment.

Daily Variables	**Overall ECMO run** (8471 days on ECMO)	**Day of the first bleeding** (342 patients)
Fluid balance, mL	170 (-327; 695)	9 (-800; 880)
Urine output, mL	2226 (833-3085)	2200 (800-3200)
CRRT, n (%)	2503 (29.5)	83 (24)
Creatinine, mg/dL	1.1 (0.7-1.8)	0.88 (0.6-1.79)
Septic shock, n (%)	1511 (17.8)	56 (16)
Cardiac SOFA	1.3 (0.5-2)	1 (0-2)
Hematocrit, %	27.6 (25.5-30.2)	27 (24.4-29.5)
Hemoglobin, g/dL	9 (8.3-9.9)	8.7 (8-9.6)
Platelets, x1000 micro/L	149 (97-198)	133 (86-200)
Fibrinogen, mg/dL	422 (336-536)	405 (281-577)
Antithrombin, %	83 (68-98)	81 (65-99)
aPTT, sec	49.5 (42.9-58.7)	54 (42-64)
QEC, L/min	4.1 (3.5-4.6)	4.1 (3.5-4.9)
QEC/eCO, %	86 (75-96)	87 (76-101)
Circuit change, n (%)	220 (2.6)	7 (2)
Major hemolysis, n (%)	152 (1.8)	5 (1.4)
Ph	7.41 (7.38-7.43)	7.42 (7.38-7.45)
HCO3, mmol/L	27.5 (24.8-30.2)	28 (24.9-31)
SaO2, %	95 (93-97)	95 (92-97)
PaO2, mmHg	84 (75-99)	77 (66-98)
PaCO2, mmHg	44 (41-48)	44 (39-49)
Lactates, mmol/L	1.5 (1.1-2)	1.4 (1-2)

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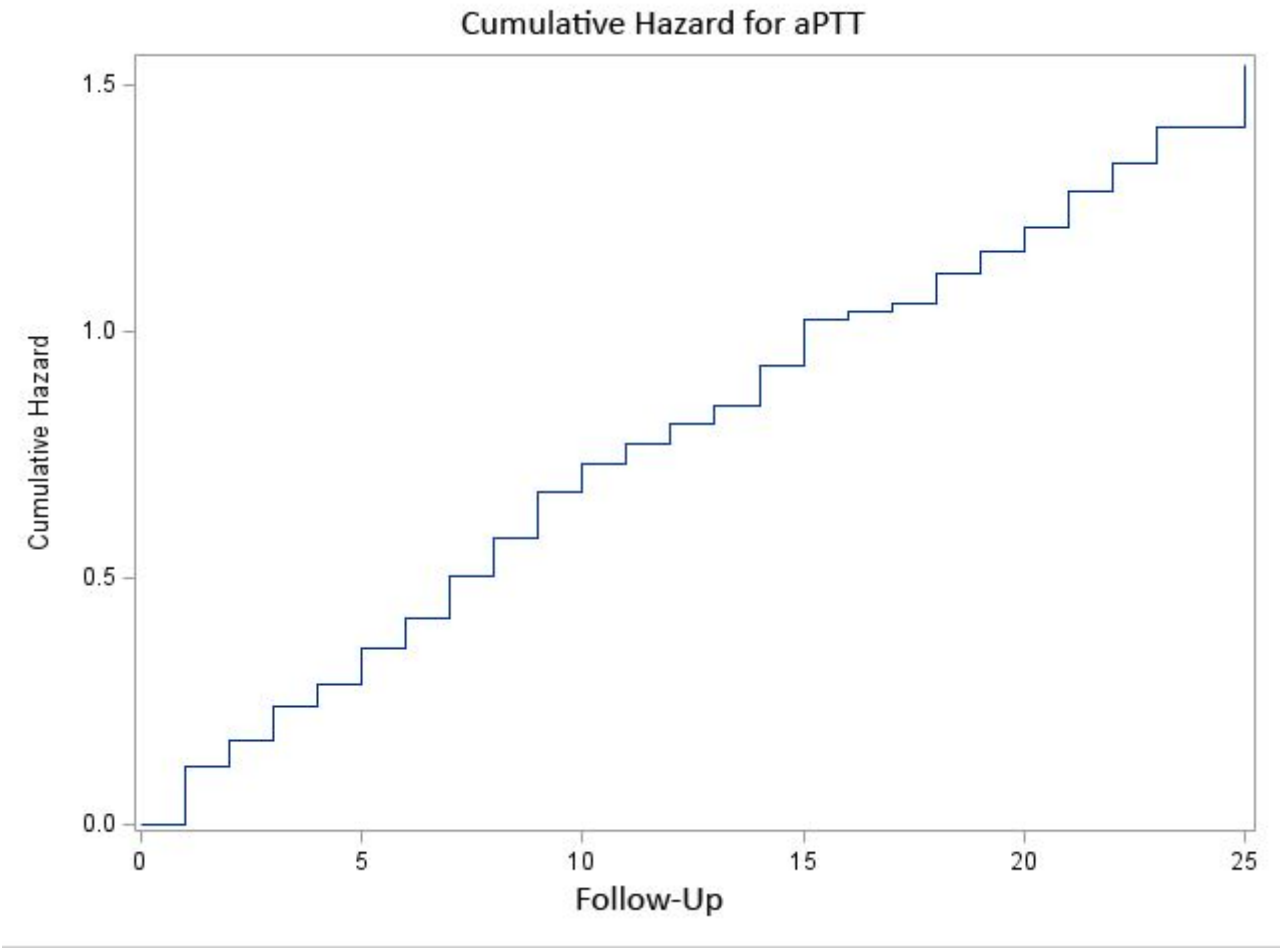
eFigure 10. Cumulative hazard of bleeding for aPTT.



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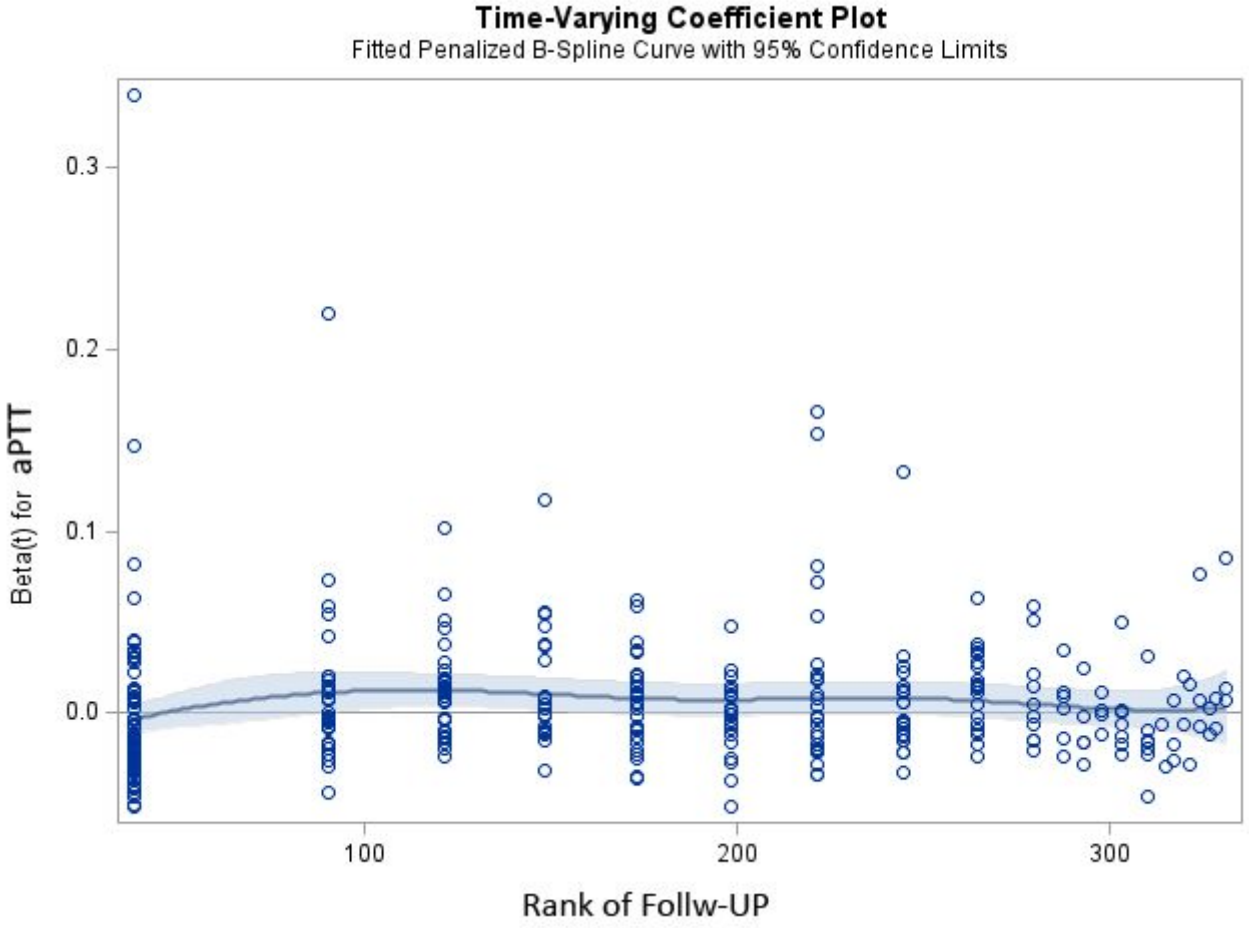
eFigure 11. Time-varying coefficient plot for aPTT in relation to bleeding.

The test of non-proportional hazard assumption is not significant, p=0.4593.



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eTable 10. Comparative features of COVID-19 and No-COVID patients in the overall cohort.

Variable	**COVID-19** n=218	**Others No-COVID-19** n=434	**P value**
Baseline Data			
Age, years	53 (43-60)	51 (38-60)	0.0080
Male gender, n (%)	181 (83)	282 (65)	<0.0001
Height, cm	172 (165-178)	170 (165-178)	0.0278
BMI, Kg/m^2	29.4 (26.2-35.5)	27.8 (24.3-33)	0.0054
SAPS 2	37 (30-54)	41 (31-55)	0.0758
SOFA score at cannulation	9 (7-12)	10 (7-12)	0.2403
PRESERVE score	3 (1-5)	4 (2-6)	<0.0001
RESP score	2 (1-4)	2 (-0.6;4)	0.0605
P/F ratio	73 (60-90)	70 (58-97)	0.8009
Pre-ECMO hospital stay, days	7.2 (4.9-11.8)	3.5 (1.1-9.8)	0.0103
Pre-ECMO ICU stay, days	5.1 (3-8.5)	2 (0.6-6)	<0.0001
Pre-ECMO mech. vent., days	4 (1.7-6.7)	1.5 (0.4-4.2)	<0.0001
Hemoglobin, g/dL	10.9 (9.6-12.3)	10.7 (9.2-12.3)	0.7174
Platelet count, x10^3/µL	244 (176-332)	186 (120-275)	<0.0001
Surgical procedure in the last 7 days, n (%)	2 (0.9)	84 (19)	<0.0001
Pregnancy or puerperium, n (%) Female n=189 Covid 37 No-Covid 152	5 (13.5)	3 (2)	0.0018
Daily Data			
Urine output, mL	2180 (1344-91)	2047 (1503-72)	0.2696
CRRT, days (%)	955 (26.4)	1545 (31.8)	<0.0001
Fluid balance, mL	342 (233-454)	326 (186-467)	0.8712
Cardiovascular SOFA	2.3 (2.1-2.5)	2.4 (2.2-2.5)	0.4965
Type of Anticoagulant, days (%)			<0.0001
UFH	2753 (76)	3458 (71)	
Bivalirudin	217 (6)	229 (5)	
Argatroban	47 (1)	73 (2)	
LMWH	21 (0.6)	57 (1)	
Nafamostat Mesylate	20 (0.6)	0	
No Anticoagulation	560 (16)	1032 (21)	
Dose of Anticoagulant,			
UFH	14.7 (13.8-15.5)	12.6 (12.1-13.1)	<0.0001
Bivalirudin	0.11 (0.07-0.15)	0.14 (0.03-0.25)	0.6823
Argatroban	1.54 (1.12-1.95)	0.44 (0.20-0.67)	0.0002
LMWH	2000 (500-3500)	4500 (3500-5500)	0.0092
Type of initial anti-coagulation, n patients (%)			<0.0001
UFH	195 (89.5)	311 (71.7)	
Bivalirudin	5 (2.3)	6 (1.4)	
Argatroban	0	2 (0.5)	
LMWH	2 (0.9)	7 (1.6)	
Nafamostat Mesylate	2 (0.9)	0	
No Anticoagulation	14 (11.5)	108 (24.9)	
Time without anticoagulant overall n (% of total days)	560 (15.5)	1032 (21.3)	<0.0001
Time without anticoagulation, for each anticoagulant			<0.0001
UFH	446/3188	482/3641	
Bivalirudin	17/97	27/79	
Argatroban	0	16/47	
LMWH	3/29	4/50	
Nafamostat Mesylate	0/42	0	
No Anticoagulation	94/263	503/1035	
Type of Coagulation Monitoring, days/total days (%)			
aPTT, sec	3163/3619 (87)	4134/4852 (85)	0.0038
aPTT ratio	1232/3619 (34)	1564/4852 (32)	0.0800
ACT, sec	834/3619 (23)	1148/4852 (24)	0.5082
r-TEG, mm	47/3619 (1.3)	174/4852 (3.6)	<0.0001
Anti-Xa, IU/mL	582/3619 (16)	606/4852 (13)	<0.0001

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Coagulation Monitoring values			
aPTT, sec	53 (41.2-65.4)	46.8 (37.5-56.7)	<0.0001
aPTT ratio	1.64 (1.29-1.97)	1.46 (1.15-1.77)	<0.0001
ACT, sec	175 (160-191)	168 (155-184)	<0.0001
r-TEG, mm	29.5 (12.7-59.8)	17.35 (9-37.2)	0.0164
Anti-Xa, IU/mL	0.33 (0.19-0.52)	0.20 (0.1-0.34)	<0.0001
Antithrombin level, % of activity	84 (80-89)	84 (80-88)	0.9324
Hemoglobin, g/dL	9 (8.9-9.2)	9.2 (9.1-9.4)	0.0147
Platelets, x1000 micro/L	178 (165-186)	145 (137-152)	<0.0001
Q_{EC}, L/min	4.5 (4.4-4.6)	3.9 (3.8-3.9)	<0.0001
Q_{EC}/eCO, %	92 (89-94)	83 (81-84)	<0.0001
Patients without PRBC transfusion, n/total patients (%)	28/218 (12.8)	83/434 (19.1)	0.0441
Patients Plasma transfusion, n/total patients (%)	166/218 (76.2)	315/434 (72.6)	0.3288
Patients without Platelet transfusion, n/total patients (%)	164/218 (75.2)	278/434 (64.1)	0.0040
Patients with at least one bleeding episode, n (%)	127 (58)	215 (50)	0.0355
Bleeding, days/total days (%) all type	548/3619 (15)	654/5852 (13.5)	0.0300
Bleeding Type, days (%) - Total episodes 1202			0.3781
Type 1	330 (60)	399 (61)	
Type 2	173 (32)	191 (29)	
Type 3	36 (7)	57 (9)	
Type 4	9 (1.6)	7 (1)	
Patients without bleeding, n (%)	91 (42)	219 (51)	0.0355
Average bleeding days for ECMO run, % of ECMO days	14	13	0.5836
Average bleeding days for ECMO run in patients with at least one bleeding, % of ECMO days	24	26	0.3269
Circuit change, n (% of total days)	93 (2.6)	127 (2.6)	0.8914
Major hemolysis, n (% of total days)	108 (3)	44 (0.9)	<0.0001
ECMO duration, days	20.7 (18.3-23.1)	13.1 (11.7-14.6)	<0.0001
Outcomes			
ECMO: successful weaning	120 (55)	325 (75)	<0.0001
ICU discharge alive	108 (50)	288 (66)	<0.0001
ICU length of stay, days	34 (22-51)	23 (14-39)	0.0003
Hospital discharge alive	105 (48)	282 (65)	<0.0001
Hospital length of stay, days	45 (27-65)	36 (21-39)	0.0009
6-month survival	102 (47)	269 (62)	0.0002

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Case Report Form

BASELINE CASE FORM

Record ID _____

Refused transfusion
- ◯ Yes
- ◯ No

Jehovah's Witness
- ◯ Yes
- ◯ No

Other reason to refuse transfusion
- ◯ Yes
- ◯ No

Included in other interventional study
- ◯ Yes
- ◯ No

Other study Specify _____

Age _____

Gender
- ◯ Female
- ◯ Male

Weight (kg) _____

Height (cm) _____

Body mass index _____

ECMO start _____

ECMO configuration
- ◯ Femoro-Jugular
- ◯ Femoro-Femoral
- ◯ Double Lumen Cannula
- ◯ Femoro-Jugular-Femoral
- ◯ Jugular-Femoral
- ◯ Subclavian-Femoral

Pre-ECMO hospital admission _____

Pre-ECMO hospital stay _____

Pre-ECMO ICU admission Pre-ECMO ICU stay _____

Pre-ECMO start of mechanical ventilation _____

Pre-ECMO days of mechanical ventilation _____

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PRE-EXISTING PULMONARY DISEASE

	No	Yes
Asthma	◯	◯
Cystic fibrosis	◯	◯
Chronic obstructive pulmonary disease	◯	◯
Pulmonary hypertension	◯	◯
Pulmonary fibrosis	◯	◯
Chronic restrictive lung disease	◯	◯
Other	◯	◯

Other-Specify _____

MAIN COMORBIDITIES

	No	Yes
Diabetes mellitus	◯	◯
Chronic renal failure	◯	◯
Ischemic heart disease	◯	◯
Heart failure	◯	◯
Chronic liver failure	◯	◯
Neurological impairment	◯	◯
Other	◯	◯

Other-Specify _____

Lung transplantation waiting list
◯ Yes
◯ No

Postoperative period <7 Days
◯ Yes
◯ No

Pregnancy or peripartum
◯ Yes
◯ No

Cause of acute respiratory failure
◯ COVID-19
◯ Bacterial pneumonia
◯ Viral pneumonia
◯ Trauma/burns
◯ Aspiration pneumonia
◯ Asthma
◯ Pancreatitis
◯ Non-respiratory and chronic respiratory diagnoses
◯ Graft failure after lung transplantation
◯ Other acute respiratory diagnosis

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Cause of ARF-non-respiratory diagnosis _____

_____

Cause of ARF-Other Diagnosis

SOFA SCORE see below

SAPS2 score _____

PaO2/FiO2 (mmHg) value _____

Glasgow Coma _____

Scale

Mean arterial pressure(mmHg) _____

Dopamine ≤5mcg/kg/minor dobutamine (any dose) ◯ Yes ◯ No

Dopamine>5mcg/kg/minoradrenaline≤0.1 mcg/kg/minor noradrenaline≤0.1mcg/kg/min. ◯ Yes ◯ No

Dopamine >15mcg/kg/minor adrenaline>0.1 mcg/kg/minor noradrenaline>0.1mcg/kg/min. ◯ Yes ◯ No

Bilirubin (mg/dl) _____

Platelets×1000/microlC _____

Creatinine (mg/dl) _____

SOFA score _____

Immunocompromised (hematologic malignancies, solid tumor, solid organ transplantation, high dose or long-term steroids, immunosuppressive agents, HIV) ◯ Yes ◯ No

Prone positioning before ECMO ◯ Yes ◯ No

PEEP<10cmH2O ◯ Yes ◯ No

Plateau pressure>30cmH2O ◯ Yes ◯ No

PRESERVE Score _____

RESP SCORE

Central nervous system dysfunction ◯ Yes ◯ No

Acute associated non-pulmonary infection ◯ Yes ◯ No

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Neuromuscular blockade before ECMO ◯ Yes ◯ No

Nitric oxide use before ECMO ◯ Yes ◯ No

Bicarbonate infusion before ECMO ◯ Yes ◯ No

Cardiac arrest before ECMO ◯ Yes ◯ No

PaCO2 ≥75mmHg/10kpa ◯ Yes ◯ No

Peak inspiratory pressure ≥42cmH2O ◯ Yes ◯ No

RESP Score _____

ECMOnet

Hematocrit (%) _____

Hemoglobin (g/dl) _____

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

DAY1

Daily data were recorded for each day on ECMO and for the first day after ECMO weaning for those patients who survived the ECMO run.

Record ID _____

Still on ECMO
- ◯ Yes
- ◯ No

Date _____

Richmond Agitation-Sedation Scale (RASS)
- ◯ +4 Combative
- ◯ +3 Very agitated
- ◯ +2 Agitated
- ◯ +1 Restless
- ◯ 0 Alert and calm
- ◯ -1 Drowsy
- ◯ -2 Light sedation
- ◯ -3 Moderate sedation
- ◯ -4 Deep sedation
- ◯ -5 Unarousable

Fluid balance in the last 24 hours
- ◯ Positive
- ◯ Negative

Fluid balance value _____

Diuresis _____

Continuous Renal Replacement Therapy
- ◯ Yes
- ◯ No

Mean arterial pressure _____

Heart rate _____

Septic shock
- ◯ Yes
- ◯ No

Vasopressor
- ◯ Yes
- ◯ No

Dobutamine (mcg/kg/min) _____

Adrenaline (mcg/kg/min) _____

Noradrenaline (mcg/kg/min) _____

Dopamine (mcg/kg/min) _____

Vasopressin (unit/hour) _____

DAILY LAB

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

Hemoglobin (g/dl) _____

Hematocrit _____

Platelet count x1000/microL _____

Creatinine [mg/dl] _____

Fibrinogen (mg/dl) _____

Coagulation Test

	No	Yes
APTT	◯	◯
APTT ratio	◯	◯
Anti-Xa	◯	◯
Other	◯	◯

APTT sec _____

APTT ratio _____

ACT sec _____

r-TEG _____

Anti-Xa (units/ml) _____

Other _____

Antithrombin III activity level _____

Hemogas analysis

pH _____

PaO2 _____

PaCO2 _____

HCO3 _____

SaO2 _____

Lactates (mmol/L) _____

Type of anticoagulation/antiaggregation

◯ Heparin IV
◯ Heparin SC
◯ Bivalirudin
◯
◯
◯
◯
◯

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

Argatroban
Other
No anticoagulant
Aspirin

Type of other anticoagulant _____

Heparin IV dose (units/hrs) _____

Heparin IV dose (units/kg/hrs) _____

Heparin SC dose _____

Bivalirudin dose _____

Argatroban dose _____

Other anticoagulant dose _____

Antithrombin III administration
◯ Yes
◯ No

Antithrombin dosage _____

ECMO SETTINGS

Revolutions per minute (RPM) _____

Blood flow (L/min) _____

Sweep gas flow _____

FiO2% _____

ECMO weaning TRIAL
◯ Yes
◯ No

ECMO removal
◯ Yes
◯ No

ECMO modification
◯ Yes
◯ No

Type of modification
◯ Add a third cannula
◯ Switch to VA o VVA
◯ Other

MAJOR EVENTS DURING THE PAST 24 HRs

Death
◯ Yes
◯ No

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

Major hemolysis	◯ Yes ◯ No
Cardiac arrest	◯ Yes ◯ No
Bleeding	◯ Yes ◯ No
Bleeding site	◯ Airway ◯ Oronasal ◯ Gastric ◯ Intestinal ◯ Intrathoracic ◯ Abdominal ◯ Urinary tract ◯ Cannulation site ◯ Cerebral
Bleeding severity (modified Bleeding Academic heparin infusion Research Consortium-BARC score)	◯Type 1 (bleeding that requires reduction of rate OR PRBC transfusion, provided Hb drop related to bleeding) ◯Type 2 (bleeding that requires reduction of heparin infusion rate AND PRBC transfusion, provided Hb drop related to bleeding, OR non-surgical procedure to stop bleeding) ◯Type3 (life-threatening bleeding that required PRBC transfusion AND surgical intervention to control the bleeding or ECMO discontinuation) ◯Type4 (any fatal bleeding)
Circuit change	◯ Yes ◯ No
Main cause for change	◯ Thrombocytopenia ◯ Hypofibrinogenemia ◯ Evidence of clots ◯ Membrane dysfunction
PRBC transfused	◯ Yes ◯ No
Reason for transfusion	◯ Low hemoglobin ◯ Hemodynamic impairment ◯ Low ECMO blood flow ◯ Bleeding ◯ Other
Other-specify	_____

PRE-TRANSFUSION

Hemoglobin (g/dl)	_____
	_____

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

SvO2

SaO2 _____

ECMO blood flow _____

ECMO RPM _____

Bleeding severity (modified Bleeding Academic Research Consortium-BARC score)

- ◯ Type 0(no bleeding)
- ◯ Type 1 (bleeding that requires reduction of heparin infusion rate OR PRBC transfusion, provided Hb drop related to bleeding)
- ◯ Type 2 (bleeding that requires reduction of heparin infusion rate AND PRBC transfusion, provided Hb drop related to bleeding, OR non surgical procedure to stop bleeding)
- ◯ Type3 (life-threatening bleeding that required PRBC transfusion AND surgical intervention to control the bleeding or ECMO discontinuation)
- ◯ Type4 (any fatal bleeding)

POST-TRANSFUSION

Hemoglobin (g/dl) _____

SvO2 _____

SaO2 _____

ECMO blood flow _____

ECMO RPM _____

TRANSFUSIONS

PRBC total transfusion (mL) in the last 24h _____

Plasma total transfusion (mL) in the last 24h _____

Platelets (mL) in the last 24h _____

Fibrinogen administration (mg) in the last 24h _____

Tranexamic acid administration (mg) in the last 24h _____

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

OUTCOME DATA

Record ID _____

Cannulation site thrombosis
◯ Yes
◯ No

Heparin-induced thrombocytopenia
◯ Yes
◯ No

Total PRBC during ECMO (mL) _____

Total plasma during ECMO (mL) _____

Total platelets during ECMO (mL) _____

Total fibrinogen during ECMO (mg) _____

Total cryoprecipitates during ECMO (mL) _____

Total antithrombin III during ECMO (Unit) _____

ECMO successful weaning
◯ Yes
◯ No
◯ Treatment withdrawal

Treatment withdrawal decision date _____

Last ECMO day _____

Total ECMO days _____

Mechanical ventilation weaning
◯ Yes
◯ No

Mechanical ventilation weaning date _____

Post-ECMO mechanical ventilation days _____

Lung transplantation performed
◯ Yes
◯ No

Lung transplantation date _____

Pre-lung Tx ECMO days _____

ICU discharge status
◯ Alive
◯ Died

Last ICU date _____

ICU length of stay _____

Hospital discharge status
◯ Alive
◯ Died

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

Last hospital stay date _____

Hospital length of stay _____

Death date _____

6-month status
◯ Alive
◯ Died

Date of death _____

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

Definitions for Data Collection

BASELINE CASE FORM

All patients on V-V ECMO with age >18 years can be enrolled, unless they refuse to be enrolled.

Register data prior to start of ECMO

Record ID	This is automatically generated by the system	
Refuse transfusion	Yes	Refusal of transfusions should be noted, but the **patient can be enrolled**
	No	
Jehovah's Witness	Yes	This is not an exclusion criterion
	No	
Other reason to refuse transfusion	Yes	This is not an exclusion criterion
	No	
Included in other interventional study	Yes	This is not an exclusion criterion
	No	
Other study (specify)	Specify the acronym of the study	
Age	Age in years	
Gender	Select female or male	
Weight (kg)	Specify weight in **kilograms**	
Height (cm)	Specify height in **centimeters**	
Body mass index	This is a calculated field	
ECMO start	The date format is DD/MM/YYYY. The time must be entered as 24h clock: 00:00-24:00. You will find a calendar and a clock.	
ECMO configuration	Specify the site of cannulation among: **femoro-jugular, femoro-femoral, double lumen cannula, femoro-jugular-femoral, subclavian-femoral**	
Pre-ECMO hospital admission	Date of hospital admission in the same admission that leads to ECMO placement. Consider the **date of the other hospital admission if the patient has arrived from another hospital.**	
Pre-ECMO hospital stay	This is a calculated field	
Pre-ECMO ICU admission	Date of ICU admission in the same admission that leads to ECMO placement. Consider the date of the **other ICU admission if the patient has arrived from another hospital.**	
Pre-ECMO ICU stay	This is a calculated field	
Pre-ECMO start of mechanical ventilation	Start date for mechanical ventilation in the same admission that leads to ECMO placement. Consider the **start date of mechanical ventilation in other ICU if the patient has arrived from another hospital.**	
Pre-ECMO days of mechanical ventilation	This is a calculated field.	

PRE-EXISTING PULMONARY DISEASE

Asthma	No	Select Yes if the patient has previously-diagnosed asthma
	Yes	
Cystic Fibrosis	No	Select Yes if the patient has cystic fibrosis
	Yes	
Chronic Obstructive Pulmonary Disease	No	Select Yes if the patient has chronic obstructive pulmonary disease

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

	Yes	
Pulmonary Hypertension	No	Select Yes if the patient had pulmonary hypertension before ECMO start
	Yes	
Pulmonary Fibrosis	No	Select Yes if the patient has pulmonary fibrosis
	Yes	
Chronic Restrictive Lung Disease	No	Select Yes if the patient has a chronic restrictive lung disease
	Yes	
Other	No	Select Yes if the patient has another pre-existing pulmonary disease
	Yes	
Other (Specify)	Specify other pre-existing pulmonary diseases if you selected Yes in the previous item	

MAIN COMORBIDITIES

Diabetes Mellitus	No	Select Yes in the case of diabetes in anamnesis
	Yes	
Chronic Renal Failure	No	Select Yes in the case of pre-ECMO dialysis, creatinine >3mg/dl, GFR <30 ml/min, previous kidney transplant
	Yes	
Ischemic Heart Disease	No	Select Yes in the case of pre-ECMO myocardial infarction, angina, previous acute coronary syndrome
	Yes	
Heart Failure	No	Select Yes in the case of pre-ECMO heart failure in NYHA class III-IV
	Yes	
Chronic Liver Failure	No	Select Yes in the case of diagnosed cirrhosis pre-ECMO. Child-Pugh class C.
	Yes	
Neurological Impairment	No	Select Yes if the patient has one or more of these conditions pre-ECMO implantation: neurotrauma, stroke, encephalopathy, cerebral embolism, seizure, epileptic syndromes
	Yes	
Other	No	Indicate Yes if the patient has any other relevant comorbidity. You will then be asked to specify it in the next item.
	Yes	
Other – Specify	Specify other relevant comorbidities	
Lung Transplantation Waiting List	Yes	Specify whether the patient was on the lung transplantation list before ECMO
	No	
Postoperative Period <7 Days	Yes	Major surgery within 7 days prior to start of ECMO
	No	
Pregnancy or Peripartum	Yes	Select Yes if the patient is pregnant or if she gave birth within 3 months prior to ICU admission.
	No	If the patient is male do not check the item.
Cause of Acute Respiratory Failure	COVID-19	
	Bacterial pneumonia	
	Viral pneumonia	
	Trauma/burns	
	Aspiration pneumonia	

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

	Asthma	
	Pancreatitis	
	Non-respiratory and chronic respiratory diagnoses	
	Graft failure after lung transplantation	
	Other acute respiratory diagnosis	
Cause of ARF – Non-respiratory Diagnosis	Specify the cause	This will open only if you click on the corresponding item in the previous field
Cause of ARF – Other Diagnosis	Specify the cause	This will open only if you click on the corresponding item in the previous field
SAPS 2 score	Please calculate the score.	
	https://www.mdcalc.com/simplified-acute-physiology-score-saps-ii	
	https://sfar.org/scores2/saps2_expanded.php	

SOFA SCORE

Report the value for the single items

PaO2/FiO2 (mmHg) value	Record the lowest PaO_2/FiO_2 ratio in **mmHg** documented prior to start of ECMO	
Glasgow Coma Scale	Report the GCS value	
Mean Arterial Pressure (mmHg)	Record the lowest mean arterial pressure in mmHg within 24 hours prior to start of ECMO	
Dopamine ≤ 5 mcg/kg/min or Dobutamine (any dose)	Yes	Select Yes if these conditions are present
	No	Select No in any other condition
Dopamine > 5 mcg/kg/min or Adrenaline ≤ 0.1	Yes	Select Yes if these conditions are present
mcg/kg/min or Noradrenaline ≤ 0.1 mcg/kg/min	No	Select No in any other condition
Dopamine > 15 mcg/kg/min or Adrenaline > 0.1	Yes	Select Yes if these conditions are present
mcg/kg/min or Noradrenaline > 0.1 mcg/kg/min	No	Select No in any other condition
Bilirubin (mg/dl)	Record the highest total **bilirubin** value **in mg/dl** within 24 hours prior to start of ECMO	
Platelets×1000/microl	Record the lowest **platelets×1000/microl** value within 24 hours prior to start of ECMO	
Creatinine (mg/dl)	Record the highest **creatinine** value **in mg/dl** within 24 hours prior to start of ECMO	
Immunocompromised	Yes	Report Yes if the patient has hematologic malignancies, solid tumor, solid organ transplantation, high dose or long-term steroids, immunosuppressive agents, HIV, cirrhosis (Child-Pugh C)
(hematologic malignancies, solid tumor, solid organ transplantation, high dose or long term steroids, immunosupppressive agents, HIV)	No	

Prone Positioning before ECMO	Yes	Select Yes if the patient has been prone-positioned for the treatment of ARDS prior to start of ECMO
	No	Select No if the patient has not been prone-positioned prior to start of ECMO
PEEP < 10 cm H2O	Yes	Select Yes if the PEEP before ECMO was < 10 cmH2O
	No	
Plateau Pressure > 30 cm H2O	Yes	Select Yes if the plateau pressure before ECMO was > 30 cm H2O
	No	
Central Nervous System Dysfunction	Yes	Select Yes if the patient, before ECMO, had neurotrauma, stroke, encephalopathy, cerebral embolism, or seizure and epileptic syndromes
	No	
Neuromuscular Blockade before ECMO	Yes	Select Yes in the case of continuous infusion or repeated boluses of neuromuscular blockade

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

	No	
Nitric Oxide Use before ECMO	Yes	Select Yes if the patient has received nitric oxide for the treatment of ARDS prior to start of ECMO
	No	
Bicarbonate Infusion before ECMO	Yes	Select Yes if the patient has received bicarbonate infusion prior to start of ECMO
	No	
Cardiac Arrest before ECMO	Yes	Select Yes if the patient had a cardiac arrest prior to start of ECMO
	No	
PaCO2 ≥75 mmHg / 10kpa	Yes	Select Yes if appropriate
	No	
Peak Inspiratory Pressure ≥42cmH2O	Yes	Select Yes if appropriate
	No	

ECMOnet

Data to complete ECMOnet score in patients affected with H1N1 Influenza A

Hematocrit (%)	Record the lowest **hematocrit** in % within 24 hours prior to start of ECMO
Hemoglobin (g/dl)	Record the lowest hemoglobin in **g/dl** within 24 hours prior to start of ECMO

Day 1 was the first day (starting at 00:00 a.m.) after the ECMO cannulation, regardless of what hour the ECMO was initiated.

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

DAILY FORM

From DAY 1 to DAY 28 or the day after ECMO removal

For Day 1 insert data, from the first day after ECMO cannulation. In this case, <24 hours may have passed

For every variable choose the value that you consider in the morning rounds between 6 a.m. and 10 a.m.

If you do not measure a variable every day you do not have to check it

Still on ECMO	Yes	Select Yes if the patient is still on ECMO
	No	Select No if the patient is not on ECMO anymore. If you have selected No here you will not have to open the form for the next day, and can go directly to the Outcome section
Date	The date format is DD/MM/YYYY. The time must be entered as 24H clock: 00:00-24:00. You will find a calendar and a clock. This is important data for you for checking the day you entered the last data, and for double checking data reliability.	
Richmond Agitation-Sedation Scale (RASS)	Chick the item most suitable for your patient	
Fluid Balance in the Last 24 Hours	Chick here **positive** or **negative** according to your patient's status	
Fluid Balance Value	Difference between fluid administered and fluid lost. Consider the morning value for the last 24 hours in **ml.** For Day 1 consider the last 24 hours or the time since cannulation.	
Diuresis	Enter the value of urine output in the last 24 hours in **ml**	
Continuous Renal Replacement Therapy	Yes	Select Yes if the patient had renal replacement therapy in the last 24 hours
	No	
Mean Arterial Pressure	Report the value recorded during the morning rounds in mmHg	
Heart Rate	Report the value recorded during the morning rounds	
Septic Shock	Yes	Select Yes if the patient is suffering from septic shock
	No	
Vasopressor	Yes	Select Yes if the patient is on vasopressor/inotropes. In this case, a new variable will open concerning the type of vasopressor/inotropes and dosage.
	No	

DAILY LAB

Hemoglobin (g/dl)	Record the morning hemoglobin in **g/dl**
Hematocrit %	Record the morning **hematocrit %**
Platelet Count x1000/microl	Record the morning platelets×1000/microl value
Creatinine [mg/dl]	Creatinine [mg/dl] value in the morning if available
Fibrinogen (mg/dL)	Fibrinogen (mg/dL) value in the morning if available

Coagulation test	Report the coagulation test that you usually adopt. Do not change your daily practice. **You may select Yes for more than one test**. For every chosen test you will be asked for the morning value in a new item that will open automatically.	
APTT	Yes	Select Yes if you monitor anticoagulation with APTT
	No	Select No if you DO NOT USE APTT to monitor coagulation
APTT Ratio	Yes	Select Yes if you monitor anticoagulation with APTT ratio

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

	No	Select No if you DO NOT USE APTT ratio to monitor coagulation
ACT	Yes	Select Yes if you monitor anticoagulation with ACT
	No	Select No if you DO NOT USE ACT to monitor coagulation
r-TEG	Yes	Select Yes if you monitor anticoagulation with r-TEG
	No	Select No if you DO NOT USE **r-TEG** to monitor coagulation
Anti-Xa	Yes	Select Yes if you monitor anticoagulation with Anti-Xa
	No	Select No if you DO NOT USE Anti-Xa to monitor coagulation
Other	Yes	Select Yes if you monitor anticoagulation with another method
	No	Select No if you DO NOT USE other methods to monitor coagulation
		In the case of Yes you may specify the type of anticoagulant adopted
Antithrombin III Activity Level	Report the value if you have measured it	

Hemogas Analysis	Register data from the arterial blood gasses in the morning	
pH	Report the value	
PaO2	Report the corresponding value in mmHg. You can find a converter from kPa to mmHg at https://www.convertunits.com/from/mm%20Hg/to/kPa	
PaCO2	Insert the corresponding value in mmHg. You can find a converter from kPa to mmHg at https://www.convertunits.com/from/mm%20Hg/to/kPa	
HCO3	Indicate the HCO^3 value in mEq/L	
SaO2	Indicate the SaO2 value	
Lactates (mmol/L)	Indicate the lactates value in (mmol/L)	
Type of Anticoagulation/ Antiaggregation	Heparin IV	For every anticoagulant that you choose, a new window will open to report the dose
	Heparin SC	
	Bivalirudin	
	Argatroban	
	Other	
	No anticoagulant	
	Aspirin	
Antithrombin III Administration	Yes	Select Yes if you administered antithrombin III
	No	
Antithrombin Dosage	Indicate the dosage if the previous answer is Yes	

ECMO SETTINGS		
Revolutions per Minute (RPM)	Report the value	
Blood Flow (L/min)	Report the value in L/min	
Sweep Gas Flow	Report the value in L/min	
FiO2 %	Report the value as ---%	
ECMO Weaning Trial	Yes	Select Yes if a weaning trial has been attempted in the last 24 hours

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

	No	
ECMO Removal	Yes	Select Yes if ECMO has been removed in the last 24 hours
	No	
ECMO Modification	Yes	Select Yes if any modification has been made in the circuit in the last 24 hours
	No	
Type of Modification	Add a third cannula	Select the appropriate type of modification according to the clinical situation
	- Switch to VA or VVA	
	- Other	

MAJOR EVENTS DURING THE PAST 24 HOURS

Death	Yes	Select Yes in the case of death. Go to the outcome form to complete the data registration
	No	
Major Hemolysis	Yes	Select Yes in the case of free hemoglobin > 50 mg/dL or if hemolysis prompts a changing of the circuit
	No	
Cardiac Arrest	Yes	Select Yes if the patient had a cardiac arrest
	No	
Bleeding	Yes	Select yes in the case of bleeding. Then specify the site and the severity according to the definitions of modified BARC score.
	No	
Bleeding Site	Tick the appropriate site of bleeding (airway – including tracheotomy, oronasal, gastric, intrathoracic, abdominal, intestinal, retroperitoneal, urinary tract, other)	
Bleeding Severity (modified Bleeding Academic Research Consortium –BARC score)	Chose the most suitable for the clinical situation, from Type 0 to Type 4. Description is provided for every item. 5 adjusted categories of the Bleeding Academic Research Consortium (BARC) score: Type 0, no bleeding; Type 1, any overt bleeding that requires reduction of heparin infusion rate or PRBC transfusion (provided Hb drop was related to bleeding); Type 2, any overt bleeding that requires reduction of heparin infusion rate and packed red blood cells transfusion or non-surgical procedure to stop bleeding (provided Hb drop was related to bleeding); Type 3, any life-threatening bleeding that required PRBC transfusion and surgical intervention for control of bleeding or ECMO discontinuation; Type 4: any fatal bleeding	
Circuit Change	Yes	Select Yes if a circuit has been changed in the last 24 hours. If you choose Yes you will be asked to specify the reason for change.
	No	
Main Cause for Change	Thrombocytopenia, Hypofibrinogenemia, Evidence of clots, Membrane dysfunction	Select the most suitable for the clinical situation
PRBC Transfused	Yes	Select Yes if a circuit has been changed in the last 24 hours
	No	
Reason for Transfusion	According to the proposed items, check the one most suitable for the clinical situation	
PRE TRANSFUSION	This item will display if you selected Yes in the item "PRBC transfused."	
	Report data within 2 hours before transfusion **if you consider and measure them in clinical practice.** You are not required to report and check anything that you would not usually do.	
Hemoglobin (g/dl)	Report the value	
SvO2	Report the value	
SaO2	Report the value	
ECMO Blood Flow	Report the value	

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

ECMO RPM	Report the value	
Bleeding Severity (modified Bleeding Academic Research Consortium –BARC score)	Chose the most suitable for the clinical situation, from Type 0 to Type 4. Description is provided for every item. This is actually not a repetition of the previous item since in here this is to establish whether the bleeding occurred before transfusion.	
POST TRANSFUSION	This item will display if you selected Yes in the item "PRBC transfused." Report data within 2 hours after transfusion if you consider them in clinical practice.	
Hemoglobin (g/dl)	Report the value	
SvO2	Report the value	
SaO2	Report the value	
ECMO Blood Flow	Report the value	
ECMO RPM	Report the value	
TRANSFUSIONS	This item is valid for every ECMO day and every patient. **If you did not administer any** of the following, please **write 0** (zero) so that it will be clear that it is **not** incomplete data.	
PRBC Total Transfusion (mL) in the Last 24h	Report the value	
Plasma Total Transfusion (mL) in the Last 24h	Report the value	
Platelets (mL) in the Last 24h	Report the value	
Fibrinogen Administration (mg) in the Last 24h	Report the value	
Tranexamic Acid Administration (mg) in the Last 24h	Report the value	

OUTCOME DATA

Cannulation Site Thrombosis	Yes	Select Yes if you have a diagnosed thrombosis in the vessel where the cannulas were placed
	No	
Heparin-induced Thrombocytopenia	Yes	Select Yes if you have a diagnosed HIT according to your center's protocols
	No	
Total PRBC during ECMO (mL)	Report the total value, also considering days on ECMO that are beyond the time frame of observations, e.g., in patients with more than 28 ECMO days, consider the total value for the whole ECMO period.	
Total Plasma during ECMO (mL)	Report the total value, also considering days on ECMO that are beyond the time frame of observations, e.g., in patients with more than 28 ECMO days, consider the total value in the whole ECMO period. **If you do not give plasma in ECMO according to your practice, insert NA.**	
Total Platelets during ECMO (mL)	Report the total value, also considering days on ECMO that are beyond the time frame of observations, e.g., in patients with more than 28 ECMO days, consider the total value in the whole ECMO period. **If you do not give platelets in ECMO according to your practice (or if it is unavailable in your institution), insert NA.**	
Total Fibrinogen during ECMO (mg)	Report the total value, also considering days on ECMO that are beyond the time frame of observations, e.g., in patients with more than 28 ECMO days, consider the total value in the whole ECMO period. **If you do not give fibrinogen in ECMO according to your practice, insert NA.**	
Total Cryoprecipitates during	Report the total value, also considering days on ECMO that are beyond the time frame of observations, e.g., in	

AJRCCM Articles in Press. Published November 09, 2023 as 10.1164/rccm.202305-0896OC

ECMO (mL)	patients with more than 28 ECMO days, consider the total value in the whole ECMO period. **If you do not give cryoprecipitates in ECMO according to your practice (or if they are unavailable in your institution), insert NA.**	
Total Antithrombin III during ECMO (unit)	Report the total value, also considering days on ECMO that are beyond the time frame of observations, e.g., in patients with more than 28 ECMO days, consider the total value in the whole ECMO period. **If you do not give antithrombin in ECMO according to your practice, insert NA.**	
ECMO Successful Weaning	Yes No Treatment withdrawal	Select Yes if the patient has been successfully weaned. Select No if the patient has not been weaned. Select treatment withdrawal if at a certain point the treatment is considered futile and palliative care is started.
Last ECMO Day	The date format is DD/MM/YYYY. The time must be entered as 24h clock: 00:00-24:00. You will find a calendar and a clock.	
Total ECMO Days	This is a calculated field	
Mechanical Ventilation Weaning	Yes No	Select Yes if the patient has been weaned from mechanical ventilation. You may select Yes also if the patient is still tracheostomized and in track mask oxygen supply.
Mechanical Ventilation Weaning Date	The date format is DD/MM/YYYY. The time must be entered as 24h clock: 00:00-24:00. You will find a calendar and a clock.	
Post ECMO Mechanical Ventilation Days	This is a calculated field	
Pre Lung Tx ECMO Days	This is a calculated field	
ICU Discharge Status	Alive Dead	
Last ICU Date	The date format is DD/MM/YYYY. The time must be entered as 24h clock: 00:00-24:00. You will find a calendar and a clock.	
ICU Length of Stay	This is a calculated field	
Hospital Discharge Status	Alive Dead	
Last Hospital Stay Date	The date format is DD/MM/YYYY. The time must be entered as 24h clock: 00:00-24:00. You will find a calendar and a clock.	
Hospital Length of Stay	The date format is DD/MM/YYYY. The time must be entered as 24h clock: 00:00-24:00. You will find a calendar and a clock.	
6-Month Status	Alive Dead	Contact the patient after 6 months from ICU discharge and report if she/he is alive or has died. If you tick the death item the date of death field will appear.
Date of Death	The date format is DD/MM/YYYY. The time must be entered as 24h clock: 00:00-24:00. You will find a calendar and a clock.	

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