Review Article

Coagulation management in patients requiring extracorporeal membrane oxygenation support: a comprehensive narrative review

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Background and Objective: Extracorporeal membrane oxygenation (ECMO) is a life-saving therapy to support respiratory or cardiorespiratory function in critically ill patients when conventional treatments fail. The exposure of the patient's blood components to the foreign surface of the ECMO extracorporeal circuit activates the inflammatory and coagulation cascades. Systemic anticoagulation is generally required to prevent thrombotic complications, assuming an increased risk of patient bleeding. Despite the increased biocompatibility of novel ECMO devices, the variety of anticoagulation drugs, and the different anticoagulation monitoring tools, there is no gold-standard hemostasis management in patients with extracorporeal life support (ECLS). We aimed to describe the underlying physiology as a rationale for the need for anticoagulation in ECMO. To describe the different alternatives for anticoagulation management, bleeding prevention, and the specific management of anticoagulation in different subgroups of patients, including coronavirus disease 2019 (COVID-19) patients.

Methods: We conducted a comprehensive literature search in the main databases, including Cochrane Database, PubMed, Google Scholar, CINAHL, and Scopus databases, with no start date until December 1st, 2023. We reviewed articles written in English and Spanish.

Key Content and Findings: Evolving evidence has been changing the current practices on anticoagulation in ECMO, and novel alternatives are available to decrease the bleeding risk in high-risk patients and for the management of bleeding complications.

Conclusions: Anticoagulation practices in ECMO are ubiquitous though variable among different geographic areas. However, as clinical experience in ECMO patients increases, best practices can be reproduced among different settings to improve patient management and patient outcomes. Some challenges remain regarding the best anticoagulation strategy in specific groups of patients.

Keywords: Anticoagulation; extracorporeal membrane oxygenation (ECMO); extracorporeal life support (ECLS); bleeding; thrombosis

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Introduction

Background and rationale

Extracorporeal membrane oxygenation (ECMO) is a life-saving therapy to support respiratory or cardiorespiratory function in critically ill patients when conventional treatments fail. Although less frequent than before, bleeding and thrombosis events remain common during ECMO support, consistent with increased morbidity and in-hospital mortality (1,2). Several risk factors for bleeding and thrombosis events have been identified, including vasopressor use, longer treatment duration, single-site cannulation, older age, overweight, initial low pH, $PaCO_2$ levels, and acute kidney injury (AKI) (2). The interaction between blood and extracorporeal circuit materials is not fully manageable, and the subsequent inflammatory and clotting responses result in a higher risk of thrombotic complications. This clotting risk is decreased with adequate anticoagulation therapy, though this prophylactic measure may significantly increase the risk of bleeding. Although thrombotic events are more common, bleeding events carry a higher risk of in-hospital mortality.

Objectives

Herein, we review the pathophysiological framework of blood components and circuit interactions, the mechanisms leading to thrombosis and bleeding, the approach to treatment and monitoring of anticoagulation treatment, transfusion strategies, and hemostatic complications during ECMO therapy in different subgroups of patients. We present this article in accordance with the Narrative Review reporting checklist (available at https://aob.amegroups.org/article/view/10.21037/aob-23-28/rc).

Methods

The methods of our research and the search strategy summary are summarized in *Table 1* (see also Figure S1).

Impact of ECMO in normal hemostasis

The interaction between blood components and the inner surface of the ECMO extracorporeal circuit triggers inflammation and coagulation cascades. ECMO circuit is one of the largest surface areas for blood contact among all medical devices. Depending on the manufacturer and size (adult or child), the oxygenator surface area ranges from 0.8 to 2.5 m^2, containing a blood volume of 75 to 250 mL (3). Also, there is a notable consumption of coagulation factors and blood components, especially platelets, due to shear forces along the ECMO circuit. This phenomenon is observed explicitly within the membrane oxygenator and centrifugal pump. Thus, two significant events result from this interaction: prothrombotic and proinflammatory states. The adverse consequences of thrombosis include oxygenator failure, pump malfunction, hemolysis, and thromboembolic complications (4).

As a result of blood contact with the ECMO circuit, fibronectin, thrombospondin, immunoglobulin E, and von Willebrand factor (vWF) bind to the inner circuit surface, and the formed protein is suitable for platelet adhesion. Then, platelets interact with vWF, a molecule that is activated by the increased shear stress forces and aberrant flow pattern. Activated platelets subsequently attach to the fibrinogen deposits (through GPIIb/IIIa receptors) and initiate the coagulation cascade by exposing tissue factor (TF) and coupling to factor VIIa (FVIIa). This event triggers the clotting process, leading to factor X (FX) activation, thrombin burst, and converting fibrinogen to soluble fibrin. This final product is transferred to an insoluble fibrin network by factor XIIIa (FXIIIa). Factors XII (FXII) and XI (FXI), high-molecular-weight kallikrein (HMWK), and prekallikrein (PK) constitute the contact activation system (after contact with a foreign surface). FXII binds to the circuit surface to be converted into the activated factor (FXIIa), cleaving PK to release kallikrein. Thus, kallikrein separates bradykinin from HMWK, creating a system responsible for the coagulation and fibrinolytic response through the immune response, intrinsic coagulation cascade, and the complement system. The blood cells bind to the circuit surface and release inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin 6. It triggers the endothelial cells again to stimulate TF generation and, via the FVII-mediated extrinsic pathway, also contributes to thrombin formation. The inevitable hemolysis generated by the ECMO circulation also promotes coagulation. The crosstalk of clotting and inflammation could have systemic consequences, such as capillary leakage and vasoplegic syndrome. Beyond contact activation phenomena, coagulopathy in ECMO is a complex syndrome due to high shear forces, hemostatic activation, altered blood flow rates, clotting factor consumption, and platelet activation and dysfunction (*Figure 1*) (5,6).

Bleeding events occur in up to 20–33% of ECMO

Table 1 The research strategy summary

Items	Specification
Date of search	From February 1st, 2023 to December 1st, 2023
Databases and other sources searched	Cochrane Database, PubMed, Google Scholar, CINAHL, and Scopus
Search terms used†	We included the following MeSH terms: ECMO OR extracorporeal life support OR extracorporeal membrane oxygenation AND anticoagulation OR thrombosis OR clotting OR heparin OR hemostasis OR management OR anticoagulation treatment OR anticoagulant OR bleeding
Timeframe	From no date to December 1st, 2023
Inclusion and exclusion criteria	Inclusion criteria: full-text articles of selected observational studies, clinical trials, systematic reviews, narrative reviews, and meta-analyses
	Exclusion criteria: books, chapters, or comments
Selection process	The main search was performed by the first author and senior author (A.F.P.R. and J.R.), and a consensus was obtained from all authors on the main manuscripts to be included after the first draft. The first draft of the manuscript was reviewed and modified by all authors. All authors approved the final document

†, see the Figure S1, which presents the detailed search strategy of one database as an example. MeSH, medical subject headings; ECMO, extracorporeal membrane oxygenation.

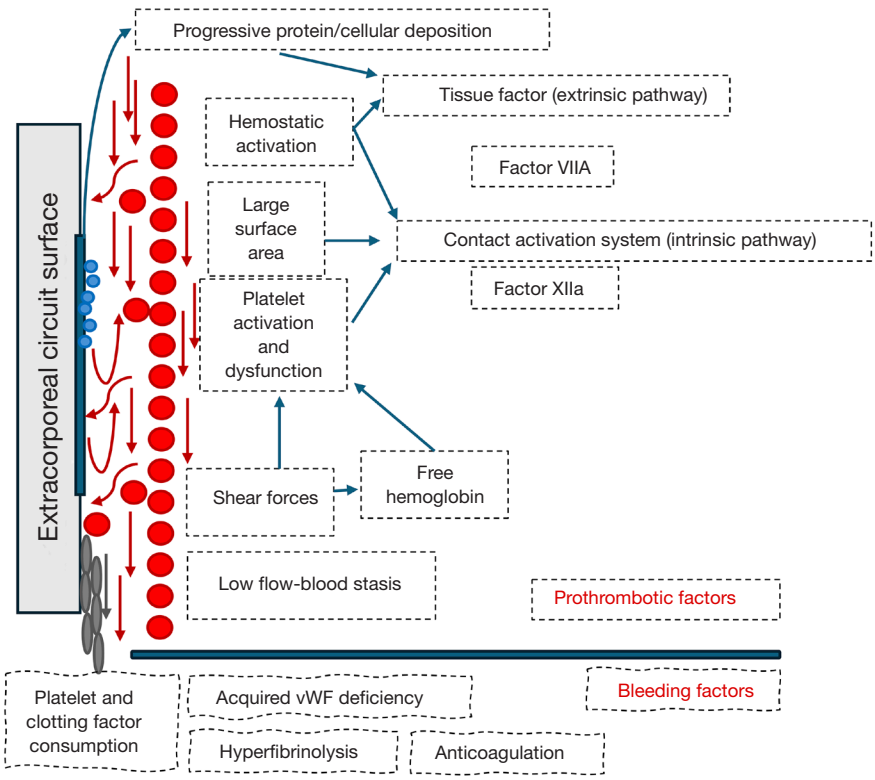

Figure 1 Main factors associated with coagulation abnormalities in ECMO patients. vWF, von Willebrand factor; ECMO, extracorporeal membrane oxygenation.

patients, more often in venoarterial (V-A) ECMO than venovenous (V-V) ECMO (approximately 30% *vs.* 20%) (7). The fibrinolytic system is activated to keep clot formation localized, and the progressive increases in D-dimer levels reflect the ongoing process of thrombosis and thrombolysis, so it can be used as a marker of the intensification of this event in ECMO (8). A low degree of disseminated intravascular consumption is observed, as well. Of note, there are patient-related causes, such as sepsis, acute liver failure, and acute kidney failure, among others, which can cause different degrees of disseminated intravascular coagulation (DIC). One of the most apparent signs of factor consumption is a reduction of platelet count by 25–40%, not attributable to heparin-induced thrombocytopenia (HIT) (9). Platelet function can also be altered due to the high shear stress, leading to acquired von Willebrand syndrome (AvWS) and FXIII deficiency during ECMO support (10-12). Some studies suggest that AvWS is one of the etiologies of bleeding diathesis in ECMO. It is believed to be caused by cleavage of large vWF multimers by the metalloprotease a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, under ECMO-associated shear stress conditions. The platelet adhesion-promoting potential of vWF decreases, contributing to bleeding (13). These events can be reverted upon withdrawal from ECMO therapy. Independent of the consumption and the subsequent decrease of pro-hemostatic factors, antithrombin levels decrease in about 50% of the cases during the first days of therapy. Still, they return to normal after this period (14,15). The initial decrease in antithrombin may be explained by unfractionated heparin (UFH) infusion, which binds antithrombin as a cofactor to inhibit coagulation. Instead, true antithrombin deficiency is associated with heparin resistance and a prothrombotic state, which causes thrombotic complications in the first days of ECMO treatment. FXIII deficiency, hypofibrinogenemia, AvWS, platelet dysfunction, and thrombocytopenia are some hemostatic abnormalities contributing to bleeding in ECMO patients (16).

One of the most significant challenges for the use of ECMO is the development of strategies to monitor and modulate the coagulation and fibrinolytic processes. According to the Extracorporeal Life Support Organization (ELSO) registry, there are approximately 0.5 thrombotic events and 0.5 bleeding events per patient run. The overall prevalence of deep vein thrombosis (DVT) is 8.1 events per 1,000 ECMO days. These two adverse events often result in a 20–30% reduction in overall survival. In a prior study, Lotz *et al.* studied patients predominantly on V-V ECMO. Eighty percent of the patients had bleeding events (17), and 19% had major bleeding episodes (18). Sy *et al.* published a meta-analysis including studies about anticoagulation in V-A ECMO patients, finding a prevalence of major bleeding in 27% (4).

The underlying technology of current ECMO devices has been developed during the last few years, especially in minimizing the size of circuits and increasing materials' biocompatibility. The intrinsic coagulation pathway predominantly mediates the coagulation during ECMO, except in patients with recent surgery, where the extrinsic coagulation pathway has an important role (19). Some novel modifications include different circuit coating strategies that mimic the endothelium surface (e.g., biomimetic surfaces, biopassive surfaces, and endothelialization of blood-contacting surfaces). Polymethylpentene oxygenators, centrifugal pumps, and heparin-coating are innovative modifications to mitigate thrombosis during ECMO. Nitric oxide (NO) is another molecule studied in experimental studies. It is normally released from the endothelium and prevents platelet aggregation. Incorporating NO into circuit surfaces reduced platelet consumption and eliminated the need for systemic heparinization in a rabbit model of extracorporeal circulation (20). Important advances in terms of biocompatibility and hemocompatibility of ECMO systems have improved patient outcomes. However, no specific bioactive surface is currently better than another (21).

Despite these advances, patients with ECMO support still need anticoagulation therapy. Its effect should be adequately monitored to balance the risk of circuit clotting and the risk of patient bleeding.

Thrombotic complications and options for anticoagulation

Thrombosis is one of the most common and feared complications of ECMO support (22), observed in 54.9% of cases, according to the ELSO report (2). ECMO patients experience an increased risk of thrombosis, mostly ECMO circuit thrombosis (23). Its incidence varies according to certain variables, including the configuration of ECMO support. Additional clotting seems more frequent in patients receiving V-A ECMO than those with V-V ECMO support (24). A certain amount of thrombosis frequently occurs in the circuit. In the most severe cases, this is accompanied by a life-threatening risk of circuit dysfunction.

In some cases, thrombotic events are not evident but could also cause other deleterious effects, such as significant increases in hemolysis (25). Hemolysis is usually produced within the high-shear stress zones within the ECMO circuit (but also inside cannulas), especially by thrombosis of the pump head, leading to occlusion of membrane oxygenation. It represents a factor that further contributes to homeostasis dysregulation. Major hemolysis is mostly due to pump clotting or highly negative pressure at the drainage cannula (26). Although extremely deleterious, causing clinically significant hematological and renal disturbances, a suitable bedside tool is lacking for monitoring hemolysis during ECMO. Free hemoglobin (fHb) in the bloodstream of ECMO patients is cytotoxic. The fHb increases the plasma vWF-mediated platelet adhesion and thrombus formation in the non-endothelial area (27). In a prior single-center analysis of 1,063 patients under ECMO support, in which 57% of patients were under V-A ECMO, Appelt *et al.* (28) described higher fHb levels in patients under V-A ECMO (4%) than patients under V-V ECMO (2%). The difference can be explained by pre-treatments [cardiac surgery or extracorporeal cardiopulmonary resuscitation (ECPR)], which are more frequently observed in the V-A ECMO group.

Thrombosis may also become evident after decannulation. In some series, DVT at the cannulation site can be as high as 70%. Femoro-femoral cannulation is the most frequent strategy related to thrombosis (29). Low circuit blood flows, hypovolemia, pump speed, kinks or flow obstruction, cannula mispositioning, the large size of ECMO cannulas, shear-stress forces, and multiple other factors leading to platelet and coagulation cascade activation contribute to the increased risk of cannula-associated DVT (30,31). The prevalence of DVT following decannulation in patients whose indication for V-V ECMO was severe respiratory failure is clinically significant, but its relationship is still unclear (30). Routine venous Doppler ultrasound following decannulation is warranted in this population (32).

Ideally, anticoagulation should inhibit clotting formation, which simultaneously generates platelet activation within the ECMO circuit while maintaining platelet function and clotting activity so as not to cause patient bleeding. Unfortunately, an anticoagulant agent fulfilling these criteria is not yet available. The Worldwide Survey performed by Protti *et al.* showed that systemic anticoagulation was routinely prescribed in 264 (96.7%) of the centers included. UFH was the most used drug in 255 (96.6%) centers (33).

UFH binds to the enzyme inhibitor antithrombin III (ATIII), causing the activation of ATIII with a conformational change, which potentiates the anticoagulant activity. The activated antithrombin then inactivates thrombin, FXa, and other proteases. The rate of inactivation of these proteases by antithrombin can increase by up to 1,000-fold due to heparin binding. The UFH-antithrombin complex immediately inhibits coagulation and significantly inhibits coagulation factors more than antithrombin alone. However, UFH inhibits available thrombin and does not prevent thrombin formation or binding to fibrin. ELSO recommends the use of UFH at the time of cannulation and by continuous infusion during ECMO support (1,34). A bolus infusion of 50 to 100 units/kg of body weight of UFH is indicated during cannulation. Afterward, UFH is given as a continuous infusion during circulatory support. Intermittent bolus infusions can be administered depending on monitoring tests and individual clinical situations. Management of HIT is discussed at the end of this section.

Although antithrombin drops during the first days after ECMO therapy initiation, the circulating antithrombin activity is routinely measured only in 50.3% of the centers registered with the ELSO. Antithrombin supplementation is usually prescribed when the anticoagulation targets cannot be achieved (UFH resistance) or when the antithrombin activity is lower than 70%. However, ELSO acknowledges that the optimal antithrombin activity during ECMO remains unknown. They suggest the correction of antithrombin deficiency in patients needing escalating or high anticoagulation requirements and in those with clinically subtherapeutic anticoagulation, especially in infants and children (1). A small randomized controlled trial assessed the association between antithrombin supplementation, UFH dosage, and the adequacy of anticoagulation in patients undergoing V-V ECMO. Antithrombin supplementation may not decrease UFH requirement nor diminish the incidence of bleeding or thrombosis in adult patients on V-V ECMO (35).

There is a lack of high-quality evidence to guide decisions regarding anticoagulation strategies when managing patients on V-V ECMO or V-A ECMO, and different anticoagulation goals are targeted ubiquitously (4,18). Some centers propose similar anticoagulation goals for V-V ECMO and V-A ECMO. However, higher levels of anticoagulation are often used for V-A ECMO, especially in patients near decannulation when ECMO flow rates are reduced (36). Other centers have performed V-A ECMO without anticoagulation in post-cardiotomy patients with significant bleeding risk after cardiopulmonary bypass (4). In

a recent report, Seeliger *et al.* compared two anticoagulation strategies (low- *vs.* high-dose UFH). They found that low-dose anticoagulation regimens were associated with a higher need for oxygenator changes than high-dose regimens. An increased rate of thromboembolic events was reported. Bleeding complications, mainly intracerebral bleeding events, were less common in the low-dose group (37). Other anticoagulant regimens that have been used include direct thrombin inhibitors (DTIs) and Nafamostat Mesylate.

DTIs are short half-life anticoagulants that directly inhibit both circulating and bound thrombin. The advantages of their use include a more predictable anticoagulant effect independently of the fluctuating antithrombin activity and more predictable dosing regimens (38). DTIs do not bind to other plasma proteins or cells, improving anticoagulant efficacy by inhibiting clot-bound and circulating thrombin, and do not cause HIT. Several ECMO centers have recently used DTIs in ECMO patients as these agents do not depend on antithrombin and have virtually no risk of HIT. DTIs have more predictable anticoagulant effects due to insignificant unspecific binding to positively charged proteins and molecules (39). However, a significant drawback of DTIs is the lack of a pharmacologic antidote or reversal agent (39). The available DITs are bivalirudin, argatroban, and lepirudin. DTIs such as argatroban and bivalirudin have been previously used in patients with HIT (38).

Bivalirudin is a specific and reversible DTI that binds to the catalytic and anionic exosite of both circulating and clot-bound thrombin, preventing thrombin-mediated cleavage of fibrinogen to fibrin monomers and the activation of FV, FVIII, and FXIII. Its onset of action is immediate, with a half-life of 25 minutes if renal function is preserved, though it can be doubled in severe dysfunction and up to 3.5 hours in dialysis patients. Its elimination is mainly through urine (20%) (40). It appears to be a safe anticoagulation agent for patients on ECMO and is not associated with increased bleeding or thrombotic complications relative to UFH (41). This agent could be used as an initial anticoagulant in ECMO therapy and for patients with HIT or UFH resistance and liver or renal dysfunction (42). A dosage reduction may be necessary in renal impairment. Argatroban is a direct DTI that reversibly binds to the active thrombin site of free and clot-associated thrombin, inhibiting fibrin formation and activation of FV, FVIII, and FXIII, protein C, and platelet aggregation (43). This drug is available for therapeutic anticoagulation in patients with confirmed or suspected HIT who develop thrombocytopenia while on ECMO support (44). Argatroban is approved in the United States and Europe for anticoagulation in patients with or at risk of HIT, while bivalirudin is used "off-label" for this indication. Besides, a dosage reduction may be necessary in case of liver impairment.

Nafamostat Mesylate, a synthetic serine protease inhibitor with antithrombin and antiplasmin effects, produces controversial effects during ECMO support. Lim *et al.* found an association with a higher bleeding risk than UFH in patients receiving V-A ECMO. In patients with bleeding tendencies, UFH is considered the safest option for anticoagulation in ECMO (45). Yet, in a single-center study, Han *et al.* reported a lower incidence of bleeding complications during ECMO without increased thromboembolic episodes with Nafamostat Mesylate (46).

Other available anticoagulants are FXa and FXIIa inhibitors. Rivaroxaban is the first new oral anticoagulant that prevents the formation of the thrombin burst by inhibiting coagulation at the amplification point. Still, there is currently limited *in vivo* evidence for its use, and it is not routinely recommended (47). Some platelet anti-aggregants have been studied for their use in ECMO. An indication for dual antiplatelet therapy due to coronary stent implantation is present in a considerable number of V-A ECMO patients in addition to anticoagulation treatment, but it increases the risk of bleeding. Prostaglandin E1 (PGE1), in addition to low-dose UFH, augments the biocompatibility of ECMO circuits without increasing bleeding risk. In a previous pilot study, add-on treatment with PGE1 was safe but did not reduce the rate of red blood cell transfusions in ECMO patients. The potential role of antiplatelets (e.g., aspirin) in ECMO must be elucidated (48). Immunotherapy is expected to have a place in ECMO anticoagulation as new evidence evolves in the near future. FXIIa inhibitory antibody is used as a coagulation prevention treatment in ECMO patients without increasing bleeding risk (49).

Patients with HIT are at risk of presenting arterial or venous thromboembolism. Therefore, they have an ongoing need for anticoagulation. Beyond holding heparin, a non-heparin anticoagulant should be administered. Fondaparinux and oral Xa inhibitors are commonly chosen initially. Depending on the urgency of anticoagulation, either a parenteral or oral anticoagulant can be used first. When there is a need for urgent reversal (high risk of bleeding, need for invasive procedures) or kidney impairment, bivalirudin and argatroban are the best choices for non-heparin anticoagulation due to their short half-lives. In the case of liver disease, argatroban should be

avoided, and bivalirudin or fondaparinux are the preferred options (50). Concomitant use of heparin with plasma exchange or potent antiplatelet agents (e.g., prostacyclin analog, tirofiban, or high-dose IV) have only been studied in patients with cardiopulmonary bypass, and there is no evidence supporting the implementation of these strategies in ECMO patients (51).

Anticoagulation monitoring

There is no gold-standard anticoagulation management in patients receiving ECMO support, and various monitoring tools are being used worldwide.

The activated clotting time (ACT) is a test used to monitor the anticoagulant effect of UFH. ACT refers to when blood forms a fibrin clot by adding various coagulation activators. ACT remains the most utilized point-of-care test in ECMO support at the bedside to make decisions. The target ACT level of 180–220 s can be achieved with an infusion rate of 20–50 units/kg/h. There are some drawbacks related to the use of ACT. The test results are influenced by platelet count and functionality, hemodilution status, coagulation factor and fibrinogen levels, blood temperature, and other various technical parameters (52). Monitoring of UFH anticoagulation by ACT has been associated with fewer major bleeding complications. Yet, there is a possible association between lower ACT targets and an increased incidence of thrombotic complications.

The activated partial thromboplastin time (aPTT) is a plasma-based assay of clot formation, reflecting the same coagulation cascade pathway as ACT. However, the results of this test are not influenced by platelet count or hematocrit. The aPTT is one of the commonly used tests to measure the effect of UFH in non-ECMO patients. The EOLIA trial used a target aPTT time of 40 to 55 s (53). Anticoagulation monitoring based on aPTT was associated with more significant bleeding complications but fewer thrombotic events (54). Confounding factors for the interpretation of aPPT during anticoagulation treatment in ECMO include inherited factor deficiencies (e.g., hemophilia A or B, vWD, FII, FV, FX, FXI, or FXII deficiencies), liver disease, combined vitamin K-dependent factor deficiency, DIC, and lupus anticoagulant-type inhibitors (55-57). In a previous study, ACT and aPTT had a low correlation with coagulation factor levels and heparin dose. The authors found anti-FXa activity (anti-Xa) to be the most specific for heparin levels, and PT was most specific for monitoring coagulation and hemostasis for patients on ECMO (58).

Anti-Xa testing has been incorporated into anticoagulation protocols in most ECMO centers. The established target value for therapeutic anticoagulation is 0.3–0.7 IU/mL. Of note, in the EOLIA trial, the study protocol considered a lower target anti-Xa, between 0.2 and 0.3 IU/mL. Clinically important bleeding events were observed in 53% of ECMO patients *vs.* 26% in the non-ECMO group, with no differences observed in massive bleeding events between both groups (53). The anti-Xa assay indirectly measures UFH effects but is not influenced by coagulopathy, thrombocytopenia, or hemodilution. However, some concurrent conditions in ECMO patients, such as hyperbilirubinemia, hemolysis, lipaemia, hyperlipidemia, and plasma-fHb, interfere with anti-Xa assay results. Some ECMO centers establish ACT targets based on anti-Xa levels, yet standardization is needed (59). The widely accepted target range for anti-factor Xa levels during ECMO is 0.3–0.7 IU/mL. Some data reflect that ECMO patients monitored by anti-Xa levels compared to ACT have less blood sampling needs for monitoring, a longer duration between circuit changes, and lower transfusions and dosages of activated FVII (60).

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) tests provide information regarding the elastic properties of the whole blood during coagulation and a rapid assessment of the need for transfusion of blood components (52). TEG and ROTEM may also provide a view of clot formation dynamics, clot strength, and clot lysis. In a feasibility pilot study, Panigada *et al.* randomized patients to one of two strategies, either TEG-based (target 16–24 min of R parameter) or aPTT-based (1.5–2 of aPTT ratio), to manage heparin protocol. The TEG-based protocol was safe for guiding anticoagulation management in ECMO patients, and it was associated with the administration of lower heparin doses than the aPTT-based protocol (61). Thus, these tests are useful for the primary treatment for early DIC. For primary hyperfibrinolysis, tranexamic acid is the preferred antifibrinolytic agent. Maintaining fibrinogen levels (>100 gr/L) and platelet counts (>80,000 cells/mm^3) during ECMO support is recommended and should be closely monitored during therapy. There are novel real-time monitoring methods such as sound, optical, fluorescent, and

electrical measurements with promising results (49).

Bleeding complications and management

Bleeding secondary to systemic anticoagulation is one of the most frequent complications during ECMO therapy and directly impacts morbidity and mortality. The definition of bleeding in ECMO varies within studies, mainly depending on the entity of the event. The ELSO defines major and minor bleedings in this context. Major bleeding is defined as any clinically overt bleeding associated with a hemoglobin fall of at least 2 g/dL, bleeding of >20 mL/kg, or the transfusion of >10 mL/kg packed red blood cell (PRBC) over 24 hours. Other major bleeding conditions are retroperitoneal, pulmonary, or central nervous system bleeding or any event requiring surgical intervention. A minor bleeding event is defined as bleeding <20 mL/kg/day or PRBC transfusions of ≤10 mL/kg. Hemorrhagic complications and the need for large volumes of PRBC are associated with increased mortality in extracorporeal life support (ECLS) therapies. In general, bleeding events can be up to 50%, with 27.5 events per 1,000 ECMO days (4,18,62).

In the recent ELSO registry analysis, bleeding events were associated with higher mortality (46.1%) than thrombotic events (36.1%) (2). Intracranial hemorrhage (73.2%), pulmonary bleeding (53.6%), and gastrointestinal bleeding (48.6%) were the types of bleeding events more associated with mortality. Bleeding events were more common in V-A ECMO than in V-V ECMO. Risk factors for bleeding were pre-ECMO vasopressor support and AKI. Bleeding events secondary to medical conditions were associated with higher mortality than surgical bleeding. Surgical events are often more susceptible to correction and less likely to induce irreversible organ damage than bleeding complications in vital organs such as the lungs, brain, or gastrointestinal tract. Longer ECMO runs, younger age, alkalosis, and <1 year of ECMO support were associated with bleeding and thrombosis. The ELSO analysis considers that the high mortality associated with bleeding from medical conditions supports studies using less intensive anticoagulation strategies (63,64).

There is no gold-standard protocol for the management of bleeding in ECMO. In general, ECMO centers should have a structured algorithm that includes different measures with progressive intensity. *Figures 2,3* detail an example of anticoagulation monitoring and bleeding management protocols in ECMO used in our unit. However, prevention and early detection are the best strategies for bleeding management.

Anticoagulation-free ECMO runs

Patients with severe bleeding and coagulopathy are candidates to receive anticoagulation-free treatment or reduced anticoagulation strategies (65). Many of these cases involve V-A ECMO in high-risk patients with ongoing bleeding, cardiogenic shock, post-cardiopulmonary resuscitation (CPR), post-cardiopulmonary bypass, and post-cardiotomy shock. Thus, routine anticoagulation is avoided. Instead, heparin-coated ECMO circuits are generally used (23). An anticoagulation-free ECMO run is feasible in clinical scenarios in which an unacceptably high risk of bleeding is present (e.g., immediate postoperative period of lung transplant or ongoing major bleeding). Most ECMO centers (96.7%) use systemic anticoagulation, and only 3.3% do not routinely prescribe anticoagulation during V-V ECMO (33). Olson *et al.*, in their systematic review, reported a total incidence of thrombosis of 22.9% in a group of 201 patients with ECMO without systemic anticoagulation for a median of 4.75 days and a total duration of anticoagulant-free ECMO of 304.7 days (63,66). In a systematic review, Fina *et al.* (64) described six studies, including 70 patients on ECMO support without anticoagulation. V-A ECMO was used in 84% of patients. Cardiac surgery was the most frequent contraindication for anticoagulation (64%), followed by active major bleeding (23%) and severe trauma (9%). Of note, successful weaning was observed in 74% of patients. Hospital discharge was possible in 58%. Lv *et al.* performed a metanalysis of low *vs.* standardized dose anticoagulation regimens for ECMO support. The authors found no significant difference in the incidence of thrombotic events (pulmonary embolism, oxygenator or pump clotting, intracardiac thrombus) between the two groups. Gastrointestinal tract and surgical site bleedings were significantly less frequent in the low-dose anticoagulation group (67). In a retrospective review, Kurihara *et al.* did not find differences in the survival of patients on ECMO with and without systemic anticoagulation (38% *vs.* 36%). However, the anticoagulation group showed a higher rate of gastrointestinal bleeding, oxygenator dysfunction, and blood product transfusions than those without anticoagulation. Both groups had no circuit thrombosis throughout ECMO support (68). Accordingly, Wood *et al.* described 203 patients on V-A ECMO that did not

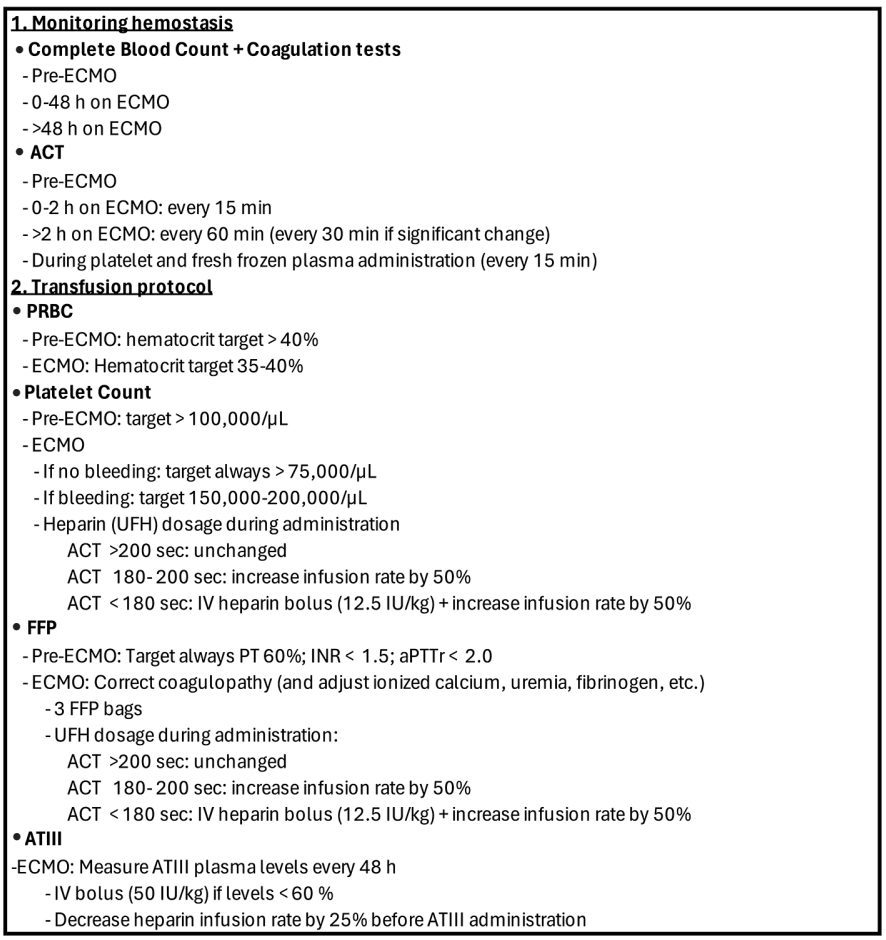

Figure 2 Institutional protocol for the management of anticoagulation in ECMO patients. ECMO, extracorporeal membrane oxygenation; ACT, activated clotting time; PRBC, packed red blood cell; UFH, unfractionated heparin; IV, intravenous; FFP, fresh frozen plasma; PT, prothrombin time; INR, international normalized ratio; aPTTr, activated partial thromboplastin time ratio; ATIII, antithrombin III.

receive anticoagulation. This group of patients had a lower incidence of hemorrhagic and thrombotic complications. The absence of routine systemic anticoagulation for patients supported on V-A ECMO was not associated with higher mortality, pump failure, or thrombotic complications (69). A recent systematic review of anticoagulant-free ECMO runs, including 443 publications, reported an incidence of circuit and patient thrombosis comparable to that in patients receiving continuous systemic anticoagulation. The total incidence of *in vivo* thrombosis was 9.5% among all cases of ECMO (including V-V and V-A ECMO runs) without continuous systemic anticoagulation. Most of these events (7%) were arterial thrombosis events. Intracardiac thrombus formation and lower-extremity ischemia were the most common, particularly in V-A ECMO patients with femoral artery cannulation (63).

There are some concerns regarding stopping anticoagulation, which leads to an increased risk of circuit thrombosis. However, recent data showed similar outcomes when anticoagulation is stopped for short periods (70). However, considering the limitations of the retrospective data, we recommend increasing the ECMO flow as much as possible when prescribing an anticoagulant-free strategy because thrombosis in the ECMO circuit is more likely to occur during periods of low flow (71,72). Two groups of patients on ECMO that usually receive anticoagulation-free ECMO runs are those with severe thrombocytopenia due to hematological diseases and recent trauma. Thrombocytopenia and coagulopathy used to be relative contraindications to ECMO therapy. In a previous

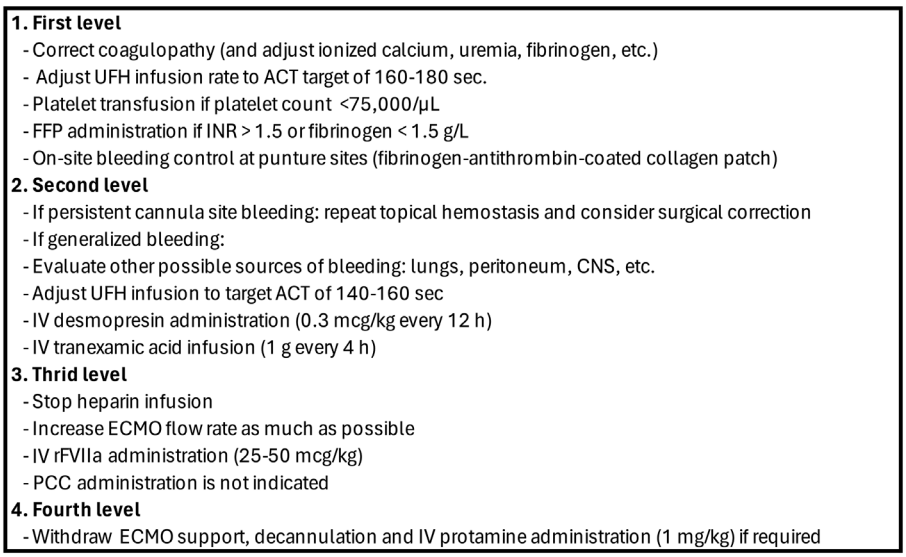

Figure 3 Institutional protocol for the management of bleeding in ECMO patients. UFH, unfractionated heparin; ACT, activated clotting time; FFP, fresh frozen plasma; INR, international normalized ratio; CNS, central nervous system; ECMO, extracorporeal membrane oxygenation; rFVIIa, recombinant activated factor VII; PCC, prothrombin complex concentrate; IV, intravenous.

single-center study, Hermann *et al.* (73) described a cohort of patients on ECMO without anticoagulation, seven of whom had thrombocytopenia or other hematologic diseases precluding anticoagulation. Patients had the anticoagulation stopped for at least 3 days while on V-V ECMO using heparin-coated systems, and a low incidence of clotting events and transfusion requirements was reported. One patient required V-V ECMO therapy for 317 days. During ECMO support, the extracorporeal system needed six exchanges. Still, the incidence of bleeding was high. One patient died due to intracerebral hemorrhage. The intensive care unit (ICU) mortality was as high as 86%. Other particular subgroups of patients, such as patients with cancer, trauma, or burns, often need anticoagulation-free ECMO.

Critically ill cancer patients who require V-V ECMO have poor survival. Thus, circulatory support should be offered to selected patients. In a recent retrospective multicenter study, Kochanek *et al.* analyzed data from 297 patients with hematologic malignancies and solid tumors (138 *vs.* 159) who developed acute respiratory failure requiring ECMO. Patients with solid tumors had a higher median 60-day survival than patients with hematologic malignancies (30% and 23%, respectively). After that 60-day period, the survival was similar between both groups of patients. The authors reported a median time from intubation to V-V ECMO initiation of 2 days. Severe bleeding occurred in 38% of patients and was the only ECMO-related complication associated with decreased survival. Most patients died within the first 30 days after ECMO therapy initiation. In the multivariable analysis, the platelet count was an independent factor associated with decreased overall survival in all cancer patients (solid and hematological cancer). Renal dysfunction was independently associated with lower overall survival in solid cancer patients. Progressive hematologic disease, hematologic cancer, and high lactate levels were independent factors associated with adverse outcomes. Of note, there was no significant difference in the survival of ECMO patients and those managed with mechanical ventilation in the propensity score analysis. However, the survival was significantly higher in ECMO patients with platelet counts of >250,000/μL than in patients requiring mechanical ventilation (74).

The management of trauma patients requiring ECMO support is burdensome. However, an anticoagulation-free strategy is possible due to the high risk of bleeding secondary to coagulopathy, especially in acute brain injury. Likewise, ECMO support is more often used in trauma-related lung injury and respiratory failure, followed by shock and severe thoracic trauma. In a multicenter retrospective cohort study, Guirand *et al.* compared the

outcome of adult trauma patients receiving V-V ECMO or mechanical ventilation for acute respiratory failure (26 and 76 patients, respectively). They demonstrated a significant survival benefit of V-V ECMO, with a survival rate of 58% (75). Ull *et al.* performed a single-center retrospective study that included a cohort of 99 patients treated with ECLS [either pumpless extracorporeal lung assist (pECLA), V-V ECMO, or V-A ECMO, including ECPR]. The patients were split into two groups: traumatic (49 patients) and non-traumatic (50 patients) groups (65). The ICU and hospital survival rates were significantly higher for the traumatic cohort. Regarding the secondary outcomes, longer ICU and in-hospital lengths of stay were reported in trauma patients. Oxygenator clotting was the main thrombotic complication in the traumatic ECLS group due to the absence of anticoagulation. Trauma patients presented a significantly lower number of primary infections and a higher number of nosocomial infections during ECLS than the non-traumatic ECLS group. Bleeding was not the main complication in the non-traumatic and traumatic cohorts. Ull *et al.* suggested V-V ECMO could provide temporary support in trauma patients awaiting pulmonary recovery, especially in hemopneumothorax, pulmonary contusion, or aspiration cases (65). Recently, Trivedi *et al.* described a survival benefit from V-V ECMO support in patients presenting acute respiratory distress syndrome (ARDS) secondary to pulmonary contusion after blunt trauma. V-A ECMO is frequently indicated for patients with cardiopulmonary failure requiring hemodynamic support, such as those with ischemic heart disease, blunt cardiac injury, and massive pulmonary embolism. Due to the multiple injuries and bleeding concerns, an anticoagulation-free strategy was performed in four of the seven patients (76). Also, Willers *et al.* systematically reviewed ECMO therapy in hemorrhagic conditions. Overall survival in the 181 identified patients was 82.3%, and anticoagulation management was modified as needed (77).

Burned patients on ECMO have some particularities. Eldredge *et al.* described seven patients with burn injuries complicated by severe ARDS treated with ECMO support (78). The median time from burn injury to ECMO was 7.5 days, and the median time on ECMO was 11 days. Wound excision prior to ECMO was a risk factor for bleeding. However, there was no difference in mortality in excised and unexcised patients. Overall survival was 87.5%, although previous publications reported mortality rates of 40% and 50%. Still, the use of ECMO in burned patients with ARDS remains infrequent and requires thoughtful patient selection (78).

Transfusion strategies

Transfusion of blood products is frequent in patients with ECMO support because increasing hemoglobin to higher levels has been considered a strategy to improve oxygen delivery in refractory hypoxemia (79).

Current transfusion guidelines suggest a restrictive approach, though they do not provide specific recommendations. In this context, the PROTECMO observational study was a multicenter, prospective study performed in 41 ECMO centers in Europe, North America, Asia, and Australia. The main aim was to describe the actual hemoglobin values and the rate and thresholds for PRBC transfusion during V-V ECMO. The study concluded that there was no universally accepted trigger for transfusion during V-V ECMO for ARDS, although the threshold appears to be lower than in previous recommendations (80).

Using high thresholds can increase transfusion requirements with associated adverse effects. An increased risk of death, transfusion-related acute lung injury, worsened ARDS, volume overload, and poor wound healing are some previously described transfusion-related complications in ECMO patients (81,82). Transfusion of PRBC was associated with lower mortality when performed when hemoglobin concentrations were less than 7 g/dL (80).

Consequently, restrictive transfusion strategies have been evaluated in clinical studies. In 2015, Agerstrand *et al.* (83) described a retrospective study of adults receiving ECMO for severe ARDS, treated with a conservative transfusion protocol (transfusion trigger <7 g/dL). A similar probability of survival and organ function improvement was observed. Lower transfusion requirements and bleeding complications were described. This study was a watershed in the management of blood transfusions, and the recommendations of restrictive strategies for transfusions have been increasing since then. However, the is a lack of more robust evidence. Singh *et al.* (79) reported a consensus of 12 Canadian ECMO centers. They recommend that a restrictive strategy with a hemoglobin threshold of up to 7 g/dL can be sought in stable, non-bleeding patients with adequate ECMO flow rates. This decision should be based on clinical judgment. In the TRAIN-ECMO survey, in which 447 centers worldwide were analyzed, mainly located in Europe, Martucci *et al.* (84) described the hemoglobin trigger to start transfusion. The hemoglobin threshold to start transfusion was significantly lower {8.4 g/dL [95% confidence interval (CI): 7.7–8.9]} in high-volume ECMO

centers (e.g., more than 2 ECMO runs per year).

Thrombocytopenia is common in ECMO patients, and its prevalence is similar in V-A ECMO and V-V ECMO patients (23.2% and 25.4%, respectively). Jiritano *et al.* showed in their meta-analysis that ECMO duration had no significant relationship with the occurrence of thrombocytopenia (85). Platelet count decline and function impairment during ECMO support have been widely studied. During the first week of ECMO, particularly within the first 48 to 72 hours of therapy, platelet counts start declining, and platelet aggregation and receptor shedding disturbances have been observed. Platelet transfusions are independently associated with the overall risk of thrombotic events, particularly circuit thrombotic events (e.g., oxygenator), which are twice more frequent than patient-related events. Between 0.5% and 5% of ECMO patients present HIT, which causes thrombocytopenia and a paradoxical prothrombotic state after heparin exposure.

Besides thrombocytopenia and impaired platelet function, multiple factors have been associated with bleeding in ECMO patients. Older age, delayed sternal closure, central cannulation, and excessive anticoagulation are the most common.

Bleeding complications and transfusions are common and associated with mortality in almost 20% of patients. There is no strict protocol for platelet transfusion. In most practices, the goal is to maintain platelets ≥20,000/μL, while the transfusion threshold can be adapted to keep the platelet count ≥50,000/μL if bleeding occurs. In the study of Singh *et al.*, a platelet transfusion threshold of 50,000/μL was suggested (79). Despite all this, unexpectedly, Oude Lansink-Hartgring *et al.* found in a retrospective study that platelet count was not associated with hemorrhagic complications (86). Platelet transfusions are frequently performed as a prophylactic measure in the absence of bleeding. Still, the optimal platelet transfusion threshold is poorly defined, and current indications for transfusion are based on expert opinion. Of note, they are associated with thrombosis, increased mortality, and a higher risk of bleeding. In a previous study, platelet transfusions were independently associated with a worsening oxygenator function in the subgroup of patients in the lowest quartile of pre-transfusion oxygenator function (87).

Particularities in coronavirus disease 2019 (COVID-19) patients

Severe COVID-19 patients are predisposed to develop thrombotic events (88). Thrombogenic conditions are decisive for the decision to start anticoagulation during ECMO support. In the ECMOVIBER study, thrombotic events were observed in 15.6% of patients with COVID-19 receiving ECMO support, and 34.7% of cases presented circuit clotting during the therapy (89), with 18% of them needed at least one circuit change.

Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic emerged, the study of the mechanisms responsible for hemostasis disturbance has risen. Klok *et al.* described a cumulative incidence of venous thromboembolism of 31%, and pulmonary embolism was the most frequent thrombotic complication (90). SARS-COV-2 infection is associated with increased D-dimer and fibrinogen levels, moderate thrombocytopenia, prolonged prothrombin time, and endotheliitis (91,92).

Sepsis-induced coagulopathy, immunothrombosis, endothelial damage, and decreased activation of the fibrinolytic cascade (hypofibrinolysis) are mechanisms promoting thrombus formation during SARS-CoV-2 infection (93,94). Guihaire *et al.* (95) described 24 patients on V-V ECMO due to critical COVID-19. The appearance of early thrombus formation immediately after cannulation and early membrane thrombosis was described. Intravenous UFH was administered: a dose of 5,000 IU before cannulation and 3,500 IU directly into the circuit. The cannulae were carefully flushed with heparinized saline using 50-mL syringes to prevent *in situ* thrombosis. Seventy-one percent of the patients were successfully weaned from ECMO. The average durability of the first circuit was 8.5±5.1 days. Beyls *et al.* (96) described 12 patients on V-V ECMO support for severe ARDS due to COVID-19 disease. In their study, four events of thrombosis (33%) were reported during percutaneous cannula insertion. Two events were sufficiently severe, leading to death, one due to major oxygenator thrombosis several minutes after starting the V-V ECMO therapy. Five patients had documented thrombosis at the cannula site despite heparin treatment. Rinsing cannulas with heparin before starting V-V ECMO therapy and a heparin bolus prior to cannulation were used. Guo *et al.* (97) described eight patients on V-V ECMO support receiving a heparin bolus before cannulation. The target for the ACT was 180–200 s. Oxygenator thrombosis was observed in seven patients.

Finally, the highly complex interactions between patients' blood and the non-endothelial surface, the activation of clotting pathways with the subsequent coagulopathy, and SARS-COV-2-induced endothelitis produce a high risk

of thrombotic events (98). Hence, the ELSO COVID-19 guideline suggests targeting the higher end of the normal range of ACT when titrating anticoagulation (99,100).

Conclusions

ECMO therapy is associated with a non-negligible risk of thrombotic and bleeding events affecting patient's prognosis. Finding the right balance between the risk for both processes may minimize morbidity and mortality. However, there is no gold standard for anticoagulation management nowadays. An adequate algorithm for bleeding management is mandatory. In extremely severe situations, an anticoagulation-free ECMO run is feasible, though associated with a higher risk of life-threatening thrombosis. A particularly challenging situation is balancing the risk of thrombosis and bleeding while managing COVID-19 patients.

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Supplementary

Database: PubMed					
1. We identified the main concepts or keywords in this topic. Then, we included some synonyms for keywords					
	Main keywords		*Related terms*		*Related terms*
Main keyword 1	*ECMO*	*OR*	*Extracorporeal life support*	*OR*	*Extracorporeal membrane oxygenation*
	AND				
Main keyword 2	*Anticoagulation*	*OR*	*Thrombosis*	*OR*	*Clotting*
	OR				
	Hemostasis	*OR*	*Management*	*OR*	*Anticoagulation treatment*
	OR				
	Bleeding	*OR*	*Heparin*	*OR*	*Anticoagulant*
2. We combined the search terms using AND - OR.					
We included the following Medical Subject Headings (MeSH) terms: ECMO OR extracorporeal life support OR extracorporeal membrane oxygenation AND anticoagulation OR thrombosis OR clotting OR heparin OR hemostasis OR management OR anticoagulation treatment OR anticoagulant OR bleeding					
3. We also used phrase searching.					
Example: “ECMO anticoagulation”			Example: “ECMO bleeding”		
We searched for different word endings.					
“anticoagulation” - “anticoagulant”					
4. We narrowed the search when necessary, using “AND” between terms					
5. We re-sorted the search results by relevance and most recent when too many results were displayed.					
6. We used the database’s thesaurus to build searches of MeSH terms.					

Main concept	Synonyms/related terms	PubMed MeSH term
ECMO	Extracorporeal life support	Extracorporeal membrane oxygenation

7. We used analysis tools offered by each database with the help of a librarian

Figure S1 Example of search strategy in PubMed database. ECMO, extracorporeal membrane oxygenation.

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