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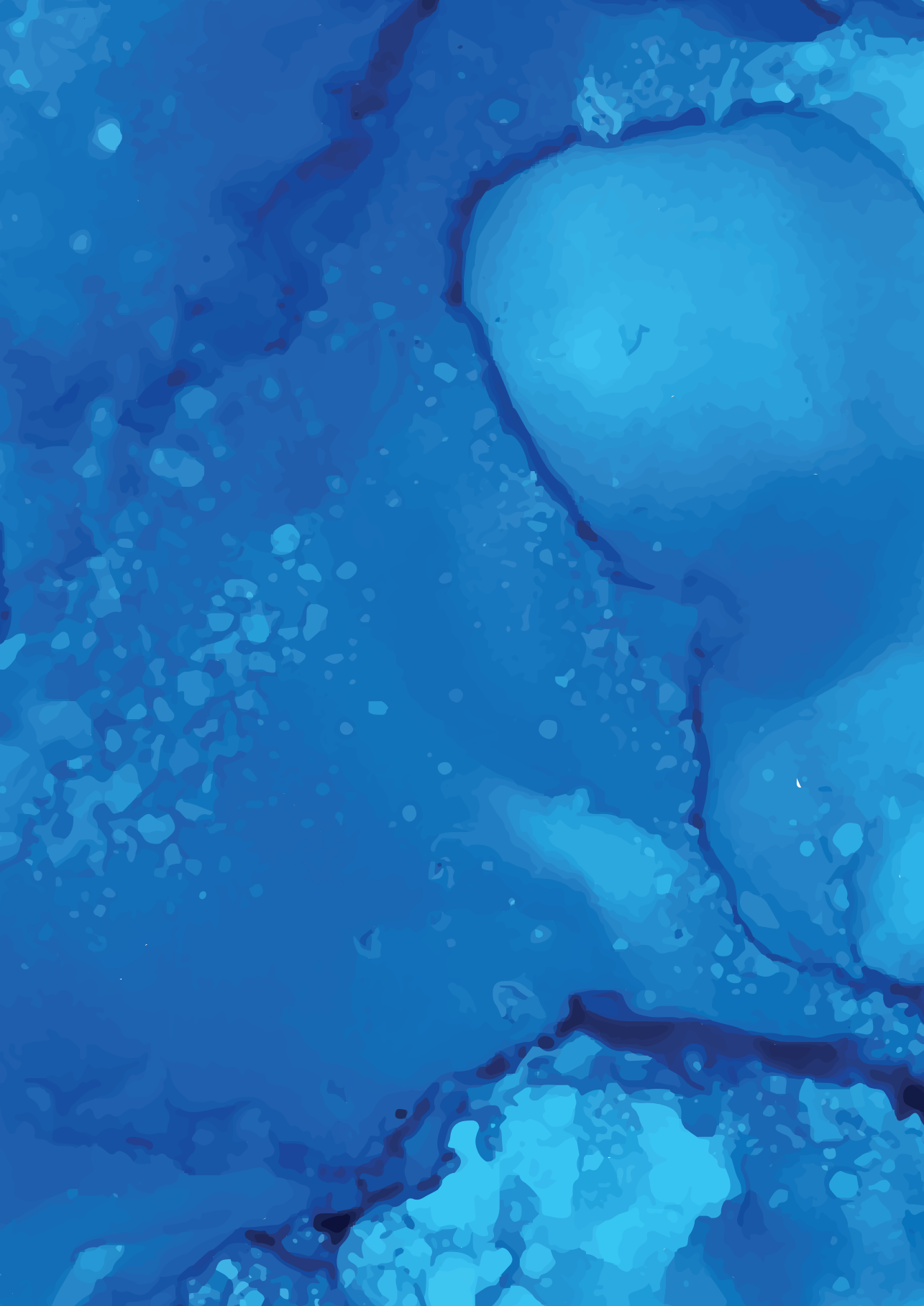

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General introduction

The Extracorporeal Life Support (ECLS), also used equivalent as Extracorporeal Membrane Oxygenation, is the mechanical device for temporarily support of the lung and/or cardiac function in cardiorespiratory failure, when conventional treatment is not sufficient [1]. The ECLS can provide gas exchange and/or circulatory support and may be used for several days to weeks or even months. The ECLS can serve as a bridge to recovery, to intervention, to decision about further treatment or to transplant providing gas exchange and maintaining adequate perfusion [2].

The history of extracorporeal life support

During the Ancient Greeks period, philosophers and physicians developed theories of a circulation system inside the human body divided in arteries and veins, with the heart as a central part of it. However, the circulatory system was considered to be open and blood diffused freely though the body.

In the 17th century William Harvey described the closed circulatory system, with connection to the lung and peripheral tissues as known today [3, 4]. After this discovery, ideas of artificial oxygenation and mechanical circulatory support were raised. In the 19th and 20th century, the knowledge of organ perfusion and blood oxygenation improved by conducting numerous animal experiments, including perfusion of blood through explanted animal organs and diffusion of air within blood [5]. Further research on hematology, such as the existence of blood groups and clotting mechanisms, improved the practical problems that were often observed during the experiments.

In 1930, Dr. John Gibbon Jr started his research on development of the cardiopulmonary bypass (CPB), and used it successfully in 1953 during an open heart surgery in a human [6-8] and during following years in multiple patients but, repeated failures led to a discouragement in the viability of CPB [9]. Research was continued in cardiac surgery in pediatric patients by Lillehei and Kirklin, who established the routine use for CPB [9]. Dr. Bartlett and Drinker used extracorporeal bypass successful for 4 days in a laboratory setting [10]. Thereafter, prolonged use of the extracorporeal bypass in respiratory and cardiac failure was introduced [9, 11] leading to further development of ECLS [12].

The main difference between ECLS and CPB is the circuit composed by closed tube system compared to the open reservoir in CPB. ECLS provides pump-driven drainage of venous blood in contrast to passive drainage into a reservoir in CPB [13, 14]. Hill et al reported the first successful case of ECLS in a human in 1972. In this case, the Bramson-membrane heart-lung machine was used to support an adult patient with adult respiratory distress syndrome (ARDS) with veno-arterial perfusion for 75 hours after a vehicle collision trauma and aortic injury repair [15]. The same year, Bartlett et al. provided veno-arterial (V-A) ECLS successfully in a

baby with cardiac failure after cardiac surgery. In 1975 the first survival of an infant with respiratory failure supported by ECLS was reported [16]. Since 1975 multiple successful veno-venous (V-V) ECLS cases were published and, as result of these efforts, a prospective randomized controlled trial (RCT) was designed by Zapol et al. This trial compared the use of V-A ECLS and invasive mechanical ventilation to mechanical ventilation without extracorporeal support in patients with severe ARDS. At this time, the benefit of lung protective ventilation was not known, and it has had presumably a negative impact on the results [17] reporting high mortality and no benefit in ECLS group. In 1994, Morris et al conducted randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. There was no significant difference in survival between the mechanical ventilation and the extracorporeal CO2 removal group. The authors did not recommend extracorporeal lung support for ARDS [17, 18]. Both trials slowed down further developments in extracorporeal organ support for almost 20 years.

After almost of four decades, survival rate increased to 70-90% in neonatal and pediatrics cohorts [11]. Device associated complications decreased over the time due to technical improvements in ECLS circuits, oxygenators and pumps as well as changes in patient's management [19].

The new era for ECLS began in 2009 after the CESAR trial was released. This trial compared use of ECLS and mechanical ventilation in severe adult respiratory failure, and the results demonstrated a survival benefit in the ECLS group [20]. During the H1N1 pandemic in 2009, the use of ECLS increased in the adult population showing improved outcomes [21, 22]. An observational study showed beneficial results in the use of ECLS in H1N1-related ARDS in the UK [23]. Similar positive effects of ECLS in H1N1 were reported in an observational study in Australia and New Zealand [24, 25]. As a result, the use of ECLS in adult populations regained attention and interest [20, 26, 27].

The trend analysis showed increasing use of ECLS and continuously improved survival since 1990 to 2015 [22]. In 2018, the EOLIA trial, a multi-center RCT of V-V ECLS in ARDS patients, was released. Among patients with severe ARDS, 60-day mortality in the ECLS group was not significantly decreased compared to conventional mechanical ventilation including ECMO as a rescue option [28]. During the COVID-19 pandemic, ECLS was also applied in severe COVID-related ARDS cases. During the first wave, a mortality around 40% was reported, whereas the reported mortality increased to 40-60% in the second wave [29-33].

As for circulatory support ECLS, the use increased after the successful outcomes of the CESAR trial and indications of V-A ECLS broadened to cardiogenic shock in myocardial infarction, myocarditis, right ventricular failure in pulmonary embolism, cardiopulmonary resuscitation and COVD-19-associated cardiogenic

shock [34]. Nowadays, the ECLS is a widely accepted organ support in specialized centers for patients where conventional treatment is not sufficient.

To improve research on ECLS, the extracorporeal life support organization (ELSO) was founded in 1989. The ELSO maintains an international registry of ECLS cases and contains voluntarily reported data of more than 130,000 ECLS runs since 1989 [35, 36]. More than 10,000 patients are entered into the ELSO Registry annually, from almost 500 active centers in 60 countries [37, 38]. Certified data managers of ELSO centers are designated and report the data via standardized case report forms [37]. Accuracy is ensured by point-of-entry data error and validity checks. Mandatory fields must be completed [37].

The circuit and components of extracorporeal life support

The ECLS system consists of three main components; a blood pump, an oxygenator for gas exchange (the membrane lung) and a supplemental heat exchanger, that are connected with medical grade tubing with catheters for vascular access [1].

Blood pumps are available with different capacities, hemocompatibility and durability. The main groups are occlusive roller pumps and nonocclusive centrifugal pumps. Currently the centrifugal pumps are most common used in adult population. Due to improved pump hemocompatibility hemolysis complications decreased [39, 40].

Membrane lung equivalent, known as oxygenator consists of a hollow fiber membrane containing small semipermeable capillaries, where gas exchange is facilitated. The hollow fibers require continuous flow of mixed gas of air and oxygen (O2), called sweep gas. Gas exchange is provided by diffusion of oxygen removing carbon dioxide (CO_2). The higher the flow of sweep gas the more CO2 might be removed from the blood. Increase of blood flow potentially increases the oxygen concentration in the blood [28].

To maintain the temperature of blood passing through the system, a heat exchanger is included in the circuit. In hypothermia (accidental or post-cardiopulmonary bypass), the ECLS can be used for rewarming [40, 41] or in post cardiac arrest for target temperature management

The circuit components are linked with polyvinyl tubing and connected to the patient via large diameter cannulas. The tubing and some types of cannulas are heparin coated to prevent clotting. The circuit contains at least two cannulas; the drainage cannula and return cannula. Via the venous drainage cannula, low saturated blood is drawn from the patient to the ECLS machine. This drainage cannula contains end and side holes to prevent obstruction and vacuum suction in the vessels. The return cannula transports oxygenated blood from the ECLS to the patients' body [13, 42]. (Figure 1 A and B)

Device related complications, such as malfunctioning of the ECLS system due to tubing rupture or disconnection, gas embolisms, or failure of one of the components occur in 25% [12]. Continuous research create further technical advances in the ECLS circuits [43].

Circuit configuration and cannulation technique

The basic modes of ECLS are veno-venous (V-V) and veno-arterial (V-A) ECLS.

Veno-venous Extracorporeal Life Support

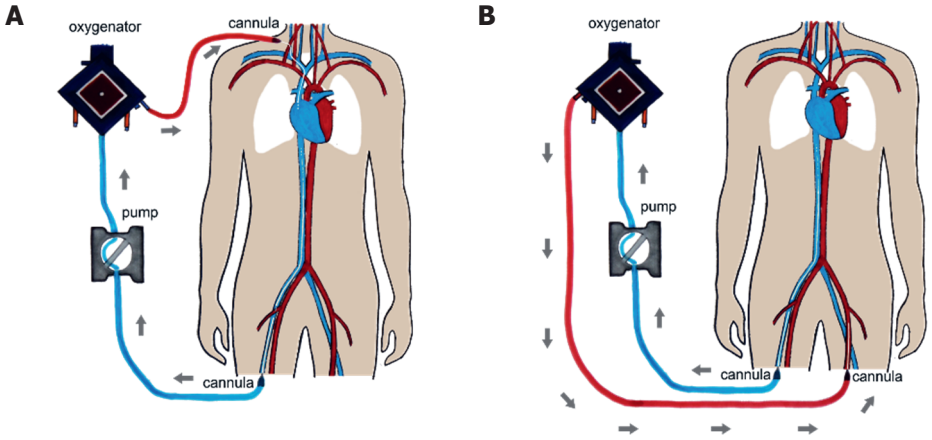
V-V ECLS is the preferred mode of extracorporeal support for respiratory failure in adults with sufficient ejection fraction [1]. For V-V ECLS cannulation is performed for the drainage and the return cannula in large veins. (Figure 1A) Cannulation of the drainage cannula in the femoral vein and the return cannula in the right internal jugular vein is the most common configuration. In this configuration, the tip of the drainage cannula should be placed within the right atrium or close to the right atrium junction in the vena cava inferior. Cannulation in both femoral veins is less common, and the tip of the return cannula should be close to the right atrium and 5-10cm from the drainage cannula to prevent recirculation [44]. Double lumen cannulas are usually placed in the internal jugular vein providing drainage and return of the blood [45].

Veno-arterial Extracorporeal Life Support

In V-A ECLS is commonly used in cardiogenic shock due to profound left or right ventricular failure [1]. The drainage cannula in this configuration is inserted in a large vein, or directly in the right atrium, and the return cannula is placed in the arterial system. (Figure 1B) By returning blood in the arteries, the lungs and heart are bypassed. The systemic continuous circulation is driven by ECLS pump. The heart can therefore continue to recover. V-A ECLS also provides a low level of respiratory support.

The cannulation site of the arterial cannulas can be centrally or peripheral. In central cannulation, the drainage cannula is inserted in the right atrium and the arterial cannula in the ascending aorta. This type of cannulation requires surgical approach, and is often used in post-cardiotomy cases [44]. Peripheral cannulation includes cannulation in the femoral artery, or alternatively with an end-to-end graft in the axillary or subclavian artery [44, 46]. Peripheral cannulas can be inserted percutaneously with the Seldinger technique. This allows cannulation outside the operating room. When better visualization of the vessels is necessary, surgical cut down can be performed with a modified Seldinger technique [44].

Figure 1. *Circuit of extracorporeal membrane oxygenation*



A) Veno-venous (V-V) extracorporeal life support provides respiratory support with circuit connection series to the heart and lung, cannulas are inserted in the large veins. B) Veno-arterial (V-A) extracorporeal life support provides both respiratory and hemodynamic support with parallel circuit connection to the heart and lungs, cannulas are inserted in a large artery and large vein.

Indications

It is important to acknowledge that ECLS is a temporary mechanical organ support and not a destination therapy because it cannot cure the underlying disease. The aim is to bridge to recovery, decision about further interventions or transplantation. Currently, indications for ECLS can roughly be divided into; respiratory failure, cardiogenic shock and cardiac arrest [12, 46, 47].

Respiratory support

Patients with pneumonia, aspiration, COVID-19 and postoperative or trauma related acute respiratory distress syndrome (ARDS) where conventional treatment is not sufficient, can benefit from the ECLS [39, 48, 49]. ECLS can provide adequate oxygenation of blood and decrease hypercapnia. Invasive mechanical ventilation settings can be decreased while adequate oxygenation is achieved on ECLS, decreasing the risks of ventilator-induced lung injury and ventilator-associated pneumoniae [12]. Supporting lung recovery, spontaneous breathing may be initiated after decreasing sedation dosage. Improving physical condition of the patient, early mobilization and nutrition could be an option in the period towards transplantation during ECLS provided as bridge to transplant [12]. ECLS can also bridge lung function during procedures or diagnostic tests where the lung function is temporarily reduced, such as in bronchoalveolar lavage or lung reduction surgery [40, 50, 51]. V-V ECLS is a configuration often used in respiratory support, however V-A ECLS might be used in respiratory failure with concomitant heart failure as well.

Cardiac support

Cardiogenic shock is defined as a low cardiac output, with inadequate systemic perfusion, resulting in organ hypoperfusion, with the following criteria; 1) systolic blood pressure <80-90 mmHg for 30 minutes or a drop of 30 mmHg below baseline with the need for vasoactive medication despite adequate fluid administration, 2) elevated biventricular filling pressures and 3) reduced cardiac index of <1.8-2.2L/min/m^2 with 4) low mixed venous blood oxygen saturation [42]. V-A ECLS decreases the preload of the right ventricle due to active drainage in the vena cava and improves systemic perfusion delivering oxygenated blood in the arterial vessels [42, 46].

Acute myocardial infarction, myocarditis, cardiac failure after cardiotoxic drugs, valvular disease, end-stage cardiomyopathy, post-cardiotomy cardiac failure and covid-19 related cardiac disfunction may cause underlying heart failure and are indications for V-A ECLS when conventional treatment is not sufficient [13, 42, 49, 52, 53]. In acute myocardial infarction, myocarditis or pulmonary embolisms, the results of support on ECLS are promising [48, 54]. Right heart failure due to pulmonary hypertension, patients may benefit from V-A ECLS. In such cases, advanced configurations with multiple cannulas have been performed [12, 55, 56].

In massive pulmonary embolisms, right ventricular failure and consecutive fluid overload may be decreased on V-A ECLS [52]. In addition, patients with refractory cardiogenic shock due to sepsis, intoxications, trauma or patients with low cardiac output syndrome after cardiac surgery may also benefit from the drainage and organ support on ECLS, however the results are variable [2, 48, 52].

In certain procedures, V-A ECLS can serve as a back-up system for circulatory support, such as high risk percutaneous coronary interventions or transcatheter aortic valve procedures or as a bridge to lung transplantation [52, 57]. V-A ECLS does provide promising outcomes in organ preservation in cardiac-death for transplantation harvesting [58].

Cardiopulmonary Resuscitation

Extracorporeal life support may also be initiated during cardiopulmonary resuscitation (CPR) [49]. First observational trials show beneficial results in survival and neurological outcomes, especially in in-hospital-cardiac arrest cases [59]. It seems that in adult extracorporeal CPR (ECPR), the hospital survival, long-term survival and neurological outcomes might be beneficial in ECPR compared to conventional cardiopulmonary resuscitation [60]. However, there are no randomized controlled trials available yet, since these designs are difficult to carry out in emergency situation [61]. A single center RCT in Prague including 264 patients, compared ECPR with standard advanced cardiac life support. Survival outcome seemed higher in the invasive treatment group. However, the primary outcome of

180-day survival with favorable neurologic status was not significantly different between the invasive group (31.5%) and standard strategy group (22%) (odds ratio, 1.63 [95% CI, 0.93 to 2.85]). Major bleeding complications including intracranial, overt and fatal bleeds, occurred more often in the invasive strategy group (31% vs 15%) [62]. The INCEPTION trial is a multicenter randomized controlled trial investigating the use of ECLS in cardiopulmonary resuscitation in witnessed out of hospital cardiac arrest cases. Official outcomes have not been published yet [59].

Contraindications

Contraindications for ECLS include irreversible conditions incompatible with life, and relative contraindications as advanced age and futile diagnosis [40] however some of them are controversial [2, 42]. Severe brain injury, or intracerebral hemorrhage, prolonged resuscitation in unwitnessed circulatory arrest, irreversible cardiac failure or malignancy in advanced stage or chronic organ dysfunction are also such relative contraindications since the potential benefits do not overweight the risk factors of the procedures.

Also, coagulopathies and major trauma are often considered relative contraindications, due to the high risk of bleeding and exsanguination [13, 28]. Difficult vascular access and vessel dissection, may also be a technical limitation in ECLS provision [2].

Survival

Survival in ECLS is depending on the underlying disease of the patient. In 2009, Peek et al. showed survival of 63% in patients with respiratory failure supported with ECLS [20]. Further meta-analyses including patients with refractory ARDS, supported by V-V ECLS reported a pooled mortality of 37.7% - 40% [63, 64].

The EOLIA trial was an RCT designed to investigate the effect of ECLS with early initiation in patients with ARDS. Mortality between ECLS and control group was not significantly different (35% vs 46%, p=0.09) [28].

Meta-analysis including 12 studies regarding acute respiratory failure, cardiogenic shock or both supported on V-A ECLS, reported a pooled mortality of 54% overall, with a mortality of 45% during ECLS [65]. For post-cardiotomy patients, a pooled hospital survival rate of 30.8% - 36,1% was reported in a meta-analysis in 2017 [66, 67]. An observational study including 121 patients after coronary artery bypass grafting submitted to V-A ECLS had a survival to hospital discharge of 46% [68].

The highest survival benefit of more than 65% was reported for myocarditis. Whereas patients with septic shock, post cardiotomy cardiac failure of cardio-myopathy show wide ranges of survival [53] in ECPR, survival between 7 and 45% has been reported [42].

Due to the data of ELSO Registry, overall survival of 58% was reported from 1990 to 2016. The international summary report of the ELSO registry in 2018 reported a survival of 66% in pulmonary support, 55% in cardiac support and 38% survival in ECPR [69].

Complications

Disease related and circuit related complications occur in about 40% of ECLS runs [63]. The most frequent complications were hemorrhagic events, renal failure and infections [22]. The underlying diseases might play a role at risk for complications. The adverse events can include vascular complications, hemodynamic changes, cerebrovascular events, renal failure, systemic inflammation or infections and hemorrhagic events [13].

Vascular complications may occur depending on cannulation site, such vessel rupture or dissection injury. Limb ischemia or compartment syndrome can occur due to diminished blood flow or thrombosis in the cannulated vessel. Ischemia occurs in 16.9% of the peripheral V-A ECLS [13, 42, 58].

Unfavorable hemodynamic changes due to ECLS include increased left ventricle afterload due to retrograde infusion of arterial blood [13]. Another hemodynamic phenomenon with negative effect is the occurrence of the Harlequin syndrome, also known as differential hypoxemia. This may occur in patients supported on peripheral V-A ECLS, when the lung function is worsening. When the native heart function is competing with the retrograde blood flow of the ECLS, reinfused oxygenated blood does not reach the cerebral and right upper extremity vessels [58, 70].

Cerebral injuries may occur due to thrombotic or air emboli and bleeding events may also lead to cerebral injury, as well as hypoperfusion. In V-A ECLS, cerebral stroke occurs in 4% (bleeding and ischemic stroke included) [13, 58].

Renal complications are reported up to 60% of patients on ECLS [13, 34, 42, 65]. Blood cells in contact to the artificial surface of the circuit may trigger systemic inflammatory response. Acute renal failure is another risk factor decreasing survival chances [71].

Further, 53% of adult patients develops an infection within 14 days after ECLS initiation [13, 14, 58]. Infections occur more often in adult population than pediatric supported on ECLS [72]. Overall prevalence of infections varies between 9-65% including pneumonia, urinary tract infections and wound infections [42, 65].

Bleeding complications are among the most frequent reported complications with an incidence of 5.3-79% and occur more often as thrombotic complications [41, 42, 63, 65, 73]. Bleeding events may include cannulation site bleeding, gastro-intestinal bleeding, hemothorax, hemopericardium, intracranial hemorrhage, pulmonary hemorrhage, surgical site bleeding [74]. The most common are surgical

site and cannulation site bleeding [73, 75-77]. The occurrence of bleeding or thrombotic complications are associated with longer ECLS duration, longer hospital length of stay and higher mortality [73, 78]. Especially hemorrhagic stroke and pulmonary bleeding are associated with higher mortality followed by gastrointestinal bleeding, tamponade and surgical site bleeding [73].

Due to the heterogeneity between studies, and different bleeding complications definitions, research outcomes are difficult to compare and trends of complications are challenging to investigate.

Challenges of hemostasis during extracorporeal life support

It is important to find a balance between minimizing thrombi forming and maintaining enough coagulation activity to prevent the frequent bleeding complications. (Figure 2)

Extracorporeal circuit coatings

In reaction to continuous contact between the large foreign body surface of the ECLS circuit and the circulating blood, the coagulation and inflammatory responses are activated [14, 79]. The exposure of blood to the artificial surface activates the contact system, which will promote coagulation and kallikrein and bradykinin driven inflammatory responses [14, 80]. Further accumulation of blood proteins on the surfaces activate the coagulation system and initiates platelet and leucocyte activation and aggregation, leaving the patient in a hypercoagulable state [79, 81]. In addition, in high left ventricular afterload in extreme cardiac dysfunction with ECLS support, the development of thrombosis increases due to minimal or no aortic valve movement [13]. Despite new and improved coatings of the ECLS components, the ideal surface coating that eliminates these responses in total has yet to be found.

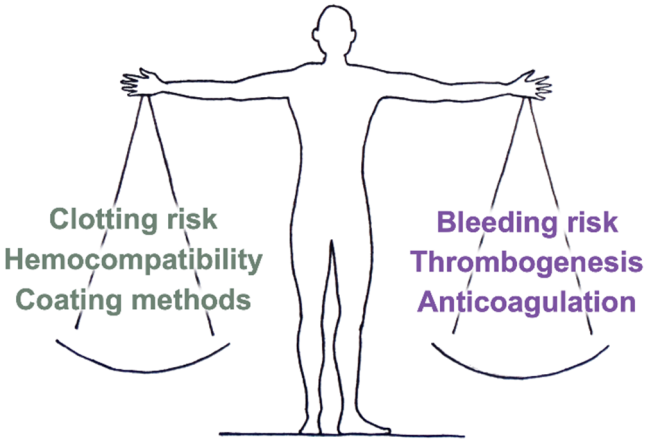
Anticoagulation management

To minimize the activation of the coagulation cascade and thrombus formation, anticoagulation is administered during ECLS. While the risk for clotting decreases with systemic administration of anticoagulation, the risk for bleeding complications may increase. Further, hemoglobin between 8-10 mg/dl was recommended previously in refractory hypoxemia on ECLS, but nowadays the benefit of higher hemoglobin levels is discussed controversial [58].

Targeting the anticoagulation, the activated clotting time (ACT), and activated partial thromboplastin time (aPTT) are monitored. However, the tests are dependent on platelet function, hypothermia, hemodilution and antithrombin levels [41]. If systemic heparin is administered, also anti-Xa plasma levels can be used to estimate the coagulation function but there is no clear consensus or protocol of

anticoagulation strategies [42] Disbalance between the coagulation and platelet function result in increased bleeding complications [82].

Figure 2. *Balance in anticoagulation*



Risk factors for bleeding complications

In neonatal and pediatric patients, risk factors for bleeding complications included hospital and ECLS duration, extracorporeal cardiopulmonary bypass resuscitation and transfer from CPB to ECLS [76]. In a small prospective cohort study, including V-A and V-V ECLS cases, hemorrhagic events occurred more often in V-A ECLS cases, but no significant risk factors were identified [83]. Current studies vary regarding the outcomes. Ried et al. reported an incidence of 23.2% bleeding complications in 418 patients on V-V ECLS. Of these bleeding complications, 40% occurred spontaneously, 37.5% postoperatively and 20% after non-operative interventions [78]. One study report higher bleeding rate in V-V ECLS compared to V-A ECLS [77]. However, it seems that bleeding complications occur more often in circulatory support cases compared to respiratory support (27% vs 24%) [12, 75, 84].

Other reported risk factors for bleeding complications during ECLS include a pulmonary infection, or specifically fungal pneumonia and renal failure [73, 75, 77]. An older age and longer ECLS duration and time to onset of ECLS seem to increase bleeding complications as well [73, 75, 78, 85]. Decreased pre-ECLS red blood cell count, platelet count, or higher alanine aminotransferase and aPTT are additional found risk factors [75]. Peripheral cannulation could reduce the risk of bleeding complications due to less invasive techniques [73, 86].

Specifically, for intracranial and gastro-intestinal bleeding, high blood pressure, decreased PaCO2 levels, lower ECLS blood flow for more than 2 hours, and gastric ulcer disease are possible risk factors [74, 87]. For intracranial hemorrhage alone, younger age, female gender, low body mass index and prior use

of antithrombotic therapy are reported risk factors, as well as previous cardiac arrest, sepsis and viral pulmonary infections. Furthermore, the following laboratory findings are associated with higher intracranial bleeding: low fibrinogen, hemolysis, thrombocytopenia, rapid PaCO2 and PaO2 shifts [88]. Another study reported diabetes mellitus and low fibrinogen levels as risk factors for intracerebral hemorrhage [89, 90].

Management of bleeding complications

Protocols for management of bleeding complications recommend, stopping anticoagulation for 24 to 48 hours, alternatively decreasing anticoagulation dose or targeting an anticoagulation free period. It seems feasible and effective to decrease bleeding complications in ECLS [89, 91]. A retrospective study including V-A ECLS cases compared conventional anticoagulation protocol versus no anticoagulation. The outcomes showed no difference in transfusion need or thrombotic complications or mortality. However, the patients without anticoagulation were more often post cardiac surgery patients with post-cardiotomy shock, with central cannulation, higher lactate levels and smaller ECLS duration [92]. In an observational study with thrombosis prophylaxis dosage, bleeding and thrombotic complications showed no higher incidence numbers compared to the available literature [93]. Also, a low-dose heparin study has shown promising outcomes compared to normal heparin dosage. But again, this study had major limitation such as the timing of protocol change instead of simultaneous comparison of protocols [94]. Another retrospective study comparing normal versus low dose heparin, showed similar outcomes between the groups. Nonetheless, the choice of anticoagulation protocol was dependent on the preference of the treating team, and there were no comprehensive baseline differences presented [95].

Limitations in current research regarding bleeding events

There are several returning limitations in the overall research to bleeding complications and adjustments to reduce the risks. First, the guidelines for anticoagulation management are suggestive, but protocols of anticoagulation management differ between every center.

Second, the definition of bleeding complications and the different type of bleeding complications also vary between centers and studies. Therefore, comparisons between studies in complication rates, and trends are difficult. Further, determining the risk factors for bleeding complications remains challenging. Since the definition of bleeding complications is not uniform, the outcomes of the studies are not comparable.

Third, in the research of adjusted anticoagulation protocols, the main disadvantage of the studies is the retrospective nature of it. The reason to adjust

the existing anticoagulation protocol must be included in the considerations of the outcomes, because the hemostatic balance is different in these patients than in the patients from the control group. Furthermore, patients with high risk for bleeding complications could benefit more from the adjusted protocols. However, determining high-risk patients is difficult since risk factors for hemorrhagic adverse events differ greatly between studies and type of cohorts.

There are no prediction models available specialized for V-A and V-V ECLS separately, and researchers will base their choice of high-risk patients on their experiences or use specific patient groups. One study reported a prediction ability for bleeding events in ECLS, in the following variables; duration of ECLS, aPTT and platelet count. These variables showed area under the ROC curves (AUC) of 0.884, 0.817, and 0.751 respectively in the predictive value for bleeding events. However, this is based on a small retrospective heterogenic cohort with V-A and V-V ECLS mixed [75]. Assessing new anticoagulation managements in high risk patients is therefore very challenging, as well as reproducing the same circumstances for following studies or to extrapolate the outcomes in clinical settings. Therefore, prediction models are warranted, to further investigate anti-coagulation management protocols.

Trauma patients on extracorporeal life support

Previously, trauma was considered as contraindication for ECLS due to the additional bleeding risk. Trauma patients with severe injuries are at risk for developing acute respiratory distress syndrome (ARDS), shock or sepsis [96]. They may also suffer airway injuries, cardiac failure due to stump thoracic trauma and pulmonary contusions [97]. Brain, spine or pelvic injuries make prone positioning in ARDS more difficult or challenging [98]. Also, the combination of simultaneously brain and pulmonary injury is challenging in terms of balanced carbon dioxide levels during protective ventilation [99]. This is where ECLS could particularly be helpful.

Between 1989 and 2017, the use of ECLS in trauma patients has increased. ECLS in trauma patients is most often initiated in cases of ARDS. In a cohort study of 196 trauma patients supported with ECLS, more than 80% complications occurred, of which almost 30% included bleeding complications. The bleeding complications occurred slightly more in V-A ECLS cases. Despite the fact that this cohort originates from 1989 to 2017, there was no information about the trends of these complications [98]. With the improvements of the circuit and components of the ECLS, systemic anticoagulation administration can be delayed. This can be a huge advantage in patients with challenging manageable bleeding sites. Arlt et al. showed a decrease of further bleeding complications in trauma patients when a heparin-free period was initiated during ECLS [100]. Chen et al. showed similar results in multi-trauma patients submitted to V-V ECLS [101]. Yet, there is no

consensus when to avoid anti-coagulation administration [97]. In a retrospective study, Kim et al. reported lower lactate and hemoglobin values in traumatic ARDS patients, as well as longer ICU and hospital stay, despite comparable ECLS duration [102]. In a systematic review including multi-trauma patients submitted to ECLS, bleeding complication rate of 22.9% and thrombosis of 19% was found. Of the 66% patients receiving systemic anticoagulation, the strategies differed among institutions [103]. It is unclear in which degree trauma patients actually suffer from ECLS complications and have a higher mortality compared to trauma patients without ECLS [104].

Aims and outline of this thesis

The aim of this thesis was to investigate the proportion of bleeding complications during ECLS, and to develop a method to identify patients at high risk for bleeding complications. Furthermore, the thesis focusses on circuit related variables interacting with coagulation homeostasis and the complications in trauma patients.

The first part (Chapters 2 and 3) of this manuscript focuses on the prevalence of bleeding complications in extracorporeal life support and the magnitude of this problem and changes of the years.
In the second part (Chapter 4 and 5), the prediction of high-risk patients for bleeding complications is research and discussed.
The third part (Chapter 6, 7, 8) is dedicated to anticoagulation and coating methods in ECLS devices and the clinical outcomes and main challenges and complications of trauma patients submitted to ECLS.

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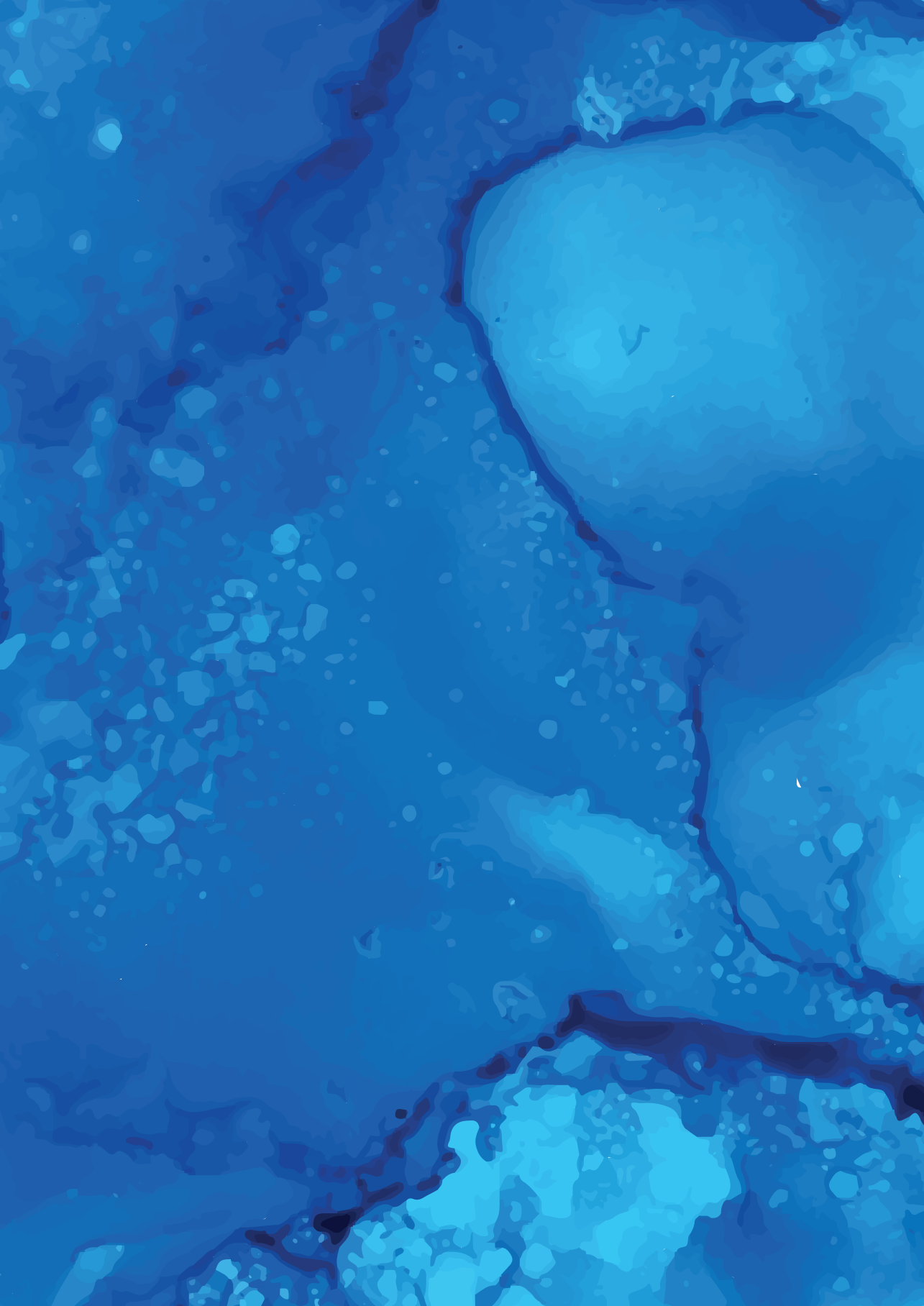

2

Extracorporeal life support in hemorrhagic conditions - A systematic review

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Abstract

Background: Extracorporeal Life Support (ECLS) is indicated in refractory acute respiratory or cardiac failure. According to the need for anticoagulation, bleeding conditions (e.g., in trauma, pulmonary bleeding) have been considered a contraindication for the use of ECLS. However, there is increasing evidence for improved outcomes after ECLS support in hemorrhagic patients based on the benefits of hemodynamic support outweighing the increased risk of bleeding.

Methods: We conducted a systematic literature search according to the PRISMA guidelines and reviewed publications describing ECLS support in hemorrhagic conditions.

Results: In total, 181 patients were, included, as identified in 74 case reports, four case series, seven retrospective database observational studies and one preliminary result of an ongoing study in a total of 86 published manuscripts. The reports included patients suffering from bleeding due to pulmonary hemorrhage (n=53), trauma (n =96), post-pulmonary endarterectomy (n=13), tracheal bleeding (n=1), postpartum or cesarean delivery (n=11) and intracranial hemorrhage (n=7). Lower targeted titration of heparin infusion, heparin-free ECLS runs until coagulation is normalized, clamping of the endotracheal tube, and other ad hoc possibilities represent potential beneficial maneuvers in such conditions. Once the patient is cannulated and circulation restored, bleeding control surgery is performed for stabilization if indicated.

Conclusions: The use of ECLS for temporary circulatory or respiratory support in critical patients with refractory hemorrhagic shock appears feasible considering tailored ECMO management strategies. Further investigation is needed to better elucidate the patient selection and ECLS management approaches.

Introduction

Circulatory shock is a life-threatening situation and is a common cause of death [1]. A relevant number of episodes of circulatory shock is caused by hypovolemia due to bleeding [1]. In trauma patients, exsanguination represents the prehospital cause of death in up to 45% of cases and 23% of total deaths, including pre- and in-hospital events [2]. Cardiogenic, hypovolemic and distributive shock and late onset multiple organ failure in are common causes of death after trauma [3]. Avoidance of late organ dysfunction by immediate hemodynamic support to prevent shock might be a lifesaving measure. An advanced option to sustain or restore circulation in shock is the use of extracorporeal life support (ECLS). ECLS supplies adequate circulation and gas-exchange assistance, but it usually requires adequate anticoagulation to prevent clotting in the ECLS-related circuit and devices.

Platelet dysfunction might also be an adverse effect of ECLS. Despite many improvements in ECLS devices, bleeding is still the most common complication of ECLS [4]. Therefore, bleeding and coagulopathy are still considered contraindications for ECLS therapy, especially in cases of hypovolemic shock caused by uncontrollable hemorrhage.

Recently, several case reports and case series described successful outcomes after ECLS treatment for respiratory and circulatory support in hemorrhagic conditions [5-7]. The aim of this review is to summarize the reported experience of supplying ECLS support in active hemorrhage. Based on this summary, various techniques for patient stabilization, restoration of circulation and prevention of further bleeding can be used in further research and development.

Methods

The search for related articles was conducted in Pubmed [8], Medline [9] and Embase [10] using the PICO (problem/patients, intervention, comparison, outcome) method [11]. Because of the aim of the review, the PICO question was converted into key words [11]. Databases were searched for the following mesh and free terms: "extracorporeal membrane oxygenation", "advanced extracorporeal therapy", "extracorporeal life support", "hemorrhage", "bleeding conditions", and "massive bleeding" [11, 12]. The inclusion criteria contained case reports, case series or observational studies describing patients undergoing ECLS during hemorrhagic events or conditions, without restrictions with respect to patient age, bleeding site or subgroup. A supplementary search in the references was conducted for additional studies.

Abstracts and titles were selected by one independent reviewer, and when there was uncertainty, the selection decision was resolved by consensus with one or two other reviewers. From each study, data such as age, reason for ECMO support, treatment, anticoagulation methods and complications were extracted. The

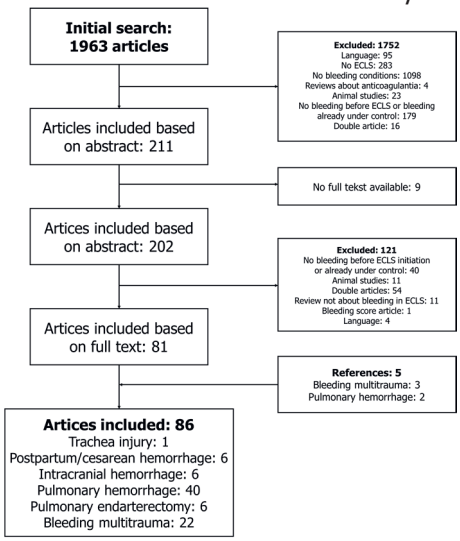
exclusion criteria were language other than English, full text not available, articles describing patients without pre-existing hemorrhage before ECLS cannulation or with already managed hemorrhage, and manuscripts that did not discuss the use of ECLS in bleeding patients. Furthermore, articles describing animal models were excluded.

In conducting this review, we aimed to meet the PRISMA criteria. This review is also registered in PROSPERO.

Results

In the end, 614 articles were found in Pubmed, 488 in Medline, 869 in Embase, and five by searching the references in publications included in the analysis. (Figure 1)

Figure 1. *PRISMA flowchart of the search and inclusion process*



The following subgroups were created based on the bleeding conditions: one patient with tracheal injury [13], eleven patients with postpartum or cesarean delivery hemorrhage [21, 37, 39, 78, 95, 97], seven patients with intracranial hemorrhage [14-19], 53 patients with pulmonary hemorrhage [5, 20-60], 13 patients with post-pulmonary endarterectomy bleeding [61-66] and 96 patients with bleeding trauma [45, 67-90]. (Tables 1-6)

Overall, 183 patients were identified in 86 included publications, namely, 67 case reports, eleven case series, five retrospective database observational studies [20, 64, 68, 71, 74], one ECPR observational cohort [73], and two observational prospective cohort studies [69, 80]. Two patients were excluded because they did not receive ECLS [24, 91]. In total, 181 patients were included in the analysis.

ECLS mode

Veno-venous (V-V) ECLS was applied in 72 75 patients, whereas veno-arterial (V-A) mode was performed in 64 cases. In 40 patients, the ECLS mode was not specified. A hybrid form of ECLS was applied in two patients [13, 71]. The conversion rate to a different mode was 15%. (Figure 2)

The indications for pulmonary support included ARDS resulting from intrapulmonary hemorrhage or trauma [17, 39, 92], pneumonia in a patient with intracranial hemorrhage [15], neurogenic pulmonary edema after trauma [19], and hypoxic respiratory failure [20, 23, 27, 31, 34, 37, 38, 40, 47, 52, 53, 62, 63, 65]. (Tables 2-6)

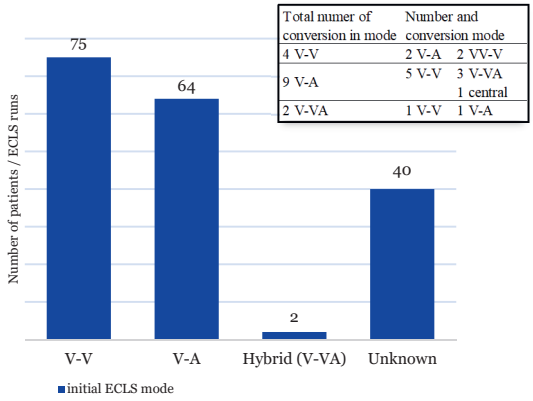
Anticoagulation

Heparin administration during a complete ECLS run, heparin-free period after cannulation and total heparin-free ECLS run strategies were described in the majority of the publications. The heparin-free period varied between four hours and two days in 12 patients [5, 16, 27, 33, 45, 59, 69, 78]. Re-start of anticoagulation was performed after damage control surgery, detection of clots in the circuit, or control of the bleeding site [17, 20, 35, 40, 47, 50, 68, 78, 88, 90]. In seven patients, the heparin-free time was not specified [65, 85, 93].

With respect to a complete heparin-free ECLS run, six articles did not mention a description of the system coating [38, 43, 44, 62, 75, 81]. One circuit was coated with Softline [72], and a heparin-coated system was used in the remaining 16 patients [18, 50, 57, 63, 64, 70, 77, 79, 94]. A few protocols mentioned the use of other anticoagulants such as nafamostat mesilate [19, 30, 42, 46], dalteparin [46], and citrate [32]. (Figure 2) One patient received nafamostat mesilate prior to the heparin bolus [19].

During the use of heparin in the complete ECLS run, activated clotting time (ACT) targets were reported in 35 patients [13, 21, 25, 31, 36, 39, 41, 48, 49, 52, 53, 55, 56, 60, 67, 73, 76, 83, 84, 86, 87, 95], and activated partial thromboplastin time (aPTT) targets were reported in ten patients [14, 15, 20, 34, 67, 89]. In the subgroup with different anticoagulation other than heparin, ACT targets were defined in four patients [30, 32, 42, 46], whereas no specific mention of anticoagulation assessment was available in the other studies [19]. For 96 patients, the targets or duration of anticoagulation management was missing [16, 18, 19, 22-24, 26, 28, 29, 36, 38, 46, 50, 51, 54, 57, 58, 61, 62, 64, 69-72, 74, 75, 77, 79-82, 85, 91, 92, 94, 96, 97].

Figure 2. *Distribution of extracorporeal life support modus*



Complications

In total, 47 (26%) patients developed bleeding complications during ECLS, and 19 developed thromboembolic complications (10.5%). (Figure 3) Ongoing coagulopathy caused bleeding complications in 8 eight patients [26, 59, 80, 91, 93], and four of them suffered fatal exsanguination. Intracranial hemorrhage occurred in three patients [61, 82, 93].

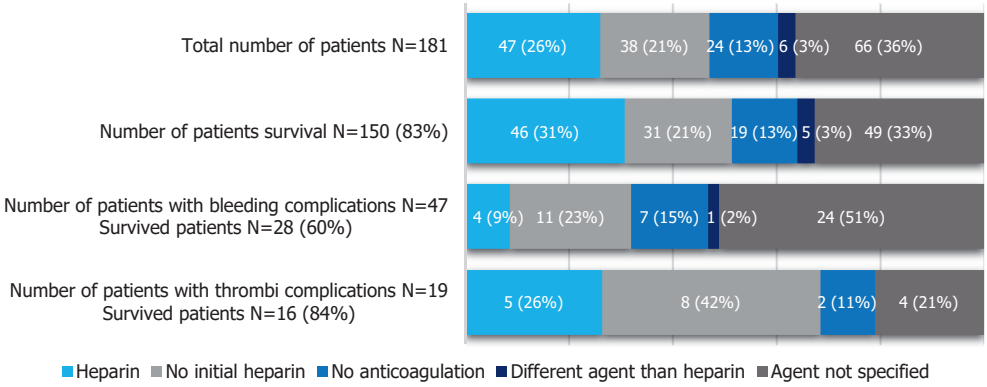
As expected, most complications occurred in the group without anticoagulation during the initial period. Clotting complications during heparin-free ECLS occurred in ten patients with a heparin-coated circuit [17, 45, 50, 63, 78], bioactive coating [35] and unknown coating [20, 47, 62, 65]. Two patients developed thrombi in the vena cava, iliac veins and deep venous thrombosis after disassembly of ECLS despite the use of heparin [83, 86].

One accidental removal of the venous cannula with consecutive bleeding was mentioned [69]. Bleeding of the cannulation site after ECLS removal occurred in three patients [28, 34, 77].

Survival

Overall survival in the 181 identified patients was 82.3% (149 patients). One patient died in hemoptysis due to tuberculosis at the four-month follow-up after discharge [63]. Lethal bleeding was caused by intracranial hemorrhage [93], retroperitoneal bleeding [68] and 3 three exsanguinations in ongoing coagulopathy [80] and in complicated ECLS cannulation [91]. Multiple organ failure and shock were the cause of death in nine patients [50, 54, 57, 64, 68, 69]. Further causes of death were cardiac arrest a few days after ECLS decannulation [20], respiratory failure [30], fat embolism [71], lethal increase in intracranial pressure [82], pulmonary hypertension [71] and ECLS futility [62]. One study did not specify the cause of death in the nine patients of the subgroup [74]. (Table 1)

Figure 3. *Anticoagulation characteristics with respect to the incidence of bleeding, clotting complications, and survival*



Bleeding control

Several procedures were performed to control bleeding. Postpartum bleeding was managed with hysterectomy and catheter embolization procedure [91, 93, 94, 96] in five and three patients, respectively, during the ECLS run. Clipping of the aneurysm was performed in two patients with intracranial hemorrhage before ECLS cannulation [14, 19]. Tracheal bleeding was controlled with a balloon in the tracheostomy and coiling embolization [13]. In post-pulmonary endarterectomy patients, bronchus blocking (with balloon or fibrin glue [64]) was frequently used to tamponade the bleeding site (5 out of 13 patients) with success [61, 63, 66], whereas local laser therapy was used in one patient [62]. Tube clamping or selective endobronchial blocking was performed in four patients in the pulmonary hemorrhage subgroup [34, 43, 57, 59], and embolization of bleeding artery was performed during ECLS in five patients [27, 38, 54, 55, 57]. Tube clamping and selective endobronchial blocking were not successful in achieving bleeding control but can be recommended as supportive during ECLS cannulation.

Five patients with pulmonary bleeding [5, 27, 78, 79] underwent surgery to control bleeding, and in six trauma patients, a surgical procedure was used to control bleeding [70, 75, 76, 78, 79] out of the 37 patients [61, 68, 71-74, 78, 79, 81, 83, 84, 86-88, 90] undergoing damage control surgery. One patient received a stent in the vena cava during fluoroscopy-guided intervention [70]. Furthermore, drugs were also used to minimize coagulopathy, such as factor VII [49, 69, 78, 93], prothrombin [25, 57, 63-65, 67], and aminocaproic acid [47, 48, 52, 67, 71]. (Table 2-6)

Discussion

Acute hemorrhage has been considered a contraindication for ECLS due to the risk of further bleeding and re- bleeding [98, 99]. Patients with hemorrhagic shock might develop further bleeding due to the lethal triad of hypothermia, hypoperfusion and acidosis, causing coagulopathy [100, 101]. The lethal triad causes hypoxia and severe acidosis, whereas acidosis causes platelet dysfunction [101]. Hypothermia slows the activity of coagulation [100]. A patient with hemorrhagic shock and coagulopathy might benefit from circulatory support such as ECLS. Rapid recovery of sufficient blood flow, oxygenation and warming of blood can be achieved immediately within cannulation of ECMO [102]. Therefore, ECMO might prevent or overcome the vicious cycle of coagulopathy in hemorrhagic shock patients [68]. A heparin-free period might be useful in these cases, especially considering the coagulopathy already existing in a hemorrhagic patient.

Zonies et al. summarized studies describing ECLS in severely injured soldiers, with an impressive survival rate of 79% and 90% [103]. Kruit et al. reported a survival rate of 75% in 52 trauma patients and a 50% incidence of bleeding complications [104]. Kruit et al. also reported a survival rate of 75% in 52 trauma patients with a 50% incidence of bleeding complications; nevertheless, they showed no exacerbation of primary traumatic injury with the use of ECMO, independent of the anticoagulation method used [104]. In the current review, 83% survival was observed in hemorrhagic trauma patients primarily stabilized with ECMO, which might be counterintuitive due to the expected bleeding risk.

Modern ECLS devices feature centrifugal pumps and a lower risk of hemolysis compared to roller pumps [103]. Primary activation of coagulation and hemolysis might be caused by clot build-up. Arlt et al. mentioned the use of shorter circuit tubes for decreased surface contact to reduce the risk of thromboembolic events and the use of heparin-coated and biocompatible circuits for decreased activation of the coagulation cascade.

Several ECLS management techniques have been described to reduce the risk of bleeding in this population. Heparin-free ECLS initiation may minimize the risk of major bleeding complications [103]. Chung et al. found no significant increased risk of oxygenator occlusion or intravascular thrombotic events between the heparin-free period and complete heparin use during ECLS in a group of 55 patients [105]. Notably, the group with a heparin-free period did have higher ACT, thrombocytopenia, bleeding complications and need for surgical procedures, since coagulation activation might result in bleeding due to consumptive coagulopathy [106].

Other diverse strategies have been described to minimize the risk of further bleeding during ECLS support in patients with active bleeding sites. One such strategy is the use of nafamostat mesilate as an anticoagulant alternative to heparin

[19, 30, 42, 46]. This synthetic serine protease inhibitor, mostly used in hemodialysis, has been investigated multiple times, but no consensus has yet been found. In 2018, Han et al. published an experimental study comparing unfractioned heparin with nafamostat mesilate [107]. In 2016, Lim et al. found conflicting results in a retrospective observational study with 320 patients in which nafamostat mesilate was compared to heparin during ECLS [108]. For both groups, an ACT and aPTT of 160-200 and 50-70 seconds were respectively set. In this article, bleeding complications are were significantly higher in the nafamostat group than in the heparin group.

ECLS is an option as a bridge to hemorrhagic control treatment. Kalavrouziotis et al. suggested that heparin-coated circuits might not even be necessary in short-term ECLS use (<1 hour) after pulmonary endarterectomy [109]. Therefore, a conventional circuit without use of heparin could be a more cost-effective solution to endobronchial bleeding after weaning from CPB. One of the complications in pulmonary endarterectomy, intraoperative bleeding, can be overcome by using V-A-ECLS in a short time period [6, 64]. Even in exceptional situations such as tracheal bleeding in a fistula or stent migration, ECLS appears to be useful in supplying hemodynamic stability until further treatment such as surgery can take place [13, 54].

A prediction model for hemorrhage risk is expected to be a useful addition for deciding the most suitable protocol or alteration. Lonergan et al. developed the hypertension, age, ECLS type (HAT) score, which shows promising validation [110, 111]. Further research is necessary to evaluate different approaches to minimizing the risk of bleeding in high-risk patients.

Limitations

The population of patients receiving ECLS includes a mix of those experiencing circulatory and respiratory failure. No randomized or observational trials exist on the use of ECLS in bleeding. There is a positive outcome bias due to the favorable outcomes and successful interventions reported in case reports and case series. Only cases with good and outstanding outcomes are published, and the other cases are not reported. Therefore, case series deserve greater emphasis because the positive outcome bias is expected to be minor.

Protocols targeting anticoagulation goals vary between the use of ACT, aPTT and/or visible clotting markers as a cut-off point for heparin administration. In particular, visible clotting and clot assessment conducted by different individuals, at different locations, and with different instruments is unlikely to be reliable. Therefore, the reproducibility is low because of the heterogeneity between publications.

Critical appraisal of the evidence is important in assessing high-cost critical care therapies. In this search, we aimed to identify complete evidence by searching multiple databases. Despite an extensive search, certain articles could be missing.

Conclusion

ECLS cannulation in hemorrhagic shock and bleeding coagulopathy is feasible for gaining central access for resuscitation. The key is the application of ECLS to buy time and provide instruments to recover from the deadly triad. ECLS is used as a bridge for circulatory support, not as a therapy for coagulopathy. The evidence based on multiple case reports and case series suggests that an acute hemorrhagic condition should not be considered an absolute contraindication to ECLS. ECLS may restore circulation and allow bridging until definitive source control of the bleeding or response to coagulopathy treatment can be attained.

Table 1. *Summary of extracorporeal life support treatment and outcomes in six subgroups*

Subgroups	N articles patients survivors (%)	ECLS mode V-A | V-V N(%)	Mean ECLS duration (hours)	Bleeding sources	Bleeding source interventions: surgery, radiological, drugs, compression devices	Supportive management, drugs, anti-coagulation reveal	Preventive management	Complications during ECLS Device related, clotting, bleeding, lethal, N (%)
Postpartum post-cesarean [14-19]	6 | 11 | 9(82)	V-A 9(82) V-A to V-V 2(18)	80	Uterine bleeding, vaginal bleeding, pulmonary hemorrhage due to thrombolysis in PE, bleeding pheochromocytoma in emergency cesarean	Bimanual compression, hysterectomy, packing, bleeding control surgery	Recombinant factor VIIa, fibrinogen transfusion, epinephrine, oxytocin	Decreased heparin, heparin free run	Clot formation in ECLS circuit (1;9) Leak out at cannula site (1;9) Intracranial bleeding (1;9) Diffuse bleeding 3 (27) Exsanguination during cannulation (1;9)
Intracranial hemorrhage [20-25]	6 | 7 | 7(100)	V-A 3(43) V-V 4(57)	186	Subarachnoid, epidural and subdural hemorrhage, aneurysm rupture, frontotemporal hemorrhage	Aneurysm clipping and coiling procedure	Inhaled nitric oxide	Decreased heparin, heparin free run, nafamostat mesilate	Leak out of percutaneous gastrostomy (1;14)
Post-pulmonary endarterectomy [67-72]	6 | 13 | 11 (85)	V-A 9(69) V-V 3(23) V-A to V-V 1(7)	45	Bleeding after pulmonary endarterectomy	Blocking of bronchus, surgery, cryotherapy, intrabronchial epinephrine	Protamin, fibrin glue	Decreased heparin, heparin free run	Clot formation in ECLS circuit (1;8) Thrombi in bronchi (2;15) Intracranial hemorrhage (1;8) Ongoing hemorrhage (1;8) Tamponade (1;8) Multiple organ failure (1;8)
Pulmonary hemorrhage [5, 26-66]	42 | 53 | 48 (90)	V-A 13 (25) V-A to V-AV 1(2) V-V 33(62) Unknown 3(6) V-V to V-A 2(4)	157*	Diffuse alveolar hemorrhage, diffuse hemorrhage in coagulopathy due to; acute respiratory distress syndrome, pneumosepsis, granulomatosis (with or without) polyangiitis, leptospirosis, influenza A, lymph angioleiomyomas, silicone embolism, Goodpasture syndrome, Wegener's disease, Wilson disease, Hurler syndrome, systemic lupus, aortic valve stenosis	Epinephrine injection, pericardiocentesis, coiling/embolization procedure, stenting, bleeding control surgery, endotracheal clamping, bronchial blocking, chest tube, protamine sulphate	Recombinant factor VII, prothrombin, cyclophosphamide, plasmapheresis	Decreased heparin, heparin free period, nafamostat mesilate, argatroban	Clot formation in ECLS circuit (5;9) Splenic, renal embolisms (1;2) Thrombi in VCI, femoral vein (1;2) Pulmonary rebleeding (7;13) Endotracheal bleeding (1;2) Epistaxis (1;2) Hematuria (1;2) Pericardial effusion (1;2) Multi organ failure (3;6) Respiratory failure (1;2) Cardiac arrest after decannulation (1;2)

Trachea bleeding [13]	1 | 1 | 1 (100)	V-VA 1(100)	528	Sliding tracheoplasty bleeding	Inflation of balloon in trachea, stent, coiling, embolization	-	Heparin, ACT target 160-180 sec	Rebleeding 1(100)
Trauma patients [51, 73-96]	25 | 96 | 84(88)**	V-A 22(23) V-V 32(33) V-V to V-A 1(1) V-VA 2(2) Unknown 39 (41)	178**	Penetrating injuries, traumatic liver, spleen laceration, hemopneumothorax, subdural hematoma, rib fractures, lung parenchymal bleeding, rupture of thoracic aorta, bronchial bleeding, pericardial effusion, subdural hematoma, crush injury lower extremities, trachea rupture	Chest drain, laparotomy, thoracotomy, pericardiostomy, wedge resection, packing, aortic stenting, repair of ventricular wall and coronary vessels lung isolation, packing, pulmonary artery locking, nitric oxygen	Epsilon-aminocaproic acid, aprotinin, temperature correction	Decreased heparin, heparin free run	DVT after decannulation (2;2) Limb ischemia (1;1) Clotting in ECLS circuit (2;2) Thrombosis vena cava inferior (1;1) Air embolism (1;1) Accidental removal of drainage cannula (2;2)*** Leak out at cannula site (2;2)*** Surgical site bleeding (7;7) Disseminated intravascular coagulopathy Gastrointestinal bleeding (2;2) No further defined bleeding (5;5) Diffuse bleeding (8;8) Pericardial effusion (1;1) Exsanguination (3;3) Intracranial hemorrhage (1;1) Fat embolism (1;1) Pulmonary hypertension (1;1) Multiorgan failure, sepsis (3;3)

Note: Days are converted to hours by multiplying with 24
*Some missing time data (4 patient with unknown ECLS duration)
**Missing data of time of ECMO (3 articles did not specify the ECLS time, 1 article did not specify the mortality)
***Some of the complications are unclear whether these occurred in ECMO patient or patients on interventional lung assist (Biderman et al)

Abbreviations: ACT = activated clotting time, aPTT = activated partial thromboplastin time, DVT = deep venous thrombosis, ECLS = extracorporeal life support, N = number, VCI = vena cava inferior, V-V = veno-venous, V-A = veno-arterial, V-VA = veno-veno-arterial, PE = pulmonary embolism, pts = patients, "→" ECLS mode conversion

Table 2. *Extracorporeal life support in post-partum and cesarean hemorrhage*

Author	N	Cause of bleeding	Treatment before and during ECLS	Management to minimize bleeding on ECLS	ECLS mode, duration (h)	Serious adverse events
Huang et al. [15]	5	Uterine atony post-delivery (3) Post-cesarean (2)	CPR, transfusion, recombinant factor VIIa, hysterectomy, trans-arterial embolization	Initial no heparin (unknown time) Flow of 2.3 L/min Circuit coating not mentioned	V-A, 32.6 ± 18.8	2 bleeding complications Amniotic fluid embolism One death due to intracranial bleeding
Itagaki et al. [17]	1	Uterine atony post-partum, coagulopathy	CPR, oxytocin, epinephrine, norepinephrine	Heparin titration to ACT 160 sec, biocompatible coating circuit, transfusion of RBC, Platelets and anti-thrombin III	V-A, 72	
Reyftmann et al. [18]	1	Uterine atony post-partum	Oxytocin prostaglandin, uterine massage, artery ligation and B-Lynch suture, emergency subtotal hysterectomy	Fibrinogen unit transfusion, heparin bound circuit	V-A, 150	Laparotomy in hemoperitoneum
Goto et al. [97]	2*	Atony of uterus post-cesarean with cardiac arrest	Hysterectomy, gauze packing, massive transfusion	Not mentioned	No ECLS	Exsanguination during ECLS cannulation
		Coagulopathy			V-A, 216	Diffuse bleeding
Arlt et al. [14][14]	1	Post-cesarean, vaginal bleeding with pulmonary hemorrhage after thrombolysis in embolism	CPR, epinephrine, norepinephrine, transfusion of RBC, FFP, emergency hysterectomy	No systemic heparin in heparin coated system	V-A, 96	
Van Zwet et al. [19] **	1	Bleeding pheochromocytoma with takotsubo cardiomyopathy, emergency cesarean delivery right before ECLS cannulation	CPR, laparoscopic adrenalectomy after ECLS	Unclear	V-A->V-V 168	

Abbreviations: ACT = activated clotting time, CPR = cardiopulmonary resuscitation, DVT = deep venous thrombosis, ECLS = extracorporeal life support, FFP = fresh frozen plasma, h= hours, L/min = Liter per minute, N= number of patients V-V = veno-venous, V-A = veno-arterial, V-VA = veno-veno-arterial, RBC = red blood cells, "→" ECLS mode conversion. * One patient did not receive ECLS, **Van Zwet et al. describes a patient with bleeding from pheochromocytoma, but because of emergency cesarean right before ECLS cannulation, we included this publication in post-partum and cesarean hemorrhage subgroup

Table 3. *Extracorporeal life support in active intracranial hemorrhage*

Author	N*	Age	Cause of bleeding	ECLS Indication	ECLS Mode	Strategy to minimize bleeding on ECLS	Supportive treatment	ECLS duration (h)	Serious adverse events
Zant et al. [20]	1	9	Frontotemporal hemorrhage and SAH after aneurysm rupture	Sepsis-induced myocardial dysfunction	V-A	aPTT 45-55 seconds, no heparin in circuit Flow 2.0L/min	Craniotomy with clipping of aneurysm	120	Hemiparesis
Hwang et al. [25]	1	28	Aneurysm rupture with right frontal base bleeding	Neurogenic pulmonary edema	V-V	3000 Units of heparin, clipping of aneurysm 4.5L/min ECLS flow Nafamostat mesilate as anti-coagulant	Craniotomy, clipping of aneurysm, hypothermia target 34 °C	168	
Biscotti et al. [21]	2	18	EDH, SAH after trauma	ARDS and pneumonia	V-V	aPTT 40-60 sec with heparin	EVD	264	
		20	SDH, SAH after trauma	ARDS	not mentioned	aPTT mean 51 sec	EVD hypothermia target 33 °C	144	
Pearson et al. [22]	1	12	SAH after struck with ball on posterior occipital area	Takotsubo cardiomyopathy	V-A	1/3 of standard heparin dose, first 53h 5Units/kg/h, later 10Units/kg/h	Intraventricular drain, chest tubes after CPR	76	Conversion to central cannulation, increase of SAH, coiling procedure
Messing et al. [23]	1	21	SDH, SAH after trauma	ARDS	V-V	Heparin bounded system without heparin until thrombi in oxygenator (day 5), ACT 180-200 sec ->160-180 sec	Not mentioned	480	Bleeding on percutaneous enterostomy
Yen et al. [24]	1	21	SDH, EDH, with midline shift after trauma	Ventricular tachycardia, cardiopulmonary	V-A	Heparin bounded system without systemic heparin	Transfusion, milrinone, inhaled nitric oxide, decompressive craniotomy	49	Renal replacement

Abbreviations: ACT = activated clotting time, ARDS = acute respiratory distress syndrome, aPTT = activated partial thromboplastin time, CPR = cardiopulmonary resuscitation, ECLS = extracorporeal life support, EDH = epidural hemorrhage, EVD = external ventricular drain, h= hours, IVH = intraventricular hemorrhage, IPH = intraparenchymal hemorrhage, L/min = Liter per minute, N = number of patients, V-V = veno-venous, V-A = veno-arterial, V-VA = veno-veno-arterial, SAH = subarachnoid hemorrhage, SDH = subdural hemorrhage, sec = second

Table 4. *Extracorporeal life support after pulmonary endarterectomy with bleeding complications*

Author	N	Age	Cause of bleeding	ECLS Indication	ECLS Mode	Strategy to minimize bleeding on ECLS	Supportive treatment	ECLS duration (h)	Adverse events
Guth et al. [70]	8	67±11	Endobronchial hemorrhage	Endobronchial bleeding and lower cardiac output	V-A	Protamin, fibrin glue, blood products, blocking of bronchus with fibrin glue No heparin, heparin bounded circuit	Not specified	0.48, 0.83, 1.17, 0.58, 0.33, 0.60, 0.42, 1.73	Multiple organ failure and lethal hypoxemia
Cronin et al. [69]	1	44	Lower and upper lobe	Inadequate gas exchange in need for lung isolation	V-V	Uni-bronchial blocker, protamine, fresh frozen plasma, platelets, heparin bonded circuit	Not specified	44	Clot formation Lethal hemoptysis due to tuberculosis after discharge
Kolnikova et al. [71]	1	50	Lower lobe	Hypoxia	V-V	Protamin, heparin after 12h, targets ACT 160-180 sec, aPTT 50-60 sec intrabronchial antifibrinolytics and epinephrine	Clot removal with bronchoscopy	96	
Yildizeli et al. [72]	1	38	Lower lobe	Hypoxia and hemodynamic instability	V-A	Target ACT 150 -200 sec Unsuccessful surgical attempt to stop bleeding Bronchus block with balloon catheter	Clot removal with bronchoscopy	72	
Caridi-Scheible et al. [68]	1	62	Pulmonary arteries	Hypoxemic respiratory failure	V-V	No heparin, unknown coating, cryotherapy	Thrombus removal; saline, perfluorodecalin lavage	264	Thrombus in main bronchus, lethal multiorgan failure
Pretorius et al. [67]	1	44	Right lung	Severe hypoxemia due to PAH	V-A	Bronchial blocker, unknown anticoagulation during ECLS and unknown coating	Not specified	96	Intracranial hemorrhage

Abbreviations: ACT = activated clotting time, aPTT = activated partial thromboplastin time, ECLS = extracorporeal life support, N = number of patients, V-V = veno-venous, V-A = veno-arterial, V-VA = veno-veno-arterial, PAH = pulmonary arterial hypertension.

Table 5. *Extracorporeal life support in pulmonary hemorrhage*

Authors	N	Patient characteristics	Bleeding source	ECLS mode, duration in days	Anticoagulation targets		Supportive treatment during ECLS	Complications during ECLS e.g. due to anticoagulation	Other complications Outcome
Vobruba et al. [65]	1	40-weeks-old neonate with coagulopathy pneumosepsis, pulmonary hypertension due to open ductus arteriosus, right-left shunt	Massive pulmonary hemorrhage	V-A, 5d	aPTT 50-60 sec	No heparin first 3 d Adjusted heparin dose after restored coagulopathy No heparin priming	Endotracheal epinephrine Endotracheal tube clamping Prothrombin	Pulmonary rebleeding	Recovery
Fagunes et al. [39]	1	46-year-old female with iatrogenic laceration of left lung during mitral and aortic valve replacement	Bleeding laceration left lung	V-V → V-A	ACT 150-180 sec	Unfractioned heparin	Surgery Attempt of removing blood clots with bronchoscopy Streptokinase endobronchial		Sepsis , lower limb paresis peripheral nerve damage Recovery
Lee et al. [49]	1	64-year-old male with microscopic polyangiitis hemoptysis, respiratory failure cardiogenic shock	Diffuse alveolar hemorrhage	V-A →V-V, 5d	ACT 133-191sec	No systemic heparin for 5 d	Endotracheal tube clamping for 15h, suction of clots Transfusion	Pericardial effusion for which pericardiocentesis was performed	Recovery
Pardinas et al. [58]	1	32-year-old male with leptospirosis with massive hemoptysis, renal failure	Diffuse alveolar hemorrhage	V-V, 18d	ACT 160-180 sec	Adjusted heparin titrated to ACT	Aminocaproic acid infusion for 6 days, platelet transfusion	Thrombocytopenia	Recovery
Vanoli et al. [64]	1	33-years-old patients wth granulomatosis polyangiitis ANCA-PR3+	Alveolar hemorrhage	Not specified	Not specified	Not specified	Plasma exchange		Renal failure, relapse alveolar hemorrhage Recovery
Liao et al. [51]	1	32-year-old male with leptospirosis, ARDS	Intrapulmonary bleeding	V-V, 6d	Not specified	Not specified	Blood transfusion Platelets		Refractory hypercapnia Recovery
Crawford et al. [35]	1	37-year-old pregnant female with ARDS influenza A lymphangioleiomyomatosis (LAM)	Diffuse alveolar hemorrhage	V-A, 14d	Not specified	Not specified	Recombinant activated factor VII endobronchial	HELLP, preeclampsia Urgent cesarean section Cysts in lung parenchyma	Continuous oxygen supplementation Recovery
Kimura et al. [46]	1	14-year-old female with SLE and hypoxic respiratory failure	Hemoptysis with massive pulmonary hemorrhage	V-V, 10d	Platelets >200.000uL, ACT 140-160 first 48h, after 180-200	Heparin infusion after surgery	Emergency pulmonary lobectomy Plasmapheresis	Hemothorax	Recovery
Choi et al. [34]	1	75-year-old female with myocardial infarction advanced cardiac life support ARDS	Diffuse alveolar hemorrhage	V-A, 5d	Not specified	Not specified		Spontaneous subarachnoid hemorrhage Ischemic left leg with fasciotomy and knee amputation	Pseudomonas sepsis, liver laceration after gastric tube placement. Discharged with severe impairment tracheostomy and gastric tube
Cao et al. [33]	1	44-year-old female with sudden hemoptysis in aneurysms of bronchial artery	Bronchial artery hemorrhage	V-V, 119h	aPTT 40-60 sec	First 4h without heparin	Embolization bronchial artery Left upper lobectomy	Rebleeding of bronchial artery	Recovery
Gutierrez et al. [42]	1	5-week-old male idiopathic pulmonary hemosiderosis, refractory respiratory failure	Massive pulmonary hemorrhage	V-V →V-A 6d	Not specified	Not specified		Bradycardia Hypotension	Recovery
		65-year-old female with							

Hohenforst et al. [43]	1	65-year-old female with granulomatosis polyangiitis Acute renal and respiratory failure, hemoptysis	Diffuse alveolar hemorrhage	V-V, 10d	ACT 160-200 sec	Argatroban No further anticoagulation	Hemofiltration	Heparin-induced-thrombocytopenia type II	Hemodialysis Recovery
Patel et al. [59]	1	28-year-old female with SLE, pericardial tamponade refractory hypoxemia ARDS	Diffuse alveolar hemorrhage	V-V, 4d	ACT >200sec	Unfractioned heparin	Hemofiltration	acute tubular necrosis	Recovery
Grimme et al. [40]	1	23-year-old pregnant female hemoptysis hypoxic cardiac arrest	Severe pulmonary hemorrhage	V-V, 8d	aPTT 50sec	Unfractionated heparin	RBCs 16U transfusion Selective endobronchial blocker for 24h	Hemothorax	Tracheostomy pulmonary hemorrhage Recovery
Dalabih et al. [37]	1	9-year-old female Goodpasture syndrome	Pulmonary hemorrhage	V-V, 6d	ACT 200-220 sec	Heparin	Plasmapheresis, renal replacement therapy	Acute renal failure	Peritoneal dialysis Recovery
Barnes et al. [29]	1	50-year-old female Wegener's granulomatosis ANCA+ hemoptysis	Alveolar hemorrhage	V-V, 6d	Not specified	Not specified	Hemodiafiltration Plasmapheresis Cyclophosphamide Methylprednisolone	Acute kidney injury	Recovery
Joseph et al. [45]	1	13-year-old male with Wegener's granulomatosis, ANCA+ hemoptysis ARDS	Pulmonary hemorrhage	V-V, 5d	ACT 130-150 sec	Reduced dose heparin	Hemofiltration Plasmapheresis		Recovery
Son et al. [61]	1	5-year-old female with Wilson disease need of liver transplantation hemoptysis	Pulmonary hemorrhage	V-A, 5d	ACT 180-200	Heparin	Emergency liver transplantation Transfusion	Hemolysis	Bile leakage Recovery
Hsu et al. [44]	1	42-year-old male with acute respiratory failure hemoptysis bronchiectasis	Bleeding to pulmonary artery fistula	V-V, 24h	Not specified	No heparin, Unknown coating	Embolization, left lower lobectomy		Recovery
Mongero et al. [53]	1	27-year-old female with silicone embolism hemoptysis	Diffuse alveolar hemorrhage	V-V, 14d	ACT 180-200 sec PTT 45-60 sec	Heparin 2000U Heparin titrated to ACT target	Switch to new circuit and start heparin again	Blood clot in circuit	Heterotopic bone formation Recovery
Morris et al. [55]	1	20-month-old male with Hurler syndrome hematopoietic stem cell transplantation ARDS	Pulmonary hemorrhage	V-A, 7d	ACT 150-170 sec	Heparin titrated to ACT target	Hemofiltration Aminocaproic acid i.v.	Blood clots in circuit	Recovery
Guo et al. [41]	1	51-year-old female with hemoptysis dyspnea systemic vasculitis (ANCA+)	Diffuse alveolar hemorrhage	V-V, 13d	ACT 150 sec	First three days no heparin, bioactive surface circuit	Changing centrifugal head transfusion plasmapheresis	Thrombus in oxygenator Hematuria	Recovery
Di Maria et al. [38]	1	13-year-old male with microscopic polyangiitis (P-ANCA+) hemoptysis	Diffuse alveolar hemorrhage	V-A, 5d	ACT 160-180 sec	Citrate anticoagulation	Plasmapheresis Renal replacement	Pneumomediastinum	Recovery

Bédard et al. [30]	1*	19-year-old male with rebleeding after Fontan surgery	Rebleeding aortopulmonary collateral	Not specified	Not specified	Not specified	Left inferior lobectomy	Thrombosis Pulmonary embolism Paradoxical embolism	Recovery
Bianchini et al. [31]	1	75-year-old female with aortic and mitral valve replacement	Bronchial hemorrhage	V-A, 2.5h	ACT 160-180 sec	Protamine sulphate	Transfusion		Embolization of pseudoaneurysm pulmonary artery Recovery
Sun et al. [62]	1	11-year-old female with idiopathic pulmonary hemosiderosis	Diffuse alveolar hemorrhage	V-V, 5d	ACT 170-200 sec	Heparin titrated to ACT, heparin bound system			Reccurence hemoptysis Recovery
Agarwal et al. [27]	1	16-year-old male microscopic polyangiitis P-ANCA+, anti MPO +	Diffuse alveolar hemorrhage	V-V, 7d	ACT 16-180 sec	Heparin infusion titrated to ACT	Plasmapheresis	No complications	Glomerulonephritis Recovery
Arokianathan et al. [28]	1	30-year-old male with leptospirosis	Diffuse alveolar hemorrhage	V-V, 183h	Not specified	Not specified	Molecular adsorption recycling system 48h		Recovery
Ahmed et al. [5]	1	26-year-old female with Wegener granulomatosis ANCA+	Diffuse alveolar hemorrhage	V-V, 12d	ACT 140-160	First 48h without heparin	Plasmapheresis, hemofiltration	Bleeding, hemothorax Thoracotomy	Recovery
Kolovos et al. [47]	8	1) 0.1-year-old female with sepsis 2) 0.25-year-old male with sepsis 3) 2-year-old female with systemic vasculitis 4) 9-year-old female with SLE 5) 13-year-old female with Wegener's granulomatosis 6) 14-year-old female Wegener's granulomatosis 7) 15-year-old female autoimmune hepatitis 8) 18-year-old male with lupus nephritis	Pulmonary hemorrhage	1pt V-A (HD instability) 7 pts V-V 1) 3d 2) 11h 3) 6 4) 5d 5) 9d 6) 6,5d 7) 5d 8) 4d	ACT 160-180 sec	Heparin titrated to ACT	3 Plasmaphereses 3 Hemodialysis		Recovery
Matsumoto et al. [52]	2	1) 19-year-old female with microscopic polyangiitis ANCA+ 2) 29-year-old male with Wegener's granulomatosis ANCA+	Pulmonary hemorrhage	1) V-A, 3d 2) V-A, 3,5d	1) ACT 150 sec 2) Not metioned	1) Dalteparin sodium heparin coated system 2) Nafamostat mesilate	1) Plasma exchange 1) Hemodiafiltration		1) Peritoneal dialysis 1) Recovery 2) Recovery
Kotani et al. [48]	1	27-year-old female after lung transplantation in end-stage pulmonary hypertension	Pulmonary hemorrhage in lung graft	V-A, 43h	ACT 180-200	Nafamostat mesilate, heparin coated circuit	Hemodiafiltration		Recovery
Uzuka et al. [63]	1	85-year-old female with congestive heart failure aortic valve replacement	Diffuse bronchial bleeding	V-A → V-V	aPTT	None, heparin coated circuit	Protamine sulfate Embolization of bilateral bronchial arteries		Lethal multiorgan failure
Pacheco et al. [56]	2	1) 33-year-old femalewith SLE 2) 36-year-old male with SLE	Diffuse bronchial bleeding	1) V-V 2) V-V, 6d	Not specified	1) Heparin coated circuit 2) Short term heparin, heparin coated	1) Hemodialysis	1) Multi organ failure, alveolar hemorrhage 2) Circuit slotting	1) Lethal septic shock 2) dialysis | Recovery
Sato et al. [60]	1	59-year-old male with tracheal fistula	Aneurysm rupture and stent migration	V-V	Not specified	Not specified	Stent removal, attempt of bronchial artery embolization		Lethal multiorgan failure

Cantwell et al. [32]	1	39-year-old male with leptospirosis hemoptysis	Diffuse bilateral hemorrhage	V-V, 8d	Not specified	Not specified	Additional membrane oxygenator blood flow about 8L/min	Epistaxis, uveitis pseudoaneurysm right femoral artery	Recovery
Pais et al. [57]	1	38-year-old female with SLE, hemoptysis	Diffuse alveolar hemorrhage	V-A, 3d	Not specified	Not mentioned, unknown coating	Plasmapheresis	Not mentioned	Recovery
Lee et al. [50]	1	56-year-old male with warfarin prior to pulmonary vein thrombosis	Diffuse alveolar hemorrhage	V-V, 5.25 d	INR 1.25-1.43 aPTT 21-33sec	No heparin Unknown coating			Recovery
Zhong et al. [66]	1	50-year-old female with microscopic polyangiitis	Diffuse alveolar hemorrhage	V-V, 12d	ACT 120-200	Heparin	Plasmapheresis Hemodialysis		Recovery
Daimon et al. [36]	1	49-year-old male with Goodpasture syndrome	Diffuse alveolar hemorrhage	Not specified 3d	ACT 150	Nafamostat mesilate	Methylprednisolone Plasmapheresis	Pulmonary rebleeding	Lethal respiratory failure
Morneault et al. [54]	1	24 hrs old infant with pneumonia coagulopathy	Bleeding via tracheal tube	V-V, 9d	ACT 160-180	Heparin Polyvinylchloride tubing	Aminocaproic acid Platelet transfusion		Recovery

Abbreviations: ACT = activated clotting time, ARDS = acute respiratory distress syndrome, aPTT = activated partial thromboplastin time, d = days, ECLS = extracorporeal life support, h = hours, N = number of patients, PFO = persistent foramen ovale, V-V = veno-venous, V-A = veno-arterial, V-VA = veno-veno-arterial, PE = pulmonary embolism, sec = seconds, "→" ECLS mode conversion, SLE = systemic lupus erythematosus

Table 6. *Extracorporeal life support in bleeding trauma patients*

Author	N	Age (y)	Injury pattern	Trauma specific treatment	ECLS Indication	Anticoagulation targets	ECLS mode duration (h)	Bleeding management on ECLS	Complications
Gatti et al. [78]	1	27	Penetrating injury	Chest drain	Cardiac arrest in bleeding	No heparin during ECLS	V-A, 1.9	350U/kg of heparin after ECLS Repair ventricular wall and coronary vessels	
Forten-berry et al. [77]	8	12,5 mean	Gunshot wound Traffic road accidents Blunt abdominal trauma multiple extremity injury	Damage control surgery	Respiratory failure hemodynamic instability	ACT 180-200 sec in bleeding 160-180 anticoagulation not specified	6 V-V 1 V-V→V-A 1 V-A 283.2 mean	Epsilon-aminocaproic acid in seven patients Aprotinin in two pts	Re-bleeding in seven pts Two lethal fat embolisms Hemofiltration in five pts
Huh et al. [79]	5	28-48	Blunt and penetrating chest trauma	Thoracotomy pericardiotomy	Hemodynamic failure	ACT 150-200 sec	5 V-A, 1.3 – 3	No heparin priming	Cerebral infarction with minor impairment
Park et al. [85]	1	40	Blunt chest trauma intracerebral hemorrhage	Not specified	Respiratory failure	Blood flow 4-5L/min	V-V, 264	Heparin coating no anti-coagulation Endobronchial clocking, Surgicell	
Jacobs et al. [80]	32**	28.9 ±1.1	Blunt chest and abdominal trauma Intracranial hemorrhage pelvic and femur fractures	Damage control surgery in 20 pts	Not specified	Not specified	V-V | V-A 207.4 mean	Surgery in 12 pts on ECLS	Five (15.6%) hemorrhagic complications Nine deaths not specified
Lee et al. [81]	1	21	Rupture of descending thoracic aorta and abdominal trauma	Laparotomy thoracotomy, aortic endograft stenting	Cardiac and respiratory failure	Not mentioned	V-VA, 264	No heparin during ECLS	Pericardial effusion drained
Liao et al. [51]	1	29	Blunt abdominal and chest trauma		Respiratory failure	ACT 180-250 sec aPTT 35-40 sec	V-V, 242	The first 24h no heparin was given in a heparin coated circuit	Clotting
Masiakos et al [83]	1	44	Blunt chest trauma	Chest drains Cardiopulmonary resuscitation	Pulmonary and cardiac failure	No anticoagulation	V-A, 168	Heparin bounded circuit	Bleeding on cannula site Tricuspid regurgitation due to cordea rupture
Reynolds et al. [87]	1	16	Chest trauma Brain contusions		Hypoxemia	No anticoagulation	V-V, 168	Middle lobe resection	Mild cognitive deficits
Yuan et al. [95]	2	18, 38	Blunt chest trauma		Respiratory failure	aPTT 40-60 sec	V-V, 240 V-V, 120	Bronchoscopy, angiography Lung separate ventilation	
Filippini et al. [76]	1	25	Blunt abdominal trauma bilateral lung contusion	Damage control surgery	ARDS	ECLS blood flow of 2 l/min to 4,5L/min	V-V, 192	Stenting vena cava injury, only heparin coated circuit, no systemic heparin	
Zhou et al. [96]	1	31	Blunt chest trauma, brain contusions and fractures of the right femur and spinous process	Damage control surgery	Hypoxemia and hypercapnia	ACT 140-180 sec ACT 120 sec after surgery	V-A, 9.1	Continuous renal replacement Damage control surgery	Vision decrease
Arlt et al. [74]	10	34.8 mean	Severe trauma with coexisting bleeding shock	Resuscitation	Hypoxemia, persistent cardiocirculatory shock	aPTT 2x normal, ACT >150sec ACT 120-140 sec after surgery	7 V-V 3 V-A Range 48-264	Heparin free initially, finally low dose heparin 5.000 units per day Damage control surgery in eight pts	Four lethal retroperitoneal bleeding Three lethal septic multiorgan failure
Sasadeusz et al. [89]	1	19	Third degree burns with blunt chest and abdominal trauma	Damage control surgery	Hypoxemia and cardiac failure	ACT 175-225 sec	Not specified 24	Heparin bonded circuit Re-warming Nitric oxygen ventilation	Deep vein thrombosis

Robba et al. [88]	4	31-58	Blunt chest and abdominal trauma, subarachnoid hemorrhage, long bone fractures	Vasopressin, chest drains, hypothermia	Hypoxemia	ACT <150sec	V-V, 48 - 144	One bolus of heparin	Lethal increase in intracerebral pressure
Voelckel et al. [93]	2	12,29	Blunt chest trauma	Chest drain	Respiratory failure	ACT 120-140 sec	Not specified 96 - 144	Heparin coated circuit Damage control surgery	
Madershahian et al. [82]	3	19-26	Blunt chest and abdominal trauma, brain injury, multiple fractures	Damage control laparotomy	Respiratory failure Hemodynamic	ACT 110-140 sec	V-A, 138 V-A, 120 V-VA, 84	Upper lobe resection in bronchial rupture	
Perchin-sky et al. [86]	6		Five patients with severe abdominal injuries and three with brain injury		Bleeding and hypoxemia	Not specified	6 V-A 5.3 - 23.7	Heparin bounded circuit Nephrectomy and damage control surgery	Three lethal coagulopathies Lower extremity amputation
Anton et al. [73]	1	8	Blunt chest and abdominal trauma	Chest drains	Respiratory failure	ACT 160-170 sec pTT 70-80 sec anti-Xa 0.3-0.4	V-V, 264	Aminocaproic acid	Bleeding on chest tube craniotomy due to intracranial bleeding
Stroehle et al. [92]	1	17	Blunt chest trauma		Respiratory failure	ACT >120 sec	V-V, 144	Aortal stenting in dissection	Extremity ischemia, vein thrombosis, cerebral edema intrapleural hematoma neurological impairment
Stoll et al. [91]	1	18	Blunt chest trauma	Chest tube	Respiratory failure	Not specified	V-V, 168	Initial no anticoagulation, heparin free time unknown, heparin bounded circuit	
Biderman et al. [75]	5	28-33-27 22-32	Blunt chest and abdominal injuries, penetrating cardiac injury, three intracranial hemorrhages Multiple long bone and rib fractures		Not specified	Not specified	228 median	No heparin in the first 48 hours recombinant factor VII	Bleeding cannulation site accidental cannula removal Two pneumothoraxes due to bronchopleural fistula Two lethal septic shock
Skarda et al. [90]	3	8, 15, 17	Blunt chest and abdominal trauma, brain injury	Resuscitation damage control surgery	Respiratory failure circulatory arrest	Anti Xa	V-V | V-A 144 -192		Right radial nerve injury Single eye blindness
Muellen-bach et al. [84]	3	16, 28, 53	Chest and abdominal injury, brain injury	Damage control surgery	Respiratory failure	aPTT 40-50 sec	V-V, 72-192	Five days heparin free, heparin bounded circuit, recombinant factor VII Damage control surgery	
Willms et al. [94]	1	18	Blunt chest trauma	Chest drains	Respiratory failure	ACT 110-150 sec	V-V, 69	Heparin bounded circuit, thoracotomy mainstem bronchus repair	

Abbreviations: ACT = activated clotting time, aPTT = activated partial thromboplastin time, ECLS = extracorporeal life support, N = number of patients, V-V = veno-venous, V-A = veno-arterial, V-VA = veno-veno-arterial, pts = patients, sec = seconds, y = years, "→" ECLS mode conversion.

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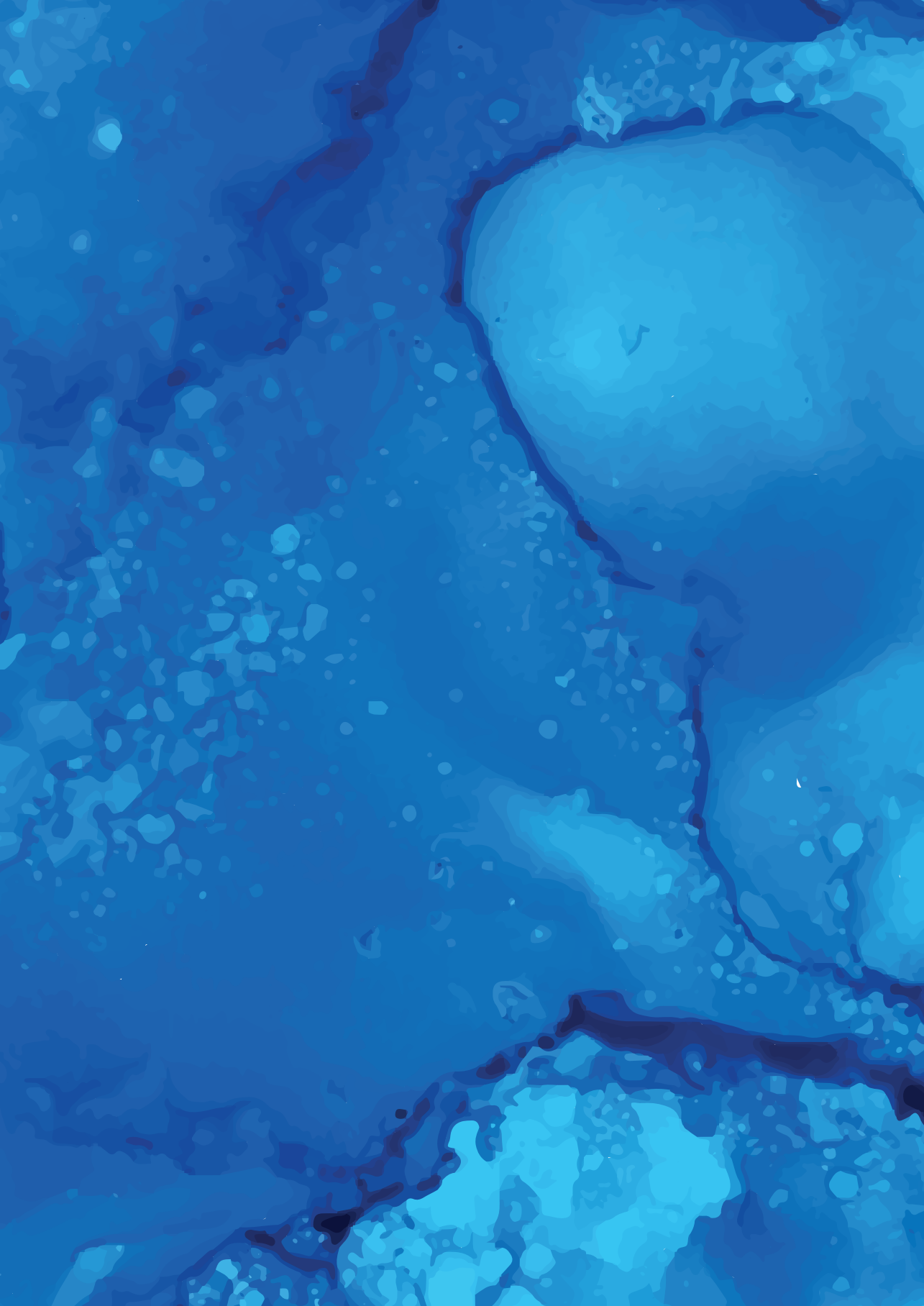

3

Longitudinal trends in bleeding complications on extracorporeal life support over the past two decades - Extracorporeal Life Support Organization registry analysis

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Abstract

Objective: Data about inhospital outcomes in bleeding complications during extracorporeal life support (ECLS) have been poorly investigated
Design: Retrospective observational study
Setting: Patients reported in Extracorporeal Life Support Organization

Patients: Data of 53.644 adult patients (greater than or equal to 18 yr old) mean age 51.4±15.9 years, 33.859 (64.5%) male supported with single ECLS run between 01.01.2000 and 31.03.2020, and 19.748 cannulated for veno-venous (V-V) ECLS and 30.696 for venoarterial (V-A) ECLS.
Interventions: Trends in bleeding complications, bleeding risk factors, and mortality

Measurement and Main Results: Bleeding complications were reported in 14.786 patients (27.6%), more often in V-A ECLS compared with V-V (30.0% vs 21.9%; $p < 0.001$). Hospital survival in those who developed bleeding complications was lower in both V-V ECLS (49.6% vs 66.6%; $p < 0.001$) and V-A ECLS (33.9 vs 44.9%; $p < 0.001$). Steady decrease in bleeding complications in V-V and V-A ECLS was observed over the past 20 years (coef., –1.124; $p < 0.001$ and –1.661; $p < 0.001$). No change in mortality rates was reported over time in V-V or V-A ECLS (coef., –0.147; $p = 0.442$ and coef., –0.195; $p = 0.139$).
Multivariate regression revealed advanced age, ecls duration, surgical cannulation, renal replacement therapy, prone positioning as independent bleeding predictors in V-V ECLS and female gender, ecls duration, pre-ecls arrest or bridge to transplant, therapeutic hypothermia, and surgical cannulation in V-A ECLS.

Conclusion: A steady decrease in bleeding over the last 20 years, mostly attributable to surgical and cannula-site–related bleeding has been found in this large cohort of patients receiving ECLS support. However, there is not enough data to attribute the decreasing trends in bleeding to technological refinements alone.Especially reduction in cannulation site bleeding is also due to changes in timing, patient selection, and ultrasound guided percutaneous cannulation. Other types of bleeding, such as CNS, have remained stable, and overall bleeding remains associated with a persistent increase in mortality

Keywords: anticoagulation; bleeding complications; ECLS; extracorporeal membrane oxygenation; Extracorporeal Life Support; registry data

Introduction

In the past decades, Extracorporeal Life Support (ECLS)–related technology and systems have improved remarkably. Roller pumps have been replaced by centrifugal pumps; surfaces of artificial lung membranes and circuit tubing have been advanced due to heparin-coated surfaces or biocompatible surfaces, and more attention has been paid to anticoagulation management and related disorders [1–6]. Despite these advances, bleeding remains a frequent complication with an occurrence rate up to 25% and is associated with increased morbidity and mortality [7–12]. When examining the current literature, standardized definitions and a lack of a comprehensive assessment of bleeding occurrence rate over time are missing. To address this limitation, we performed an analysis of the Extracorporeal Life Support Organization (ELSO) Registry to examine the trends in occurrence rate and risk factors in bleeding complications over the past 20 years in patients undergoing ECLS in venovenous (V-V ECLS) and venoarterial (V-A ECLS) modes across the world. The authors hypothesized decreasing rates of bleeding complications in ECLS, attributable to improvements in equipment development, for example, membrane surfaces as well as better understanding of anticoagulation management.

Materials and Methods

Data source and population

The ELSO Registry contains voluntarily reported data on more than 130,000 ECLS runs since 1989 [13, 14]. The data submission is standardized and ensures all mandatory fields are completed [15]. ELSO Registry data of adult patients (greater than or equal to 18 yr old) supported with ECLS between January 1, 2000, and March 31, 2020, were included. Patients with multiple ECLS runs were excluded to prevent bias of cumulative effects and dependency in the data. Overall characteristics contained patients with V-V ECLS, V-A ECLS, hybrid mode, conversion, and unknown configurations.

Statistical analysis

Comparative analysis covered runs of V-V or V-A ECLS. Means, continuous variables, and the independent-sample t test were used. Pearson chi-square test was used to compare categorical data, and the Fisher exact test in the case of expected count was less than five cells in 20% of the cells. Significance was set at a two-sided p value of less than 0.05. Uni- and multivariable logistic regressions were performed in the V-V and V-A ECLS group to evaluate predictive factors for bleeding. Associations were quantified as odds ratio including 95% CI. Variables with $p<0.20$ in the univariable analysis were considered potentially important predictors and were included in the multivariable logistic regression analysis. Linear regression analysis was used to test whether the percentages of bleeding complications and mortality

increased or decreased over the years. An additional comparison was made between the first and last decades to see whether there was a substantial difference in the last decade, since techniques have been changed in this time. Analyses were performed with the Statistical Package for the Social Sciences (SPSS) statistical software (Version 26.0, IBM, Armonk, NY).

Outcomes and co-variates

ELSO registry data definitions were used for data assessment with error and validity checks. Reported mortality was inhospital mortality. For analysis, patients discharged on ECLS were coded as alive as of the date of discharge; however, they were censored at the discharge date, as they remained at risk but were no longer observed.

The primary outcome was defined as the occurrence of any bleeding complication. ELSO Registry definitions of bleeding complications include requirement of packed RBC (PRBC) transfusion of greater than 20mL/kg/24hr or greater than 3 units/24hr, endoscopic interventions for bleeding, CT-, ultrasound- or MRI imaging for gastrointestinal, cannulation site, surgical site, CNS, and pulmonary bleeding complications.

Secondary outcomes were different types of bleeding complications, including gastrointestinal, pulmonary, CNS, cannulation and surgical site bleeding, and tamponade due to bleeding.

Ethics committee approval

Each institution participating in ELSO Registry approves data reported to the registry through their local institutional review board. This study involved only analysis of preexisting deidentified data from an international registry, and as such, no ethics approval was required. Similarly, no patient consent was required. Deidentified data are available to member centers for scientific research and publication without need for further institutional research board approval.

Results

In total, 57.020 runs were identified. After exclusion of 3.376 multiple ECLS runs, data of 53.644 runs, and thus, patients were analyzed, among them 19.748 patients received V-V ECLS, 30.696 patients V-A ECLS, 596 patients underwent ECLS with a hybrid configuration, 1.991 with conversion of configuration, and 613 with unknown configuration. Of the total cohort, the mean age was 51.4 years (±sd, 15.9 yr), and 64.5% were male. Mean weight was 85.4kg (±sd, 25.6) and height 170.7cm (±sd, 11.0), with a calculated body mass index (BMI) of 29.7 (±sd, 10.5). Overall, mean duration of ECLS was 8.2 days (± sd 11.5). V-V ECLS patients were younger, had a

higher BMI, and were supported longer and their inhospital survival was significantly higher compared with V-A ECLS group. (Table 1)

Overall bleeding complications were reported in 27.6% and occurred more often in V-A ECLS (30.0%) compared with V-V (21.9%) ($p < 0.001$). However, CNS and pulmonary hemorrhage occurred more often in V-V ECLS (3.4% and 3.9%) than in V-A ECLS (2.2% and 2.3%); $p < 0.001$. (Table 1)

Characteristics bleeding and non-bleeding groups

ECLS duration was significantly longer in both, V-V and V-A ECLS if bleeding complications occurred. (Table 2) In the V-V group, duration of ECLS run, and surgical cannulation were independently associated with bleeding complications. Other independent bleeding predictors included pre-ECLS support with cardiopulmonary bypass (CPB) and renal replacement therapy (RRT), vasodilatory agents and anti-hypotensive agents. Increasing age was associated with lower risk of bleeding, especially if categorized in 10-year groups. In the V-A group, independent associated factors included female sex, ECLS duration and surgical cannulation, pre-ECLS support with CPB, vasodilatory agents and anti-hypotensive agents. (Table 3)

Temporal trend of bleeding complications

In V-V and V-A groups, bleeding complications decreased significantly with 1.124% per year (95% CI 0.750-1.497%), $p<0.001$ and 1.661% per year (95% CI 1.960 - 1.362%), $p<0.001$. (Table 3) In V-V ECLS, bleeding complications declined to 15.5% with a negative coefficient of 1.124 (95% CI 0.750 - 1.497, $p<0.001$) between 2010 and 2019. (Figure 1, Table 4, 5) A steady decrease in bleeding complications in V-A group was noticeable since 2013. Between 2010 and 2019, the decrease coefficient of bleeding complications was 1.945 (95% CI 1.303 – 2.587, p 0.001) in V-A ECLS. (Figure 1, Table 4, 5)

Table 1. *Patient characteristics, pre-cannulation support and bleeding complications in overall cohort and veno-venous and veno-arterial extracorporeal life support*

	All patients N=53644	Veno - Venous ECLS N=19748	Veno -Arterial ECLS N=30696	P value
Characteristics				
Sex male n (%)	33.930 (64.5)	11752 (60.6)	20200 (67.2)	<0.001
Weight KG (±SD)	85.389 (25.551)	87.999 (28.894)	83.598 (22.975)	<0.001
Height cm (±SD)	170.650 (11.025)	170.086 (11.059)	170.973 (10.941)	0.383
Body Mass Index (±SD)	29.740 (10.543)	30.717 (11.597)	29.077 (9.939)	<0.001
Age categories	-	-	-	<0.001
18-40 years	13.795 (25.7)	6964 (35.3)	5943 (19.4)	-
40.1-60 years	21.536 (40.1)	8221 (41.6)	12010 (39.1)	-
60.1-80 years	17.485 (32.6)	4495 (22.8)	12004 (39.1)	-
80 or older	828 (1.5)	68 (0.3)	739 (2.4)	-
Days on ECLS mean (±SD)	8.228 (11.464)	11.656 (14.340)	5.584 (7.380)	<0.001
Pre-ECLS cardiac arrest n (%)	16.167 (30.1)	1750 (8.9)	13433 (43.8)	<0.001
Bridge to transplant n (%)	2.916 (5.4)	1028 (5.2)	1620 (5.3)	0.724
Surgical cannulation	15.085 (28.1)	2073 (10.5)	11.783 (38.4)	<0.001
Reported pre-extracorporeal life support				
CPB n (%)	5.896 (11.0)	579 (2.9)	4853 (15.8)	<0.001
VADs n (%)	9.347 (17.4)	514 (2.6)	829 (26.7)	<0.001
Berlin heart n (%)	*6 (0.0)*	*0 (0)*	*6 (0.0)*	*0.088*
BiVAD n (%)	*122 (0.2)*	*36 (0.2)*	*64 (0.2)*	*0.518*
LVAD n (%)	*1.452 (2.7)*	*175 (0.9)*	*1155 (3.8)*	*<0.001*
RVAD n (%)	*336 (0.6)*	*117 (0.6)*	*171 (0.6)*	*0.607*
PVAD n (%)	*1.241 (2.3)*	*54 (0.3)*	*1065 (3.5)*	*<0.001*
IABP n (%)	*6.926 (12.9)*	*267 (1.4)*	*6274 (20.4)*	*<0.001*
Cardiac pacemaker n (%)	2.308 (4.3)	166 (0.8)	1992 (6.5)	<0.001
RRT n (%)	3.445 (6.4)	1466 (7.4)	1725 (5.6)	<0.001
Prone positioning n (%)	1.228 (2.3)	1091 (5.5)	55 (0.2)	<0.001
Therapeutic hypothermia n (%)	734 (1.4)	110 (0.6)	561 (1.8)	<0.001
Beta-blockage n (%)	282 (0.5)	91 (0.4)	181 (0.6)	0.006
Vasodilatory agents n (%)	6.707 (12.5)	2976 (15.1)	3221 (10.5)	<0.001
Anti-hypotensive agents n (%)	36.468 (68.0)	11665 (59.1)	22517 (73.4)	<0.001
Patient outcomes				
Bleeding overall n (%)	14.786 (27.6)	4332 (21.9)	9202 (30.0)	<0.001
Gastro-intestinal hemorrhage n (%)	*2.452 (4.6)*	*976 (4.9)*	*1234 (4.0)*	*<0.001*
Cannulation site bleeding n (%)	*6.456 (12.03)*	*1.537 (7.78)*	*4.359 (14.20)*	*<0.001*
Surgical site bleeding n (%)	*5.615 (10.5)*	*1232 (6.2)*	*3886 (12.7)*	*<0.001*
Pulmonary hemorrhage n (%)	*1.709 (3.2)*	*777 (3.9)*	*721 (2.3)*	*<0.001*
Tamponade bleeding n (%)	*1.396 (2.6)*	*183 (0.9)*	*1061 (3.5)*	*<0.001*
Central nervous system hemorrhage n (%)	*15.04 (2.8)*	*681 (3.4)*	*683 (2.2)*	*<0.001*
Discharged alive n (%)	26.482 (49.4)	12.422 (62.9)	12.760 (41.6)	<0.001

Abbreviations: ECLS; extracorporeal life support, V-V; veno-venous, V-A; veno-arterial, CPB; cardiopulmonary bypass, VADs; ventricular assist device, BiVAD; biventricular assist device, LVAD; left ventricular assist device, RVAD; right ventricular assist device, PVAD; percutaneous ventricular assist device, IABP; intra-aortic balloon pump, RRT; renal replacement therapy

Table 2. *Characteristics and outcomes of bleeding and non-bleeding patients separated in veno-venous and veno-arterial extracorporeal life support groups*

Patient Characteristics	***Veno - venous ECLS***			***Veno - arterial ECLS***		
Variables	**No bleeding N=15416 (78.1%)**	**Bleeding N=4332 (21.9%)**	***P* value**	**No bleeding N= 21494 (70.0%)**	**Bleeding N= 9202 (30.0%)**	***P* value**
Patient characteristics						
Sex male, *n* (%)	9174 (60.8)	2578 (60.0)	0.947	14206 (67.8)	5994 (65.6)	<0.001
Weight, *kg* (±SD)	88.3 (28.9)	87.0 (28.8)	0.525	83.6 (22.9)	83.6 (23.0)	0.459
Length, *cm* (±SD)	170.2 (11.0	169.6 (11.2)	0.151	171.1 (10.8)	170.7 (11.3)	0.038
Body mass index (±SD)	30.8 (11.8)	30.4 (10.7)	0.752	29.0 (9.3)	29.3 (11.5)	0.410
Age categories			<0.001			0.056
18-40 yr	5362 (34.8)	1602 (37.0)	-	4137 (19.2)	1806 (19.6)	-
40.1-60 yr	6397 (41.5)	1824 (42.1)	-	8512 (39.6)	3498 (38.0)	-
60.1-80 yr	3597 (23.3)	898 (20.7)	-	8342 (38.8)	3662 (39.8)	-
80 or older	60 (0.4)	8 (0.2)	-	503 (2.3)	236 (2.6)	-
Days on ECLS (±SD)	10.3 (12.3)	16.5 (19.3)	<0.001	5.0 (6.7)	6.9 (8.7)	<0.001
Pre-ECLS cardiac arrest, *n* (%)	1411 (9.2)	339 (7.8)	0.007	9524 (44.3)	3909 (42.5)	0.003
Bridge to transplant, *n* (%)	797 (5.2)	231 (5.3)	0.671	1171 (5.4)	449 (4.9)	0.043
Surgical cannulation, *n* (%)	1481 (9.6)	592 (13.7)	<0.001	7148 (33.3)	4635 (50.4)	<0.001
Pre-ECLS interventions						
Cardiopulmonary bypass, *n* (%)	430 (2.8)	149 (3.4)	0.025	2619 (12.2)	2234 (24.3)	<0.001
Ventricular assist devices, *n* (%)	382 (2.5)	132 (3.0)	0.038	5286 (24.6)	2923 (31.8)	<0.001
Berlin heart, n (%)	-	-	-	*3 (0.0)*	*3 (0.0)*	*0.373*
Biventricular assist device, n (%)	*25 (0.2)*	*11 (0.3)*	*0.211*	*37 (0.2)*	*27 (0.3)*	*0.037*
Left ventricular assist device, n (%)	*124 (0.8)*	*51 (1.2)*	*0.021*	*722 (3.4)*	*433 (4.7)*	<0.001
Right ventricular assist device, n (%)	*92 (0.6)*	*25 (0.6)*	*0.881*	*115 (0.5)*	*56 (0.6)*	*0.453*
Percutaneous ventricular assist device, n (%)	*44 (0.3)*	*10 (0.2)*	*0.543*	*727 (3.4)*	*338 (3.7)*	*0.207*
Intra-aortic balloon pump, n (%)	*196 (1.3)*	*71 (1.6)*	*0.064*	*4000 (18.6)*	*2274 (24.7)*	<0.001
Cardiac pacemaker, *n* (%)	121 (0.8)	45 (1.0)	0.106	1185 (5.5)	807 (8.8)	<0.001
Renal replacement therapy, *n* (%)	1081 (7.0)	385 (8.9)	<0.001	1184 (5.5)	541 (5.9)	0.203
Prone positioning, *n* (%)	825 (5.4)	266 (6.1)	0.045	40 (0.2)	15 (0.2)	0.762
Therapeutic hypothermia, *n* (%)	86 (0.6)	24 (0.6)	0.976	342 (1.6)	219 (2.4)	<0.001
Beta-blockage, *n* (%)	65 (0.4)	16 (0.4)	0.634	132 (0.6)	49 (0.5)	0.415
Vasodilatory agents, *n* (%)	2078 (13.5)	898 (20.7)	<0.001	1954 (9.1)	1267 (13.8)	<0.001
Anti-hypotensive agents, *n* (%)	8810 (57.1)	2855 (65.9)	<0.001	15215 (70.8)	7302 (79.4)	<0.001
Outcomes						
Mechanical complications, *n* (%)	2.794 (18.1)	1.532 (35.4)	<0.001	2538 (11.8)	2133 (23.2)	<0.001
Renal complications, *n* (%)	4.709 (30.5)	2.261 (52.2)	<0.001	6.688 (31.1)	5.011 (54.5)	<0.001
Infection, *n* (%)	1261 (8.2)	895 (20.7)	<0.001	1.321 (6.1)	1.102 (12.0)	<0.001
Limb complications[a], *n* (%)	143 (0.9)	78 (1.8)	<0.001	1.134 (5.3)	745 (8.1)	<0.001
Discharged alive, *n* (%)	10272 (66.6)	2150 (49.6)	<0.001	9641 (44.9)	3.119 (33.9)	<0.001

Abbreviations: ECLS; extracorporeal life support

[a]Limb complications including limb ischemia, compartment syndrome, fasciotomy, and amputation

Table 3. *Binary logistic regression analysis for occurrence of bleeding complications occurrence in veno-venous and veno-arterial extracorporeal life support*

		Univariable			Multivariable	
Variables	**OR**	**CI 95%**	***p***	**OR**	**CI 95%**	***p***
Veno-venous ECLS						
Sex female	1.035	0.966-1.109	0.330			
Weight in kilograms	0.998	0.997-1.000	0.010	1.000	0.999-1.001	0.737
Age categories	0.914	0.874-0.955	<0.001	0.949	0.904-0.995	0.032
Weeks on ECLS	1.215	1.194-1.236	<0.001	1.234	1.212-1.257	<0.001
Pre-ECLS cardiac arrest	0.843	0.745-0.954	0.007	0.955	0.837-1.089	0.494
Bridge to transplant	1.033	0.889-1.201	0.671			
Surgical cannulation	1.489	1.345-1.649	<0.001	1.224	1.095-1.360	<0.001
Pre-ECLS cardiopulmonary bypass	1.241	1.027-1.500	0.025	1.487	1.214-1.822	<0.001
Pre-ECLS ventricular assist devices	1.237	1.012-1.512	0.038	1.137	0.909-1.423	0.260
Pre-ECLS cardiac pacemaker	1.327	0.941-1.871	0.107	1.162	0.806-1.676	0.421
Pre-ECLS renal replacement therapy	1.293	1.145-1.461	<0.001	1.339	1.174-1.526	<0.001
Prone positioning	1.157	1.003-1.334	0.045	1.353	1.161-1.577	<0.001
Therapeutic hypothermia	0.993	0.631-1.563	0.976			
Use of beta blockage	0.876	0.506-1.514	0.634			
Use of vasodilatory agents	1.678	1.539-1.831	<0.001	1.308	1.190-1.437	<0.001
Use of anti-hypotensive agents	1.449	1.351-1.555	<0.001	1.324	1.225-1.431	<0.001
Year on ECLS	0.915	0.907-0.924	<0.001	0.908	0.898-0.918	<0.001
Veno-arterial ECLS						
Sex female	1.106	1.050-1.165	<0.001	1.113	1.054-1.175	<0.001
Weight in kilograms	1.000	0.999-1.001	0.895			
Age categories	1.017	0.986-1.049	0.282			
Weeks on ECLS	1.275	1.242-1.309	<0.001	1.311	1.275-1.349	<0.001
Pre-ECLS cardiac arrest	0.928	0.884-0.975	0.003	1.142	1.082-1.205	<0.001
Bridge to transplant	0.890	0.796-0.995	0.041	0.777	0.689-0.877	<0.001
Surgical cannulation	2.037	1.938-2.141	<0.001	1.520	1.438-1.606	<0.001
Pre-ECLS cardiopulmonary bypass	2.311	2.170-2.460	<0.001	1.916	1.787-2.054	<0.001
Pre-ECLS ventricular assist devices	1.427	1.353-1.506	<0.001	1.225	1.157-1.298	<0.001
Pre-ECLS cardiac pacemaker	1.647	1.501-1.808	<0.001	1.272	1.152-1.406	<0.001
Pre-ECLS renal replacement therapy	0.196	0.965-1.190	0.196	1.057	0.946-1.180	0.327
Prone positioning	0.876	0.484-1.586	0.661			
Therapeutic hypothermia	1.508	1.270-1.790	<0.001	1.358	1.135-1.624	0.001
Use of betablockade	0.866	0.624-1.204	0.392			
Use of vasodilatory agents	1.597	1.481-1.722	<0.001	1.139	1.050-1.235	0.002
Use of anti-hypotensive agents	1.586	1.496-1.681	<0.001	1.228	1.153-1.308	<0.001
Year on ECLS	0.927	0.921-0.934	<0.001	0.935	0.929-0.942	<0.001

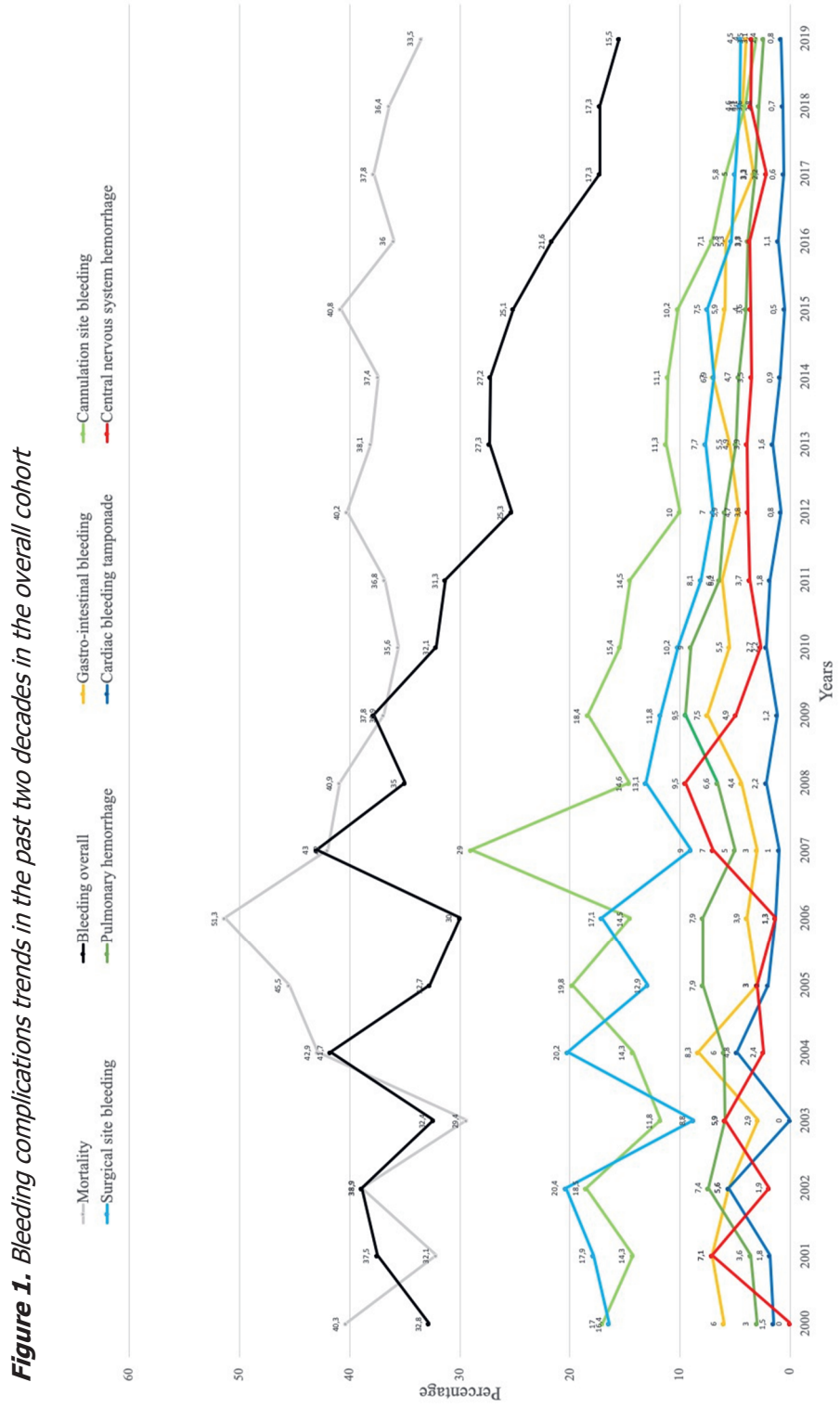


Figure 1. *Bleeding complications trends in the past two decades in the overall cohort*

Subtypes of bleeding complications

Cannulation site and surgical site bleeding were the most common bleeding complications, but markedly declined in the last 2 decades. (Table 4, 5) In contrast, central nervous system, gastrointestinal bleeding, and bleeding tamponade, all less frequent than the former bleeding complications, reached a stable rate between 2008 and 2010. (Figure 2) Compared to V-V group, in V-A ECLS cannulation site, surgical site and bleeding tamponade were more frequent. Gastro-intestinal, intracranial, and pulmonary hemorrhage were more frequent in V-V ECLS. (Table 1) In V-V ECLS, all subtypes of bleeding showed a decrease, of which tamponade bleeding, cannulation site and surgical site bleeding were significant, with negative coefficients of -0.112, -0.715 and -0.763 consecutively.

In V-A ECLS, gastro-intestinal and central nervous system showed a small increase of bleeding rates, of which gastro-intestinal bleeding was significant +0.165 (95% CI 0.033 - 0.296), p=0.017. All other bleeding complications showed a significant decreasing trend. (Figure 1, Table 4, 5)

Figure 2. *Indexed temporal trends of bleeding complications in the veno-venous and veno-arterial extracorporeal life support groups.*

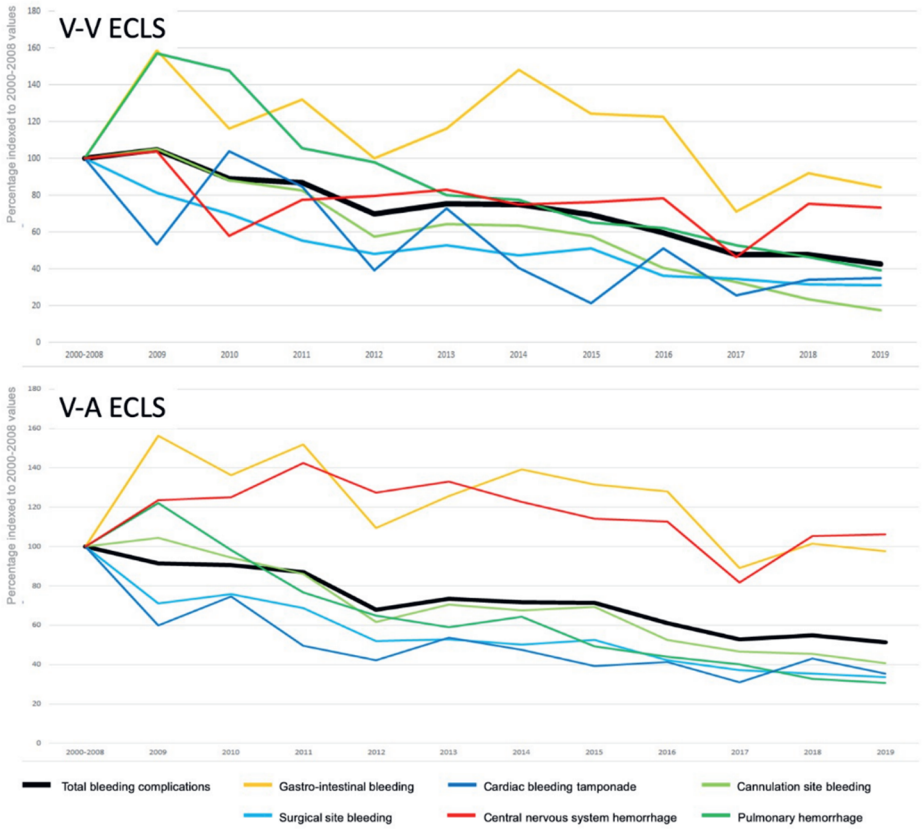


Table 4. *Trends of bleeding complications and mortality of veno-venous and veno-arterial extracorporeal life support in the past two decades (2000-2019)*

	Veno - venous ECLS				*Veno - arterial ECLS*			
	Direction trend	Coefficient	CI 95%	P value	Direction trend	Coefficient	CI 95%	P value
Mortality	D	0.147	-0.247 - 0.542	0.442	D	0.195	-0.070 - -0.460	0.139
Overall bleeding	D	1.124	0.750 - 1.497	<0.001	D	1.661	1.362 - 1.960	<0.001
GI bleeding	D	0.037	0.094 - 0.169	0.557	I	0.165	0.033 - 0.296	0.017
Cannulation bleeding	D	0.715	0.335 - 1.075	0.001	D	0.761	0.454 - 1.068	<0.001
Surgical bleeding	D	0.763	0.542 - 0.984	<0.001	D	1.450	1.247 - 1.652	<0.001
Pulmonary bleeding	D	0.138	0.025 - 0.300	0.093	D	0.290	0.114 - 0.465	0.003
Tamponade bleeding	D	0.112	0.013 - 0.211	0.029	D	0.530	0.376 - 0.684	<0.001
CNS bleeding	D	0.013	0.169 - 0.196	0.881	I	0.071	0.000 - 0.142	0.051

Abbreviations: ECLS; extracorporeal life support, CI; confidence interval, GI; gastro-intestinal, CNS; central nervous system, I; increase, D; decrease

Table 5. *Trends of bleeding complications and mortality veno-venous and veno-arterial extracorporeal life support groups overviewed in 2000-2009 and 2010-2019 decades*

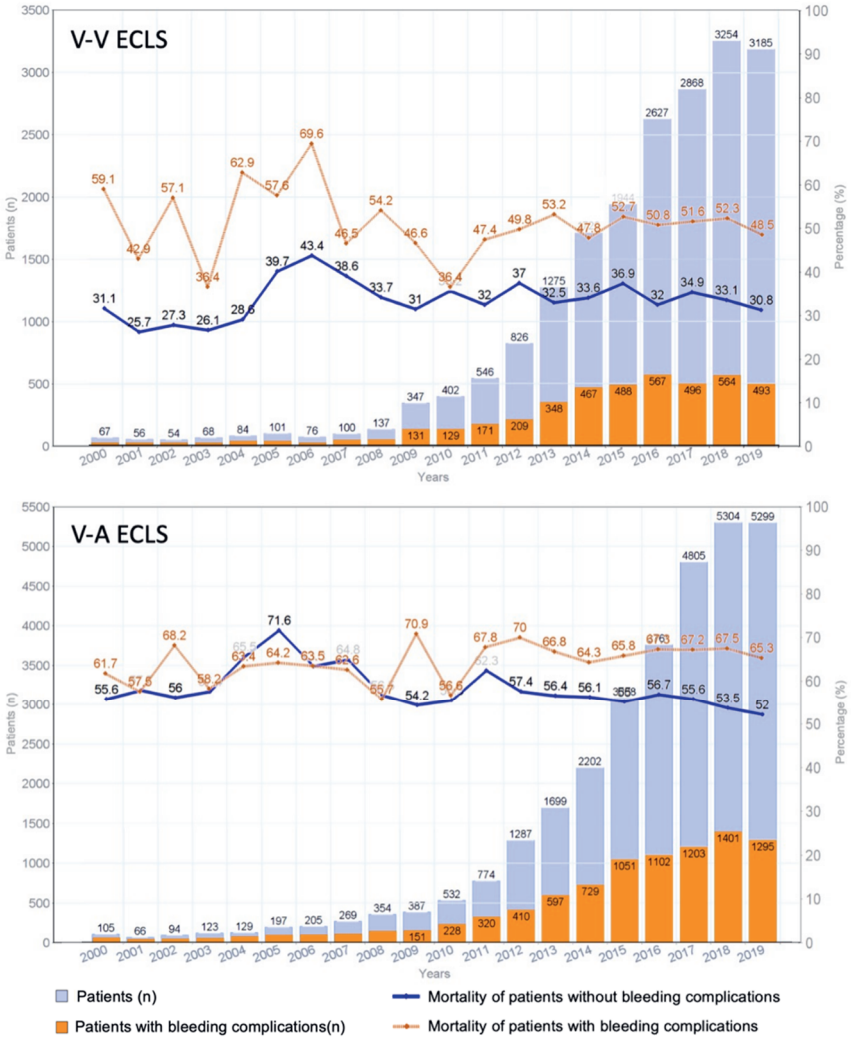
	2000 - 2009				2010 - 2019			
	Direction trend	Co-efficient	CI 95%	P-value	Direction trend	Co-efficient	CI 95%	P-value
Veno-venous ECLS								
Mortality	I	0.693	-0.905 – 2.291	0.346	D	0.218	-0.335 -0 .771	0.389
Overall bleeding	I	0.196	-0.938 - 1.329	0.701	D	1.858	-1.404 - 2.313	<0.001
GI bleeding	D	0.126	-0.408 - 0.660	0.602	D	0.204	-0.043 - 0.452	0.093
Cannulation bleeding	I	0.443	-0.808 - 1.694	0.438	D	1.325	1.027 - 1.623	<0.001
Surgical bleeding	D	0.690	-0.307 - 1.687	0.149	D	0.557	0.375 - 0.739	<0.001
Pulmonary bleeding	I	0.459	0.059 - 0.858	0.029	D	0.617	0.460 - 0.789	<0.001
Tamponade bleeding	D	0.132	-0.318 - 0.583	0.517	D	0.147	0.044 - 0.251	0.011
CNS bleeding	I	0.443	-1.182 - 0.296	0.204	D	0.160	- 0.126 – 0.158	0.801
Veno-arterial ECLS								
Mortality	I	0.227	-0.755 - 1.209	0.608	D	0.435	-0.203 - 1.074	0.155
Overall bleeding	D	2.098	0.956 - 3.240	0.003	D	1.945	1.303 - 2.587	<0.001
GI bleeding	I	0.513	0.091-0.935	0.023	D	0.221	0.077 – 0.366	0.008
Cannulation bleeding	D	0.243	1.033 - 1.519	0.672	D	1.111	0.700 - 1.522	<0.001
Surgical bleeding	D	2.202	1.623 - 2.781	<0.001	D	1.345	0.980 - 1.710	<0.001
Pulmonary bleeding	D	0.007	0.769 - 0.783	0.984	D	0.321	0.212 - 0.429	<0.001
Tamponade bleeding	D	1.027	0.499 - 1.554	0.002	D	0.248	0.109 - 0.387	0.003
CNS bleeding	D	0.044	0.180 - 0.268	0.662	D	0.158	0.098 - 0.218	<0.001

Abbreviations: CI; confidence interval, GI; gastro-intestinal, CNS; central nervous system, I; increase, D; decrease

Other complications and mortality in bleeding patients

In both V-A and V-V groups, patients with bleeding complications had a significantly higher incidence of mechanical complications, acute kidney injury and RRT and infections. In V-A support, limb ischemia, compartment syndrome, fasciotomy and amputation incidences were significantly higher in patients with bleeding complications. (Table 2) As might be expected, mortality was higher in patients with bleeding complications. In V-V ECLS, overall mortality was 50.4% in bleeding vs 33.4% ($p<0.001$) in non-bleeding patients. In V-A group, mortality was 66.1% in bleeding vs 55.1% ($p<0.001$) in non-bleeding patients. (Figure 3, Table 2)

Figure 3. *Mortality of bleeding and non-bleeding patients in veno-venous and veno-arterial extracorporeal life support patients over the past two decades*



Discussion

Bleeding complications during ECLS remain feared and frequent, and lead to high morbidity and mortality [1, 6, 17, 18]. Our analysis aimed to investigate the course of bleeding complications and mortality of bleeding patients in the past 20 years. Our main finding is a steady, overall decrease in bleeding complications during the last 20 years (figure 1), which was most relevant for surgical site and cannulation site–related bleeding in V-A and V-V ECLS. In the ELSO registry, overall cohort including all configurations, hybrid forms, and conversions bleeding complications amounted to 30%, and to 21.9% and 30.0% in V-V and V-A ECLS, respectively. Our findings regarding bleeding complications were consistent with previous literature [7–12]. A meta-analysis, including a majority of patients supported on V-A ECLS, revealed bleeding to be the most frequent complication (33%) besides requirement of renal replacement therapy (52%) and pneumonia (33%) [12]

Another meta-analysis including acute coronary syndrome patients on ECLS described bleeding event rate of 25% [10]. Meta-analyses in the postcardiotomy setting yielded the pooled rates of surgery due to bleeding complications of 42.9% and 50%, respectively [7, 11].

Although comparing the first and second decades, the decrease of bleeding complications was most significant in the last 10 years. (Figure 1) Finally, higher mortality was found in patients with bleeding complications during ECLS compared with patients without bleeding. Furthermore, we found a difference in subtypes of bleeding between the V-V and V-A groups. Cannulation site, surgical site, and tamponade bleeding occurred more often in V-A, whereas gastrointestinal, pulmonary hemorrhage, and brain hemorrhage were more observed in V-V ECLS. In addition, these differences deserve ad hoc investigations, particularly with regard to cerebral bleeding.

The occurrence rate of bleeding complications in V-A was higher than in V-V ECLS, even though V-V support and exposure to artificial surfaces were longer. This may be explained by a possibly higher risk for bleeding in arterial cannulation and more frequent pre-ECLS cardiac surgical procedures. Other authors reported that bleeding occurred more frequently than thrombo-embolism, and bleeding was associated with decrease.survival in V-V ECLS [1, 17–23]. Presumably, the higher

anticoagulation targets also may increase bleeding risk.

A bundle of physiologic responses and derangements occur with the patient's exposure to the artificial circuit that promotes thrombosis. Anticoagulation is typically needed to maintain patency of the extracorporeal circuit and to achieve a hemostatic balance during ECLS [24]. Although decreasing, hemocompatibility-related adverse events remain common during V-A ECLS and have a cumulative association with survival [25]. In addition, in V-V ECLS, bleeding is more frequent than thrombotic events and associated with decreased survival [6].

Cannulation site bleeding was the most frequent subtype of bleeding complications in the ELSO Registry cohort and was mainly observed in V-A ECLS; however, it decreased over the years. In addition, the venous site cannulation might play a role, as observed in the V-V group. Paden et al. [26] found cannulation bleeding complications in 17.2% and 20.9% of V-V and V-A ECLS, retrospectively. Higher rates of bleeding complications in V-V ECLS were found in the EOLIA trial (53%) [16] and of 22% in the ANZ-ECMO study [27]. Thus, cannulation site bleeding has been reported as high occurrence rate bleeding site, but literature is nonconclusive about arterial or venous cannulation site bleeding in terms of higher frequencies or risk for bleeding. A meta-analysis comparing peripheral and central cannulation did show a higher bleeding occurrence rate in central cannulation compared withperipheral cannulation (51.9% vs 32.9%) in postcardiotomy patients [28].

In the annual ELSO Registry report of 2012, surgical site bleeding percentages of 16.7% and 25% were observed in adults undergoing V-V and V-A ECLS, respectively [26], which is similar to our findings in terms of bleeding distribution between V-V and V-A ECLS. Cheng et al [8] conducted a meta-analysis of 1,866 adults and found a range of rethoracotomy due to bleeding or tamponade between 16.1% and 86.7% in V-A ECLS. In our analysis, surgical site bleeding in cumulative 20 years was 6.2% and 12.7% in V-A and V-V ECLS in our analysis, showing a possible decrease overall. This might be explained by the decreasing numbers of surgical site bleeding complications, especially in the last decade, due to improved surgical techniques, intensively coagulation monitoring perioperatively, and increasing trend to heparin-free ECLS runs postoperatively.

The report of gastrointestinal bleeding complications in ECLS varies considerably. Our data show gastrointestinal bleeding in 4.0% and 4.9% in V-A and V-V ECLS. Percentages of these bleeding complications can vary due to underdiagnoses and different definitions of gastrointestinal bleeding. In the literature, Otani et al [9] reported an occurrence rate of 24% after extracorporeal life support resuscitation. In postcardiotomy shock or cardiogenic shock and V-A support, an occurrence rate of 0.9% was found [29]. Reported occurrence rate of gastrointestinal bleeding in V-V ECLS ranges between 6.2% and 14% [27, 30–32] and may be causative for significant longer ECLS support and higher mortality [33, 34].

Previous ELSO registry analysis reported intracranial hemorrhage rates of 1.8% and 3.6% in V-A and V-V ECLS, respectively [18, 35], whereas this analysis showed 2.2% and 3.4% in V-A and V-V ECLS. In the EOLIA trial, hemorrhagic stroke occurred in 2% of the patients [16]. Other authors reported an occurrence rate of 9% up to 14.4% [27, 30]. Fletcher-Sandersjöo et al [19] reported preexisting anticoagulation as an additional risk factor for intracranial hemorrhage in a cohort

of 253 adults supported with V-V and V-A ECLS. The same authors performed a systematic review on the occurrence rate, outcomes, and predictors of ECLS-associated intracranial hemorrhage in adults. An increased risk of intracranial hemorrhage was associated with ECLS duration, therapeutic anticoagulation, altered intrinsic coagulation, renal failure, transfusion, and too quickly corrected hypercapnia [20]. Compared with other bleeding sources, no significant decrease over the last 2 decades was recorded in gastrointestinal bleeding or cerebral bleeding [36]. The reasons behind the variance in occurrence rate between V-V and V-A ECLS are presumably due to differences in risk factors and in the underlying clinical condition and comorbidities [20]. In V-A groups, factors related to cardiogenic shock (low cerebral blood flow, hypoxia, acidosis, and liver failure) and reperfusion injury at ECLS initiation may precipitate brain injury.

Our analysis is the first to show a steady decreasing trend in bleeding complications during ECLS. This could be related to a number of important temporal changes in the technology of ECLS, including the use of heparin-coated and biocompatible circuits for decreased activation of the coagulation cascade, allowing even heparin-free run for limited time [3, 37] and the use of shorter circuit tubes for decreased surface contact to reduce the risk of thromboembolic events that may have a protective effect reducing bleeding risk. In addition, modern ECLS devices include centrifugal pumps and a lower risk of hemolysis compared with roller pumps. If technology was main driver behind these trends, all types of bleeding should have possibly decreased, but as we do not have enough granular data, the complexities of device patient interactions, pathophysiology of ECMO, and iatrogenesis all intersect. However, some patients bleed more than the others. We also know that using the same technology, different centers are achieving different outcomes, so patient selection, timing decision to cannulation, improvements in clinical application, education, and experience all are at play. Anticoagulation policies may also have been adjusted due to advanced monitoring including viscoelastic tests of clotting function like thromboelastography (TEG) and rotational thromboelastrometry (ROTEM). Further, the use of ECLS has increased exponentially over the observation period, and it is possible that patients with different pathologies have been exposed to the treatment. In addition, this also might have led to an increase in expertise in high-volume centers, which resulted in an improved management of patients with bleeding risks and may have contributed to an improved outcome [38, 39]. Nevertheless, it is reasonable to hypothesize a causality on all discussed factors and conclude that this decrease in overall trend is multifactorial.

Risk factors for bleeding and thrombotic complications were identified in the previous ELSO Registry analysis performed by Chung et al [25]. In addition, Sy at al [40] evaluated the effect of anticoagulation in V-A ECLS on outcomes reporting the

prevalence of 27% for major bleeding and for inhospital mortality of 59% (95% CI, 52–67%; I2 = 78%). Nakasato et al [41] found thrombocytopenia, postcardiotomy extracorporeal support, pneumonia, previous antithrombotic therapy, platelet count decline, and age to be risk factors for bleeding complications.

The rate of bleeding complications changed over the years, but the lack of standardized definitions regarding the bleeding severity and amount of the blood was the main hurdle in comparing different cohorts. Burrell et al [42] described definitions of bleeding complications analyzing 28 publications investigating outcomes in V-A ECLS. The common definition was "requirement of RBC transfusion," with a threshold ranging from greater than 1 to greater than 5 units. "Surgery requirement," "gastroscopy," or "bleeding on cannulation or surgical site" are referred to bleeding complications [42].

Previous studies have largely been metanalyses of single-center studies. This article provides a clear overview in the development of bleeding complications during ECLS in the past 20 years and includes classification of bleeding into subtypes. A major strength of this study is the use of the largest database analysis on this topic, spanning multiple countries, and geographical regions, and it enables an unprecedented temporal analysis across the world. The use of a standardized data collection increases the generalizability of our findings. With steadily growing numbers of ECLS patients and a knowingly high rate of bleeding complications, this research topic is of high interest. The findings are largely confirmative with respect to previous findings of investigations with smaller patient numbers. However, employing the international ELSO registry for analyses with an impressive number of patients treated in numerous centers worldwide adds significant validity, not only to the approach of this study but furthermore and importantly to the findings, respectively.

This analysis has several limitations as observational design and retrospective aspect of the analyzed data, with corresponding missing data. The probability of experiencing a bleeding complication during ECLS therapy is inherently dependent on the time of being at risk for an ECLS-related bleeding complication, accounted for competing risks precluding the occurrence of the primary outcome (e.g., death or discharge), making interpretation of the results difficult. The outcome bleeding is influenced by changes of case-mix, which is likely to occur over 2 decades, and changes, as the authors hypothesize, of improvement of equipment and coagulation management. The ELSO Registry does not contain specific information on anticoagulation strategies, amount of blood loss, timing, impact, and pre-ECLS bleeding sites, which makes it difficult to understand the underlying mechanisms of bleeding and changes in the past 20 years. However, ELSO guidelines suggest that unfractionated heparin (or a similar antithrombotic agent) is administered as an initial bolus of 50–100 units/kg and a continual dose of 20–50

units/kg/hr to ensure an activated clotting time (ACT) range of 180–220 s [43]. Further, not all subtypes of bleeding are mandatory fields in the registry form, resulting in possible underestimation of the prevalence of certain types of bleeding complications. In addition, no variables regarding chronic and acute conditions are reported because these are not included in the ELSO database oriented more on process dedicated variables. Even the outcome bleeding is indirect derived from treatment and diagnostic proxies (number of PRBCs transfused or diagnostic for bleeding) remaining the main limitation of this analysis.

Nonetheless, it remains unclear whether the reduction in bleeding over time was due to changes in management, or differences in subsets of patients being treated with ECLS, or both. Whether further reduction in bleeding complications is possible by improving the ECLS systems or supportive therapy, or whether these complications are secondary to the clinical conditions of the patients, and determining the explanation for these trends, requires further dedicated research.

Conclusions

In this large cohort of patients receiving ECLS support, a steady decrease in bleeding has been found over the last 20 years, mostly attributable to surgical and cannula-site–related bleedings. However, there are not enough data to attribute the decreasing trends in bleeding to technological refinements alone. Especially reduction in cannulation site bleeding is also due to changes in timing, patient selection, and ultrasound-guided percutaneous cannulation. Other types of bleeding, such as CNS, have remained stable, and overall bleeding remains associated with a persistent increase in mortality. Further research perspective includes development of accurate and usable prediction models to manage anticoagulation and to prevent bleeding complications.

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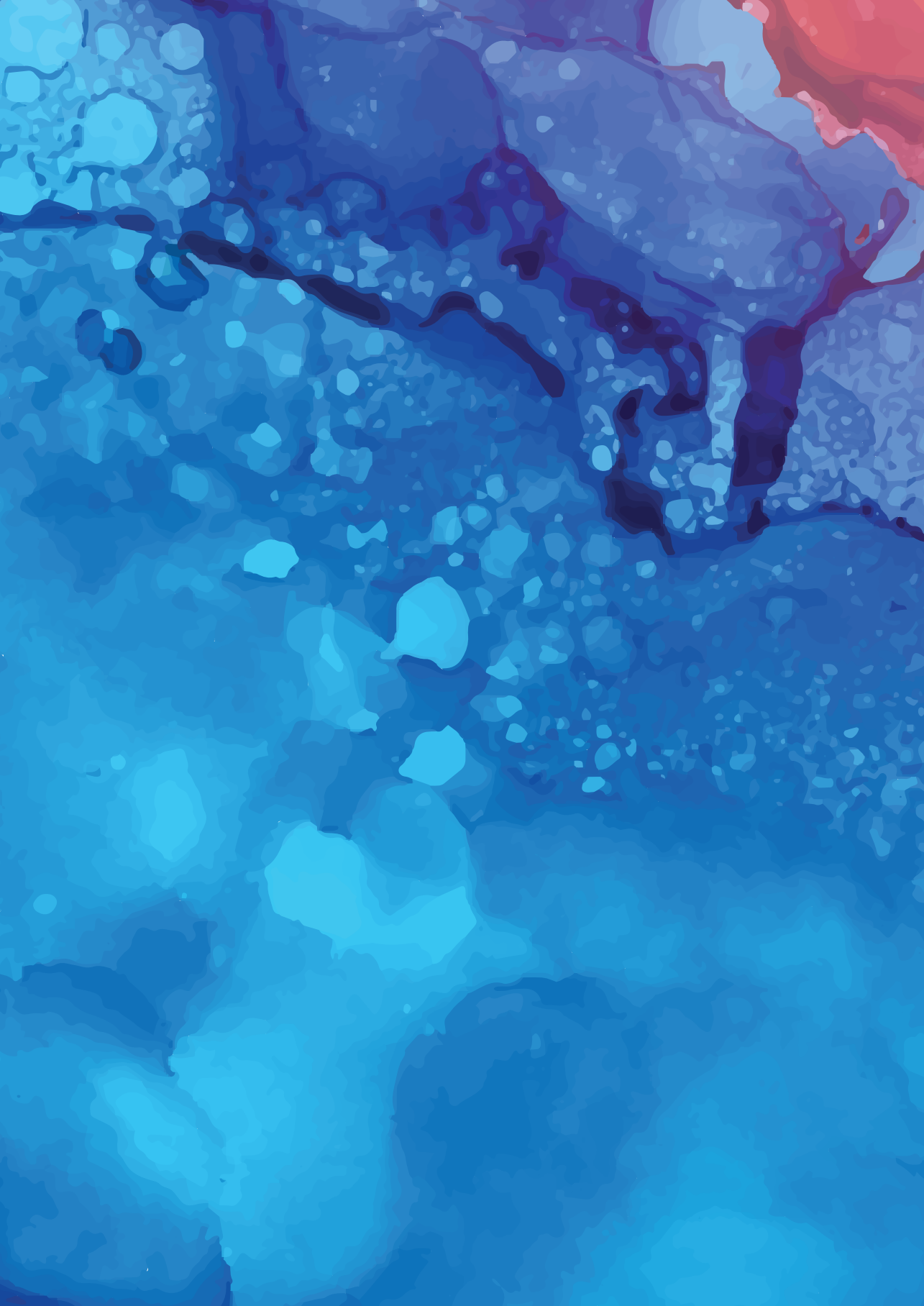

4

HEROES V-V
HEmoRrhagic cOmplications in Veno-Venous Extracorporeal life Support - Development and internal validation of a multivariable prediction model in adult patients

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Abstract

Background: During extracorporeal life support (ECLS), bleeding is one of the most frequent complications, associated with high morbidity and increased mortality, despite continuous improvements in devices and patient care. Risk factors for bleeding complications in veno-venous (V-V) ECLS applied for respiratory support have been poorly investigated.
We aim to develop and internally validate a prediction model to calculate the risk for bleeding complications in adult patients receiving V-V ECLS support.

Methods: Data from adult patients reported to the extracorporeal life support organization (ELSO) registry between the years 2010 and 2020 were analyzed. The primary outcome was bleeding complications recorded during V-V ECLS. Multivariable logistic regression with backward stepwise elimination was used to develop the predictive model. The performance of the model was tested by discriminative ability and calibration with receiver operating characteristic curves and visual inspection of the calibration plot.

Results: In total, 18658 adult patients were included, of which 3933 (21.1%) developed bleeding complications. The prediction model showed a prediction of bleeding complications with an AUC of 0.63. Pre-ECLS arrest, surgical cannulation, lactate, pO2, HCO3, ventilation rate, mean airway pressure, pre-ECLS cardiopulmonary bypass or renal replacement therapy, pre-ECLS surgical interventions, and different types of diagnosis were included in the prediction model.

Conclusions: The model is based on the largest cohort of V-V ECLS patients and reveals the most favorable predictive value addressing bleeding events given the predictors that are feasible and when compared to the current literature. This model will help identify patients at risk of bleeding complications, and decision making in terms of anticoagulation and hemostatic management.

Keywords: anticoagulation, bleeding complications, prediction model, registry data, veno-venous ext racorporeal life support, V-V ECLS

Introduction

Veno-venous (V-V) extracorporeal life support (ECLS) is used for respiratory support, most commonly for acute respiratory distress syndrome (ARDS), including respiratory failure due to COVID-19 [1–4]. However, bridge to lung transplant, pulmonary hemorrhage, and traumatic injury are also increasingly common indications [5,6]. Also, underlying diseases or conditions, such as vasculitis or trauma, may further contribute to the risk of bleeding [7–9].

Bleeding represents the most frequently reported adverse event during ECLS [10]. The pathophysiology of bleeding while on ECLS is complex, although not completely understood, [11] is likely multifactorial, depending on the exposure to artificial surfaces and anticoagulation. Underlying patients' primary diagnoses and/or comorbidities, such as vasculitis or trauma, may con- tribute to an increased risk of bleeding [6–9]. Artificial surfaces can trigger platelet and coagulation activation, ultimately giving rise to coagulation factor consumption leading to impaired hemostasis. Activation of platelets can lead to thrombi forming and secondary thrombocytopenia, but also to functional impairment. Furthermore, the priming of the circuit can dilute the coagulation factors and platelets as well [12]. Necessary systemic anticoagulation to avoid circuit clotting also modifies the inflammatory and prothrombotic responses on the non-endothelial surfaces of tubing and the oxygenator membranes [13]. However, there is a fine balance between bleeding complications and clotting of circuit components, [12] and excessive anticoagulation may lead to bleeding [14].

Bleeding complications remain frequent with high morbidity and mortality [11,15–20]. The reported incidence of bleeding complications ranges between 24% and 56% [18,21,22]. The management of these complications is complex, involving transfusion support and interventions to control bleeding. Contact of blood components to circuit tubes and membrane surfaces cause hemolysis which in conjunction with anticoagulation agents, perturbs balance of hemostasis [12, 23–31]. Transfusions are also associated with additional risks, including acute hemolytic reactions, allergic reactions, and transfusion- related lung injury [32–34]. It also has been shown that the utilization of red cell transfusion varies by a factor of three between V-V and V-A modalities [35]. A prediction of bleeding complications specific to V-V ECLS could enable clinicians to identify patients at higher risk of bleeding and allow adjustment of anticoagulation or correction of other modifiable risk factors to limit the need for blood transfusion.

There are no specific bleeding prediction scores for patients undergoing V-V ECLS. Studies validating prediction scores were based on a mixed cohort of V-V and veno- arterial (V-A) ECLS patients [16,36–38]. Thus, we aimed to develop and validate a prediction model for bleeding com- plications in adult patients receiving V-V ECLS support.

Methods

Data source and patient selection

International registry of ECLS cases among the member centers is maintained by the Extracorporeal Life Support Organization (ELSO). The ELSO Registry contains voluntarily reported data of more than 130 000 ECLS runs since 1989 [39,40]. More than 10 000 patients have entered into the ELSO Registry annually, from almost 500 active centers in 60 countries [41,42]. As a result of the significant changes in ECLS management over time, including changes in circuits and anticoagulation management, ELSO registry data of adult patients (≥18 years old) supported with V-V ECLS between January 1, 2010 and March 31, 2020 were chosen to be most representative of current practice for the development of the prediction model. Patients with multiple ECLS runs were excluded to prevent bias of cumulative effects and dependency in the data.

Variables analyzed included diagnosis, demographics, pre-ECLS and on-ECLS assessment, reported interventions, and complications. The data entry rules in the ELSO registry data definitions were used for data assessment with error and validity checks, for example, for the weight (<10 kg and >500 kg) and height (<70 cm and >250 cm) and blood gas analysis, hemodynamic blood pressures and ventilator settings [43]. The ELSO registry does not contain specific information on anticoagulation strategies, amount of blood loss, timing, impact, and pre-ECLS bleeding sites.

Co-variates and outcomes

Age was divided into categories of 18–40, 40.1–60, 60.1–80, and 80.1 years or older, as age above 80 was not reported as a continuous variable. Body mass index (BMI) was calculated as weight (kg)/squared height in meters. Variables were clustered as follows: ventricular assist devices (VAD) include Berlin Heart, biventricular assist device, left ventricular assist device, right ventricular assist device, and percutaneous ventricular assist device. Anti-hypotensive agents include the use of epinephrine, norepinephrine, dopamine, dobutamine, vasopressin, phenylephrine, metaraminol, and/or the old definition code for vasopressor/inotropics. Vasodilatory agents include nicardipine, nitroglycerine, nitroprusside, nitric oxide, sildenafil, tolazoline, and/or the old definition vasodilators codes. Pre-ECLS interventions and diagnosis were also clustered into groups based on current procedural terminology (CPT) codes for interventions and International Classification of Diseases (ICD) ICD-9 and ICD-10 codes for diagnosis. (Tables 1 and 2) The pre-ECLS assessment includes arterial blood gasses values, ventilator settings and hemodynamic values closest to ECLS start (within 6 h prior to ECLS start).

The primary outcome was defined as the occurrence of any bleeding complication. ELSO registry definitions of bleeding complications include the

requirement of red blood cell transfusion (RBCs) of >20 ml/kg/24 h or >3 Units/24 h, endoscopic interventions for bleeding, CT-, ultrasound- or MRI-imaging for gastro-intestinal, cannulation site, surgical site, central nervous system, and pulmonary bleeding complications. Tamponade bleeding was defined as cardiac tamponade during ECLS run requiring pericardial drainage or mediastinal washout of blood.

Statistical analysis

Demographic, clinical, pre-operative support and intervention details, and complications were compared between patients with or without bleeding complications, using the independent sample t-test for continuous variables and the Pearson's chi-square test for categorical variables. In case expected cell counts were less than 5, Fisher's exact test was used. Statistical significance was set at a two-sided p-value of less than 0.05.

The sample size was determined as the amount of available V-V ECLS adult patients in the ELSO registry between January 1, 2010 and March 31, 2020. The number of potential predictor variables was determined using the 10 events-per-variable rules of thumb [44].

Missing data were imputed using stochastic regression imputation using predictive mean matching. 18.658 missing values were identified in 16.657 (89.28%) cases due to many missing values in pre-ECLS lactate and mean air- way pressure values. As pre-lactate values and mean airway pressure were thought to be important predictors for bleeding complications, these variables were included in the imputation. (Table 3) Single imputation method was preferred as more feasible in such a large dataset compared to multiple imputation.

The development of the prediction model was per- formed according to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) Statement [45,46]. (Table 4)

Potential predictors were identified based on biological and clinical plausibility, as well as previously published risk factors for bleeding complications. We did not have an a priori hypothesis that one of the variables would have a non-linear association between the continuous variable and the outcome. Therefore, continuous predictors were modeled linearly.

Univariable logistic regression was used to assess the crude overall association of the variables, for example, between potential predictor variables and bleeding complications. Variables with $p < 0.20$ were considered important covariates and submitted to multivariable logistic regression analysis to assess the association of duration of ECLS and bleeding complications.

To ensure transparency of our model development, internal validation was performed separately. We included regression coefficients to calculate the model

and association measures like the odds ratio, which for face validity and are easier to understand for clinicians.

For the model, multivariable logistic regression analysis using backward Wald with stepwise elimination was used to arrive at a model with only independent predictors of bleeding complications and end up with the best significant predictors. All variables tested in the univariable regression analysis were used in the formation of the prediction model. For feasibility reasons, mean blood pressure, instead of systolic and diastolic pressure, pneumonia instead of specific types of pneumonia, and shock instead of specific types of shock, were included.

The performance of the prediction model was quantified as discriminative ability and calibration. Discrimination of the predictive model included the area under the receiver operating characteristic (ROC) curve with a 95% confidence interval or area under the ROC curve (AUC). An AUC of 0.5 indicates no discrimination; an AUC of 1 indicates perfect discrimination. A calibration plot was built and assessed visually. The calibration plot displays the agreement between the predicted probabilities and pseudo-observed event status and should follow a 45-degree line of perfect agreement.

Internal validation of the model

As the contribution of predictor variables to outcome prediction is often overestimated in model development, especially in performance among future patients. To address this, internal validation was performed using bootstrapping. This resulted in a constant that was subsequently used to shrink regression coefficients toward zero to prevent extreme predictions in future patients and second, a measure of optimism in the AUC which was subtracted from the apparent AUC to compute the optimism-corrected AUC.

Analyses were performed with commercially available statistical software SPSS (Version 26.0, IBM, Armonk, New York, USA) and R (Version 4.0.4 R Core Team (2017) R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 20 967 patients were supported with V-V ECLS during 2010–2020. Among them, 18 658 patients were included in the cohort after the exclusion of multiple ECLS runs. (Table 5)

Bleeding complications occurred in 3 933 patients (21.1%). Patients with bleeding complications were significantly smaller and had increased weight. (Table 5)

Table 5. *Characteristics of patients supported on veno-venous extracorporeal life support*

Characteristics		Total cohort n=18658 (100%)	Non-bleeding n= 14725 (78.9%)	Bleeding n= 3933 (21.1%)	*p* value
Patient characteristics	Male *n* (%)	11133 (60.9)	8793 (61.1)	2340 (60.0)	0.209
	Weight kg (±SD)	88.26 ±29.06	88.51 ± 29.03	87.32 ± 29.14	0.026
	Height cm (±SD)	170.09 ±11.06	170.19 ± 11.03	169.61 ± 11.20	0.045
	Body Mass Index	30.72 ± 11.60	30.80 ± 11.78	30.36 ± 10.71	0.151
	Age categories				0.030
	18-40 years *n* (%)	6394 (34.3)	5014 (34.1)	1380 (35.1)	
	40.1-60 years *n* (%)	7815 (41.9)	6139 (41.7)	1676 (42.6)	
	60.1-80 years *n* (%)	4383 (23.5)	3514 (23.9)	869 (22.1)	
	80.1 or older *n* (%)	66 (0.4)	58 (0.4)	8 (0.2)	
	Days on ECLS mean (±SD)	11.78 ±14.5	10.38 ± 12.42	17.03 ± 19.63	<0.001
	Cardiac arrest *n* (%)	1664 (9.2)	1351 (9.5)	313 (8.1)	0.005
	Bridge to transplant *n* (%)	1016 (5.8)	789 (5.7)	227 (5.8)	0.580
	Surgical cannulation *n* (%)	1814 (9.7)	1312 (8.9)	502 (12.8)	<0.001
Blood gas closest to ECLS start	Lactate mmol/L (±SD)	3.69 ±4.07	3.705 ± 4.05	3.598 ± 4.16	0.448
	pH (±SD)	7.23 ±0.15	7.23 ± 0.15	7.24 ± 0.14	0.005
	PaO_2 mmHg (±SD)	76.20 ± 65.07	77.02 ± 65.14	73.39 ± 64.79	0.004
	$PaCO_2$ mmHg (±SD)	63.31 ±26.72	63.27 ± 26.92	63.44 ± 26.04	0.749
	HCO3 mmol/L or mEq/L (±SD)	25.30 ± 7.47	25.10 ± 7.36	26.01 ± 782	<0.001
	SaO_2 % (±SD)	85.61 ± 12.51	85.72 ± 12.52	85.24 ± 12.45	0.063
Ventilator settings closest to ECLS start	Rate bpm (±SD)	22.91 ± 7.84	22.78 ± 7.72	23.34 ± 8.21	0.001
	FiO_2 % (±SD)	92.78 ±15.06	92.64 ± 15.34	93.25 ± 14.09	0.031
	PEEP cm H2O (±SD)	12.68 ± 5.44	12.63 ± 5.41	12.83 ± 5.52	0.076
	PIP cm H2O (±SD)	33.96 ± 8.69	33.80 ± 8.55	34.49 ± 9.15	0.001
	Mean AP cm H2O (±SD)	22.22 ± 6.98	22.00 ± 6.84	22.96 ± 7.41	<0.001
Hemodynamics closest to ECLS start	SBP mmHg (±SD)	108.39 ±27.74	108.71 ± 27.65	107.33 ± 27.99	0.013
	DBP mmHg (±SD)	59.00 ±15.65	59.32 ± 15.83	57.97 ± 15.01	<0.001
	MBP mmHg (±SD)	73.42 ±17.70	73.64 ± 17.66	72.71 ± 17.81	0.012
Pre-ECLS support	CPB *n* (%)	560 (3.0)	419 (2.8)	141 (3.6)	0.016
	IABP *n* (%)	247 (1.3)	186 (1.3)	61 (1.6)	0.161
	VADs *n* (%)	290 (1.6)	217 (1.5)	73 (1.9)	0.085
	RRT *n* (%)	1455 (7.8)	1073 (7.3)	382 (9.7)	<0.001
	Prone positioning *n* (%)	1091 (5.8)	825 (5.6)	266 (6.8)	0.006
	Vasodilatory agents *n* (%)	2561 (13.7)	1831 (12.4)	730 (18.6)	<0.001
	Anti-hypotensive agents *n* (%)	10859 (58.2)	8305 (56.4)	2554 (64.9)	<0.001

Abbreviations; ECLS – extracorporeal life support, PaO_2 - partial pressure of oxygen, $PaCO_2$ - partial pressure of carbon dioxide, HCO3 - bicarbonate, SaO_2 - saturation of oxygen, FiO_2 - fraction of oxygen supplied on ventilator, PEEP - positive end expiratory pressure, PIP - peak inspiratory pressure, MeanAP - mean airway pressure, SBP - systolic blood pressure, DBP - diastolic blood pressure, MBP – mean blood pressure,

Surgical cannulation and ECLS duration were associated with this complication. Furthermore, blood gas values and ventilation settings except lactate values, pCO2, saturations, and positive end-expiratory pressure (PEEP) were significantly different

between bleeding and non-bleeding patients. Pre-ECLS support of cardio-pulmonary bypass (CPB), renal replacement therapy (RRT), prone positioning, vasodilatory, and anti-hypotensive agents was significantly more common in patients with bleeding complications. (Tables 5 and 6)

The most frequent underlying diseases were an acute respiratory failure, pneumonia, ARDS, systemic inflammatory syndrome (SIRS), and/or sepsis and shock other than septic shock, of which all except ARDS were more frequently found in patients with bleeding complications. (Table 7)

Significantly higher number of other complications such as mechanical complications, renal failure, infections, limb complications, and a higher mortality was observed in patients with bleeding complications. (Table 8)

Risk factors for bleeding complications

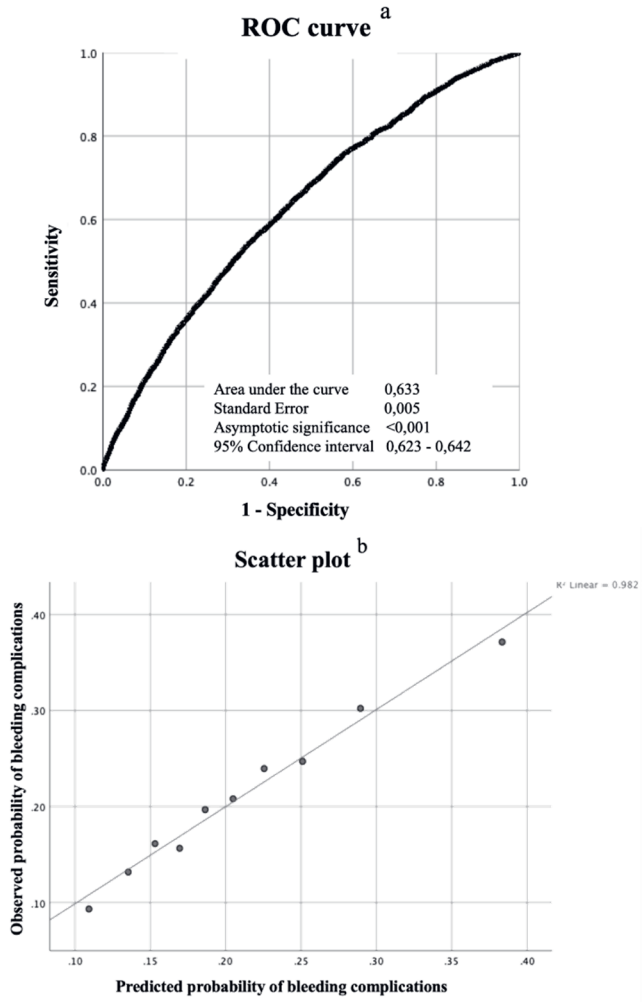
In univariate regression analysis, multiple variables showed a significant association with bleeding com- plications. Odds ratios (ORs) of several variables were above 1,5 and the ORs of pericardiocentesis, thoracic drainage, hypovolemic and postoperative shock, bronchiectasis, pulmonary vessel disease, pre-ECLS hemorrhage/hematoma/laceration of the circulatory system, and hypothermia exceeded 2,0. (Table 9) The duration of ECLS in hours was highly associated with bleeding complications after the correction for other variables with an OR of 1.001 (95%CI 1.001–1.001, $p < 0.001$).

Model performance

The model that was derived excluded many variables during the backward elimination process. All predictors increased the risk of bleeding complications except for diastolic blood pressure, which was protective, except for pO2 and surgery on the nervous system. The full model with regression coefficients is depicted in Table 10. In total, 25 variables were included in the final model, among them are pre-ECLS lactate, renal replacement therapy, diagnosis of respiratory failure, pneumonia, and pulmonary vessel disease. (Table 10) In the modeling process, we have mitigated effects on model performance associated with the major limits of the database. For instance, we have selected an imputation method to complete missing values based on multivariable modeling of the missing data mechanism (i.e., we used stochastic regression imputation).

The AUC of this model was 0.633 (95% CI: 0.623– 0.642, $p < 0.001$). (Figure 1A) A calibration plot was made to assess the agreement between observed and predicted probabilities. As deciles of patients with similar predicted probability lie close to the ideal line of 45 degrees, it can be assumed that the model is well-calibrated. (Figure 1B)

Figure 1. *Discrimination and calibration of the prediction model*



A) Receiver operating characteristic (ROC) curves discrimination, B) Calibration scatter plot

Internal validation yielded a shrinkage factor of 0.960. The optimism in the AUC was 0.004, indicating that the expected AUC in future patients is 0.633–0.004 = 0.629. The prediction model can be used to calculate an individual's risk score at the initiation of ECLS for experiencing bleeding complications with the formula (Figure 2), or as a proposed website-based calculator (Figure 3).

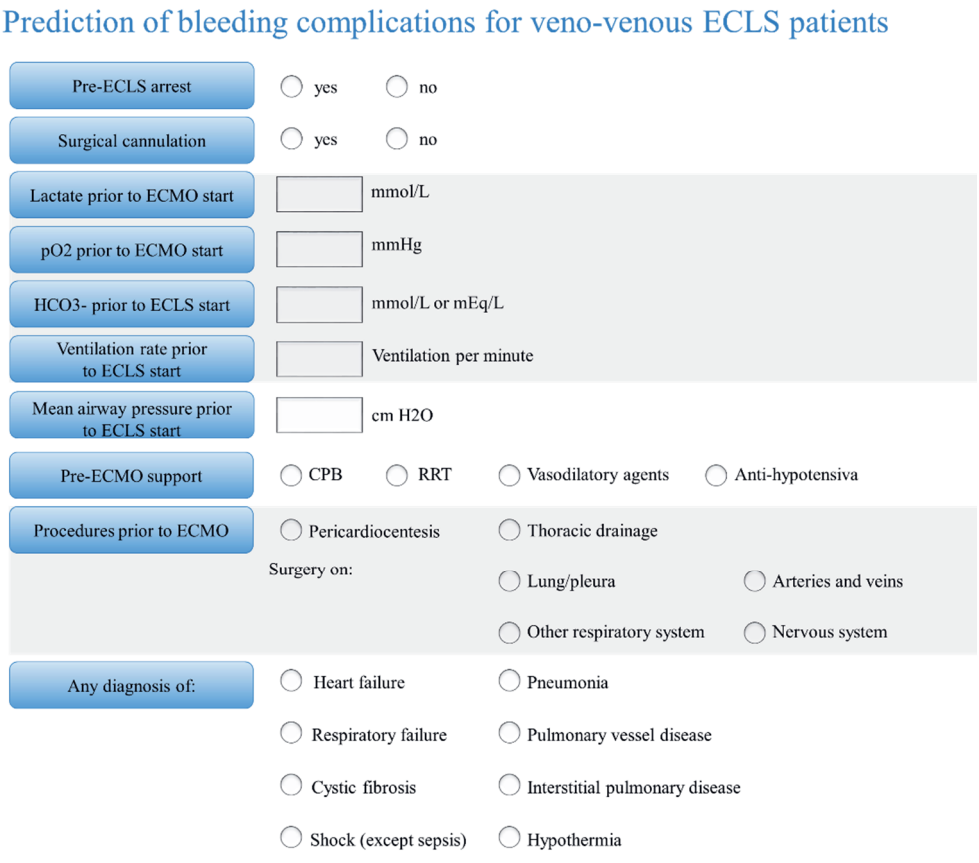
Figure 2. *Formula for prediction model of bleeding complication in veno-venous extracorporeal life support*

$$P(\text{bleeding complication}) = 1/(1+e^{-(\text{linear predictor})}), \text{ in which}$$

Linear predictor = -2.905 + (-0.176 • pre ECLS cardiac arrest) + (0.351 • surgical cannulation*) + (0.012 • pre ECLS lactate) + (-0.001 • pO2-) + (0.021 • HCO3-) + (0.006 • ventilation rate) + (0.016 • mean airway pressure) + (0.278 • CPB*) + (0.229 • RRT*) + (0.297 • vasodilatory agents*) + (0.280 • anti-hypotensive*) + (1.682 • pericardiocentesis*) + (0.593 • thoracic drainage*) + (0.224 • surgery on lung or pleura*) + (0.263 • surgery on other parts of respiratory system*) + (0.190 • surgery on arteries/veins*) + (-1.196 • surgery on the nervous system*) + (0.194 • diagnosis of heart failure*) + (0.122 • diagnosis of shock*) + (0.200 • diagnosis of respiratory failure*) + (0.407 • diagnosis of cystic fibrosis*) + (0.325 • diagnosis of pneumonia*) + (0.832 • pulmonary vessel disease*) + (0.160 • interstitial pulmonary disease*) + (1.278 • hypothermia*)

*; yes = 1, ECLS; extracorporeal life support, pO2; partial pressure of oxygen, HCO3-; hydrogencarbonate, CPB; cardiopulmonary bypass, RRT; renal replacement therapy

Figure 3. *Web-based prediction model calculator for prediction of bleeding complications for veno-venous extracorporeal life support patients*



Discussion

Despite the increasing experience and improved technology, bleeding complications during ECLS remain a frequent complication with high mortality [16, 17, 38, 47, 48]. There is a need to identify patients with a higher risk of bleeding complications to allow clinicians to tailor anticoagulation, including clinical monitoring. Furthermore, such a predictive model could be used to inform future trials, for example, on different anticoagulation management and to identify patients that could benefit from tailored anticoagulation management.

From the 18 658 V-V ECLS patients included in our analysis, 21.1% developed bleeding complications. Duration and surgical cannulation of ECLS was highly associated with bleeding outcome, as well as hemodynamic status prior to ECLS. Pre-ECLS support in terms of RRT, prone positioning and vasodilatory, and anti-hypotensive agents were found to be possible risk factors, as well as different types of surgery prior to ECLS.

Several score systems to predict bleeding complications have previously been reported [16, 37, 49, 50]. The assessment of blood consumption (ABC) score, used to predict massive red cell transfusion, was developed for adult trauma patients and includes penetrating trauma, positive ultrasound for abdominal fluids, systolic blood pressures of ≤90 mm Hg, and a pulse of >120 bpm, with a reported AUC of 0.833 to 0.903 [51]. The Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies score (SWEDEHEART) to predict bleeding risks in patients with the acute coronary syndrome has an AUC of 0.81. The model includes predictors such as hemoglobin, age, sex, creatinine, and cardiopulmonary resuscitation (CPR) [52]. The WILL BLEED risk score was developed to predict severe bleeding (>4 units of red blood cells or reoperation for bleeding) after coronary artery bypass grafting. Predictors of severe bleeding were postoperative anemia, female gen- der, estimated glomerular filtration rate (eGFR) <45 ml/ min/1.73 m2, antiplatelet drugs discontinued <5 days, critical preoperative state, acute coronary syndrome, and the use of low molecular weight heparin/fondaparinux/ unfractionated heparin. The discriminative ability was good with an AUC of 0.725 [53].

The HAT score is the only score developed to predict bleeding events in ECLS [37]. This score was tested on a merged V-V and V-A ECLS group and was based on pre- ECLS variables with strong associations for coagulopathy bleeding, including hypertension, age older than 65 years, and ECLS mode. It was compared to the HAS-BLED score, a predictive score for patients using anticoagulation for atrial fibrillation, in V-V and V-A ECLS [37, 54]. The HAT and the HAS-BLED score had an AUC of 0.66 and 0.64, respectively. However, a major limitation of the HAT score was the small cohort of 112 patients, which limits its generalizability [37, 54]. Furthermore, the HAT score was not specifically created for V-V ECLS patients.

Limitations and strengths of HEROES V-V model

HEROES V-V model aims to predict the probability of bleeding complications specifically for V-V ECLS using data from the ELSO registry. It provides a debatable discriminatory performance. The shrinkage factor was remarkably close to 1 and the measures of optimism close to, concluding that the HEROES V-V model was not particularly overfitted and did not need much penalization. Although the HEROES V-V AUC appears comparable to the HAT AUC, such comparison is not reliable, as preferably the models should be tested on the same external dataset to ensure a fair comparison. Moreover, the AUC of our model showed increased accuracy because of the large data set and the specification for V-V ECLS patients. However, the HEROES V-V model has several limitations. A number of important characteristics are associated with bleeding, that are not, or cannot be recorded. As these are not available, it is unlikely the model can be improved substantially over the current performance. For model application, the use of cut-off thresholds resulting in dichotomized prediction results (e.g., "low risk" and "high risk") is necessary, as this ensures reproducible decisions regardless of the user. We have not determined one or more cut-off values as the choice of which value is best is determined by many factors, among others the intended use (rule out or rule in), the prevalence of bleeding complications in the specific setting, and the cost of misclassification. We think that the intended user should decide, based on characteristics of the local setting, what cut-off value should be used. Moreover, whether discrimination is important depends on the intended use of the model. It appears they envision this being used by clinicians to make individual patient care decisions, rather than as a benchmarking tool to characterize entire cohorts. If this is a clinical prediction tool, the AUROC provides very little insight into model performance. The practicing clinician may well be more interested in sensitivity and positive predictive value, among other more interpretable metrics.

We performed bootstrapping as an internal validation method as this employs all data for both model development and for model validation. This is widely accepted as an internal validation method and has several advantages over other internal validation methods, such as testing on a held-out dataset. We kindly refer the reviewer to the prediction model risk of bias assessment tool (PROBAST) in which bootstrapping is regarded as a competent means to internally validate.

Bleeding events will always be difficult to predict because of unpredictable events such as surgical procedures which are difficult to anticipate and prognosticate. Previous risk scores included laboratory findings such as hemoglobin (Hb) and/or the use of anticoagulation. Aubron et al found that an activated partial thromboplastin time (aPTT) >70 s prior to ECLS initiation, higher APACHE III score, and postsurgical ECLS were independently associated with bleeding [16]. Data on anticoagulation, transfusion, and several laboratory results (platelets, Hb, D-dimers)

are not available in the ELSO registry. Also, the use of a retrospective dataset is complicated by missing values. To minimize bias, we chose an imputation method that allows for unbiased estimates after imputation when the missingness mechanism has been considered in the imputation model. The stochastic regression imputation was based on a large number of covariates that were likely associated with missing values, as these variables were selected from demography, disease characteristics, ECMO characteristics, and outcomes, as per data imputation guidelines. As we believed lactate and mean airway pressure to be important potential predictor variables, we imputed these as well despite a higher percentage of missingness. This likely caused more uncertainty in the estimated regression coefficients as reflected by the confidence intervals. Finally, this model needs to be externally validated in an independent cohort to be used in clinical settings.

We acknowledge that p-value-based selection methods should be avoided when possible as the selection is unlikely to be completely reproducible in other datasets and yields testimation bias. However, we have selected this method as we had far too many candidate predictors to allow to be included in a multivariable prediction model, if only for practical purposes, and too little is known on predictors of bleeding to perform the selection based on the available literature and expert opinion only. To counteract the effect of testimation bias (i.e., coefficients are biased away from the null due to the p-value-based selection), shrinkage of coefficients was performed based on the internal validation results.

Despite these limitations, the HEROES V-V predictive score has a number of strengths. The internal validity of the developed risk model is robust because of the analysis using the largest V-V ECLS cohort to date. Even after the exclusion of ECLS runs before 2010, this analysis included over 18 500 patients from almost 500 active centers internationally. External validity is likely to be high due to the multi-center international design of the registry.

By constructing a prediction model for adult patients on V-V ECLS only, more homogeneity was created. There are likely significant differences in pathology and effects according to the type of ECLS configurations, underlying condition, and across neonatal, pediatric, and adult patient populations.

In the HEROES V-V model, the measure of the AUC of 0.629 after adjustment for optimism is highly accurate due to the analysis of a large dataset. Further research may increase the performance of this model by identifying other important predictors. The development of an online prediction tool might simplify the use of the model. (Figure 3) Future studies, which include other relevant variables such as hemoglobin and anticoagulation, may improve the model. Furthermore, prospective, and external validation is needed to confirm usefulness for the prediction of bleeding risk.

Conclusion

We developed and internally validated a prediction model for bleeding complications in patients supported with V-V ECLS. The model is based on the largest multi-center cohort worldwide including over 18 500 adult patients supported with V-V ECLS. We assumed, there are many factors related to bleeding, but these characteristics are not or cannot be recorded, are thus not available. With an AUC of 0.63, compared to available literature, this is the best available predictive model addressing bleeding events during V-V ECLS given the predictors that are feasible. This model will help identify patients at risk of bleeding complications, and decision making in terms of anticoagulation and hemostatic management.

Table 1. *Clustering of pre-extracorporeal life support interventions based on current procedural terminology*

Procedure	SPSS code	CPT Code
Pericardiocentesis	90	3202, 33010, 33015
Thoracic drainage	00	32000, 32020
Fine needle biopsy	1	10004-10021
Surgical procedures on integumentary system	2	10030-19499
Surgical procedures on musculoskeletal system	3	20100-29999
Surgery on the respiratory system	4	30000-31899
Surgery on lungs and pleura	5	32035-32999
Surgery on heart and pericardium	6	33016-33999
Surgery on arteries and veins	7	34001-37799
Surgery on hemic and lymphatic system	8	38100-38999
Surgery on mediastinum	9	39000-39499
Surgery on diaphragm	10	39501-39599
Surgery on the digestive system	11	40490-49999
Surgery on the urinary system	12	50010-53899
Surgery on the male genital system	13	54000-55899
Surgery on the reproductive system	14	55920
Surgery of intersex	15	55970-55980
Surgery on the female genital system	16	56405-58999
Surgery of maternity care and delivery	17	59000-59899
Surgery on the endocrine system	18	60000-60699
Surgery on the nervous system	19	61000-64999
Surgery on the eye and ocular adnexa system	20	65091-68899
Surgery on the auditory system	21	69000-69979
Surgery on microscopic surgery	22	69990
Anesthesia procedures	30	00100-01999
Radiology procedures	40	70010-79999
Pathology and laboratory interventions	50	80047-89398
Services and procedures	60	90281-99607
Management	70	99201-99499

Table 2. *Clustering of diagnostical International Classification of Diseases-codes*

Diagnosis	ICD-10	ICD-9
Heart failure	I50, I50.1-2-20-21-22-23-3-30-31-32-33-4-40-41-42-43-8-81-810-811-812-813-814-82-84-89-9	428, 428.0-1-2-21-22-23-31-33-4-41-42-43-9
Cardiac arrest	I46, I46.2, I46.8, I46.9	427.5
Hypothermia	T68, T68.XXX, T68.XXXA	991.6
Cardiomyopathy	I25.5, I42, I42.0-1-2-3-4-5-6-7-8-9	425.0-1-18-3-4-5-9, 414.8
Chronic ischemic heart disease	I25, I25.1-10-11-111-1118-119-2-3-4-41-42-5-6-7-70-700-701-708-709-710-719-720-729-730-79-798-799-8-81-810-811-812-82-83-84-89-9	414.0-00-01-04-05-06-1-10-11-12-19-2-8-9
Endocarditis	I33, I33.0-1-9, I38, I39	421.0-1-9
Heart transplant failure	T86.2-20-21-22-23-29-290-298-3-30-31-32-33-39	966.83, V42.1, Z94.1
Failure of transplantation other than heart transplantation	T86, T86.0-00-01-02-03-09-1-10-11-12-13-19-4-40-41-42-43-49-5-8-81-810-811-812-818-819-820-821-822-828-829-83-830-831-832-838-839-84-840-8401-8402-8403-8409-841-8411-8412-8413-8419-842-8421-8422-8423-8429-848-8481-8482-8483-8489-849-8491-8492-8493-8499-85-850-851-852-858-859-89-890-891-892-898-899-9-90-91-92-93-99	996.8-80-81-82-84-85-86-87-88-89
Myocardial infarction	I21, I21.0-01-02-09-1-11-19-2-21-29-3-4-9-A1-A9, I22, I22.0-1-2-8-9	410, 410.0-01-09-1-10-11-2-21-3-4-41-5-6-70-71-72-9-90-91-92
Myocarditis	B33.22, I40, I40.0-1-8-9, I51.4	422, 422.0-9-90-91-92-99, 429.0
SIRS and/or sepsis	R65, R65.1-10-11-2-20-21, A40, A40.0-1-3-8-9, A41, A41.0-01-02-1-2-3-4-5-50-51-52-53-59-8-81-89-9	995.91-9-90-91-92-93-94, 785.52, 38, 038, 038.0-1-10-11-12-19-2-3-4-40-41-42-43-44-49-8-9
Other specified bacterial diseases	A48.8	040.8-89
Shock (excl. septic shock)	R57, R57.0-1-8-9, T81.1, T79.4, T75.01, T78.0-2, T88.3-6	785.5-50-51-52, 998, 998.0-00-01-02-09, 785.59
Hypovolemic shock	R57.1	785.50
Cardiogenic shock	R57.0	785.51, 998.01
Postoperative shock	T81.1	998.01-02
Unspecified shock	R57.9-8, T79.4, T75.01, T78.0-2, T88.3-6	785.59
Atrial fibrillation and flutter	I48, I48.0-1-11-19-2-20-21-3-4-9-91-92	427.3-31-32
Other cardiac arrhythmias	I49, I49.0-01-02-1-2-3-4-40-49-5-8-9	427.9
Ventricular fibrillation and flutter	I49.01-02	427.4-41-42
Acute respiratory failure	J96, J96.0-00-01-02-1-10-11-12-2-20-21-22-9-90-91-92, R06.03	518, 518.0-1-12-4-5-50-51
ARDS	J80	518.82-7
Bronchiectasis	J47, J47.0-1-9	494, 494.0-1
Cystic fibrosis	E84, E84.0-1-11-19-8-9	277.0-00-01-02-03-09
Overall pneumonia	Combined subgroups of pneumonia	Combined subgroups of pneumonia
Subgroup pneumonia aspiration	J69, J69.0-1-8	507, 507.0-1-8
Subgroup pneumonia bacterial	J13, J14, J15, J15.0-1-2-20-21-211-212-29-3-4-5-6-7-8-9, J16.0-8, J17, A48.1, A69.8	481, 482, 482.0-1-2-3-30-31-32-39-4-40-41-42-49-8-81-82-83-84-89-9, 483, 483.0-1-8, 104.8
Subgroup pneumonia viral	J12, J12.0-1-2-3-8-81-89-9, J09.X1, J10.0-00-01-08, J11, J11.0-00-08	480, 480.0-1-23-8-9, 488, 488.0-01-02-09-1-11-12-19-8-81-82-89, 487, 487.0
Subgroup pneumonia unspecified	J18, J18.0-1-2-8-9	486
COPD	J44, J44.0-1-9	491.20-21-22, 493.20-21-22, 496
Acute pulmonary edema	J81, J81.0-1	518.4, 514, 514.8
Pulmonary embolism	I26, I26.0-01-02-09-9-90-92-93-94-99	451, 451.1-11-12-13-5
Pulmonary hypertension	I27.0-2-20-21-22-23-24-29	416, 416.0-2-8-9
Pulmonary vessel disease	I28, I28.0-1-8-9	417, 417.0-1-8-9

Respiratory arrest	R09.2	799.1
Bronchiolitis interstitial lung disease	J84.115	995.94
Other interstitial lung disease	J84, J84.0-01-02-03-09-1-10-11-111-112-113-114-115-116-117-17-170-178-89-9-2-8-81-82-83-84-841-842-843-848	515, 516, 516.0-1-2-3-30-31-32-33-34-35-36-37-4-5-6-61-62-63-64-69-8-9
Intra- and post procedure complications of the respiratory system	J95, J95.0-00-01-02-03-04-09-1-2-3-4-5-6-61-62-7-71-72-8-81-811-82-821-822-83-830-831-84-85-850-851-859-86-860-861-862-88-89	997.3-31-32-88-89
Post cardiotomy syndrome	I97.0	429.4
Intra- and post procedure cardiac functional disturbances	I97.1-11-110-111-12-120-121-13-130-131-19-190-191-7-71-710-711-79-790-791	429.4, 997.1
Post procedure hemorrhage/ hematoma/ puncture laceration of circulatory system	I97.4-41-410-411-418-42-5-51-52-6-610-611-618-62-620-621-63-630-631-638	998.1-11-12-2-3-30-31-32-33
Other intra- and post procedure complications of the circulatory system	I97, I97.8-81-810-811-82-820-821-88-89	997.1

Table 3. *Numbers and percentages of missing data and cut-off values*

Patients' characteristics ECLS data **Monitoring values**	Missing data in total cohort *n* = 18 658	Missing data %	Lower limit	Upper limit
Sex	364	2,00%	-	-
Weight (kg)	961	5,15%	10	500
Height (cm)	9020	48,34%	70	250
BMI	9041	48,46%	10	100
Age	0	0,00%	18	-
ECLS duration	175	0,94%	-	-
Pre-ECLS arrest	580	3,11%	-	-
Bridge to transplant	1012	5,42%	-	-
Pre-ECLS values				
Lactate	13.046	69,92%	-	40
pH	3046	16,33%	6,00	8,00
PaO2 (mmHg)	3317	17,78%	0	760
PaCO2 (mmHg)	3908	20,95%	10	250
HCO3 (mmol/L)	4096	21,95%	0	70
SaO2 (%)	5264	28,21%	1	100
Ventilation rate (bpm)	5290	28,35%	0	90
FiO2 (%)	3917	20,99%	10	100
PEEP (cm H2O)	5188	27,81%	0	40
PIP (cm H2O)	7357	39,43%	0	80
MeanAP (cm H2O)	10.861	58,21%	0	60
SBP (mmHg)	4875	26,13%	0	300
DBP (mmHg)	4942	26,49%	0	250
MBP (mmHg)	6095	32,67%	0	250

Abbreviations: BMI - body mass index, PaO_2 - partial pressure of oxygen, $PaCO_2$ - partial pressure of carbon dioxide, HCO3 - bicarbonate, SaO_2 - saturation of oxygen, FiO_2 - fraction of oxygen supplied on ventilator, PEEP - positive end expiratory pressure, PIP - peak inspiratory pressure, MeanAP - mean airway pressure, SBP - systolic blood pressure, DBP - diastolic blood pressure, MBP – mean blood pressure

Table 4. *TRIPOD checklist: prediction model development and validation*

Section/Topic	Item		Checklist Item	Page
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Provided
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Provided
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	Provided
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	Provided
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	Provided
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Provided
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centers.	Provided
	5b	D;V	Describe eligibility criteria for participants.	Provided
	5c	D;V	Give details of treatments received, if relevant.	Provided
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	Provided
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	N/a
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Provided
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	N/a
Sample size	8	D;V	Explain how the study size was arrived at.	Provided
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Provided
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	Provided
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	Provided
	10c	V	For validation, describe how the predictions were calculated.	Provided
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Provided
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	N/a
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	N/a
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Provided
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Provided, table 2
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Tables 1-4
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Tables 5-6

Model development	14a	D	Specify the number of participants and outcome events in each analysis.	Table 6
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Table 6-7
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Provided, table 7
	15b	D	Explain how to the use the prediction model.	Figures 2-3
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	Provided
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	N/a
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as non-representative sample, few events per predictor, missing data).	Provided
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	Provided
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	Provided
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	Provided
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Tables 8-9, figure 3
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	Provided

Abbreviations: D – development, V - validation

Table 6. *Interventions and surgery procedures prior to extracorporeal life support initiation*

Intervention and surgery procedures	Total cohort n=18658 (100%)	Non-bleeding n= 14725 (78.9%)	Bleeding n= 3933 (21.1%)	*p* value
Pericardiocentesis	12 (0.1)	4 (0.0)	8 (0.2)	0.001
Thoracic drainage	264 (14)	160 (1.1)	104 (2.6)	<0.001
Surgery integumentary system	20 (0.1)	17 (0.1)	3 (0.1)	0.783
Surgery musculoskeletal system	71 (0.4)	50 (0.3)	21 (0.5)	0.079
Surgery on other respiratory system	2106 (4.8)	1482 (10.2)	624 (15.9)	<0.001
Surgery on lung or pleura	890 (4.8)	652 (4.4)	238 (6.1)	<0.001
Surgery on heart and pericardium	1127 (6.0)	821 (5.6)	306 (7.8)	<0.001
Surgery on arteries and veins	1431 (7.7)	996 (6.8)	435 (11.1)	<0.001
Surgery on hemic and lymphatic system	49 (0.3)	32 (0.2)	17 (0.4)	0.019
Surgery on diaphragm	3 (0.0)	2 (0.0)	1 (0.0)	0.508
Surgery on digestive system	363 (1.9)	271 (1.8)	92 (2.3)	0.044
Surgery on urinary system	38 (0.2)	27 (0.2)	11 (0.3)	0.234
Surgical on maternity care and delivery	21 (0.1)	18 (0.1)	3 (0.1)	0.597
Surgery on endocrine system	4 (0.0)	3 (0.0)	1 (0.0)	1.000
Surgery on the nervous system	37 (0.2)	33 (0.2)	4 (0.1)	0.125
Anesthesia procedure	30 (0.2)	25 (0.2)	5 (0.1)	0.553

Table 7. *Underlying diseases before veno-venous extracorporeal support*

Underlying diseases	Total cohort n=18658 (100%)	Non-bleeding n= 14725 (78.9%)	Bleeding n= 3933 (21.1%)	*p* value
Heart failure	808 (4.3)	581 (3.9)	227 (5.8)	<0.001
Cardiac arrest	705 (3.8)	562 (3.8)	143 (3.6)	0.597
Hypothermia	11 (0.1)	6 (0.0)	5 (0.1)	0.062
Cardiomyopathy	282 (1.5)	203 (1.4)	79 (2.0)	0.004
Chronic ischemic heart disease	448 (2.4)	333 (2.3)	115 (2.9)	0.016
Endocarditis	109 (0.6)	89 (0.6)	20 (0.5)	0.483
Heart transplant failure	47 (0.3)	38 (0.3)	9 (0.2)	0.745
Failure of transplantation other than heart transplantation	568 (3.0)	436 (3.0)	132 (3.4)	0.200
Myocardial infarction	315 (1.7)	230 (1.6)	85 (2.2)	0.010
Myocarditis	31 (0.2)	23 (0.2)	8 (0.2)	0.518
SIRS and/or sepsis	3289 (17.6)	2450 (16.6)	839 (21.3)	<0.001
Other specified bacterial diseases	41 (0.2)	30 (0.2)	11 (0.3)	0.366
Shock (excl. septic shock)	1647 (8.8)	1198 (8.1)	449 (11.4)	<0.001
Hypovolemic shock	141 (0.8)	87 (0.6)	54 (1.4)	<0.001
Cardiogenic shock	668 (3.6)	513 (3.5)	115 (3.9)	0.170
Postoperative shock	10 (0.1)	5 (0.0)	5 (0.1)	0.040
Not specified shock	763 (4.1)	602 (4.1)	161 (4.1)	0.988
Atrial fibrillation and flutter	719 (3.9)	523 (3.6)	196 (5.0)	<0.001
Other cardiac arrhythmias	112 (0.6)	84 (0.6)	28 (0.7)	0.308
Ventricular fibrillation and flutter	90 (0.5)	69 (0.5)	21 (0.5)	0.599
Acute respiratory failure	8408 (45.1)	6384 (43.4)	2024 (51.5)	<0.001
ARDS	4583 (24.6)	3598 (24.4)	985 (25.0)	0.430
Asthma	933 (5.0)	768 (5.2)	165 (4.2)	0.009
Bronchiectasis	100 (0.5)	64 (0.4)	36 (0.9)	<0.001
Cystic fibrosis	212 (1.1)	154 (1.0)	58 (1.5)	0.024
Overall pneumonia	6653 (35.7)	4952 (33.6)	701 (43.2)	<0.001
Subgroup pneumonia aspiration	767 (4.1)	588 (4.0)	179 (4.6)	0.117
Subgroup pneumonia bacterial	2538 (13.6)	1849 (12.6)	689 (17.5)	<0.001
Subgroup pneumonia viral	2466 (13.2)	1767 (12.0)	699 (17.8)	<0.001
Subgroup pneumonia unspecified	1488 (8.0)	1156 (7.9)	332 (8.4)	0.224
COPD	527 (2.8)	383 (2.6)	144 (3.7)	<0.001
Acute pulmonary edema	343 (1.8)	257 (1.7)	86 (2.2)	0.067
Pulmonary embolism	378 (2.0)	293 (2.0)	85 (2.2)	0.498
Pulmonary hypertension	558 (3.0)	400 (2.7)	158 (4.0)	<0.001
Pulmonary vessel disease	45 (0.2)	26 (0.2)	19 (0.5)	<0.001
Respiratory arrest	44 ().2)	35 (0.2)	9 (0.2)	0.919
Pulmonary embolism	378 (2.0)	293 (2.0)	85 (2.2)	0.498
Pulmonary hypertension	558 (3.0)	400 (2.7)	158 (4.0)	<0.001
Pulmonary vessel disease	45 (0.2)	26 (0.2)	19 (0.5)	<0.001
Respiratory arrest	44 ().2)	35 (0.2)	9 (0.2)	0.919
BILD	50 (0.3)	37 (0.3)	13 (0.3)	0.393
OILD	1107 (5.9)	848 (5.8)	259 (6.6)	0.051
Intra- and post procedure complications of the respiratory system	442 (2.4)	328 (2.2)	114 (2.9)	0.014
Post cardiotomy syndrome	13 (0.1)	9 (0.1)	4 (0.1)	0.492
Intra- and post procedure cardiac functional disturbances	41 (0.2)	29 (0.2)	12 (0.3)	0.198
Hematoma/ puncture laceration of circulatory system	65 (0.3)	32 (0.2)	33 (0.8)	<0.001
Other intra- and post procedure complications of the circulatory system	28 (0.2)	19 (0.1)	9 (0.2)	0.151

Abbreviations: ECLS - extracorporeal life support, ARDS - acute respiratory distress syndrome, COPD – chronic obstructive pulmonary disease, BILD - bronchiolitis interstitial lung disease, OILD - other interstitial lung disease, n - number

Table 8. *Complications of veno-venous extracorporeal life support in patients with bleeding compared to non-bleeding*

Complications	All patients n=18658 (100%)	Non-bleeding n= 14725 (78.9%)	Bleeding patients n= 3933 (21.1%)	*p* value
Mechanical problems	3966 (21.3%)	2606 (17.7%)	1360 (34.6%)	<0.001
Mechanical cannula problems	821 (4.4%)	482 (3.3%)	339 (8.6%)	<0.001
Circuit change	559 (3.0%)	396 (2.7%)	163 (4.1%)	<0.001
Thrombosis/clots in components	84 (0.5%)	60 (0.4%)	24 (0.6%)	0.092
Clot and air emboli	5 (0. %)	3 (0. %)	2 (0.1%)	0.285
Clots hemofilter	199 (1.1%)	120 (0.8%)	79 (2.0%)	<0.001
Air in circuit	195 (1.0%)	102 (0.7%)	93 (2.4%)	<0.001
Clots in circuit components	1857 (10 %)	1179 (8%)	678 (17.2%)	<0.001
Oxygenator failure	1009 (5.4%)	625 (4.2%)	384 (9.8%)	<0.001
Pump failure	186 (1.0%)	117 (0.8%)	69 (1.8%)	<0.001
Rupture of raceway tubing	3 (0%)	2 (0. %)	1 (0 %)	0.508
Other tubing rupture	21 (0.1%)	16 (0.1%)	5 (0.1%)	0.789
Heat exchanger malfunction	13 (0.1%)	7 (0. %)	6 (0.2%)	0.038
Cracks in pigtail connectors	34 (0.2%)	20 (0.1%)	14 (0.4%)	0.004
Renal creatinine 1.5-3.0	2223 (11.9%)	1453 (9.9%)	770 (19.6%)	<0.001
Renal creatinine >3.0	1153 (6.2%)	771 (5.2%)	382 (9.7%)	<0.001
Renal replacement therapy	5180 (27.8%)	3540 (24%)	1640 (41.7%)	<0.001
Infection	1934 (10.4%)	1147 (7.8%)	787 (20 %)	<0.001
Overall limb complications	221 (1.2%)	143 (1.0%)	78 (2 %)	<0.001
Limb ischemia	156 (0.8%)	97 (0.7%)	59 (1.5%)	<0.001
Compartment syndrome	38 (0.2%)	24 (0.2%)	14 (0.4%)	0.017
Limb fasciotomy	51 (0.3%)	34 (0.2%)	17 (0.4%)	0.032
Limb amputation	25 (0.1%)	20 (0.1%)	5 (0.1%)	0.895
In-hospital survival	11765 (63.1%)	9808 (66.6%)	1957 (49.8%)	<0.001

Table 9. *Univariable logistic regression analysis of bleeding risk factors in patients undergoing veno-venous extracorporeal membrane oxygenation*

Groups	Values	Beta	OR	95% CI limits Lower-Upper	*P* value
Patient characteristics	Gender male	0.043	1.044	0.972-1.122	0.239
	BMI	0.000	1.000	0.998-1.003	0.850
	Age categories				
	18-40 years				0.032
	40.1-60 years	-0.008	0.992	0.915-1.075	0.843
	60.1-80 years	-0.107	0.899	0.817-0.988	0.028
	80 or older	-0.691	0.501	0.239-1.052	0.068
	Hours on ECLS	0.001	1.001	1.001-1.001	<0.001
	Days on ECLS	0.028	1.029	1.026-1.031	<0.001
	Weeks on ECLS	0.199	1.221	1.199-1.242	<0.001
	Pre ECLS-cardiac arrest n (%)	-0.167	0.846	0.745-0.961	0.010
	Bridge to transplant n (%)	0.048	1.049	0.904-1.218	0.529
	Surgical cannulation	0.403	1.496	1.341-1.669	<0.001
Blood gas closest to ECLS start	Lactate mmol/L	0.004	1.004	0.995-1.013	0.418
	pH	0.219	1.245	0.981-1.580	0.072
	PaO2 mmHg	-0.001	0.999	0.998-0.999	<0.001
	PaCO2 mmHg	0.000	1.000	0.999-1.002	0.555
	HCO3 mmol/L or mEq/L	0.017	1.017	1.012-1.022	<0.001
	SaO2 %	-0.004	0.996	0.993-0.999	0.003
Ventilator settings closest to ECLS start	Rate	0.009	1.009	1.004-1.013	<0.001
	FiO2 %	0.003	1.003	1.001-1.005	0.011
	PEEP cm H2O	0.012	1.012	1.005-1.018	<0.001
	PIP cm H2O	0.013	1.014	1.010-1.018	<0.001
	Mean airway pressure cm H2O	0.022	1.022	1.017-1.027	<0.001
Hemodynamics closest to ECLS start	Systolic blood pressure mmHg	-0.002	0.998	0.997-1.000	0.009
	Diastolic blood pressure mmHg	-0.006	0.994	0.991-0.996	<0.001
	Mean blood pressure mmHg	-0.004	0.996	0.994-0.998	<0.001
Reported pre-ECLS support	Cardiopulmonary bypass	0.239	1.270	1.046-1.542	0.016
	Intra-aortic balloon pump	0.208	1.231	0.920-1.648	0.161
	Ventricular assist devices	0.235	1.264	0.968-1.652	0.086
	Renal replacement therapy	0.314	1.369	1.211-1.547	<0.001
	Prone positioning	0.201	1.222	1.059-1.410	0.006
	Vasodilatory agents	0.473	1.605	1.461-1.763	<0.001
	Anti-hypotensive agents	0.359	1.432	1.331-1.540	<0.001
Reported interventions prior to ECLS	Pericardiocentesis	2.015	7.501	2.258-24.923	0.001
	Thoracic drainage	0.905	2.473	1.927-3.173	<0.001
	Musculoskeletal system surgery	0.455	1.576	0.945-2.626	0.081
	Surgery on other respiratory system	0.522	1.685	1.523-1.864	<0.001
	Surgery on lung or pleura	0.330	1.390	1.193-1.620	<0.001
	Surgery on heart and pericardium	0.357	1.429	1.247-1.637	<0.001
	Surgery on arteries and veins	0.539	1.714	1.522-1.930	<0.001
	Surgery hemic and lymphatic system	0.690	1.993	1.106-3.593	0.022
	Surgery on digestive system	0.245	1.278	1.006-1.623	0.045
	Surgery on urinary system	0.423	1.527	0.757-3.081	0.237
	Surgical procedures on maternity care and delivery	-0.472	0.624	0.184-2.118	0.449
	Surgery on nervous system	-0.791	0.453	0.160-1.280	0.135
	Anesthesia procedure	-0.290	0.748	0.26-1.956	0.555
Diagnosis	Heart failure	0.400	1.491	1.274-1.746	<0.001
	Cardiac arrest	-0.050	0.951	0.789-1.146	0.597
	Hypothermia	1.139	3.123	0.953-10.237	0.060
	Cardiomyopathy	0.383	1.466	1.128-1.906	0.004
	Chronic ischemic heart disease	0.264	1.302	1.050-1.614	0.016
	Endocarditis	-0.174	0.841	0.517-1.367	0.484

Heart transplant/heart transplant failure	-0.121	0.886	0.428-1.835	0.745
SIRS and sepsis	0.306	1.359	1.244-1.483	<0.001
Other specified bacterial diseases	0.318	1.374	0.688-2.744	0.368
Other complications of transplanted organs other than heart	0.129	1.138	0.934-1.387	0.200
Myocardial infection	0.331	1.392	1.083-1.790	0.010
Myocarditis	0.265	1.303	0.582-2.915	0.520
All types of shock (cardiac, other, unspecified, hypovolemic)	0.375	1.455	1.298-1.632	<0.001
Subgroup hypovolemic shock	0.851	2.342	1.665-3.295	<0.001
Subgroup cardiogenic shock	0.128	1.137	0.946-1.365	0.171
Subgroup postoperative shock	1.321	3.747	1.084-12.951	0.037
Subgroup unspecified shock	0.001	1.001	0.838-1.196	0.988
Atrial fibrillation and flutter	0.354	1.424	1.204-1.685	<0.001
Other cardiac arrhythmias	0.223	1.250	0.814-1.920	0.309
Ventricular fibrillation and flutter	0.131	1.140	0.699-1.861	0.599
Respiratory failure	0.326	1.385	1.291-1.486	<0.001
ARDS	0.033	1.033	0.953-1.121	0.430
Asthma	-0.228	0.796	0.670-0.945	0.009
Bronchiectasis	0.750	2.116	1.405-3.188	<0.001
Cystic fibrosis	0.348	1.416	1.045-1.919	0.025
Pneumonia	0.408	1.504	1.400-1.616	<0.001
COPD	0.353	1.423	1.171-1.729	<0.001
Acute pulmonary edema	0.230	1.258	0.983-1.611	0.068
Pulmonary embolism	0.084	1.088	0.852-1.389	0.498
Pulmonary hypertension	0.405	1.499	1.242-1.808	<0.001
Pulmonary vessel disease	1.010	2.744	1.517-4.964	0.001
Respiratory arrest	-0.038	0.963	0.462-2.004	0.919
Respiratory bronchiolitis interstitial lung disease	0.275	1.316	0.699-2.479	0.394
Other interstitial pulmonary disease	0.143	1.154	0.999-1.32	0.051
Intra- and postprocedural complications of the respiratory system	0.270	1.310	1.056-1.626	0.014
Post cardiotomy syndrome	0.510	1.665	0.512-5.408	0.397
Other intra- and post procedure cardiac functional disturbances	0.439	1.551	0.791-3.042	0.202
Postoperative hemorrhage/hematoma/puncture laceration of circulatory system	1.357	3.885	2.386-6.326	<0.001
Other intra- and postprocedural complications of the circulatory system, not elsewhere classified	0.574	1.775	0.803-3.927	0.157

Table 10. *Prediction model with beta and shrunken beta coefficients*

		Shrunken		95% CI for EXP (B)	
	Beta	**Beta**	**OR**	**Lower - Upper**	**Sig.**
Pre-ECLS cardiac arrest	-0,184	-0.176	0,832	0,727 - 0,953	0,008
Surgical cannulation	0,366	0.351	1,442	1,287 - 1,615	<0,001
Lactate	0,012	0.012	1,012	1,002 - 1,022	0,017
pO2	-0,001	-0.001	0,999	0,999 - 1,000	0,013
HCO3	0,022	0.021	1,022	1,017 - 1,027	<0,001
Ventilation rate	0,006	0.006	1,006	1,002 - 1,011	0,009
Mean airway pressure	0,017	0.016	1,017	1,012 - 1,023	<0,001
Pre ECLS CPB	0,290	0.278	1,336	1,085 - 1,645	0,006
Pre-ECLS Renal replacement therapy	0,238	0.229	1,269	1,116 - 1,442	<0,001
Vasodilatory agents	0,310	0.297	1,363	1,236 - 1,503	<0,001
Anti-hypotensive agents	0,291	0.280	1,338	1,237 - 1,448	<0,001
Pericardiocentesis	1,752	1.682	5,768	1,714 - 19,413	0,005
Thoracic drainage	0,618	0.593	1,855	1,430 - 2,406	<0,001
Surgery on the respiratory system other than lung and pleura	0,274	0.263	1,316	1,179 - 1,468	<0,001
Surgery on the lung and or pleura	0,233	0.224	1,263	1,073 - 1,486	0,005
Surgery on arteries and or veins	0,198	0.190	1,219	1,070 - 1,387	0,003
Surgery on the nervous system	-1,246	-1.196	0,288	0,100 - 0,825	0,020
Diagnosis of heart failure	0,202	0.194	1,224	1,036 - 1,447	0,018
Diagnosis of shock (any type except septic shock)	0,127	0.122	1,135	1,003 - 1,286	0,045
Diagnosis of respiratory failure	0,208	0.200	1,231	1,143 - 1,326	<0,001
Diagnosis of cystic fibrosis	0,424	0.407	1,529	1,115 - 2,096	0,008
Diagnosis of pneumonia	0,339	0.325	1,404	1,301 - 1,514	0,000
Diagnosis of pulmonary vessel disease	0,867	0.832	2,380	1,284 - 4,410	0,006
Diagnosis of interstitial pulmonary disease	0,167	0.160	1,181	1,014 - 1,376	0,032
Diagnosis of hypothermia	1,332	1.278	3,787	1,089 - 13,171	0,036
Constant	-2,988	-2.905	0.050		0,000

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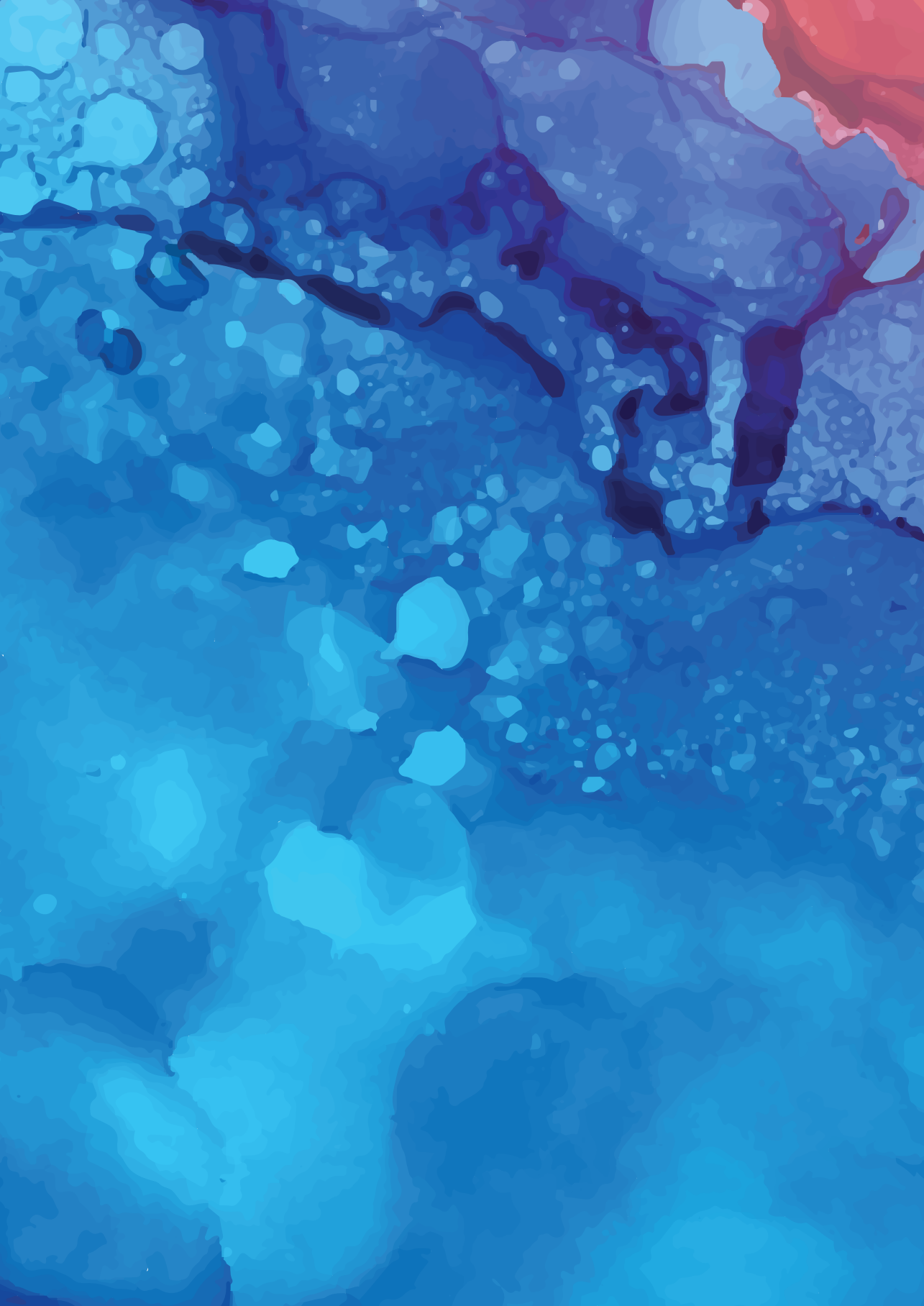

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HEROES V-A
HEmoRrhagic cOmplications in veno-arterial Extracorporeal life Support - Development and internal validation of a multivariable prediction model in adult patients

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Abstract

Background: Risk factors for bleeding complications during extracorporeal life support (ECLS) indicated for cardiac support remain poorly investigated. The aim is to develop and internally validate a prediction model to calculate the risk for bleeding complications in adult patients receiving veno-arterial (V-A) ECLS.

Methods: Data of the Extracorporeal Life Support Organization (ELSO) registry of adult patients undergoing V-A ECLS between 2010 and 2020 were analyzed. The primary outcome was bleeding complications recorded during V-A ECLS. Multivariable logistic regression with backward stepwise elimination was used to develop the prediction model. Performance of the model was tested by discriminative ability and calibration with receiver operator characteristic (ROC), area under the curve (AUC) and visual inspection of the calibration plot. Internal validation was performed to detect overfitting of the model.

Results: In total 28.767 adult patients were included, of which 29,0% developed bleeding complications. Sex, BMI, surgical cannulation, pre-ECLS respiratory and hemodynamic variables, pre-ECLS support and interventions and different type of diagnosis were included in the prediction model. This prediction model showed a predictive capability with an AUC of 0.66.

Conclusion: The model is based in the largest cohort of V-A ECLS patients and is the best available predictive model for bleeding events given the predictors that are available in V-A ECLS compared to current literature. The model can help identifying patients at high risk for bleeding complications and will help in developing further research and decision making in terms of anticoagulation management. External validation is warranted to extrapolate this model in the clinical setting.

Keywords: anticoagulation, bleeding complications, hemorrhagic complications, prediction model, registry data, veno-arterial extracorporeal life support.

Introduction

The use of veno-arterial (V-A) extracorporeal life support (ECLS) is most used in refractory cardiogenic shock, post-cardiotomy cardiac failure or cardiac arrest. The use has been increasing over time, with expanding indications [1, 2]. Patients supported on ECLS have impaired hemostasis due to blood contact to artificial surfaces, use of anticoagulation and underlying conditions [3, 4]. Bleeding complications in V-A ECLS are the most frequent adverse events, followed by renal failure, vascular complications, and infections [5, 6]. Rates of bleeding complications are reported between 22.3% and 46% [7, 8] but the incidence may be higher than 80% [5]. Bleeding events within the first 48 hours of V-A ECLS initiation have been found in 46% [8] and for patients undergoing post-cardiotomy ECLS, the rate of re-thoracotomy for hemorrhage or tamponade was 41.9% [9].

The underlying mechanisms of development of bleeding complications on ECLS is not completely understood and is likely multifactorial; comorbidities can also contribute to a higher risk for bleeding complications [1, 10, 11].

Many small observational studies have found an association of potentially modifiable risk factors with bleeding complications. It was found that therapeutic hypothermia (32-34 degrees Celsius) after cardiac arrest did not increase the risk for bleeding complications, but lactate values prior to hypothermia and 24 and 48 hours post cardiac arrest did. A platelet count below 60 x 109/L was associated with major bleeding complications [12]. High blood pressure and low CO2 were reported independently associated with intracranial bleeding [13]. Also, duration, use of anti-thrombotic therapy, renal failure and female gender were found to be risk factors for intracranial hemorrhage [14]. Another study reported central cannulation, hypertension, male sex as risk factors for bleeding complications [15].

Bleeding complications are associated with higher need for transfusion, increased morbidity, and mortality [4, 15]. Thus, it would be beneficial and helpful to recognize patients at higher risk for bleeding complications and to protect them adjusting or avoiding anticoagulation for limited time. Therefore, a prediction score for bleeding complications is warranted. Further, separate risk prediction models for V-A and V-V are necessary, since the underlying pathophysiology and diseases, ECLS duration and anticoagulation needs differ between the configurations. There are no specific prediction scores for bleeding complications in V-A ECLS. Thus, we aimed to develop and validate a prediction model for bleeding complications in adult patients receiving V-A ECLS support using the largest international registry dataset available.

Methods

Data source and patient selection

The analyzed data was provided by the ELSO registry, an international registry maintained by the Extracorporeal Life Support Organization (ELSO). This registry

collects data on all ECLS runs worldwide of ELSO centers since 1989. Almost 500 centers in 60 countries are voluntarily contributing data in this registry. Data entry is performed by certified data managers of ELSO centers and is regulated by standardized case report forms and error and validity checks [16-18]. Data of demographics, pre- and on-ECLS assessments, diagnosis, interventions, and complications are collected. Since bleeding complications have been decreased the last ten years, possibly due to significant improvements of ECLS devices, we included data from adult (≥18 years old) patients undergoing V-A ECLS between 01.01.2010 and 31.03.2020. Only patients with one ECLS run were eligible to prevent bias of cumulative effects and dependency in the data. Patients undergoing ECPR were also included.

Variables analyzed included demographics, pre-ECLS and on-ECLS assessment, reported interventions and complications. The data entry rules in the ELSO registry data definitions were used for data assessment with error and validity checks, e.g. for weight, height and other continuous variables such as blood gas analysis, hemodynamic blood pressures and ventilator settings [19]. Information on laboratory findings (hemoglobin, platelet count, Activated Clotting Time (ACT), activated Partial Thromboplastin Time (aPTT)) amount of blood loss, timing, and impact and pre-ECLS bleeding sites and use of anticoagulation agents are not sampled in the registry.

Ethic statement

Each institution participating in ELSO Registry approves data reported to the registry through their local institutional review board. This study involved only analysis of pre-existing de-identified data from an international registry, and as such no ethics approval was required. Similarly, no patient consent was required. De-identified data are available to member centers for scientific research and publication without need for further institutional research board approval.

Co-variates and outcomes

To obtain practical variables, we clustered age, pre-ECLS support, medication, interventions, and diagnosis into groups. Age was divided in categories: 18-40 years, 40.1-60 years, 60.1-80 years, 80.1 years or older, since age above 80 was not continuous reported. Body Mass Index (BMI) was calculated as weight (kg)/squared height in meters. Ventricular assist devices (VADs) include Berlin Heart, biventricular assist device (BiVAD), left ventricular assist device (LVAD), right ventricular assist device (RVAD), and percutaneous ventricular assist device (PVAD). Anti-hypotensive agents include use of epinephrine, norepinephrine, dopamine, dobutamine, vasopressin, phenylephrine, metaraminol and/or the old definition code for vasopressor/inotropics. Vasodilatory agents include the use of nicardipine,

nitroglycerine, nitroprusside, nitric oxide, sildenafil, tolazoline, and/or the old definition vasodilators codes. Therapeutic hypothermia was defined as induces hypothermia of 35 degrees Celsius or lower.

Furthermore, pre-ECLS assessment include arterial blood gasses, ventilator settings and hemodynamic values closest to ECLS start (no more than 6 hours before ECLS start). Pre-ECLS interventions and diagnosis were also clustered into groups based on CPT codes for interventions and ICD-9 and ICD-10 codes for diagnosis (Supplemental Table 1, 2). The pre-ECLS assessment include arterial blood gasses values, ventilator settings and hemodynamic values closest to ECLS start (within 6 hours prior to ECLS start).

The primary outcome was defined as occurrence of any type of bleeding complication. The definition of bleeding complications defined by ELSO registry includes requirement of packed red blood cell transfusion (PRBCs) of >20ml/kg/24hrs or >3 Units/24hrs, endoscopic intervention for bleeding, CT-, ultrasound- or MRI-imaging for gastro-intestinal, cannulation site, surgical site, central nervous system, and pulmonary bleeding complications. Tamponade bleeding was defined as tamponade during ECLS run requiring pericardial drainage or mediastinal washout of blood.

Statistical analysis

Baseline characteristics were expressed as percentages for ordinal and categorical variables and mean +/- standard deviation (SD) for continuous variables. Baseline characteristics and complications were compared between patient with or without bleeding complications and between patients, who underwent extracorporeal cardiopulmonary resuscitation (ECPR) or V-A ECLS for other underlying diseases than cardiac arrest. Differences between means and continuous variables were tested with the independent samples T-test. The Pearson chi-square test was used to compare categorical data. The Fisher exact test was used when the expected count was less than 5 in at least 20% of the cells. Statistical significance was set at a two-sided p-value of less than 0.05. The sample size was determined pragmatically as the amount of available V-A ECLS adult patients in the ELSO registry between 01.01.2010 and 31.03.2020. The number of potential predictor variables was determined using the 10 events-per-variable rules of thumb [20].

Missing data were imputed using stochastic regression imputation using predictive mean matching. (Table 1) Single imputation was used due to feasibility reasons in such a large dataset compared to multiple imputation methods. Missing values were mostly on mean airway pressure, lactate values, and peak inspiratory pressure (PIP). Since these variables were initially assumed to be important risk factors and potential predictors for bleeding complications, the variables were included in the imputation method. (Table 1)

Table 1. *Numbers and percentage of missing data and cut-off values*

Patients´ characteristics ECLS data Monitoring values	N missing of total n=28.767	% Missing data	Lower limit	Upper limit
Sex	611	2.12%	-	-
Weight (kg)	1.537	5.34%	10.0	500.0
Height (cm)	12.594	43.78%	70.0	250.0
BMI	12.655	43.99%	10.0	100.0
Age	0	0.00%	18	-
ECLS duration	291	1.01%	-	-
Lactate	19.948	69.34%	-	40
pH	8.462	29.42%	6.00	8.00
PaO_2 (mmHg)	9.088	31.59%	0	760
PaO_2 (mmHg)	9.345	32.49%	10	250
HCO_3 (mmol/L)	9.448	32.84%	0	70
SaO_2 (%)	11.567	40.21%	1	100
Ventilation rate (bpm)	13.759	47.83%	0	90
FiO_2 (%)	11.625	40.41%	10	100
PEEP (cm H_2O)	14.128	49.11%	0	40
PIP (cm H_2O)	17.446	60.65%	0	80
Mean AP (cm H_2O)	20.202	70.23%	0	60
Mean BP (mmHg)	12.636	43.93%	0	250

Abbreviations; BMI - body mass index, PaO_2 - partial pressure of oxygen, $PaCO_2$ - partial pressure of carbon dioxide, HCO_3 - bicarbonate, SaO_2 - saturation of oxygen, FiO_2 - fraction of oxygen supplied on ventilator, PEEP - positive end expiratory pressure, PIP - peak inspiratory pressure, Mean AP - mean airway pressure, mean BP – mean blood pressure

Designing, conducting, and analyzing the developed prediction model was performed according to the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) Statement to guarantee transparent and complete reporting of the prediction model development [21, 22]. (Supplemental Table 3) Potential predictors were identified based on clinical reasoning and previous published risk factors for bleeding complications [4, 7, 13, 23-26]. Continuous predictors were modelled as linear since we did not have an a priori hypothesis of non-linear associations between continuous variables and the outcome.

Univariable logistic regression was used to assess crude associations between potential predictor variables and bleeding complications on the imputed data. Variables with a $p < 0.20$ were considered important potentially covariates and submitted to multivariable logistic regression analysis to assess the association of duration of ECLS and bleeding complications. We computed correlations between potential predictor variables to make sure no predictors with very high correlation (i.e. >0.8) were added simultaneously in the multivariable model.

All variables tested in the univariable logistic regression analysis were used in the formation of the prediction model. Using multivariable regression with backward elimination process, the most significant variables were included while

other variables were excluded based on the least strong associations. For feasibility reasons, mean blood pressure instead of systolic and diastolic pressure was included and shock overall instead of specific types of shock.

Performance of the prediction model was quantified as discriminative ability and calibration. Discrimination of the predictive model included the area under the Receiver Operating Characteristic (ROC) curve with 95% confidence interval, or Area Under the Curve (AUC). An AUC of 0,5 indicates no discriminative ability; an AUC of 1 indicates perfect discriminative ability. A calibration plot was built and assessed by visual inspection. The calibration plot shows the agreement between predicted probabilities and pseudo-observed event status and should follow a 45-degree line of perfect agreement.

Internal validation of the model

In general, the contribution of predictor variables is overestimated when developing a model. Moreover, measures of predictive performance may be too optimistic when compared to actual performance in future patients. Therefore, internal validation was performed using standard bootstrapping methods, with B = 1000. In each bootstrap sample, modelling steps were repeated, and model performance was evaluated on the bootstrap and the original sample. From this, we extracted the shrinkage factor and measures of optimism in model performance. The internal validation was performed separately from the model building to ensure transparency. This resulted in a constant that was subsequently used to shrink regression coefficients towards zero to prevent too extreme predictions in future patients and secondly, a measure of optimism in the AUC which was subtracted from the apparent AUC to compute the optimism-corrected AUC.

Analyses were performed with commercially available statistical software SPSS (Version 26.0, IBM, Armonk, New York, USA). and R (Version 4.0.4 R Core Team (2017) R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 28.767 adult patients supported with V-A ECLS were included in the analysis, after exclusion of 3.794 patients with multiple runs. Patient characteristics are summarized in the tables. (Table 2, 3, 4) Bleeding complications occurred in 8.343 (29,0%) patients.

Patients with bleeding complications were more likely to be male, older, longer ECLS duration, and more often surgically cannulated. Pre-ECLS blood pressures, ventilation rate, fraction of inspired oxygen (FiO2) and positive end expiratory pressure (PEEP) were significantly different between the bleeding and non-bleeding group, as well as PaO2 and SaO2 in the blood gas analysis. Pre-ECLS support therapies were significantly more used in the bleeding group. (Table 2) Most

surgical interventions were more frequent in the bleeding group. (Table 3) Shock was the most frequent diagnosis (40.6%), followed by cardiac arrest (21.7%), heart failure (20.2%), myocardial infarction (18.0%) and chronic ischemic heart disease (15.3%). These diagnoses were significantly more observed in the bleeding group, except for cardiac arrest. (Table 4) Baseline values were compared between patients undergoing ECPR support versus V-A ECLS. Patient characteristics, ECLS duration and cannulation, pre-ECLS support and complications were almost all significantly different between these two groups. (Table 5) Incidence of mechanical complications, renal failure, infection, limb complications and hospital mortality were all significantly higher in the bleeding group. (Table 6)

Risk factors for bleeding complications

In the univariate regression analysis, multiple variables were found to be potential prediction variables with a significant association to bleeding complications. Variables with odds ratios exceeding 2.0 were surgical cannulation; CPB; thoracic drainage; surgery on heart; surgery on arteries and veins; pulmonary vessel disease; aortic aneurysms and dissections without rupture; ruptured aneurysms of the aorta; postoperative hemorrhage of the circulatory system and other intra- or postoperative complications of the circulatory system. (Table 7)

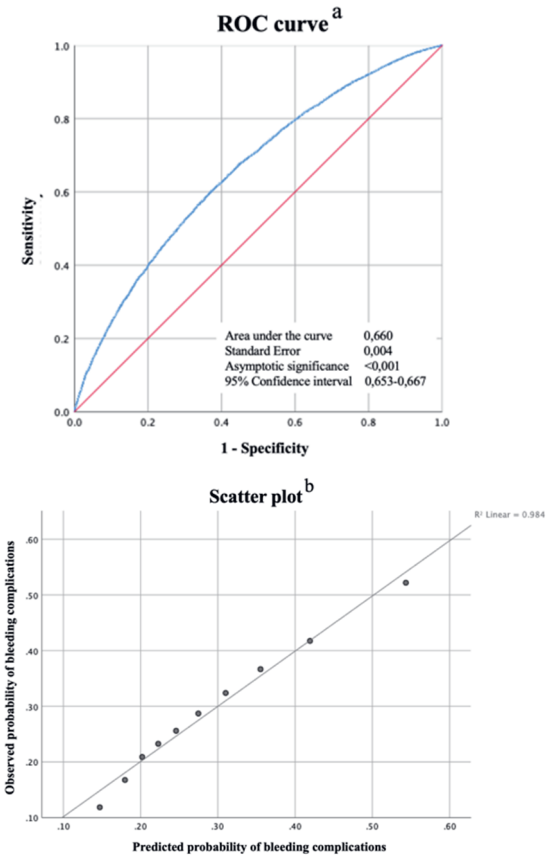
Model performance

In the final model sex, BMI, surgical cannulation, pre-assessment values, intervention and diagnosis are included. Many variables were excluded due to the backward elimination process based on the impact on the prediction, including ECPR support. In total 30 variables were included. Notably in the final model pH, PEEP, mean airway and blood pressure and therapeutic hypothermia were found to be predictive variables for bleeding complications. BMI, pH, PEEP and surgery on the musculoskeletal system and intra- and postoperative complications of the circulatory system other than hemorrhage were protective variables for bleeding complications. The full model with regression coefficients is presented in Table 8. Discrimination of the model revealed an AUC of 0.660 (95% CI: 0.653 – 0.667, p<0,001). (Figure 1a)

The model is assumed to be well-calibrated, based on the calibration plot. (Figure 1b) In this figure, the predicted and observed probability between the deciles of patients is close to the ideal line of 45 degrees, indicating good calibration. Internal validation showed limited overfitting with a shrinkage factor of 0.990. Optimism of the AUC was 0.002, which concluded in an expected AUC in patients outside of the cohort of 0.660 - 0.002 = 0.658.

To calculate an individual's risk score at initiation of ECLS for experiencing bleeding complications with this model, the formula (Figure 2), or a proposed website-based calculator (Figure 3) can be used.

Figure 1. *Discrimination and calibration of the predictive model*



A) ROC discrimination curves and B) calibration scatter plot

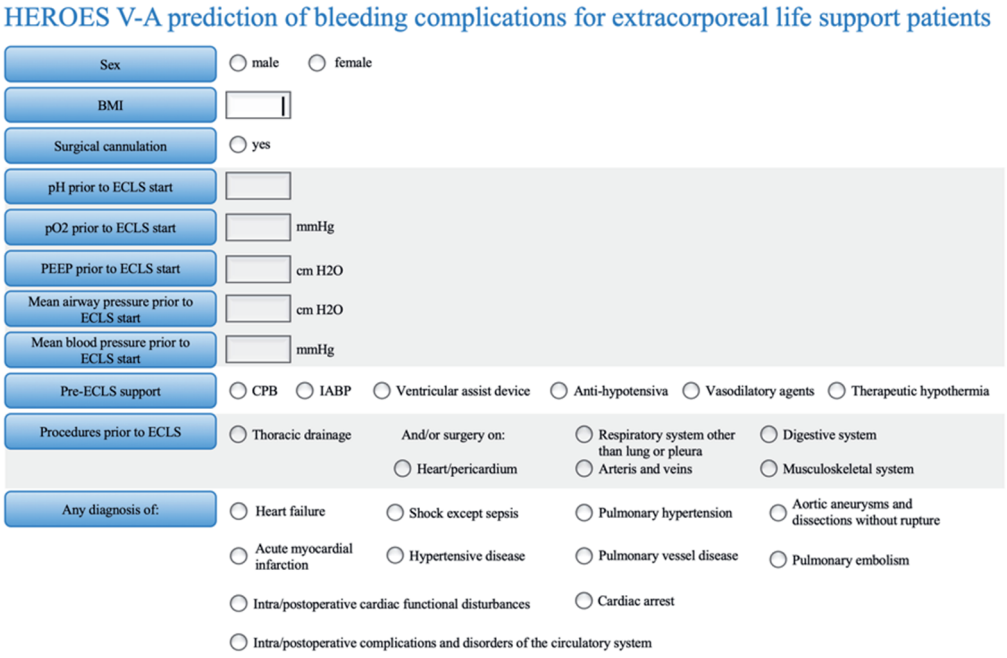
Figure 2. *Formula for prediction model of bleeding complications in veno-arterial extracorporeal life support*

$$P(\text{bleeding complication}) = 1/(1+e^{-(\text{linear predictor})})$$, in which

linear predictor = 1,193 + (0,098 • Male*) + (-0,005 • BMI) + (0,468 • Surgical cannulation *) + (-0,366 • pH) + (0,000 • pO2) + (-0,010 • PEEP) + (0,007 • MeanAP) + (-0,004 • MBP) + (0,477 • CPB*) + (0,159 • IABP*) + (0,243 • VAD*) + (0,195 • Therapeutic hypothermia*) + (0,096 • vasodilatory agents*) + (0,237 • anti-hypotensive agents*) + (0,381 • thoracic drainage*) + (-0,541 • surgery on musculoskeletal system*) + (0,234 • surgery on respiratory other than lung or pleura*) + (0,430 • surgery on heart/pericardium*) + (0,360 • surgery on arteries/veins*) + (0,467 • surgery on digestive system*) + (0,190 • heart failure*) + (0,147 • cardiac arrest*) + (0,109 • acute myocardial infarction*) + (0,226 • shock*) + (0,274 • pulmonary embolism*) + (0,647 • pulmonary hypertension*) + (1,052 • pulmonary vessel disease*) + (0,412 • aortic aneurysm or dissection without rupture*) + (0,547 • hypertensive diseases*) + (0,258 • intra/postoperative cardiac functional disturbances*) + (-1,098 • intra/postoperative complications of the circulatory system other than hemorragic complications*)

*; yes = 1, pO2; partial pressure of oxygen, PEEP; positive end-expiratory pressure, MeanAP; mean airway pressure; MBP; mean blood pressure; CPB; cardiopulmonary bypass, IABP; intra-aortic balloon pump, VAD; ventricular assist device

Figure 3. *Website-based prediction model calculator*



Discussion

In our analysis 29,0% patients supported on V-A ECLS developed bleeding complications. Identified risk factors were ECLS duration, anticoagulation, post-cardiotomy ECLS, previous surgery, higher BMI, lower hemoglobin, fibrinogen levels, pH, and fungal pneumonia, comparable to available literature [3, 8, 14]. Duration of ECLS was highly associated with bleeding complications. Possible risk factors for bleeding complications in this large cohort of 28.767 adult patients were surgical cannulation, the use of CPB, VADs or intra-aortic balloon pump IABP prior to ECLS and surgical interventions on the heart, lung and pleura, arteries and veins, digestive system. Diagnosis of pulmonary hypertension and pulmonary vascular disease, as well as aortic aneurysms (with or without rupture) and hypertensive diseases.

Our bleeding prediction model showed an AUC of 0.658 after correction for optimism. As expected, and according to the literature, surgical interventions and pre-CPB, gender and pH were included in our model. ECPR was used as a possible predictive value instead of separate prediction model for this subgroup. The regression coefficients of the multivariable analysis of the ECPR and non-ECPR group were compared, and despite differences in baseline between ECPR and non-ECPR patients, the regression coefficients were comparable to each other. Meaning, the separation of models between ECPR and non-ECPR patients would not yield significant differences between the groups and would not benefit the predictive value

of the models. With multivariable analysis, ECPR did not have a superior predictive value, compared to other variables. ECPR as a predictive variable, was therefore not included in the final model due to the backward elimination process. Of note, the presence of a cardiac arrest at any point during the four hours prior to ECLS was included in the model. Furthermore, we checked if the use of subgroups of shock (hypovolemic, cardiogenic, postoperative, and unspecified shock) acted differently in the model compared to shock overall. We found no difference in the models, so the variable shock remained an overall variable due to feasibility reasons.

Prediction scores for bleeding complications were developed for several non-ECLS settings. (Table 9) In trauma, the assessment of bleeding consumption (ABC) and revised assessment of bleeding and transfusion (RABT) scores were developed to predict the need for mass transfusion [27, 28]. A significant increase in mortality in trauma patients was observed as the average number of transfusions per hospital day (significance level 0.024, Exp (B) 4.378, 95% confidence interval for Exp (B) 1.212 to 15.810) [29]. The ABC score includes penetrating trauma, systolic blood pressure (SBP) <90mmHg, heart rate >102 bpm, positive FAST (Focus Assessment Sonography in Trauma) as predictive variables, whereas the RABT score used the shock index ≥ 1 and pelvic fractures instead of SBP and heart rate [27, 28].

In acute myocardial infarction, numerous risk scores were developed to predict major in-hospital bleeding complications. The CRUSADE score includes sex, heart rate, SBP, history of diabetes, prior vascular disease, signs of congestive heart failure, baseline hematocrit <36%, and creatinine clearance [30]. The ACTION score includes similar variables, but uses other medical history and includes weight, and the use of anticoagulation drugs [31, 32]. In a meta-analysis, these risk scores were compared with an additional ACUITY score. In acute coronary syndrome patients, the three scores performed similarly, as well as for STEMI patients [33]. Multiple groups performed comparisons of the performance of the CRUSADE, ACTION and ACUITY-HORIZON scores in different cohorts. The CRUSADE and ACTION scores are more favorable based in the predictive value for bleeding complication [34-37]. The SWEDEHEART score including hemoglobin, age, sex, creatinine, and CRP, developed for patients with acute myocardial infarction in 2019 seems to be superior to the CRUSADE and ACTION scores [38]. The HAS-BLED score is a score developed to estimate the risk of major bleeding in patients with atrial fibrillation using anticoagulation [39]. This score includes hypertension, abnormal renal or liver function, stroke, bleeding history or predisposition, labile international normalized ratio, age over 65 years and use of drugs or alcohol concomitantly. It is mostly used to support clinical decisions regarding to antithrombotic therapy start or withdrawal in patients with atrial fibrillation [39].

Cardiac surgery setting seems to be the most comparable to V-A ECLS. Four major risk scores exist to predict bleeding complications: the Papworth score,

TRUST, TRACK, and WILL BLEED [40-43]. The Papworth score is based on a prospective cohort of almost 12.000 patients undergoing CPB supported cardiac surgery and has been developed to predict early bleeding complications (blood loss >2ml/kg/h) within 3 hours of ICU admission. Variables of this model include surgery priority, type of surgery, aortic valve disease, BMI, and age [40]. Hemoglobin, sex, redo-surgery and creatinine as predictors for bleeding complications are additionally included in TRUST score [41]. Hematocrit instead of hemoglobin is used in the TRACK score [42]. The WILL BLEED score included sex, hemoglobin, eGFR <45 ml/min/1.73 m2, antiplatelet drugs (clopidogrel and ticagrelor) discontinued less than five days, acute coronary syndrome (ACS) and the use of low molecular weight heparin, fondaparinux and/or unfractionated heparin as predictors for bleeding [43]. All these risk scores had a predictive value with AUC around 0,70-0,75.

The only prediction score for bleeding complications validated in V-A ECLS is the HAT Score [44]. This score includes hypertension, age older than 65, and ECLS type as predictive variables and may allow bleeding risk stratification in adult patients undergoing ECLS. With an AUC of 0.66, it showed a superior predictive performance compared to the HAS-BLED score. Also REMEMBER score was specifically developed for post-coronary arterial bypass grafting in V-A ECLS; however, to predict mortality [45]. Older age left main coronary artery disease, inotropic score, CK-MB, creatinine, and platelet levels are included in this score and has an AUC of 0.85 (95% CI 0.79-0.91).

Table 9. *Prediction scores for bleeding complications in several patient populations*

Reference	Score	Population	Outcomes	AUC
Cotton et al [27]	ABC	Trauma patients	Massive transfusion	0.83 (95% CI 0.77-0.90) 0.90 (95% CI 0.87-0.94)
Hanna et al [28]	RABT	Trauma patients	Massive transfusion	0.89 (95% CI 0.86-0.91)
Mathews et al [32] Desai et al [31]	ACTION	ACS	In hospital major bleeding	0.74
Subherwal et al [30]	CRUSADE	NSTEMI	Risk major bleeding	0.71
Simonsson et al [38]	SWEDEHEART	AMI	Bleeding complications	0.80 (95% CI 0.79-0.81)
Pisters et al [39]	HAS-BLED	Atrial fibrillation	Risk major bleeding with anticoagulation	0.72
Vuylsteke et al [40]	Papworth	Cardiac surgery	Early postoperative bleeding	Not mentioned
Alghamdi et al [41]	TRUST	Cardiac surgery	Need for blood transfusion	0.78 (SE 0.0052) 0.81 (SE 0.0006)
Ranucci et al [42]	TRACK	Cardiac surgery	Need for blood transfusion	0.71 (95% CI 0.69-0.73)
Biancari et al [43]	WILL BLEED	Cardiac surgery	Identify high risk bleeding	0.73 (95% CI 0.69-0.76)
Lonergan et al [44]	HAT	V-V | V-A ECLS	Bleeding complications	0.66

Strengths and limitations of the HEROES V-A predictive model

The HEROES V-A model for bleeding complications in V-A ECLS is based on the largest cohort available, including over 28.000 patients even after exclusion of ECLS runs before 2010. We used single imputation based on drawing from the posterior distribution conditional on the imputation model. The only major difference between single and multiple imputation in this case is the fact that single imputation

may yield results that tend to be too precise. We chose for single imputation nonetheless as the study was primarily concerned with estimation, not null-hypothesis testing, and because multiple imputation would have yielded many practical and statistical challenges. For one, the already very large dataset would have been multiplied M times, resulting in large intervals between executing commands and getting analysis results. This is especially prevalent when combining multiple imputation with bootstrap resampling. Moreover, although Rubin's rules to pool results into a single inference can easily be applied to regression coefficients, it does not provide methods to pool measures of model performance. Further, we abided by the rule of thumb to prevent (severe) overfitting which is more likely the more variables are studies given a fixed set of events. Appropriateness of the model has been evaluated in terms of performance of the model for the sample we collected and verified using internal validation using bootstrapping. We have expanded the text on the bootstrap validation. Therefore, internal validation was performed using standard bootstrapping methods, with B = 1000. In each bootstrap sample, modelling steps were repeated, and model performance was evaluated on the bootstrap and the original sample. From this, we extracted the shrinkage factor and measures of optimism in model performance.

We used backward elimination process; however, it could cause overfitting of the model. As a matter of fact, this was one of the reasons we additionally performed the bootstrap resampling to get an estimate of overfitting and optimism. However, the amount of candidate predictors was far too large for any practical application, and no other methods (e.g., expertise, previous literature) was considered sufficient to base our decisions on.

Due to the use of the large cohort, the developed risk model is robust. It provides a debatable discriminatory performance. The shrinkage factor was remarkably close to 1 and the measures of optimism close to, concluding that HEROES V-A model was not particularly over-fitted and did not need much penalization. External validity is expected to be high, because of the multi-center international design of the registry. By focusing on V-A ECLS runs and including only adult patients, we created more homogeneity. Multiple runs were also excluded to prevent bias by cumulative effects and to create even more homogeneity in the cohort.

The HEROES V-A model has also several limitations. A number of important characteristics are associated with bleeding, that are not, or cannot be recorded. As these are not available, it is unlikely the model can be improved substantially over the current performance. Laboratory findings (hemoglobin, platelets count) and anticoagulation agent information are not recorded in the ELSO Registry. However, anticoagulation agents, hemoglobin and creatinine are included in the risk scores of bleeding complications in other patient populations, especially for cardiac surgery

population. For model application, the use of cut-of thresholds resulting in dichotomized prediction results (e.g. 'low risk' and 'high risk') is necessary, as this ensures reproducible decisions regardless of the user. We have not determined one or more cut-of values as the choice which value is best is determined by many factors, amongst others the intended use (rule out or rule in), the prevalence of bleeding complications in the specific setting, and the cost of misclassification. We think that the intended user should decide, based on characteristics of the local setting, what cut-of value should be used. Moreover, whether discrimination is important depends on the intended use of the model. It appears they envision this being used by clinicians to make individual patient care decisions, rather than as a benchmarking tool to characterize entire cohorts. If this is a clinical prediction tool, the AUROC provides very little insight into model performance. The practicing clinician may well be more interested in sensitivity and positive predictive value, among other more interpretable metrics.

We performed bootstrapping as an internal validation method as this employs all data for both model development and for model validation. This is widely accepted as internal validation method and has several advantages over other internal validation methods, such as testing on a held-out dataset. We kindly refer the reviewer to the Prediction model Risk Of Bias ASsessment Tool (PROBAST) in which bootstrapping is regarded as a competent means to internally validate.

Further limitation is the use of a retrospective database, patient data being limited to the recorded information only, with the obvious problem of incomplete cases or missing values. To minimize bias, we chose an imputation method that allows for unbiased estimates after imputation when the missingness mechanism has been considered in the imputation model. The stochastic regression imputation was based on a large number of covariates that were likely associated with missing values, as these variables were selected from demography, disease characteristics, ECMO characteristics, and outcomes, as per data imputation guidelines. Since we believed lactate and mean airway pressure to be important potential predictor variables, we imputed these as well despite a higher percentage of missingness. This likely caused more uncertainty in the estimated regression coefficients as reflected by the confidence intervals. The size of the database helped us to limit potential bias related to the missing data. Patient outcomes are limited to the in-hospital course, because the ELSO registry does not include follow-up data after transfer from the hospital to other facilities. Furthermore, external validation in an independent cohort is warranted to be able to use this model in clinical settings.

We acknowledge that p-value based selection methods should be avoided when possible as the selection is unlikely to be completely reproducible in other datasets and yields estimation bias. However, we have selected this method as we had far too many candidate predictors to allow to be included in a multivariable

prediction model, if only for practical purposes, and too little is known on predictors of bleeding to perform the selection based on the available literature and expert opinion only. To counteract the effect of testimation bias (i.e. coefficients are biased away from the null due to p-value based selection), shrinkage of coefficients was performed based on the internal validation results.

The HEROES V-A model showed a predictive discriminative capability with an AUC or 0.658 after adjustment for optimism. Due to the analysis of a large dataset, this is highly accurate, reflected by a small 95% CI of 0.653-0.667. Further research may improve the model by identifying and adding other important predictors. External validation is needed to implement the model in clinical settings; however, the model might already be used for research purposes and crude estimates in bleeding risk. Development of an online prediction tool could make the model more accessible to other researchers and clinicians (Supplemental Figure 1).

The major barriers of the HEROES V-A score that were raised are: AUC at 0.66, lack of external validation, and the absence of laboratory variables in ELSO registry data. The ability to predict outcomes is still preserved despite the lack of anticoagulation data, thus explored variables may strongly influence bleeding and clotting despite any anticoagulation or lack thereof. The data span a decade that saw a rapid increase in the use of ECLS with many changes in practice e.g. circuit design, surface coatings, cannulation techniques leading to development of new anticoagulation agents and paradigm changes in anticoagulation management (e.g. anticoagulation free ECLS run) [11, 46]. That might be an era effect for the variables that were protective against bleeding [11, 46]. Finally, the main question might be to estimate the risk of bleeding complications and to adjust the anticoagulation lever or to leave it out for the limited time.

Conclusion

HEROES V-A for bleeding complications in patients support with V-A ECLS is an internally validated prediction model based on the largest multi-center cohort including over 28.000 patients. We assumed, there are many factors related to bleeding, but these characteristics are not or cannot be recorded, are thus not available. The model showed a prediction with an AUC of 0.66. This is the best available predication model for bleeding complications in adult V-A ECLS patients, compared to available literature, given the predictors that are available. The model can help identifying patients at high risk for bleeding complications and will help in developing further research and decision making in terms of anticoagulation management. External validation is warranted to extrapolate this model in the clinical setting.

Table 2. *Characteristics prior to veno-arterial extracorporeal life support*

Groups	Values	Total n=28767	Non-bleeding n=20.424 (71.0%)	Bleeding n=8.343 (29.0%)	*p* value
Patient characteristics	Male n (%)	18.916 (67.2)	13.476 (67.8)	5.440 (65.7)	0.001
	Weight KG (±SD)	84.29 ±23.04	84.17 ±22.97	84.55 ±23.21	0.224
	Height cm (±SD)	170.98 ±10.94	171.09 ±10.80	170.68 ±11.32	0.040
	BMI	28.82 ±6.96	28.79 ± 6.96	27.84 ± 6.97	0.005
	Age categories				0.005
	18-40 years n (%)	5.338 (18.6)	3818 (18.7)	1.520 (18.2)	
	40.1-60 years n (%)	11.243 (39.1)	8.084 (39.6)	3.159 (37.9)	
	60.1-80 years n (%)	11.476 (39.9)	8.037 (39.4)	3.439 (41.2)	
	80 or older n (%)	710 (2.5)	485 (2.4)	225 (2.7)	
	Days on ECLS mean (±SD)	5.63 ±7.48	5.08 ±6.73	6.99 ±8.91	<0.001
	Support type				<0.001
	- Pulmonary n (%)	1.363 (4.7)	998 (4.9)	365 (4.4)	
	- Cardiac n (%)	20.520 (71.3)	14.324 (70.1)	6.196 (74.3)	
	- ECPR n (%)	6884 (23.9)	5.102 (25.0)	1.782 (21.4)	
	Cardiac arrest n (%)	12.735 (44.3)	9.160 (44.8)	3.575 (42.9)	0.002
	Bridge to transplant n (%)	1.509 (5.2)	1.111 (5.4)	398 (4.8)	0.021
	Surgical cannulation n (%)	10.425 (36.2)	6.399 (31.3)	4.026 (483)	<0.001
Pre-ECLS blood gas closest to ECLS start	Lactate mmol/L (±SD)	8.40± 6.06	8.39 ±6.19	8.44 ±5.74	0.696
	pH (±SD)	7.24 ±0.18	7.24 ±0.18	7.24 ±0.18	0.686
	PaO_2 mmHg (±SD)	141.75 ±122.23	137.56 ±118.99	150.88 ±128.55	<0.001
	$PaCO_2$ mmHg (±SD)	47.37 ±22.31	47.57 ±22.76	46.94 ±2127	0.064
	HCO3 mmol/L or mEq/L (±SD)	19.38 ±6.41	19.36 ±6.46	19.41 ±6.29	0.665
	SaO_2 % (±SD)	89.43 ±15.69	89.22 ±15.86	89.87 ±15.31	0.009
Ventilator settings closest to ECLS start	Rate bpm (±SD)	17.90 ±6.44	18.03 ±6.41	17.61 ±6.49	<0.001
	FiO_2 % (±SD)	84.63 ±23.15	84.29 ±23.43	85.40 ±22.52	0.003
	PEEP cm H2O (±SD)	7.95± 4.00	8.04 ±3.99	7.74 ±4.00	<0.001
	PIP cm H2O (±SD)	26.26 ±8.17	26.28 ±8.16	26.24 ±8.17	0.829
	Mean AP cm H2O (±SD)	15.20 ±6.85	15.26 ±6.74	15.04 ±7.11	0.174
Hemodynamics closest to ECLS start	SBP mmHg (±SD)	85.82 ±29.69	86.94 ±29.95	83.36 ±28.96	<0.001
	DBP mmHg (±SD)	52.47 ±19.41	53.16 ±19.70	50.94 ±18.66	<0.001
	MBP mmHg (±SD)	62.23 ±20.54	62.83 ±20.75	60.94 ±20.03	<0.001
Pre-ECLS support therapy	CPB n (%)	4.510 (15.7)	2.469 (12.1)	2.041 (24.5)	<0.001
	IABP n (%)	5.704 (19.8)	3.700 (18.1)	2.004 (24.0)	<0.001
	VADs n (%)	2.336 (8.1)	1.532 (7.5)	804 (9.6)	<0.001
	- Berlin Heart n (%)	6 (0.0)	3 (0.0)	3 (0.0)	0.365
	- BiVAD n (%)	60 (0.2)	36 (0.2)	24 (0.3)	0.060
	- LVAD n (%)	1.122 (3.9)	704 (3.4)	418 (5.0)	<0.001
	- RVAD n (%)	149 (0.5)	104 (0.5)	45 (0.5)	0.746
	- PVAD n (%)	1.065 (3.7)	727 (3.6)	338 (4.1)	0.045
	RRT n (%)	1.705 (5.9)	1.174 (5.7)	531 (6.4)	0.045
	Therapeutic hypothermia (<35 degrees Celsius) n (%)	556 (1.9)	339 (1.7)	217 (2.6)	<0.001
	Vasodilatory agents n (%)	2.785 (9.7)	1.741 (8.5)	1.044 (12.5)	<0.001
	Anti-hypotensive agents n (%)	20.988 (73.0)	14.379 (70.4)	6.609 (79.2)	<0.001

Abbreviations: ECLS - extracorporeal life support, ECPR - extracorporeal cardiopulmonary resuscitation, FiO_2 - fraction of inspired oxygen, PEEP - positive end expiratory pressure, PIP - peak inspiratory pressure, MeanAP - mean airway pressure, SBP - systolic blood pressure, DBP - diastolic blood pressure, MBP - mean blood pressure, CPB - cardiopulmonary bypass, IABP - intra-aortic balloon pump, VADs - ventricular assist devices, BiVAD - biventricular assist device, LVAD - left ventricular assist device, RVAD - right ventricular assist device, PVAD - percutaneous ventricular assist device, RRT - renal replacement therapy, +SD - standard deviation, n - number

Table 3. *Reported interventions and surgery procedures prior to veno-arterial extracorporeal life support initiation*

Interventions and surgical procedures	Total n=28.767	Non-bleeding n=20.424 (71,0%)	Bleeding n=8.343 (29,0%)	*p* value
Pericardiocentesis	92 (0.3)	58 (0.3)	34 (0.4)	0.092
Thoracic drainage	152 (0.5)	70 (0.3)	82 (1.0)	<0.001
Surgery on musculoskeletal system	143 (0.5)	104 (0.5)	39 (0.5)	0.648
Surgery on lung or pleura	605 (2.1)	338 (1.9)	217 (2.6)	<0.001
Surgery on other respiratory system	836 (2.9)	504 (2.5)	332 (4.0)	<0.001
Surgery on heart and pericardium	7671 (26.7)	4.512 (22.1)	3.159 (37.9)	<0.001
Surgery on arteries and veins	2005 (7.0)	1.130 (5.5)	875 (10.5)	<0.001
Surgery hemic and lymphatic system	28 (0.1)	16 (0.1)	12 (0.1)	0.106
Surgery on digestive system	316 (1.1)	177 (0.9)	139 (1.7)	<0.001
Surgery on urinary system	49 (0.2)	28 (0.1)	21 (0.3)	0.032
Surgery on maternity care and delivery	39 (0.1)	24 (0.1)	15 (0.2)	0.193
Surgery on nervous system	33 (0.1)	23 (0.1)	10 (0.1)	0.869

Table 4. *Underlying diagnosis during veno-arterial extracorporeal support*

Underlying diseases	Total n=28.767	Non-bleeding n=20.424 (71.0%)	Bleeding n=8.343 (29.0%)	*p* value
Heart failure	5.807 (20.2)	3.682 (18.0)	2.125 (25.5)	<0.001
Cardiac arrest	6.247 (21.7)	4.399 (21.5)	1.848 (22.2)	0.253
Cardiomyopathy	2.745 (9.5)	1.852 (9.1)	893 (10.7)	<0.001
Chronic ischemic heart disease	4.409 (15.3)	2.770 (13.6)	1.639 (19.6)	<0.001
Endocarditis	466 (1.6)	297 (1.5)	169 (2.0)	<0.001
Heart transplant/heart transplant failure	665 (2.3)	441 (2.2)	224 (2.7)	0.007
Complications of transplanted organs other than heart	287 (1.0)	182 (8.9)	105 (1.3)	0.004
Myocardial infarction	5.184 (18.0)	3.519 (17.2)	1.665 (20.0)	<0.001
Myocarditis	793 (2.8)	559 (2.7)	234 (2.8)	0.750
All types of shock	11.670 (40.6)	7.807 (38.2)	3.863 (46.3)	<0.001
- Subgroup hypovolemic shock	170 (0.6)	92 (0.5)	78 (0.9)	<0.001
- Subgroup cardiogenic shock	10.836 (37.7)	7.325 (35.9)	3.511 (42.1)	<0.001
- Subgroup postoperative shock	97 (0.3)	46 (0.2)	51 (0.6)	<0.001
- Subgroup unspecified shock	7.642 (26.6)	5.356 (26.2)	2.286 (27.4)	0.040
Atrial fibrillation and flutter	1.995 (6.9)	1231 (6.0)	764 (9.2)	<0.001
Other cardiac arrhythmias	1.114 (3.9)	759 (3.7)	355 (4.3)	0.032
Ventricular fibrillation and flutter	1.282 (4.5)	869 (4.3)	413 (5.0)	0.009
Pneumonia	1.428 (5.0)	940 (4.6)	488 (5.8)	<0.001
COPD	531 (1.8)	354 (1.7)	177 (2.1)	0.026
Acute pulmonary edema	687 (2.4)	438 (2.1)	249 (3.0)	<0.001
Pulmonary embolism	1.469 (5.1)	1.032 (5.1)	437 (5.2)	0.518
Pulmonary hypertension	1.186 (4.1)	738 (3.6)	448 (5.4)	<0.001
Pulmonary vessel disease	48 (0.2)	24 (0.1)	24 (0.3)	0.001
Respiratory arrest	60 (0.2)	45 (0.2)	15 (0.2)	0.494
BILD	30 (0.1)	19 (0.1)	11 (0.1)	0.355
OILD	399 (1.4)	316 (1.5)	83 (1.0)	<0.001
SIRS and sepsis	1.620 (5.6)	1.082 (5.3)	538 (6.4)	<0.001
Other specified bacterial diseases	40 (0.1)	30 (0.1)	10 (0.1)	0.577
Aortic aneurysms and dissection without rupture	937 (33)	502 (2.5)	435 (5.2)	<0.001
Ruptured aneurysms of aorta	58 (0.2)	29 (0.1)	29 (0.3)	<0.001
Hypertensive diseases	2.914 (10.1)	1.784 (8.7)	1.130 (13.5)	<0.001
Intraoperative and postprocedural complications of respiratory system	444 (1.5)	284 (1.4)	160 (1.9)	0.001
Post cardiotomy syndrome	309 (1.1)	183 (0.9)	126 (1.5)	<0.001
Other intra/post-procedure cardiac functional disturbances	658 (2.3)	394 (1.9)	264 (3.2)	<0.001
Postoperative hemorrhage/hematoma/puncture laceration of circulatory system	345 (1.2)	127 (0.6)	218 (2.6)	<0.001
Other intraoperative and post procedure complications and disorders of the circulatory system. not elsewhere classified	107 (0.4)	56 (03)	51 (6.1)	<0.001
Hypothermia	59 (0.2)	44 (0.2)	15 (0.2)	0.544

Abbreviations: ECLS - extracorporeal life support, BILD - bronchiolitis interstitial lung disease, OILD - other interstitial lung disease, SIRS - systemic inflammatory response syndrome, n - number

Table 5. *Differences between extracorporeal cardiopulmonary resuscitation and non extracorporeal cardiopulmonary resuscitation groups*

Groups	Values	ECPR n=6.884 (23.9%)	Non-ECPR n=21.883 (76.1%)	*p* value
Patients´ characteristics	Gender male n (%)	4.690 (69.6)	14.226 (66.4)	<0.001
	Weight KG (±SD)	83.47 ±22.65	84.54 ±23.16	0.001
	Height cm (±SD)	171.17 ±10.42	170.92 ±11.11	0.198
	Age categories n (%)			<0.001
	18-40 years	1.299 (18.9)	4.039 (18.5)	
	40.1-60 years	2.719 (39.5)	8.524 (39.0)	
	60.1-80 years	2.654 (38.6)	8.822 (40.3)	
	80 or older	212 (3.1)	498 (2.3)	
	Pre-ECLS cardiac arrest n (%)	6.683 (97.1)	6.052 (27.7)	<0.001
	Bridge to transplant n (%)	162 (2.4)	1.347 (6.2)	<0.001
	MBP mmHg (±SD)	56.97 ±26.78	63.60 ±18.49	<0.001
ECLS characteristics	Surgical cannulation n (%)	1.756 (25.5)	8.669 (39.6)	<0.001
	Days on ECLS mean (±SD)	4.05 ±5.72	6.13 ±7.89	<0.001
Pre-ECLS support	CPB n (%)	272 (4.0)	4.238 (19.4)	<0.001
	IABP n (%)	658 (9.6)	5.046 (23.1)	<0.001
	Ventricular assist devices n (%)	259 (3.8)	2077 (9.5)	<0.001
	RRT n (%)	261 (3.8)	1.444 (6.6)	<0.001
	Therapeutic hypothermia n (%)	143 (2.1)	413 (1.9)	0.318
	Vasodilatory agents n(%)	313 (4.5)	2.472 (11.3)	<0.001
	Anti-hypotensive agents n(%)	4.936 (71.7)	16.052 (73.4)	0.007
Outcomes	Hemorrhage n (%)	1.782 (25.9)	6.561 (30.0)	<0.001
	G-I bleeding n (%)	317 (4.6)	848 (3.9)	0.007
	Cannulation bleeding n (%)	930 (13.5)	2.972 (13.6)	0.880
	Surgical site bleeding n (%)	470 (6.8)	2.944 (13.5)	<0.001
	Brain hemorrhage n (%)	659 (2.3)	475 (2.2)	0.015
	Tamponade bleeding n (%)	132 (1.9)	792 (3.6)	<0.001
	Pulmonary hemorrhage n (%)	165 (2.4)	447 (2.0)	0.076
	Mechanical problems n (%)	861 (12.5)	3.082 (14.1)	0.001
	RRT n (%)	1.628 (23.6)	5.969 (27.3)	<0.001
	Infection n (%)	395 (5.7)	1.651 (7.5)	<0.001
	Limb ischemia n (%)	361 (5.2)	943 (4.3)	0.001
	In-hospital survival n (%)	2.031 (29.5)	9.982 (45.6)	<0.001

Abbreviations: ECLS - extracorporeal life support, ECPR - extracorporeal cardiopulmonary resuscitation, MBP - mean blood pressure, CPB - cardiopulmonary bypass, IABP - intra-aortic balloon pump, VADs - ventricular assist devices, RRT - renal replacement therapy, G-I - gastro-intestinal, +SD - standard deviation, n - number

Table 6. *Complications on extracorporeal life support in bleeding and non-bleeding patients*

Complications	Total n=28.767	Non-bleeding n=20.424 (71.0%)	Bleeding n=8.343 (29.0%)	*p* value
Mechanical problems n (%)	3.942 (13.7)	2.171 (10.6)	1.772 (21.2)	<0.001
mechanical cannula problems	893 (3.1)	432 (2.1)	461 (5.5)	<0.001
circuit change	305 (1.1)	162 (0.8)	143 (1.7)	<0.001
thrombosis/clots circuit components	163 (0.6)	97 (0.5)	66 (0.8)	0.001
oxygenator failure	844 (2.9)	479 (2.3)	365 (4.4)	<0.001
pump failure	175 (0.6)	101 (0.5)	74 (0.9)	<0.001
roller pump rupture of raceway tubing	3 (0.0)	3 (0.0)	-	0.561
other tubing rupture	24 (0.1)	17 (0.1)	7 (0.1)	0.986
heat exchanger malfunction	9 (0.0)	4 (0.0)	5 (0.1)	0.133
clot and air emboli	19 (0.1)	11 (0.1)	8 (0.1)	0.208
clots hemofilter	155 (0.5)	82 (0.4)	73 (0.9)	<0.001
air in circuit	267 (6.5)	117 (0.6)	150 (1.8)	<0.001
clots in circuit components	1.860 (6.5)	1.024 (5.0)	836 (10.0)	<0.001
cracks in pigtail connectors	48 (0.2)	21 (0.1)	27 (0.3)	<0.001
Renal creatinine 1.5-3.0 n (%)	4.345 (15.1)	2.410 (11.8)	1.935 (23.2)	<0.001
Renal creatinine >3.0 n (%)	2.362 (8.2)	1.389 (6.8)	973 (11.7)	<0.001
Renal replacement therapy n (%)	7.597 (26.4)	4.295 (21.0)	3.302 (39.6)	<0001
Infection n (%)	2.046 (7.1)	1.108 (5.4)	938 (11.2)	<0.001
Limb ischemia n (%)	1.304 (4.5)	791 (3.9)	513 (6.1)	<0.001
Limb compartment syndrome n (%)	333 (1.2)	171 (0.8)	162 (19)	<0.001
Limb fasciotomy n (%)	608 (2.1)	361 (1.8)	247 (3.0)	<0.001
Limb amputation n (%)	169 (0.6)	102 (0.5)	67 (0.8)	0.002
In-hospital mortality n (%)	16.754 (58.2)	11.212 (54.9)	5.542 (66.4)	<0.001

Abbreviations: n - number

Table 7. *Univariate logistic regression analysis for associations with bleeding complications in veno-arterial extracorporeal life support*

		UNIVARIATE			
Groups	**Values**	**Beta**	**OR**	**CI 95% limits Lower - Upper**	***p* value**
Patient characteristics	Sex male	-0.094	0.91	0.862 - 0.961	0.001
	BMI	0.00	1.000	0.997 - 1.004	0.793
	Age categories				
	18-40 years				0.005
	40.1-60 years	-0.019	0.982	0.913 - 1.055	0.614
	60.1-80 years	0.072	1.075	1.001 - 1.155	0.048
	80 or older	0.153	1.165	0.984 - 1.380	0.076
	Hours on ECLS	0.001	1.001	1.001 - 1.002	<0.001
	Cardiac arrest prior to ECLS	-0.121	0.886	0.842 - 0.993	<0.001
	Bridge to transplant	-0.215	0.807	0.723 - 0.901	<0.001
	Surgical cannulation	0.715	2.044	1.940 - 2.153	<0.001
	E-CPR support	-0.204	0.816	0.767 - 0.867	<0.001
Blood gas analysis closest to ECLS initiation	Lactate mmol/L	0.004	1.004	1.000 - 1.008	0.051
	pH	0.046	1.047	0.913 - 1.201	0.507
	PaO_2 mmHg	0.001	1.001	1.001 - 1.001	<0.001
	$PaCO_2$ mmHg	-0.001	0.999	0.997 - 1.000	0.009
	HCO_3 mmol/L or mEq/L	0.001	1.001	0.997 - 1.005	0.716
	SaO_2 %	0.003	1.003	1.001 - 1.004	0.001
Ventilator settings closest to ECLS initiation	Rate bpm	-0.009	0.991	0.987 - 0.995	<0.001
	FiO_2 %	0.001	1.001	1.000 - 1.002	0.017
	PEEP cm H_2O	-0.019	0.981	0.975 - 0.998	<0.001
	PIP cm H_2O	0.004	1.004	1.000 - 1.007	0.024
	Mean airway pressure cm H_2O	-	1.000	0.996 - 1.004	0.983
Hemodynamics closest to ECLS initiation	Systolic blood pressure mmHg	-0.004	0.996	0.995 - 0.997	<0.001
	Diastolic blood pressure mmHg	-0.006	0.994	0.993 - 0.995	<0.001
	Mean blood pressure mmHg	-0.006	0.994	0.993 - 0.995	<0.001
Pre-ECLS support	Cardiopulmonary bypass	0.857	2.355	2.206 - 2.514	<0.001
	Intra-aortic balloon pump	0.357	1.429	1.344 - 1.520	<0.001
	Ventricular assist devices	0.274	1.315	1.203 - 1.438	<0.001
	Renal replacement therapy	0.108	1.115	1.003 - 1.239	0.045
	Therapeutic hypothermia	0.459	1.582	1.332 - 1.880	<0.001
	Vasodilators	0.428	1.535	1.415 - 1.665	<0.001
	Anti-hypotensive agents	0.471	1.602	1.508 - 1.703	<0.001
Pre-ECLS interventions	Pericardiocentesis	0.362	1.437	0.940 - 2.196	0.094
	Thoracic drainage	1.060	2.886	2.096 - 3.975	<0.001
	Surgery on the musculoskeletal system	-0.086	0.918	0.635 - 1.327	0.648
	Surgery on the other respiratory system	0.493	1.639	1.423 - 1.886	<0.001
	Surgery on the lung or pleura	0.321	1.379	1.166 - 1.631	<0.001
	Surgery on the heart and pericardium	0.765	2.149	2.034 - 2.271	<0.001
	Surgery on the arteries and veins	0.693	2.001	1.824 - 2.194	<0.001
	Surgery on the hemic and lymphatic system	0.608	1.837	0.869 - 3.885	0.111

	Surgery on the digestive system	0.662	1.938	1.550 - 2.424	<0.001
	Surgery on the urinary system	0.609	1.838	1.043 - 3.239	0.035
	Surgical procedures on maternity care and delivery	0.426	1.531	0.803 - 2.920	0.196
	Surgery on the nervous system	0.062	1.064	0.506 - 2.237	0.869
	Anesthesia procedure	0.318	1.374	0.824 - 2.291	0.223
Diagnosis	Heart failure	0.247	1.280	1.149 - 1.425	<0.001
	Cardiac arrest	-0.174	0.841	0.773 - 0.914	<0.001
	Cardiomyopathy	-0.063	0.939	0.802 - 1.100	0.434
	Chronic ischemic heart disease	0.204	1.227	1.070 - 1.407	0.003
	Endocarditis	0.250	1.285	0.953 - 1.732	0.101
	Heart transplant/heart transplant failure	0.097	1.102	0.818 - 1.486	0.522
	Other complications of transplanted organs other than the heart	0.326	1.385	0.935 - 2.053	0.104
	Myocardial infarction	-0.024	0.976	0.891 - 1.069	0.603
	Myocarditis	-0.176	0.839	0.688 - 1.022	0.081
	All types of shock (cardiac. other. unspecified. hypovolemic)	0.181	1.198	1.129 - 1.272	<0.001
	Atrial fibrillation and flutter	0.204	0.816	0.463 - 1.437	0.481
	Other cardiac arrhythmias	-0.582	0.559	0.368 - 0.849	0.006
	Ventricular fibrillation and flutter	-0.190	0.827	0.591 - 1.156	0.267
	Pneumonia	-0.080	0.924	0.680 - 1.254	0.610
	COPD	-1.339	0.262	0.080 - 0.862	0.028
	Acute pulmonary edema	-0.663	0.515	0.175 - 1.515	0.228
	Pulmonary embolism	0.060	0.942	0.814 - 1.089	0.419
	Pulmonary hypertension	0.457	1.580	1.211 - 2.062	0.001
	Pulmonary vessel disease	1.332	3.789	1.774 - 8.093	0.001
	Respiratory arrest	-0.491	0.612	0.130 - 2.882	0.534
	BILD	-0.491	0.612	0.068 - 5.476	0.661
	OILD	-0.409	0.665	0.468 - 0.943	0.022
	SIRS and sepsis	-0.202	0.817	0.647 - 1.031	0.088
	Other specified bacterial diseases	-0.258	0.773	0.309 - 1.936	0.582
	Aortic aneurysms and dissection without rupture	0.676	1.967	1.646 - 2.350	<0.001
	Ruptured aneurysms of aorta	0.763	2.144	1.046 - 4.395	0.037
	Hypertensive diseases	0.586	1.796	1.200 - 2.689	0.004
	Intraoperative and postprocedural complications and disorders of respiratory system	-0.386	0.680	0.337 - 1.370	0.280
	Post cardiotomy syndrome	0.336	1.400	1.049 - 1.868	0.022
	Other intraoperative/postprocedural cardiac functional disturbances	0.408	1.540	1.194 - 1.894	0.001
	Postoperative hemorrhage/hematoma/puncture laceration of circulatory system	1.184	3.267	1.376 - 7.757	0.007
	Other intraoperative and postprocedural complications and disorders of the circulatory system. not elsewhere classified	-1.340	0.262	0.113 - 0.608	0.002
	Hypothermia	-0.204	0.816	0.384 - 1.735	0.597

Abbreviations: ECLS - extracorporeal life support. ECPR - extracorporeal cardiopulmonary resuscitation. FiO_2 - fraction of inspired oxygen. PEEP - positive end expiratory pressure. PIP - peak inspiratory pressure. CPB - cardiopulmonary bypass. COPD - chronic obstructive pulmonary disease. BILD - bronchiolitis interstitial lung disease. OILD - other interstitial lung disease. SIRS - systemic inflammatory response syndrome

Table 8. *VA HEROES prediction model with beta and shrunken beta coefficients*

Values	B	Shrunken B	OR	95% C.I. for EXP(B)		Sig.
				Lower	Upper	
Male	0.098	0.096	1.103	1.042	1.167	0.001
BMI	-0.005	-0.005	0.995	0.991	0.999	0.014
Surgical cannulation	0.478	0.468	1.612	1.524	1.706	0.000
pH	-0.373	-0.366	0.688	0.588	0.806	0.000
pO2	0.000	0.000	1.000	1.000	1.001	0.014
PEEP	-0.011	-0.010	0.989	0.982	0.997	0.009
Mean airway pressure	0.007	0.007	1.007	1.002	1.011	0.006
Mean blood pressure	-0.004	-0.004	0.996	0.995	0.997	0.000
Cardiopulmonary bypass	0.487	0.477	1.627	1.509	1.755	0.000
Intra-aortic balloon pump	0.162	0.159	1.176	1.099	1.258	0.000
Ventricular assist device	0.248	0.243	1.282	1.165	1.410	0.000
Therapeutic hypothermia	0.199	0.195	1.220	1.018	1.462	0.032
Vasodilatory agents	0.098	0.096	1.103	1.011	1.204	0.027
Anti-hypotensive agents	0.242	0.237	1.274	1.194	1.359	0.000
Thoracic drainage	0.389	0.381	1.476	1.049	2.076	0.026
Surgery on the musculoskeletal system	-0.541	-0.530	0.582	0.395	0.859	0.006
Surgery on the respiratory system other than lung or pleura	0.239	0.234	1.270	1.092	1.477	0.002
Surgery on the heart and pericardium	0.438	0.430	1.550	1.458	1.649	0.000
Surgery on arteries and veins	0.368	0.360	1.445	1.307	1.597	0.000
Surgery on the digestive system	0.476	0.467	1.610	1.273	2.037	0.000
Diagnosis of heart failure	0.194	0.190	1.214	1.080	1.364	0.001
Diagnosis of cardiac arrest	0.150	0.147	1.162	1.057	1.277	0.002
Diagnosis of acute myocardial infarction	0.111	0.109	1.118	1.011	1.237	0.031
Diagnosis of shock (except septic shock)	0.231	0.226	1.259	1.175	1.350	0.000
Diagnosis of pulmonary embolism	0.279	0.274	1.322	1.131	1.545	0.000
Diagnosis of pulmonary hypertension	0.660	0.647	1.935	1.466	2.556	0.000
Diagnosis of pulmonary vessel disease	1.074	1.052	2.926	1.346	6.360	0.007
Diagnosis of aortic aneurysms or dissection without rupture	0.420	0.412	1.522	1.259	1.840	0.000
Diagnosis of hypertensive diseases	0.558	0.547	1.748	1.145	2.668	0.010
Other intraoperative/postprocedural cardiac functional disturbances	0.263	0.258	1.301	1.021	1.660	0.034
Other intraoperative and postprocedural complications and disorders of the circulatory system. not elsewhere classified	-1.121	-1.098	0.326	0.137	0.773	0.011
Constant	**1.293**	**1.193**	**3.645**			**0.027**

Abbreviations: Sex - male 0 and female 1, BMI - body mass index, pO2 - partial pressure of oxygen, PEEP - positive end-expiratory pressure

Supplemental Table 1. *Clustering of pre-ECLS interventions based on Current Procedural Terminology (CPT) codes.*

Procedure	SPSS code	CPT Code
Pericardiocentesis	90	3202, 33010, 33015
Thoracic drainage	00	32000, 32020
Fine needle biopsy	1	10004-10021
Surgical procedures on integumentary system	2	10030-19499
Surgical procedures on musculoskeletal system	3	20100-29999
Surgery on the respiratory system	4	30000-31899
Surgery on lungs and pleura	5	32035-32999
Surgery on heart and pericardium	6	33016-33999
Surgery on arteries and veins	7	34001-37799
Surgery on hemic and lymphatic system	8	38100-38999
Surgery on mediastinum	9	39000-39499
Surgery on diaphragm	10	39501-39599
Surgery on the digestive system	11	40490-49999
Surgery on the urinary system	12	50010-53899
Surgery on the male genital system	13	54000-55899
Surgery on the reproductive system	14	55920
Surgery of intersex	15	55970-55980
Surgery on the female genital system	16	56405-58999
Surgery of maternity care and delivery	17	59000-59899
Surgery on the endocrine system	18	60000-60699
Surgery on the nervous system	19	61000-64999
Surgery on the eye and ocular adnexa system	20	65091-68899
Surgery on the auditory system	21	69000-69979
Surgery on microscopic surgery	22	69990
Anesthesia procedures	30	00100-01999
Radiology procedures	40	70010-79999
Pathology and laboratory interventions	50	80047-89398
Services and procedures	60	90281-99607
Management	70	99201-99499

Supplemental Table 2. *Clustering of diagnostical International Classification of Diseases codes*

Diagnosis	ICD-10	ICD-9
Heart failure	I50, I50.1-2-20-21-22-23-3-30-31-32-33-4-40-41-42-43-8-81-810-811-812-813-814-82-84-89-9	428, 428.0-1-2-21-22-23-31-33-4-41-42-43-9
Cardiac arrest	I46, I46.2, I46.8, I46.9	427.5
Hypothermia	T68, T68.XXX, T68.XXXA	991.6
Cardiomyopathy	I25.5, I42, I42.0-1-2-3-4-5-6-7-8-9	425.0-1-18-3-4-5-9, 414.8
Chronic ischemic heart disease	I25, I25.1-10-11-111-1118-119-2-3-4-41-42-5-6-7-70-700-701-708-709-710-719-720-729-730-79-798-799-8-81-810-811-812-82-83-84-89-9	414.0-00-01-04-05-06-1-10-11-12-19-2-8-9
Endocarditis	I33, I33.0-1-9, I38, I39	421.0-1-9
Heart transplant failure	T86.2-20-21-22-23-29-290-298-3-30-31-32-33-39	966.83, V42.1, Z94.1
Failure of transplantation other than heart transplantation	T86, T86.0-00-01-02-03-09-1-10-11-12-13-19-4-40-41-42-43-49-5-8-81-810-811-812-818-819-820-821-822-828-829-83-830-831-832-838-839-84-840-8401-8402-8403-8409-841-8411-8412-8413-8419-842-8421-8422-8423-8429-848-8481-8482-8483-8489-849-8491-8492-8493-8499-85-850-851-852-858-859-89-890-891-892-898-899-9-90-91-92-93-99	996.8-80-81-82-84-85-86-87-88-89
Myocardial infarction	I21, I21.0-01-02-09-1-11-19-2-21-29-3-4-9-A1-A9, I22, I22.0-1-2-8-9	410, 410.0-01-09-1-10-11-2-21-3-4-41-5-6-70-71-72-9-90-91-92
Myocarditis	B33.22, I40, I40.0-1-8-9, I51.4	422, 422.0-9-90-91-92-99, 429.0
SIRS and/or sepsis	R65, R65.1-10-11-2-20-21, A40, A40.0-1-3-8-9, A41, A41.0-01-02-1-2-3-4-5-50-51-52-53-59-8-81-89-9	995.91-9-90-91-92-93-94, 785.52, 38, 038, 038.0-1-10-11-12-19-2-3-4-40-41-42-43-44-49-8-9
Other specified bacterial diseases	A48.8	040.8-89
Shock (excl. septic shock)	R57, R57.0-1-8-9, T81.1, T79.4, T75.01, T78.0-2, T88.3-6	785.5-50-51-52, 998, 998.0-00-01-02-09, 785.59
- Subgroup hypovolemic shock	R57.1	785.50
- Subgroup cardiogenic shock	R57.0	785.51, 998.01
- Subgroup postoperative shock	T81.1	998.01-02
- Subgroup unspecified shock	R57.9-8, T79.4, T75.01, T78.0-2, T88.3-6	785.59
Atrial fibrillation and flutter	I48, I48.0-1-11-19-2-20-21-3-4-9-91-92	427.3-31-32
Other cardiac arrhythmias	I49, I49.0-01-02-1-2-3-4-40-49-5-8-9	427.9
Ventricular fibrillation and flutter	I49.01-02	427.4-41-42
Overall pneumonia	Combined subgroups of pneumonia	Combined subgroups of pneumonia
- Subgroup pneumonia aspiration	J69, J69.0-1-8	507, 507.0-1-8
- Subgroup pneumonia bacterial	J13, J14, J15, J15.0-1-2-20-21-211-212-29-3-4-5-6-7-8-9, J16.0-8, J17, A48.1, A69.8	481, 482, 482.0-1-2-3-30-31-32-39-4-40-41-42-49-8-81-82-83-84-89-9, 483, 483.0-1-8, 104.8
- Subgroup pneumonia viral	J12, J12.0-1-2-3-8-81-89-9, J09.X1, J10.0-00-01-08, J11, J11.0-00-08	480, 480.0-1-23-8-9, 488, 488.0-01-02-09-1-11-12-19-8-81-82-89, 487, 487.0
- Subgroup pneumonia unspecified	J18, J18.0-1-2-8-9	486
COPD	J44, J44.0-1-9	491.20-21-22, 493.20-21-22, 496
Acute pulmonary edema	J81, J81.0-1	518.4, 514, 514.8
Pulmonary embolism	I26, I26.0-01-02-09-9-90-92-93-94-99	451, 451.1-11-12-13-5
Pulmonary hypertension	I27.0-2-20-21-22-23-24-29	416, 416.0-2-8-9
Pulmonary vessel disease	I28, I28.0-1-8-9	417, 417.0-1-8-9
Respiratory arrest	R09.2	799.1
Bronchiolitis interstitial lung disease	J84.115	995.94
Other interstitial lung disease	J84, J84.0-01-02-03-09-1-10-11-111-112-113-114-115-116-117-17-170-178-89-9-2-8-81-82-83-84-841-842-843-848	515, 516, 516.0-1-2-3-30-31-32-33-34-35-36-37-4-5-6-61-62-63-64-69-8-9
Aortic aneurysms and dissection without rupture	I71, I71.0-00-01-02-03-2-4-6-9	441, 441.0-01-00-02-03-2-4-7-9
Ruptured aneurysms of aorta	I71.1-3-5-8	441.1-3-5-6
Hypertensive diseases	I10, I11, I11.0-9, I12, I12.0-9, I13, I13.0-1-10-11-2, I15.0-1-2-8-9, I16, I16.0-1-9	401, 401.0-1-9, 402, 402.0-00-01-1-10-11-9-90-91, 403, 403.0-00-01-1-10-11-9-90-91, 404, 404.0-00-01-02-03-1-10-11-12-13-9, 405.11-19-9-91-99
Intra- and post procedure complications of the respiratory system	J95, J95.0-00-01-02-03-04-09-1-2-3-4-5-6-61-62-7-71-72-8-81-811-82-821-822-83-830-831-84-85-850-851-859-86-860-861-862-88-89	997.3-31-32-88-89
Post cardiotomy syndrome	I97.0	429.4
Intra- and post procedure cardiac functional disturbances	I97.1-11-110-111-12-120-121-13-130-131-19-190-191-7-71-710-711-79-790-791	429.4, 997.1
Post procedure hemorrhage/ hematoma/ puncture laceration of circulatory system	I97.4-41-410-411-418-42-5-51-52-6-610-611-618-62-620-621-63-630-631-638	998.1-11-12-2-3-30-31-32-33
Other intra- and post procedure complications of the circulatory system	I97, I97.8-81-810-811-82-820-821-88-89	997.1

Supplemental Table 3. *TRIPOD Checklist: Prediction Model Development and Validation*

Title and abstract			Checklist Item	Page
Title		V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract		V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	1
Introduction				
Background and objectives	a	V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	2
	b	V	Specify the objectives, including whether the study describes the development or validation of the model or both.	3
Methods				
Source of data	a	V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	3-4
	b	V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	3
Participants	a	V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centers.	3
	b	V	Describe eligibility criteria for participants.	3
	c	V	Give details of treatments received, if relevant.	
Outcome	a	V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	4
	b	V	Report any actions to blind assessment of the outcome to be predicted.	5-6
Predictors	a	V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6
	b	V	Report any actions to blind assessment of predictors for the outcome and other predictors.	6
Sample size		V	Explain how the study size was arrived at.	3,7
Missing data		V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	5
Statistical analysis methods	a		Describe how predictors were handled in the analyses.	6
	b		Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	5-7
	c		For validation, describe how the predictions were calculated.	n/a
	d	V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	6-7
	e		Describe any model updating (e.g., recalibration) arising from the validation, if done.	n/a
Risk groups	1	V	Provide details on how risk groups were created, if done.	n/a
Development vs. validation	2		For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	6
Results				
Participants	a	V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	7
	b	V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	7-8
	c		For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	n/a
Model development	a		Specify the number of participants and outcome events in each analysis.	7
	b		If done, report the unadjusted association between each candidate predictor and outcome.	n/a
Model specification	a		Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	8
	b		Explain how to the use the prediction model.	8,9
Model performance	6	V	Report performance measures (with CIs) for the prediction model.	8
Model-updating	7		If done, report the results from any model updating (i.e., model specification, model performance).	n/a
Discussion				
Limitations	8	V	Discuss any limitations of the study (such as non-representative sample, few events per predictor, missing data).	12-14
Interpretation	a		For validation, discuss the results with reference to performance in the development data, and any other validation data.	9-11
	b	V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	12-14
Implications	0	V	Discuss the potential clinical use of the model and implications for future research.	14-15
Other information				
Supplementary information	1	V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	9
Funding	2	V	Give the source of funding and the role of the funders for the present study.	n/a

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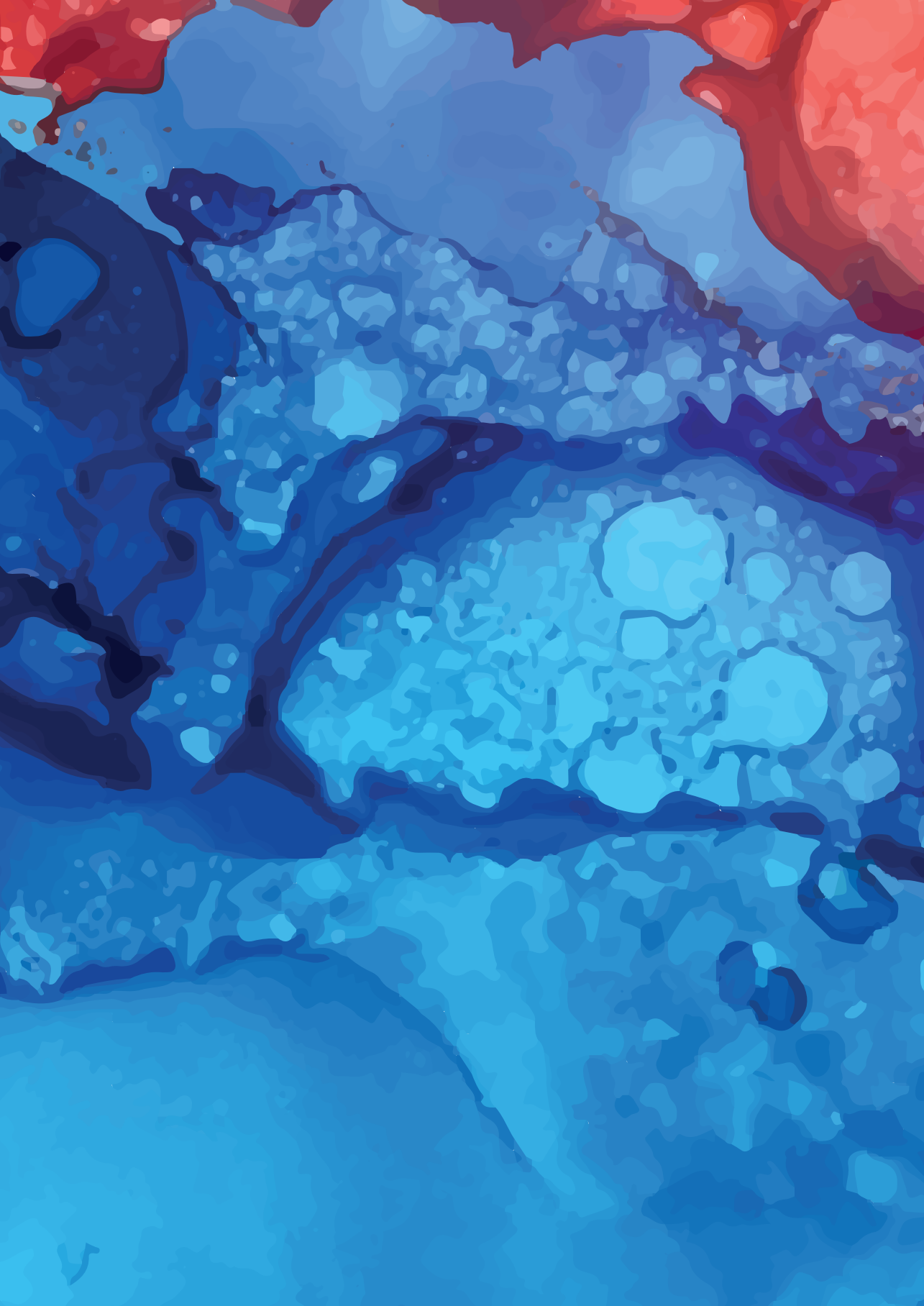

6

New trends, advantages and disadvantages in anticoagulation and coating methods used in extracorporeal life support devices

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Abstract

Background: The use of extracorporeal life support (ECLS) devices has significantly increased in the last decades. Despite medical and technological advancements, a main challenge in the ECLS field remains the complex interaction between the human body, blood, and artificial materials. Indeed, blood exposure to artificial surfaces generates an unbalanced activation of the coagulation cascade, leading to hemorrhagic and thrombotic events. Over time, several anticoagulation and coatings methods have been introduced to address this problem. This narrative review summarizes trends, advantages, and disadvantages of anticoagulation and coating methods used in the ECLS field.

Methods: Evidence was collected through a Pubmed search and reference scanning. A group of experts was convened to openly discuss the retrieved references.

Key content and findings: Clinical practice in ECLS is still based on the large use of unfractionated heparin and, as an alternative in case of contraindications, nafamostat mesilate, bivalirudin, and argatroban. Other anticoagulation methods are under investigation, but none is about to enter the clinical routine. From an engineering point of view, material modifications have focused on commercially available biomimetic and biopassive surfaces and on the development of endothelialized surfaces. Biocompatible and bio-hybrid materials not requiring combined systemic anticoagulation should be the future goal, but intense efforts are still required to fulfill this purpose.

Keywords: Extracorporeal life support; extracorporeal membrane oxygenation; anticoagulation; circuit modifications; coating methods

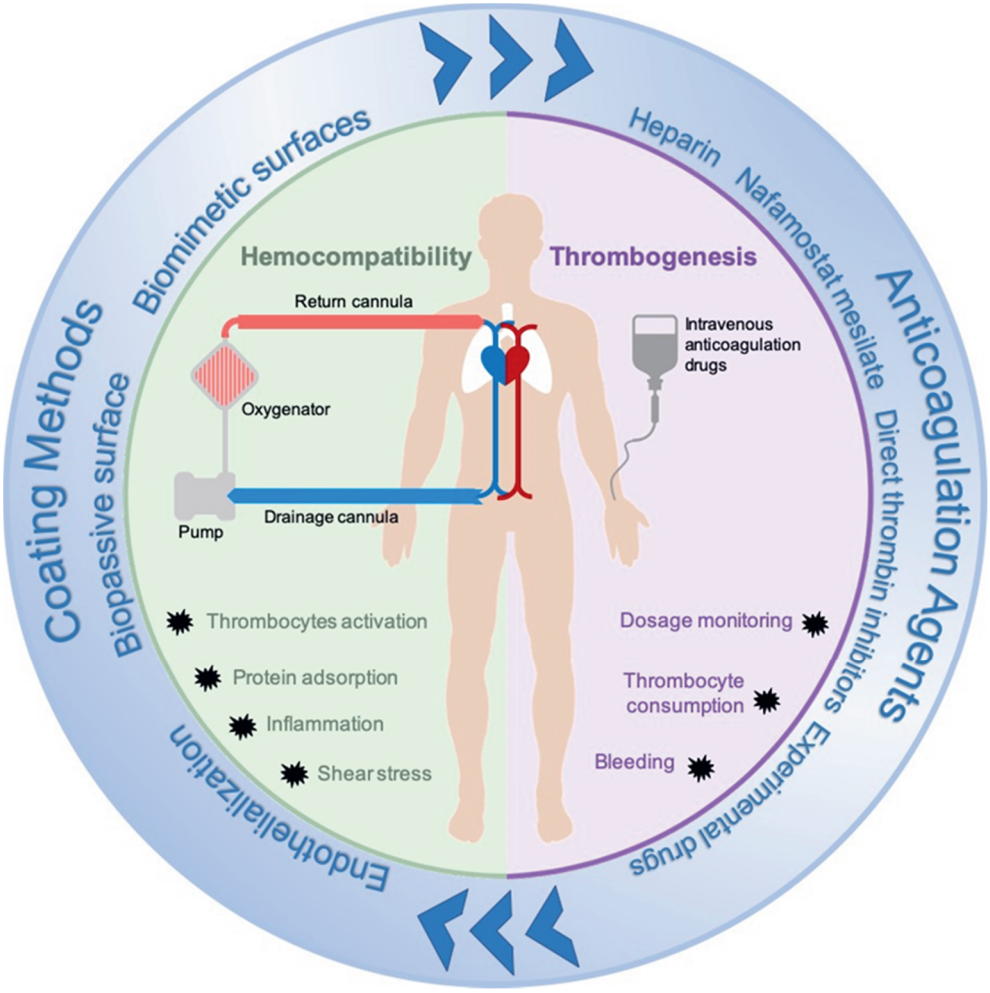
Introduction

Extracorporeal life support (ECLS) devices are used for cardiac or/and pulmonary support as a bridge to recovery, bridge to surgery or treatment, to decision, or to transplant in the presence of cardio-circulatory or respiratory refractory compromise. Overall, hospital survival of adult patients undergoing ECLS for respiratory support is reported to be 69% while survival in cardio-circulatory support is 59% [1].

The effects of ECLS assistance, however, are not consistently positive. Compared to cardio-pulmonary bypass (CPB), ECLS devices provide support for several days or weeks. Consequently, blood is exposed to the artificial tubing and membrane surfaces for a long time, leading to activation of the patient's inflammatory response and coagulation [2]. Prolonged ECLS duration may increase the risk of clot formation, which can result in severe complications (e.g., oxygenator failure, thrombosis, or emboli) and are associated with a decreased survival to discharge. Indeed, clotting inside the circuit or vessels thrombosis may occur, such as in the case of oxygenator failure reported in 9.1% and 6.6% of respiratory and cardiac adult patients, respectively [3,4]. Thus, anticoagulation is necessary to prevent these adverse events. Bleeding events are also frequently reported, and they are twice as common as thrombotic events [3]. Therefore, improvement of ECLS clinical results is necessary bonded to the reduction of thrombotic and hemorrhagic ad-verse events. Based on the complex interaction between the patient's homeostasis and the ECLS circuit, these two players are the main targets to be addressed to prevent thrombo-embolic problems. Indeed, in the last decades, efforts have been done to develop new anticoagulant medications able to reduce embolic events while preventing bleedings in the patient´s body. Similarly, ECLS components and materials have been modified to improve their hemocompatibility and reduce the effects of blood-material contact. The interaction between hemocompatibility and thrombogenesis during extracorporeal life support and the adopted strategies to control it through anticoagulation agents and coating methods are summarized in Figure 1.

Despite significant improvements, clinical evidence highlights the persistent need for further research on hemocompatibility and anticoagulation agents in ECLS. This narrative review provides a state-of-the-art overview of currently available anticoagulation agents, the most recent circuit hemocompatibility improvements, and their expected future developments.

Figure 1. *Visual summary of the interaction between hemocompatibility and thrombogenesis during extracorporeal life support and the adopted strategies to control it through anticoagulation agents and coating methods.*



Materials and Methods

To provide a broad presentation of the anticoagulation strategies and available coatings for ECLS, a search of PubMed/Medline was performed from inception to March 2021. Terms used for the search included 'Extracorporeal Life Support', 'Anticoagulation', 'Heparin', 'Unfractionated heparin', 'Thrombin inhibitors', 'Hirudin', 'Nafamostat Mesilate', 'Factor Xa inhibitors', 'Factor IIa inhibitor', 'Coatings', 'Circuit surfaces', and 'Endothelialization'.

We included randomized clinical trials, controlled before-and-after studies, prospective and retrospective cohort studies, cross-sectional studies and case-

control studies, reviews, and animal studies. Conference abstracts, books or grey literature, articles not written in English were excluded. Articles reporting on anticoagulation methods in patients supported with ECLS and research papers on coatings of ECLS components were retrieved. References were scanned for further information.

Based on the original study design, a group of experts was convened to openly discuss the references retrieved from the literature. The final evidence was summarized as a narrative review.

Results

1. Anticoagulation Agents

To minimize the risk of thrombosis or clotting in the circuit, and subsequently the failure of the ECLS system, patients receive systemic anticoagulation. An optimal anti-coagulation agent should be easy to administer and monitor and have a moderate risk for bleeding complications while maintaining the anti-thrombotic effects. Moreover, it should have an antidote or short half-life to ensure possible counteraction or fast extinguishing effect. Currently, multiple anticoagulant drugs are available, but each of them has specific advantages and disadvantages, implying the fact that the perfect agent still needs to be found. (Table 1)

Table 1. *Overview of the different anticoagulation agents described for clinical and experimental use in extracorporeal life support.*

	Anticoagulation Agent	Inhibition Site	Monitoring	Half-Time	Antidote	Advantages	Disadvantages
Clinically Used Anticoagulation Agents	Unfractionated Heparin	Factor Xa and thrombin inhibition	Anti-factor Xa, ACT, aPTT	1–3 h	Protamine-sulfate	Saturable clearance mechanism and renal clearance, widely used most experience	Risk of HITT, variable effects on APTT, no linear effect
	Nafamostat mesilate	Serine protease inhibitor	ACT, aPTT	8–10 min	No antidote	Short half time anti-inflammatory effect	No large prospective trials available, short half time, higher costs than UFH
	Bivalirudin	Direct thrombin inhibitor	ACT, aPPT, PTT	25 min	No antidote	Renal clearance no risk for HITT easy titration	May interfere with APTT, less effective inhibition in areas of stasis
	Argatroban	Direct thrombin inhibitor	ACT, aPTT	45–50 min	No antidote	Hepatic clearance No risk for HITT Good dose response	Can interfere with INR, lesser coagulation inhibition in areas of stasis
Anticoagulant Agents Under Investigation	Low-molecular-weight-heparin	Factor IIa and Xa inhibition	Anti-factor Xa, aPTT	3–6 h	Protamine-sulfate	lower risk of HITT partially effective	Anti-Xa levels, accumulation in renal impairment
	Lepirudin	Direct thrombin inhibitor	ACT, aPTT, ECT	1–2 h	No antidote	Renal clearance No risk for HITT	Limited evidence in ECLS, risk for anaphylaxis, no longer available
	Rivaroxaban	Direct-Xa inhibitor	Anti-factor Xa	5–9 h	Andexanet alfa	Rapid onset of action, few drug interactions	No clear laboratory monitoring available, only oral administration possible

Abbreviations: ACT: Activated Clotting Time, aPTT: activated Partial Thromboplastin clotting Time, HITT: Heparin Induced Thrombocytopenia and Thrombosis.

Currently used anticoagulation agents can be divided into three groups: heparin group, nafamostat group, and direct thrombin inhibitors. Other anticoagulants have been described in experimental models or case-reports and include recombinant forms of hirudin, oral anticoagulants and experimental factor XIIa antibodies.

1.1. Clinically Used Anticoagulation Agents

Unfractionated Heparin

The most commonly used anticoagulation during ECLS is unfractionated heparin (UFH). It has an inhibitory effect by binding the enzyme inhibitor antithrombin and increasing its inhibitory potential toward coagulation enzymes factor Xa and thrombin [5,6]. UFH is administered continuously and usually titrated based on activated clotting time (ACT), antifactor Xa activity levels, or activated partial thromboplastin time (aPTT) [5]. Though, these measurements do not always correlate correctly with the heparin dose and effect, leading to some uncertainty in the monitoring of patients' anticoagulation status [7]. Anti-Xa does correlate superiorly on heparin concentrations compared to ACT and aPTT, on the other hand, it does not represent the overall hemostatic state of the patient [8].

Thromboelastography (TEG) and thromboelastometry (ROTEM) have been studied in ECLS populations, where ROTEM showed moderate correlation with standard coagulation test and [9] ROTEM has been found to be a good indicator of anticoagulation status in pediatric patients undergoing ECLS as well [10]. Furthermore, UFH might stimulate the development of antibodies against heparin-platelet factor 4 complexes, which induce heparin-thrombocytopenia and thrombosis (HITT) [11]. The incidence of HITT varies between 0.36% [12] and 3.1% [13], and 50% of ECLS patients diagnosed with HITT develop clinically significant thrombotic events if no alternative anticoagulant is given [12]. While circulating UFH is surely related to HITT, it is unclear if heparin-coated circuits may induce HITT [14].

Regardless, in the case of HITT, alternative anticoagulants should be administered, and all sources of heparin should be removed, including heparin-coated components [12,15]. In addition, protamine sulfate can be administered to reverse the effects of UFH. To summarize, UFH is still the most used anticoagulation agent used in ECLS patients but its monitoring uncertainty and the risk of HITT prompt exploring of new anticoagulant agents [16].

Nafamostat Mesilate

A possible alternative for UFH is nafamostat mesilate (NM). NM is a synthetic serine protease inhibitor, often used as an anticoagulant for patients with a high bleeding risk on hemodialysis. It inhibits thrombin, factor Xa, and XIIa, the kallikrein-kinin

system, complement system, and lipopolysaccharide-induced nitric oxide production. There is no antidote available, but NM has a short half-life of 8–10 min [17].

A study comparing NM to UFH in dogs on ECLS revealed decreased hemoglobin levels after 1 hour of ECLS in all animals. However, the NM group experienced no cannulation site bleeding as opposed to the UFH group. Thrombo-elastography and aPTT results were comparable between groups, but pro-inflammatory cytokine levels were lower with NM [18]. A retrospective study of patients on ECLS showed a longer duration of oxygenators, less transfusion of red blood cells, fresh frozen plasma, and cryoprecipitate when NM was used as an anticoagulation agent compared to UFH. In addition, the rate of bleeding, thrombosis, and mortality was higher in the heparin group [19]. Similarly, Han et al. observed more bleedings with UFH, but 3 cases of intracerebral hemorrhage with NM. Survival was higher in the NM group (38.2% vs. 13.6%) and heparin was found to be the only independent predictor of bleeding complications [20]. Conflicting results were presented in another retrospective study based on propensity-matched data. In this case, bleeding events occurred more in the NM group, probably because of the lack of an antidote for NM [21]. In conclusion, evidence on NM is still controversial and it is mainly used as an alternative anticoagulation agent, especially in patients with a high bleeding risk on hemodialysis.

Direct Thrombin Inhibitors

Direct thrombin inhibitors are known alternatives for heparin in HITT patients. These agents bind directly to thrombin and inhibit the actions of thrombin, including feedback-activation of factors V, VIII, and XI, and conversion of fibrinogen to fibrin, and the stimulation of platelets [22].

Bivalirudin, a synthetic hirudin, is a direct thrombin inhibitor peptide often used as anticoagulation in HITT patients or patients with heparin resistance [6]. There is no antidote available, however the half-time of bivalirudin is 25 min and the onset of action is within 4 min [23]. It is mostly cleared by the kidneys and dosages should be adjusted in renal dysfunction [22,24]. It can be monitored by aPTT but also with ROTEM [25]. Bivalirudin has been used as an off-label anticoagulation therapy in ECLS with no significant increased risk of bleeding or thrombosis [24]. In post-cardiotomy ECLS patients, bivalirudin-based anticoagulation, compared to conventional heparin, has been associated with less bleeding and transfusion rates [26]. Similar outcomes were found in a mixed ECLS adult cohort, where bivalirudin showed less bleeding complications and a lower rate of thrombosis compared to heparin. In the same study, heparin was associated with higher aPTT variations compared to bivalirudin [27]. Indeed, it has been demonstrated that time within the therapeutic range is better with bivalirudin, especially in high-intensity anticoagulation protocols [28]. On the other hand, other studies failed to show the

significant superiority of bivalirudin in terms of mortality and adverse events. For example, Kaseer et al. was not able to demonstrate any differences in 30-day and in-hospital mortality, major bleedings, renal and hepatic impairment, and thrombotic events between heparin and bivalirudin [29]. Again, bivalirudin showed more consistency than heparin in ACT and aPTT levels without higher risk for bleeding in patients with normal hepatic function [29,30]. However, dose adjustment is required in patients with hepatic impairment due to possible false and unpredictable aPTT prolongation and changes [31]. Different dosages of bivalirudin have been reported in studies with ACT and aPTT as monitoring tools to test the effect of medication [30]. Indeed, the optimal bivalirudin dosage still needs to be defined.

Argatroban is a small molecule direct thrombin inhibitor and can also be an alternative for UFH in patients with a contraindication for UFH and renal failure. Differently from bivalirudin, argatroban binds to the active site of thrombin (univalent), whereas bivalirudin binds to the active site and an additional exosite-1 on thrombin (bivalent) [22]. The onset of action is within 30 min and the half-life of this agent is around 45 min, with no antidote available [24]. Argatroban is eliminated by hepatic metabolism, and liver dysfunction requires dosage change [22,32,33]. No randomized controlled trials are available on argatroban, and its clinical use is justified based on case series and case reports [24]. A preclinical study showed lower fibrinolytic levels and higher platelet count in animals treated with argatroban compared to heparin and supported with CPB, using circuit components with or without heparin coating [34]. Another study tested three sham ECLS circuits with blood priming and demonstrated that thrombin formation was lower in the argatroban anticoagulated circuits compared to heparin, despite a less prolonged aPTT [35]. Even in ARDS patients requiring ECLS, argatroban administration was found feasible and safe, and comparable to heparin. Outcomes of bleeding complications, requiring transfusion, thrombotic complications, and replacement of ECLS components did not differ between heparin or argatroban anticoagulated patients [36]. The use of argatroban has been reported in patients simultaneously receiving continuous renal replacement therapy (CRRT) and veno-venous (V-V) ECLS. In these patients, a dosage of 2 μg/kg/min resulted in bleeding complications, and lowering the dose to 0.2 μg/kg/min showed promising effects [33]. The use of argatroban is associated with higher aPTT values and requires more frequent measurements to titrate the drug to an optimal therapeutic level [37].

As for bivalirudin, a standard dosage for argatroban is still difficult to be defined.

1.2. Anticoagulation under Investigation

Low Molecular Weight Heparin

Low molecular weight heparin (LMWH) has been described as anticoagulation during ECLS with promising results in clinical trials, even if its use is uncommon. The standard test for monitoring LMWH is an anti-Xa essay [38]. Thromboelastography is an assay to measure the stages of clot development and has also been described as a monitoring assay for LMWH. However, it has not been proven superior to anti-Xa assays. ROTEM does not fully detect the effects of LMWH [38,39]. Since LMWH selectively targets factor Xa through antithrombin, it has more predictable pharmacokinetics and therefore does not need routine monitoring [40]. The risk for HITT is also lower with LMWH [7]. Krueger et al. reported a rate of 18% relevant bleeding complications in 61 patients undergoing V-V ECLS support for 7 days with only LMWH as anticoagulation. In 4 (6.5%) patients severe thrombotic events occurred, but all after more than 5 days of ECLS [41]. In lung transplantation patients, similar outcomes were found. Of 102 patients with peri-operative ECLS during lung transplant 80 patients received LMWH, and the remaining 22 received UFH as anticoagulation. No significant differences in bleeding complications were found between both groups, but thromboembolic events occurred more often in the UFH group [40]. LMWH seems promising, but it is difficult to predict the ending of its effect in the case of need and it cannot be considered as an alternative to UFH in the case of HITT due to the potential remaining risk of HITT antibody formation [42].

Recombinant Forms of Hirudin

Hirudin has been reported as a possible alternative for UFH. It is a naturally occurring anticoagulant in the salivary glands of leeches, and different recombinant (and synthetic) forms are available as anticoagulants but none of them is paired to an antidote.

Lepirudin is a recombinant form of hirudin. It is a bivalent direct thrombin inhibitor, binding to the catalytic site and exosite-1 of thrombin. It is approved by the Food and Drug Administration (FDA) as an alternative drug for heparin in the occurrence of HITT. The half-life of lepirudin is 1–2 h and administration by bolus can increase aPTT to a maximum within 10 min. Due to the renal elimination route, dosages must be adjusted in acute kidney injury [43]. This agent has been used in patients undergoing ECLS with contra-indications for UFH. The literature reports two pediatric cases of lepirudin use in patients diagnosed with HITT and suffering from biventricular heart failure requiring ECLS [44]. Another two cases reported on lepirudin use in adults with similar conditions [45,46]. In both cases, aPTT and ACT were used to titrate dosages, and, in one case, a lower dose was required based on

acute kidney injury. In all described patients, no bleedings or thromboses occurred. Since 2013, lepirudin is no longer available on the market [24].

Desirudin is another recombinant-DNA form of hirudin with an irreversible inhibition action to thrombin. It has been proven to be more effective than UFH or LMWH in reducing the risk of deep venous thrombosis [47] and to have a similar effect compared to argatroban in the treatment of HITT [48]. However, there are no case reports or case series discussing the use of desirudin during ECLS.

Due to these agents' exogenous protein character, an immune reaction can be triggered and cause anaphylaxis [43].

Direct Oral Anticoagulants

Direct factor Xa inhibitors, such as rivaroxaban, apixaban, edoxaban (factor Xa inhibitors), and direct thrombin inhibitors such as dabigatran are direct oral anticoagulants (DOACs) or non-vitamin K antagonist oral anticoagulants (NOACs) used for secondary prophylaxes in atrial fibrillation and treatment of deep venous thrombosis (DVT) and venous thromboembolism (VTE). One case-report report addressed the uneventful use of rivaroxaban for 10 days in a COVID patient on V-V ECLS with suspected HITT, with no other intravenous anticoagulation alternatives. In this case, anti-Xa assays were used to monitor the rivaroxaban levels [49]. So far, no further evidence for the use of direct factor Xa inhibitors in ECLS as anticoagulation is available [50].

2. Circuit Modifications: Coating Methods

The complex interaction between inflammation and coagulation significantly affects a patients' safety, but it has also important consequences on the ECLS devices as well, especially in terms of durability. Despite the routine patient's systemic anticoagulation, deposition of blood proteins onto the artificial ECLS surfaces may still occur, leading to inefficient membrane functioning, insufficient gas transfer, and finally, device failure [51]. This is a major limitation for the long-term use of ECLS systems and a major obstacle toward the development of totally implantable durable devices [52,53]. The main limiting factors are related to platelet and coagulation activation leading to clot formation within the system, and protein adsorption which gradually impairs gas exchange in the oxygenator [52]. For these reasons, research efforts are aiming to improve hemocompatibility of foreign surfaces, optimize gas and blood flows, miniaturize ECLS systems, and decrease the imbalance of coagulation and inflammation [52].

From an engineering point of view, the new ECLS circuits should aim to mimic the physiologic conditions in order to avoid hemolysis and reduce the shear stress and/or the stasis zones [54–57]. The artificial surface area of the ECLS systems should be minimized by simplifying the circuit, reducing shear stress and

stasis, while maintaining or increasing usability [58]. On the other hand, the ultimate goal is to mimic healthy endothelial tissue in circuits´ surfaces such as oxygenators´ membranes and housing parts, pumps, cannula, and tubing to eliminate both the systemic inflammatory and the coagulation pathway responses.

Normally, anticoagulant regulation of procoagulant processes is regulated by the endothelium which is absent at the artificial surfaces of the ECLS circuit. The artificial surfaces not only activate platelets and factor XII, but also adsorb plasma proteins like fibrinogen, immunoglobulins, hemoglobin, fibronectin, and van Willebrand factor, in varying amounts depending on the material, but especially on hydrophobic surfaces [59]. This protein adhesion is thought to be the initiating factor of the procoagulant response [60]. As a consequence, to improve the hemocompatibility of these artificial ECLS surfaces, a replication of the anti-thrombotic and anti-inflammatory properties of the endothelium would be ideal. According to Ontaneda and Annich, surface modifications addressing this goal can be classified into three major groups [61]: bioactive surfaces (also called bio-mimetic surfaces); biopassive surfaces; and endothelialization of blood-contacting surfaces.

An overview of the commercially available hemocompatibility improving coatings for extracorporeal circulation systems is available in Table 2.

Table 2. *Overview of the commercially used coatings in extracorporeal life support circuit components*

	Main Coating Compound(s)	Commercial Name of Coating	Company
Bioactive	Heparin	Cortiva Bioactive surface	Medtronic
	Heparin	Rheoparin	Xenios/Fresenius
	Albumin + Heparin	Bioline	Maquet/Getinge
	Albumin + Heparin	X.ellence	Xenios/Fresenius
Biopassive	Albumin	Rheopak	Chalice Medical
	Albumin	Recombinant Albumin Coating	Hemovent
	Albumin	Safeline (discontinued)	Maquet/Getinge
	Albumin	X.eed	Xenios/Fresenius
	Phosphorylcholine	PC phosphorylcholine	Eurosets
	Phosphorylcholine	PH.I.S.I.O Coating	Liva Nova
	poly(2-methoxyethylacrylate) (PMEA)	Xcoating	Terumo
	Sulphate and sulphonate groups and polyethylene oxide (PEO)	Balance Biosurface	Medtronic
	Sulphonate groups, polyethylene oxide (PEO) and heparin	Trillium Biosurface	Medtronic
	Amphyphilic polymer	Softline	Maquet/Getinge

2.1. Bioactive Surfaces

Heparin-coated systems for ECLS were developed to reduce the hemorrhagic risk by lowering the systemic heparinization [62–65]. The first heparin coating to become commercially available was developed by the company Carmeda in 1983 [66,67]. From that time on, several new coatings with different bonding techniques have

been developed and became available in the market. The local release of heparin can minimize the negative effects of foreign materials coming in contact with blood [68]. In an early study, Videm et al. found that heparin coatings have the ability to reduce complement activation by 45% [69]. Wendel and Ziemer analyzed several studies and assumed that oxygenators coated with heparin can reduce the following effects in comparison to un-coated devices: activation of contact activation of coagulation, complement system activation, alteration of granulocytes, inflammation, and pulmonary complications, activation of platelets, disturbance of homeostasis, loss of blood, and cerebral damage [70]. However, the utility of heparin-coated materials has been questioned. Covalently- and ionic-bonded heparin coating on oxygenators reduced some effects of the inflammatory response, thrombi formation, but other complications remained the same when compared to uncoated oxygenators [60]. In general, these studies need to be interpreted with some caution as most were performed either in 6 h in vitro tests or in short-term use in CPB. Thus, their relevance for long-term ECLS is limited, but no evident contraindications are reported so far [71].

Nitric Oxide (NO) is also known as an endothelium-derived relaxing factor and is released by endothelial cells to induce vasodilatation. NO activates an increase in cyclic guanosine monophosphate (GMP) in platelets and vascular smooth muscle cells [61]. Indeed, coatings with NO-catalytic bioactivity can inhibit collagen-induced platelet activation and adhesion, proliferation, and migration of arterial smooth muscle cells through the cGMP signaling pathways. Studies showed good anti-thrombogenic properties in extracorporeal circuits [61,72]. Moreover, stents implanted in rabbits with this coating showed improved endothelial mimetic microenvironment, stronger recovery to the endothelium, and had less restenosis and thrombosis after 4 weeks [73]. A significant reduction in platelet consumption and activation was also observed in animal studies. The latest generation of NO coating is characterized by a lipophilic NO donor complex embedded into plasticized PVC to prevent uncontrolled NO release in the circulatory system. This technology showed not only platelet inhibition but also less fibrinogen consumption. The main disadvantage with NO is the fact that its storage cannot exceed 4 weeks. This can be a problem in long-term ECLS runs [61,72]. So far, NO-coatings have not been used commercially. However, NO was clinically used as a fraction of the sweep gas (20 ppm) of the oxygenator in 31 pediatric ECLS runs in order to use its anti-thrombotic properties by diffusion through the gas exchanger membrane [74].

To further improve hemocompatibility, a novel covalent **C1-esterase inhibitor (C1-INH)** coating has been introduced by Gering et al. [53]. Besides complement inhibition, C1-INH also prevents factor XII (a) activation, an early event of contact phase activation at the crossroads of coagulation and inflammation [53]. This coating is still under development and thus not commercially available.

2.2. Biopassive Surfaces

Albumin has been used as coating material since 1980 and it is often indicated in case of contraindications from heparin [75]. Albumin coating is used as a base layer with a hydrophilic surface, which reduces the biological response to hydrophobic surfaces [23]. Albumin lacks binding sequences for platelets, leukocytes, and coagulation enzymes and therefore slows down the platelet activation when used as a coating. Nevertheless, albumin coatings do not last long due to displacement by procoagulant proteins [75]. Some manufacturers use albumin as part of a multi-layer, bioactive coating in alternating layers with heparin (Table 2: Bioline and X. ellence coatings).

Phosphorylcholine (PC) is anti-thrombogenic, protein resistant, antibacterial, and has anti-fouling properties [67]. Coatings with phosphorylcholine (PC) have been developed as an alternative to heparin-bound systems. PC is a hydrophilic polar headgroup of phospholipids. It contains a negatively charged phosphate bonded to a positively charged choline. Phospholipids containing PC are non-thrombogenic. PC coatings in extracorporeal circuits have been found to induce plateau formation of thromboxane B2 and thromboglobulin and even reduce thrombin formation [76]. However, other studies did not find PC favorable over heparin-coated circuits [61]. A study by Thiara et al. compared heparin-albumin coating with PC coating in elective cardiac surgery patients. The PC group showed significantly higher lactate dehydrogenase, thus hemolysis, but this was allocated to the fact that the group had significantly longer aortic clamping time and CPB duration. Further, hemoglobin, platelet counts, numbers of leukocytes and cytokines, levels of complement activation, and endothelial shedding molecule syndecan-1 were not significantly different between the two coating groups [77].

Poly(2-methoxy-ethyl-acrylate) (PMEA) is a blood-compatible polymer composed of a hydrophobic polyethylene chain and a mild hydrophilic tail. This combined hydrophobic and hydrophilic polymer allows the polymer to adhere to the hydrophobic site to different materials and create a hydrophilic surface for the blood to contact with the other side. Proteins and platelets will not denature or adhere to the hydrophilic surface [59]. Animal studies involving CPB revealed suppression of the complement system activation [61]. Compared to non-coated systems in patients undergoing coronary artery bypass grafting, PMEA coating was superior in reduction of platelet adhesion, aggregation, and protein adsorption [78]. However, other studies found a higher risk of postoperative leukopenia and systemic inflammatory response syndrome (SIRS) without a decrease in platelet aggregation [79]. Finally, there is no consensus on whether or not PMEA is superior to heparin-bound systems.

Polyethylene oxide (PEO), commercially used in combination with negatively charged sulphonate groups and sulphate, is used as a biopassive coating, which has been proposed as an alternative to the heparin-loaded coatings. In an ex

vivo study with human blood (n = 40), Teliguia et al. found no differences in coagulation activation (factor IIa, prothrombin fragment 1 + 2 were assessed) when compared to a heparin coating. All groups demonstrated similar adhesion scores following ultrastructural oxygenator assessment by scanning electron microscopy and no difference in the pressure gradients of the oxygenators was observed [80].

Poly (MPC-co-BMA-co-TSMA) (PMBT), a zwitterionic copolymer, is also a polymer with both positive and negative charged components [81]. PMBT coating was shown to be stable on polypropylene hollow fiber membranes, tested by Wang et al. by elution with ethanol and washing and sterilizing solutions of peracidin. In the same study in animal models, almost no change in fibrinogen and platelets in the blood after blood circulation through PMBT copolymer circuits was observed. In the uncoated circuits, fibrinogen and platelets were significantly reduced due to absorption and consumption. Thrombus formation was significantly lower in the PMBT circuits. PMBT's influence on gas exchange was not tested in the study [82]. The mimetic surface seems promising and might be applicable in artificial lung systems, however, it is not commercially available yet.

In an in vitro study by Preston et al., different coatings were tested in ECLS circuits with bovine blood. Coatings were tested regarding the adsorption of morphine and fentanyl. Safeline® coating—a synthetic albumin (Maquet), Softline® coating—a heparin free polymer (Maquet), Bioline® coating—recombinant albumin and heparin (Maquet), Xcoating®—poly2methoxylacetylate (Terumo), Carmeda® coating—covalently bonded heparin (Metronic), and Trillium®—covalently bonded heparin (Metronic) were com-pared to one another. All circuit coatings were associated with the loss of drugs. The Carmeda® and Xcoating® had significantly more morphine adsorption than Safeline®, Softline®, Bioline® and Trillium®. Fentanyl was adsorbed more in Safeline®, Softline®, Bioline®, and Trillium® compared to Carmeda® and Xcoating®, but was not statistically significant [83].

2.3. Endothelialization

Surface endothelialization is a technique where an endothelial layer is created onto circuit surface areas by seeding cells onto the surface to achieve complete hemocompatibility between blood and materials. Creating a surface with endothelial cells would achieve higher hemocompatibility than replicating specific thrombo-regulatory aspects of the endothelium. Few studies have investigated the feasibility of establishing an endothelial monolayer on the gas exchange ECLS membranes [51], although it is known that endothelial cells do not adhere easily to hydrophobic surfaces [75]. To provide an endothelial monolayer, the base of the material must enable endothelial attachment and bonding while preserving the viability of the endothelial cells. Heparin/albumin-coated PMP membrane fibers were found to be a good base for a viable and confluent endothelial monolayer of endothelial cells.

Moreover, the heparin/albumin coating avoids thrombogenic events in areas not covered with cells [84]. Pflaum et al. demonstrated the effectiveness of a stable titanium dioxide (TiO2) coating achieved by pulsed vacuum cathodic arc plasma deposition (PVCAPD) technique on hydrophobic poly(4-methyl-1-pentene (PMP) membranes, with a functional monolayer of endothelial cells as a result. Although the use of the TiO2 coating resulted in a reduction in the oxygen transfer rate (OTR) of the membrane by 22%, it successfully mediated EC attachment. The endothelial layer was resistant to shear stress and able to repair itself when monolayer disruption appeared. [51].

A study experimented with endothelial cell seeding from cells derived from juvenile sheep carotid arteries and searched for the best protein coating for endothelial cell attachment. Seeding endothelial cells to uncoated oxygenator membranes was ineffective, and using gelatin, fibrinogen, and collagen IV did not enhance the cell seeding process. Cornellissen et al. considered fibronectin to be a good base for cell attachment on flat sheet membranes, however, they did not perform gas exchange performance tests [85]. However, current research on how to establish a single layer of endothelial tissue on the gas exchange of ECLS equipment is not advanced [23]. In addition, the shelf life of an endothelialized oxygenator can, under hypothermic conditions, be stretched up to two weeks [86] compared to the shelf life of an otherwise coated oxygenator being typically 2 years. This would result in complex resource planning and management for both manufacturers and ECLS centers. The use of immune-silenced cells might at least help in quicker response times as production for a particular patient would not depend on the availability of autologous cells. Indeed, Wiegmann et al. showed that the rejection of allogeneic endothelial cells could be prevented by silencing HLA-class I expression [87]. However, many questions in relation to costs, timely production, quality assurance, and approval of endothelialized oxygenators remain open, leaving a wide field of potential research.

Future Perspective and Conclusions

Since the first successful ECLS application, technological and medical progress has led to a wide application of ECLS devices with improved patient outcomes. As the evolution process of ECLS systems continues, the application of this support is likely to increase in the future, based also on the growing population suffering from acute and chronic heart and lung failure. To further improve the ECLS circuits, the aim is to find the materials that are comparable to the human body, require no or limited anticoagulation (thereby limiting bleeding-related complications), and do not initiate a thrombogenic and inflammatory response without compromising the oxygenation. It is thus mandatory to prompt the research field toward the development of better anticoagulant molecules and improved ECLS

components. A combination of stable ECLS anti-adsorbent and anti-coagulant coatings with (low dose) systemic anticoagulant and antiplatelet therapy might be an optimal first line of defense against ECLS-induced thrombotic and bleeding complications.

In parallel, new ECLS bio-hybrid materials are being developed to prevent the initiation of the thrombogenic and inflammatory response triggered by the blood–surface interaction, without compromising the gas exchange process. With the onset of the endothelialization technique, creating complete biocompatible materials seems achievable. For example, 3D stem cell printing is a technique on the rise even though the limited life span of the stem cells and long-term engraftment remain a major difficulty [88].

Overcoming these problems could lead to further use of life support systems, without risk for systemic inflammatory reactions and with less need for anticoagulation. Finally, this will make possible the development of totally implantable lung and heart devices and long-term ECLS without interferences to the hemostasis of the body.

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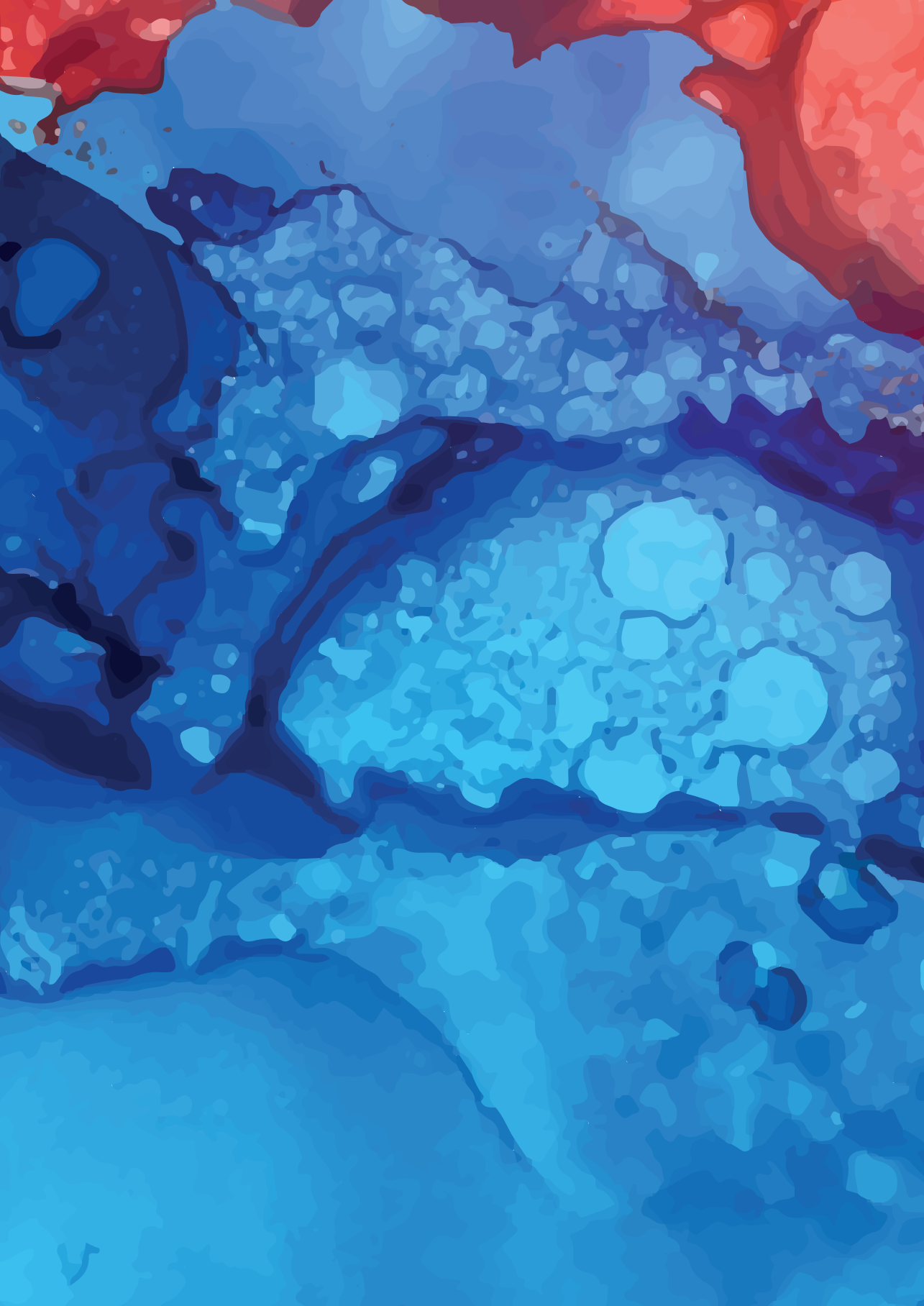

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EMBARGO

Complications of extracorporeal life support in trauma patients – Analysis of the ELSO registry and systematic review of the literature

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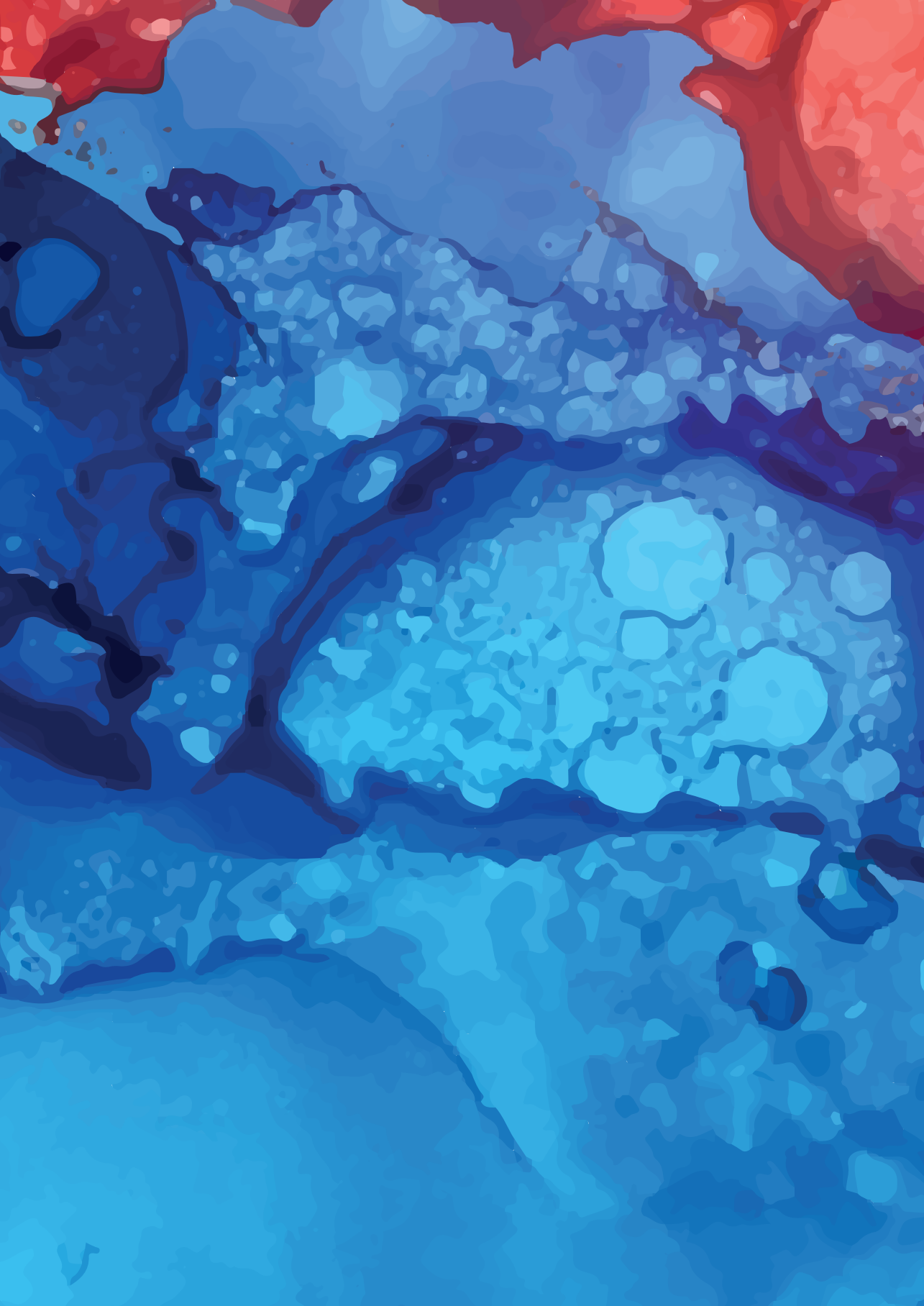

8

Extracorporeal life support in thoracic emergencies – a narrative review of current evidence

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Abstract

Background and objective: Resuscitative therapies for respiratory and cardiac failure are lifesaving and extended by using extracorporeal life support (ECLS) as mechanical circulatory support (MSC). This review informs the debate to identify the life-threatening thoracic emergencies in which patients may be cannulated for ECLS support.

Methods: An advanced search was performed in PubMed, Google Scholar and references query, assessed in June 2022, identified 761 records. Among them, 74 publications in English were included in the current narrative review.

Key content and findings: ECLS is an additional tool for organ support in life-threatening thoracic emergencies. It provides bridging to recovery or to decision about destination as definitive therapy, intervention, or surgery. Non-traumatic emergencies include mediastinal mass, acute lung injury, aspiration, embolisms, acute and chronic heart failure. However, based on the current evidence, trauma, and especially blunt thoracic trauma, is one of the main indications for ECLS use in thoracic emergencies, among others in chest wall fractures, blunt and penetrating lung injuries. ECLS use is always individualized to patient's needs, injury pattern and kind of organ failure, circulatory arrest inclusive, depending on if respiratory or cardiac and circulatory support is needed. Further, ECLS offers the possibility for fast volume resuscitation and rewarming, thus preventing the lethal of trauma: hypothermia, hypoperfusion and acidosis. Anticoagulation may be omitted for some hours or days. Interdisciplinary cooperation between the intensivists, surgeons, anesthesiologists, emergency medical services, an appropriately organized and trained staff, equipment resources and logistical planning are essential for successful outcomes.

Conclusions: ECLS use in selected life-threatening thoracic emergencies is increasing. The summarized findings appeal to policymakers, and we hope that our summary of recommendations may impact clinical practice and research.

Keywords: Thoracic emergencies, extracorporeal life support, extracorporeal membrane oxygenations, hemorrhage, trauma.

Introduction

Background

The early pioneering cardiopulmonary bypass (CPB) technology [1], besides the application to perform planned cardiac surgery operations to treat acquired or congenital heart diseases, was used as temporary life support for patients with acute cardiac or respiratory failure. In 1972, a severe injured patient suffered several thoracic emergencies, among others including transection of thoracic aorta, as well multiple pelvic and lower limb fractures, after being struck by a motor vehicle [2, 3]. Four days later, he developed worsening acute respiratory distress syndrome (ARDS). On his sixth postoperative day, the first successful use of extracorporeal life support (ECLS), with a peripheral veno-arterial configuration using a Bramson membrane heart-lung machine, was performed and continued for a total of 75 hours [3, 4].

Rationale and knowledge gap

Over the last five decades, the use of ECLS has increased exponentially. ECLS provides temporary support of circulation and/or gas exchange bridging to recovery or to decision about destination as definitive therapy, intervention, or surgery. Historically, ECLS in trauma was considered as contraindication, due to coagulopathies and hemorrhage, difficulties in prone positioning, and need for further interventions and surgery [5, 6]. Due to advances in hemostatic resuscitation, percutaneous vascular cannula insertion, centrifugal pump technologies, and improvements in membrane oxygenators, there has been significant improvement in ECLS management and broadened indications for its use. However, its use in the trauma population remained controversial for a long time [6, 7]. An outcome analysis from Extracorporeal Life Support Organization (ELSO) registry showed that less than 1% of the adult ELSO registry population is diagnosed with a traumatic injury [6]. In this cohort, thoracic injury was the most common diagnosis. The survival rates, comparable to other non-trauma groups, was reported by 70% at decannulation and 61% at hospital discharge [6]. In parallel, the evidence for beneficial outcomes in hemorrhagic patients supported with ECLS is increasing [8]. The benefits of hemodynamic support may outweigh the increased risk of bleeding since anticoagulation free protocols have been established thereby reducing or even preventing anticoagulation-related bleeding worsening due to ECLS application and support [8]. Early stabilization with ECLS might prevent or overcome the vicious circle of the lethal triad of trauma: hypothermia, hypoperfusion and acidosis, causing coagulopathy [8-10].

ARDS is the most common, non-traumatic indication for respiratory support on ECLS. CESAR trial published in 2009, was the randomized study which compared ECLS with conventional treatment and highlighted the importance of involving

specialized units, lung-protective ventilation, indicating ECLS as a valuable option in refractory respiratory failure [11]. The results of EOLIA study brought further results suggesting a possible superior clinical advantage of ECLS used for respiratory support over conventional measures, particularly when ECMO is used early. Conventional therapies, including prone positioning, had a high failure rate, necessitating rescue ECLS. Even if the mortality at day 60 in ECLS 44/124 (35%) vs. control group 57/125 (46%) was not significant [12], based on the previous evidence ECLS is a well-established organ support and becoming a standard practice. The Bayesian analysis of EOLIA stated that ECLS did prove to be superior to conventional therapy and, therefore, is now a well-established and accepted organ support in lung failure and ARDS, as also shown in the COVID-19 period. [13]. The outcomes of V-V ECLS in patients with severe COVID-related ARDS showed similar results as patients with non-COVID-related ARDS. [14]

Respiratory and cardiac failure are commonly seen in the out-of-hospital scene, emergency department (ED), intensive care unit (ICU), and operating room (OR). Initial resuscitative therapies for these conditions are lifesaving and nowadays extended by using extracorporeal life support (ECLS) and mechanical circulatory support (MSC) techniques.

Objective

This review addresses the application of ECLS in the life-threatening thoracic emergencies. The new developed classification of trauma and non-trauma categories in thoracic emergencies in which patients may be cannulated for ECLS support is also presented. Finally, the findings in accordance with the narrative review reporting checklist (Supplemental material 1) are also reported.

Description and classification of thoracic emergencies

Respiratory and/or cardiac failure are common due to trauma or non-traumatic underlying diseases. They may also result in circulatory, distributive, or obstructive and hypovolemic shock. ECLS is an additional, advanced tool for lung and/or heart organ support and does not represent the treatment of the underlying disease. Mostly used application modes of ECLS are veno-venous (V-V) and veno-arterial (V-A). V-V ECLS is aimed for respiratory support in which cardiovascular function is not severely compromised. V-A ECLS targets supporting cardiac or combined cardiopulmonary failure. Another support option for combined cardiopulmonary failure is veno-arterial-venous hybrid mode (V-AV), which included V-A and V-V support [15]. Regarding the definition and classification of thoracic emergencies with potential use of ECLS, the list of the newly categorized patterns and indications are shown in Table 1.

Table 1. *Classification of thoracic emergencies (Trauma and non-trauma, cardiac, parenchymal)*

Organs or region		**Trauma**	**Non-trauma**
Respiratory	chest wall	ribs, sternum, spine cord fractures	chest wall tumor mass, compression, bleeding
	lung parenchyma	contusion post trauma ARDS penetrating injuries bleeding	acute lung injury atelectasis hemorrhagic condition (anticoagulants, coagulopathies due to hematological or rheumatological underlying disease)
	pleural	pneumothorax tension- or hemopneumothorax	tension-, spontaneous pneumothorax hemopneumothorax (post- interventional complication)
	tracheobronchial system	tracheal or bronchial rupture difficult airway intubation aspiration (blood, stomach content)	compression due to cervical mass (lymphoma, goiter) trachea- or bronchial fistulas tracheal cannulae dislocation difficult airway intubation aspiration (fluids, blood, stomach content, meconium in newborns)
	others	burns, blast, and inhalation injury drowning avalanche injury	Anterior mediastinal mass
Cardiac	cardiac organ	penetrating heart or great vessels injury	chronic or acute heart failure due to underlying disease cardiogenic shock
		aortic rupture or dissection contusio cordis, luxatio cordis	aortic dissection
	circulatory	hemorrhagic shock (penetrating injury or bleeding coagulopathy)	circulatory arrest
		traumatic air embolism (due to long bone fracture)	embolism (pulmonary artery embolism, amnion fluid embolism, air embolism)
Others	mediastinal	esophageal rupture trachea-esophageal fistula	compression due to mediastinal tumor mass (lymphoma, retrosternal goiter) Boerhaave Syndrome (spontaneous esophageal rupture)
	hypothermia	due to drowning or avalanche injury due to traumatic bleeding coagulopathy	accidental post- surgery due to bleeding coagulopathy

Methods

An advanced search of Pubmed, Embase and Google Scholar through their databases using the following Medical Subject Headings (MeSH) terms: "Extracorporeal Membrane Oxygenation" AND "Wounds and Injuries" OR "Burns" OR "Hypothermia" OR "crush injuries" OR "wounds, penetrating" OR "wounds, nonpenetrating", OR "mediastinal mass" and free terms: "ECLS" OR "ECMO" OR "extracorporeal life support" AND "thoracic emergency" OR "blunt trauma" OR "penetrating trauma" OR "combat" OR "critical airway" OR "REBOA" assessed in June 2022, identified 761 records. From those, 74 publications in English language were analyzed. Reference lists of assessed full texts were screened for further relevant studies [16].

We included prospective and retrospective cohort studies, cross-sectional studies, case-control studies, case series and case reports. Studies reporting on use of any type of ECLS in thoracic, lung and cardiac trauma, hemorrhage, combat and burn thoracic injuries, and airways emergencies were considered eligible (Table 2). Available evidence was summarized using narrative review methodology.

Table 2. *Summary of proceeding the database search for related publications*

Items	Specification
Date of Search	June 2022
Databases and other sources searched	PubMed/EMBASE, Google Scholar
Search terms used	Mesh: extracorporeal membrane oxygenation, wound and injuries, wounds – non penetrating, wounds – penetrating, crush injuries, hypothermia, burns, mediastinal mass Free terms: extracorporeal life support, ECLS, ECMO, thoracic emergency, blunt trauma, penetrating trauma, combat, critical airway, REBOA
Timeframe of studies	1958- June 2022
Inclusion and exclusion criteria	Studies reporting on use of any type of ECLS in thoracic trauma, cardiac trauma, thoracic hemorrhage, combat and burn thoracic injuries, and airways emergencies were considered eligible. Randomized clinical trials, controlled before-and-after studies, prospective and retrospective cohort studies, cross-sectional studies, case-control studies, case series and case reports. Conference abstracts, books, articles not written in English, and animal studies were excluded.
Selection process	All the authors (A.W, S.M, J.S, R.L., J.M.) conducted the literature search and assessed the selected articles for inclusion. Consensus was reached when all the authors agreed on all studies.

Mediastinal mass

Mediastinal masses are often initially asymptomatic. The late symptoms of the appear usually from either mass effects on adjoining structures, or paraneoplastic effects. Enlargement of mediastinal structures can cause severe

respiratory impairment due to compression of the trachea and/or main bronchi. The stenosis of trachea and superior vena cava obstruction are secondary to compression from an enlarged mediastinal mass. Airway stents may provide effective and timely relief in patients with central airway obstruction. But severe, life- threatening respiratory failure may occur during such interventions. Thus, V-V ECLS is usually recommended in patients suffering severe hypoxemia and/or hypercapnia during invasive mechanical ventilation with exacerbating the risks of the mechanical ventilation induced lung injury (VILI). When committing an immunosuppressed patient to ECLS, patient selection and timing of initiation of these supports are the key considerations. ECLS use in immunocompromised patients with ARDS is increasing with 5% to 31% of patients receiving ECMO in recent studies. Because encouraging rates for hospital and long-term survival of immunocompromised patients in ICUs have been described, these patients are more likely to receive invasive therapies, also ECLS. Regarding the choice to perform ECLS or not, mainly due to possible complications of ECLS, as severe bleeding, the intensivists must take into account the future benefits of these patient.

Currently, ECLS may also be used as a protective bridging before, during and after interventions and procedures as among others, during induction chemotherapy and bronchoscopy intervention with stent placement preventing life-threatening deterioration. It leads to a paradigm shift in the pulmonary research.

Early V-V ECLS cannulation for respiratory support may improve survival in patients with mediastinal mass malignancies causing trachea obstruction and severe respiratory impairment. As configuration, femoro-femoral V-V cannulation is recommended as it enables stable blood flow avoiding the complications of superior vena cava obstruction.

ECLS in V-A configuration is used as a rescue management of anterior mediastinal masses with extrinsic compression on the airways and mediastinal vessels as well as during an emergent peri-arrest setting [17-20].

Tracheobronchial emergencies

The tracheobronchial tree plays a key role in ventilation. Any trauma, disruption or obstruction on these structures may be life-threatening and their treatment challenging, as in tracheal stenosis, tracheomalacia, tracheal tumors, iatrogenic tracheal injuries and foreign body aspiration. In these cases, emergency tracheostomy or coniotomy, cross field jet ventilation, direct cannulation of the distal trachea and small-bore endotracheal tubes can be employed [21]. In several circumstances conventional ventilation is impossible. In such situation, ECLS may provide adequate oxygenation without the need for endotracheal intubation [22]. This allows for an adequate respiratory support while performing surgery to restore the airway anatomy.

Iatrogenic tracheal injuries are a rare but life-threatening complication of endotracheal intubation. Moreover, in 0.8% of blunt thoracic trauma victims, tracheobronchial injuries occur [23]. Although a conservative approach is advised where possible, there are some cases which require surgical intervention [24]. In distal airway ruptures, an endotracheal double lumen tube may prevent air leakage, tension pneumothorax or pneumomediastinum occluding the injured site. One-lung ventilation might be necessary but not sufficient for safe oxygenation [25, 26] . In such situations, a V-V ECLS can be used for respiratory support during surgery and post-operatively [24, 27-31]. V-V ECMO has been used during intraoperatively even for more complex procedures such as the repair of a tracheoesophageal fistula [32].

Further example of a critical airway condition foreign body aspiration. These patients can deteriorate fast due to asphyxia. Removing the foreign body with bronchoscopy is necessary but the bronchoscopy itself can cause intermittent complete airway occlusion due to manipulation in the main airways, aggravating the respiratory distress. V-V ECLS can support the respiratory system during the intervention, while extraction of the foreign body is performed [25].

Chest trauma and parenchymal injury

Thoracic trauma accounts for 20-25% of all trauma-related deaths [33-35]. Thoracic injuries may include injuries to the airways, lungs, or parts of the cardiovascular system. The pathophysiologic mechanisms of a thoracic injury are multiple and include thoracic bone injuries, tracheobronchial injuries, pulmonary contusions or lacerations, pneumothorax and pleural effusion, acute airway obstruction, barotrauma, or restrictive intra-thoracic spaces [36]. Overall, the survival of patients with thoracic trauma depends on the extent of injury and the techniques of support [37]. Trauma itself and surgery in trauma patients require volume and blood products administration and can cause systemic inflammation and an increase of vascular permeability in alveolar capillaries. This results in fluid shifts, edema forming and alveolar damage, leading to decreased gas exchange and eventually to acute lung injury (ALI) and ARDS [35, 38]. Furthermore, ventilator-associated pneumonia (VAP) is a frequent complication. ARDS requires protective lung ventilation with low tidal volumes and safe positive expiratory pressure (PEEP) limits. In all these cases, ECLS could be an option to minimize the ventilatory settings when standard and advanced ventilation are failing and protective ventilation is required [35]. ECLS initiation and cannulation strategy should be carefully chosen in thoracic trauma patients since several injuries may limit the insertion of a cannula through the traditional ways [36]. Overall, V-V ECLS is the most used ECLS configuration for respiratory support while V-A ECLS is chosen in case of respiratory and circulatory support. In case of concomitant lung and right heart failure, a temporary right ventricular assist device with oxygenator (OxyRVAD) might be considered.

Results of ECLS use in chest trauma patients have been reported as positive by several small studies [39-41]. Guirand et al. demonstrated that V-V ECMO was even associated with higher survival compared to conventional mechanical ventilation [41], mirroring the results of much larger studies performed in ARDS patients [42-45].

Prolonged mechanical ventilation (defined previously as longer than 7 days) was considered a relative contraindication for ECLS a decade or two decades ago, e.g as an exclusion criterium for the CESAR trail [11]. This exclusion criterium was chosen based on the rare use of lung protective ventilation in ICUs, and the frequent lung damage due to baro- and volu-trauma. On the other hand, the EOLIA trial, although known as „negative trial", showed that the conventional management (including prone positioning) had a high failure rate, necessitating „rescue" ECLS cannulation [12]. Thus, based on the ELSO guidelines and available literature, prolonged ventilation is not considered as an ECLS contraindication anymore. [46, 47]

TRALI, ARDS and VAP may also lead to severe lung failure with life threatening complications, thus ECLS in chest trauma and parenchymal lung injury should be carefully considered. However, based on the current evidence, trauma, and especially blunt thoracic trauma is one of the main indications for ECLS in thoracic emergencies. Trauma patients are younger than non-trauma patients, and they have less comorbidities. In large cohort studies, the outcomes of trauma patients supported on ECLS are comparable to non-trauma patients, and not worse than them [6, 48]

Thoracic penetrating injuries and hemorrhagic shock

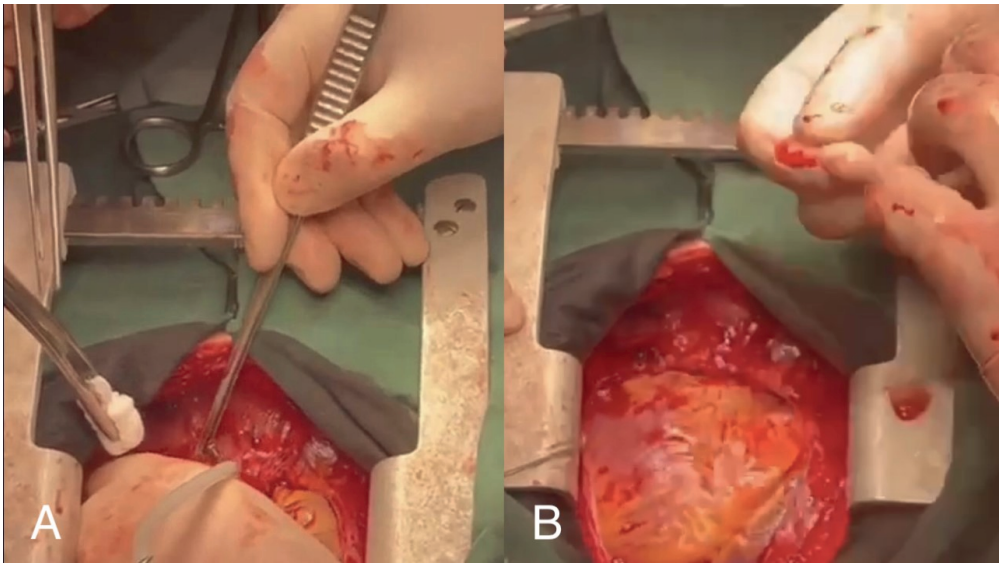
Most penetrating injuries include direct damage to the intercostal or mammary arteries, pleura or lung tissue [34] and can be managed non-operatively with thorax drainage and conventional resuscitation techniques [35]. However, in 10-15% of cases, an operative management is necessary. The main cause of morbidity and mortality in these patients is the hemorrhagic shock which is the second most frequent cause of death in trauma patients after nervous system injuries [49]. Hemorrhagic shock and hemothorax can be a result of penetrating injury due to laceration of tine intercostal or mammary arteries, thoracic spine arteries, lung parenchyma, great vessels, thoracic aorta, and the heart. (Figure 1)

Hemorrhagic shock after thoracic injury is managed by volume resuscitation and mass transfusion [8, 34]. Mass transfusion may lead to transfusion related lung injury (TRALI) as well. The pathophysiology of TRALI is quite similar to ARDS [50]. Multiple cases of V-V ECLS has been reported successful to support patients with TRALI where conventional treatment was not sufficient [51-54].

Historically, bleeding has been considered a contraindication [8, 55, 56]. However, due to the systematic review performed by Willers et al. [8]. ECLS for temporary circulatory support in refractory hemorrhagic shock is feasible based on tailored devices and adequate patient management. However, ECLS is not designed for bleeding control and it should not be considered as such "therapy". ECLS provides circulatory support that allows clinicians to gain time and bridge the patient to an appropriate medical, surgical, or interventional strategy for bleeding control, transfusions and coagulation supporting agents. Furthermore, new strategies and devices allows for a safer ECLS management in terms of anticoagulation [55].

ECLS might be indicated to support adequate tissue perfusion after the hemorrhagic shock, provide massive and quick transfusions, reduce systemic hypoxia and acidosis and prevent or treat hypothermia [8]. Through these mechanisms, ECLS plays a pivotal role preventing or overcoming the vicious cycle of coagulopathy in hemorrhagic shock patients [57]. Management of bleeding control, (surgical, or interventional), transfusions and coagulation supporting agents is a separate strategy.

Figure 1. *Projectile penetrating myocardium resulting in heart injury*



A) Splinter found in penetrating myocard injury after combat injury in Ukraine. A. In situ corpus alienum pointed out by the forceps. B) The corpus alienum is extracted from the patients, pointed out by the surgeon.

Aortic injuries

A direct penetrating injury or a complete transection of the aorta may cause exsanguination with pre-hospital death in 90% and 44% mortality of patients who make it to the emergency or operating room [58]. An aortic injury due to a blunt chest trauma is not always immediately lethal. Shearing forces due to rapid acceleration and deceleration on the aorta in blunt trauma may cause aortic dissection, typically at the ligamentum arteriosum where the aorta arch is fixed [59-61]. Similarly, partial thickness injuries cause contained hematomas in the aortic walls. Patients with aortic injury need emergency surgery on CPB. However, these patients may rapidly deteriorate in the emergency department, aortic dissection may be misdiagnosed and/or cardiac surgery may not be available in every hospital. In such conditions, ECLS may be considered as a bridge to surgery and circulatory support but the evidence for ECLS in aortic injury is very scarce and controversial [15].

V-A ECLS is a potential option for refractory cardiogenic shock and cardiac arrest because it quickly improves hemodynamics and can be initiated rapidly. The most feared complication is the injury of the dissection membrane during the cannulation. In selected cases, the resuscitative endovascular balloon occlusion of the aorta (REBOA) might be required to control the massive hemorrhage from major vessels [62]. Deployment of REBOA in the supra-diaphragmatic location (Zone I) allows for control of lower torso/abdominal or lower extremity bleeding. Zone II implies the placement of a REBOA between the celiac trunk and the renal arteries. Zone III involves REBOA placement below the renal arteries but proximal to the iliac bifurcation. ECLS can be applied also in combination with REBOA and a selective aortic arch perfusion (SAAP) to restore the circulation of the upper body in case of concomitant cardiac arrest or profound shock [63]. In these cases, SAAP is a technique that combines thoracic aortic occlusion with a large-lumen balloon occlusion catheter inserted via a femoral artery and positioned between the left subclavian artery and diaphragm. The SAAP catheter lumen allows for extracorporeal perfusion with flow limited to the upper body to allow for adequate control of the hemorrhagic focus while maintaining the perfusion of the upper body. Although the concept of SAAP has been extensively evaluated in preclinical studies, its clinical use has not yet been described [63].

Emergency preservation and resuscitation (EPR) is a novel approach to the management of patients who have suffered a cardiac arrest from trauma such as in case of major thoracic hemorrhage or penetrating cardiac injury [63]. This technique involves rapid cooling of the body and a period of circulatory arrest to allow for surgical hemostasis and a subsequent rewarming phase through ECLS. Profound hypothermia is induced by large-volume cold fluid infusion into the thoracic aorta and blood drainage from the right atrial appendage. Surgical

hemostasis is then achieved under ECLS. This technique in currently under clinical investigation [64].

Blunt thoracic trauma

Based on the current evidence, trauma, and especially blunt thoracic trauma, is one of the main indications for ECLS use in thoracic emergencies. Indeed, the use of ECLS in trauma is broadly increasing.[6, 15, 57, 65, 66]. Blunt thoracic trauma is often caused by high-energy trauma with compression, deceleration or inertial forces due to falls, motor vehicle collisions or by direct forces from assault. Blunt trauma forces on the thorax often cause rib fractures, resulting in higher mortality and risk for pneumonia, especially in elderly patients. An extensive trauma including four or more rib fractures increases the risk for intensive care unit (ICU) admission, intubation and ventilation [34]. Furthermore, a high-energy impact on the thorax can cause pulmonary contusions, damage to lung parenchyma, alveolar lacerations and hemorrhage, followed by edema. This clinical picture can lead to ALI or ARDS [23, 34], and to a ventilation-perfusion mismatch that will eventually result in shunting. In these cases, ECLS can be indicated to provide respiratory support as bridge to recovery [23]. V-V ECLS is the first choice in case of good cardiac function, due to its lower bleeding risks. Overall, promising outcomes of V-V ECLS in trauma-related hypoxemia are reported, even when emergency surgery is performed. [39, 67-69]

Previous studies report a survival rate of almost 75-80% in thoracic blunt trauma supported by ECLS. V-V ECLS is the most often ECLS configuration used. Damage control surgery or invasive measurements were performed in 15-30% and hemorrhagic complications are reported between 29% of the cases, mostly at the surgical site and cannula site. [39, 70]

Cardiac trauma and traumatic cardiac arrest

Cardiac arrest caused by trauma is associated to a low survival rate, with a high incidence of permanent neurologic disability in survivors [71]. The etiology of traumatic cardiac arrest can be categorized in three main groups: penetrating injuries, blunt injuries and hemorrhage-induced traumatic cardiac arrest [63, 72].

Penetrating injury of the heart is nowadays rare in European countries. This kind of injury is one of the possible indications for ECLS, e.g. as bridging to surgery in case of hemorrhagic shock (Figure 1 A and B). Penetrating trauma is associated with better outcome than blunt mechanisms, but the location of the injury greatly affects survival [63]. Indeed, some studies report a 94% pre-hospital mortality in patients with penetrating cardiac injury [23] and chances of survival to the hospital are reported between 6-19.3% [34]. In most cases, survival depends on the rapidity of the patient transfer to a cardiac surgery center [73]. Active bleeding and tamponade are the reason for severe hemodynamic instability in both penetrating

and blunt injuries. Secondary myocardial contusion, myocardial stunning and/or infarction further complicate the clinical picture with acute heart failure. In these cases, the surgical control of the hemorrhage and the tamponade decompression are the treatment of choice. Simultaneously, V-A ECLS can provide adequate organs perfusion, rapid cooling of the body in case a circulatory arrest is required, therapeutic hypothermia and left ventricular unloading.

Blunt cardiac injuries include a wide range of clinical presentations, from ECG abnormalities to myocardial rupture and cardiogenic shock [23]. In vehicle collisions, between 20-76% of death at scene is caused by blunt cardiac injuries [34] which usually include myocardial bruises, septal rupture with or without valvular injury, coronary artery injury and free wall ruptures. These injuries can result in direct congestive heart failure, myocardial infarctions and tamponade. Also arrhythmias can occur due to blunt chest trauma [34]. When the cardiac function is not sufficient, an intra-aortic balloon pump can help to unload the left ventricle [23]. However, unloading the left ventricle does not always secure sufficient cardiac function to maintain adequate tissue perfusion. In cases where cardiac function is significantly reduced, tissue perfusion must be supported with chronotropic and inotropic medications. ECLS can further support patients with deteriorated heart function whenever medical support is not sufficient [74]. Indeed, patients with rupture of major vessels or cardiac rupture, cardiac arrest or valvular injury after blunt chest trauma have been successfully supported with ECLS [73, 75-79].

Combat injuries

Recent years have witnessed a growing interest in the use of ECLS in military settings [80]. Major traumas in battlefields are caused by explosions and are associated with inhalation, burn and blast injuries. There are four major types of blast injuries: direct tissue damage from pressurized waves, secondary injuries from penetrating wounds from projectiles, tertiary injuries from blunt or penetrating trauma caused by blast winds, and quaternary injuries including burns, radiation, and inhalation injuries [81]. Soldiers exposed to explosions are thus at risk for multiple trauma injuries, including pulmonary injury. Blast lung injuries evolve to ARDS in 3-14% of patients sustaining primary blast injuries, associated with confined spaces [82, 83]. Trauma patients in combat settings could benefit from fast respiratory and circulatory stabilization with ECLS so to allow a safer transport to a treatment facility. Literature reports few successful cases where interventional lung assists systems (iLA) were implanted to secure oxygenation during air transport as bridge to further treatments [84-86]. Similarly, ECLS has been applied in ARDS after blast lung injury [87]. Moreover, interfacility transport of patients submitted to ECLS has been improved and has proven to be safe an effective [88], supporting the growing role of ECLS as clinical approach for combat injuries [89]. However, specialized teams are necessary

to provide safe use of ECLS circuits and due to environmental factors, the use of ECLS on combat scenes is still very challenging.

Burn injuries

Burn and smoke inhalation injuries result in overwhelming inflammation activation with intra alveolar and intra bronchial damage with edema and hemorrhage. As a result, the lung compliance decreases, and alveolar gas exchange deteriorates. Finally, pulmonary shunting occurs, and hypoxemic respiratory failure can develop [90, 91]. Inhalation injury and sepsis leading to ARDS, multi-organ failure and shock have driven burn-related morbidity and mortality with 60% total body surface area involvement being a predictor of negative outcomes [92, 93]. Overall mortality of patients with burn inhalation injuries is reported between 16 and 85% in pediatric patients and 90% in the overall population [94, 95]. Successful use of ECLS in major burn injuries, with secondary ARDS, has been reported [90, 96-103]. Survival rates in these reports ranged between 28% and 87% [90, 100, 104]. Nevertheless, limited evidence is reported. No large cohorts have been described and evidence of successful use of ECLS is only based on case series or case reports which might be biased and overestimate the survival rate of this specific patient group.

Benefits of ECLS in trauma patients

Trauma patients are conventionally treated with fluid resuscitation, ventilatory support and chest tube drainage. In cases of traumatic cardiorespiratory arrest, survival decreases to 17% [105]. ECLS used during the cardiopulmonary failure can restore the lethal triad characterized by metabolic acidosis, coagulopathy and hypothermia [106] (Figure 2). ECLS may quickly restore the circulatory volume allowing for a resuscitation of 4L within 30 minutes with the use of normal to large size cannulas. With resuscitation and continuous cardiac support, circulation is restored and can therefore correct the metabolic acidosis. Furthermore, accidental hypothermia can be corrected with central rewarming via ECLS. Whenever there is cerebral injury, ECLS can be used in blood cooling to protect the cerebral tissue. By reversing hypothermia, coagulopathy can be reversed as well [57].

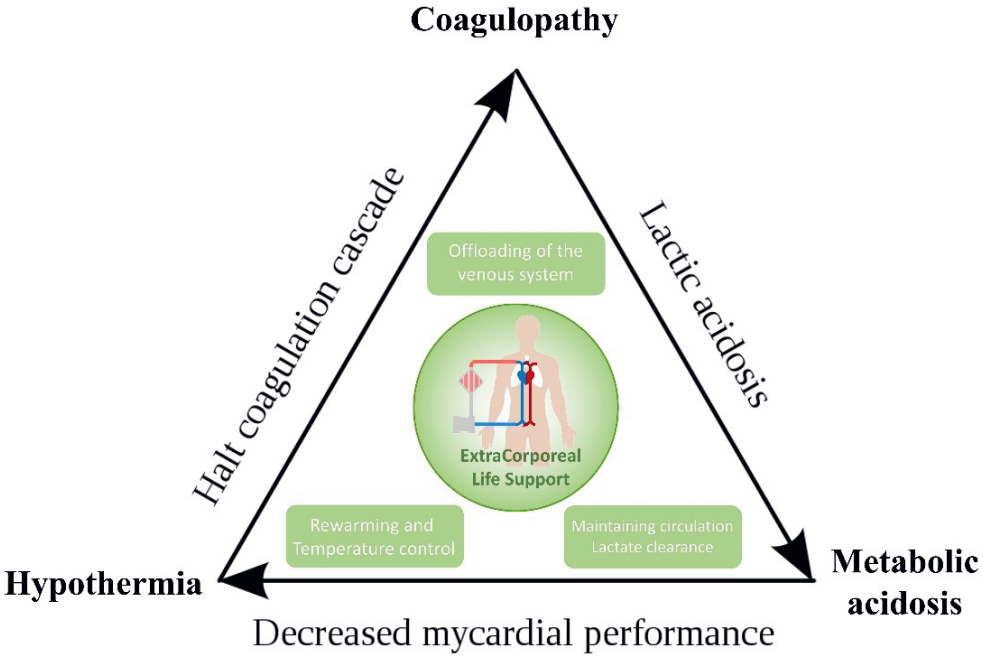
Limitations of ECLS in trauma patients

There are still concerns to the use of ECLS in trauma patients. First, by reversing hypothermia, coagulopathy can be prevented. But the use of ECLS, with foreign body cannulas and surfaces and the use of systemic anticoagulation, may promote the development of coagulopathy. In addition, the specific concern in trauma patients is further exsanguination during ECLS. In the past few years, the knowledge and experience with the use of ECLS has been expanding rapidly. ECLS systems have been improved with heparin bonding and modifications in the systemic

anticoagulation management have been developed, decreasing the incidence of bleeding complications [35, 57]. A systematic review of patient with pre-existent hemorrhage, showed good outcomes of ECLS support with a survival rate of 82.3%. Only 26% of patients developed bleeding complications. Multiple solutions to minimize the risk of further bleeding, include an initial heparin-free period, lower heparin targets or clamping of the tube in pulmonary bleeding [8]. However, anticoagulation strategies and timing of ECLS initiation in trauma patients are still controversial [107].

Further research is needed to improve the use of ECLS in trauma. However, a low number of trauma patients submitted to ECLS complicates this. Most papers are case series of small cohorts. Research on prediction of survival is therefore difficult. Adding a trauma addendum to the previously mentioned ELSO registry, could contribute to further research.

Figure 2. *The triad of hypothermia, acidosis and coagulopathy causing further bleeding in hemorrhagic shock*



ECLS used during the cardiopulmonary failure can restore the lethal triad characterized by metabolic acidosis, coagulopathy and hypothermia.

Conclusion

ECLS use in thoracic emergencies is increasing. The summarized findings appeal to policymakers, and we hope that our summary of recommendations may impact clinical practice and research. ECLS use is always individualized to patient's needs, injury pattern and kind of organ failure, circulatory arrest inclusive, depending on if respiratory or cardiac and circulatory support is needed. It is recommended to adjust anticoagulation targets to patients' condition. Anticoagulation may be omitted for some hours or days. Daily, routine oxygenator checks are obligatory. ECLS is an additional tool for organ support and cannot be understand as a treatment of the underlying disease. ECLS provides bridging to recovery or to decision about destination as definitive therapy, intervention, or surgery. Interdisciplinary cooperation between the intensivists, surgeons, anesthesiologists, emergency medical services, an appropriately organized and trained staff, equipment resources and logistical planning are essential for successful outcomes.

Supplemental material 1. *Narrative Review Checklist*

Section/ Topic	**Item No**	**Item**	**Page**	**Paragraph**
Title	1	Identify the report as a Narrative Review or Literature Review.	1	Not applicable
Structured summary	2	Provide a structured summary with the subsections as: Background and Objective, Methods, Key Content and Findings, Conclusions.	2	Not applicable
Rationale/ background	3	Describe the rationale for the review in the context of what is already known.	3-4	Introduction
Objectives	4	Specify the key question(s) identified for the review topic.	3-4	Introduction
Research selection	5	Specify the process for identifying the literature search (eg, years considered, language, publication status, study design, and databases of coverage).	4	Methods
Narrative	6	Discuss: 1) research reviewed including fundamental or key findings, 2) limitations and/or quality of research reviewed, and 3) need for future research.	1.4-14 2.14 3.14	Not applicable
Summary	7	Provide an overall interpretation of the narrative review in the context of clinical practice for health professionals, policy development and implementation, or future research.	15	Summary

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9

General discussion

Bleeding-related events are among the most frequent complications reported during extracorporeal life support (ECLS) [1]. Therefore, acute bleeding was previously considered a contraindication for ECLS initiation. Due to improved ECLS circuits, increased knowledge and experiences, bleeding has now become only a relative contra-indication. The manuscript herein presented elaborates on the magnitude of bleeding complications during ECLS and the possible solutions, but also on the use of ECLS in the treatment of bleeding-related conditions.

Due to several ECLS-based peculiarities, including cardio-circulatory support in the presence of refractory hypotension, provision of high volume of fluid and blood-related components in a short time, and the quick correction of metabolic and gas inbalances, ECLS could help prevent the lethal triad of hypothermia, hypoperfusion and acidosis, and thereby overcome the vicious cycle of coagulopathy in hemorrhagic shock patients [2]. The included case-reports and case series reported different strategies to stop and/or prevent continuous or recurrence of bleeding. Multiple solutions have been presented to prevent further bleeding complications, such as shorter circuits with secondary a decrease in anticoagulation dosages, heparin free or heparin free periods during ECLS or lower targets for anticoagulation. An overall survival of 82.3% was found in these circumstances. The high survival rate could be overrated due to publication bias and randomized or observational trials are lacking. Despite the lack of large data studies, pre-existing hemorrhagic conditions should no longer be considered an absolute contra-indication for ECLS. Further research is necessary to evaluate different approaches to minimize the risk for bleeding and to evaluate patients at high risk for bleeding complications. (Chapter 2)

The incidence of bleeding adverse events during ECLS varies a great deal among published studies. In a retrospective study describing cohorts of veno-arterial (V-A) and veno-venous (V-V) ECLS patients, 60% of the complication episodes included bleeding events [3]. In a study with post-cardiotomy patients on ECLS, a prevalence of 45% was reported [4]. Meta-analyses of V-A ECLS and V-V ECLS cases respectively showed a summary bleeding complications prevalence of 27% and 29.3% [5, 6]. Other meta-analysis of mixed V-A and V-V ECLS showed a variation of bleeding events between 16.6 and 50.7% [7]. The different bleeding complications rates are explainable due to heterogeneity of the study cohorts and the use of different definitions of bleeding complications. As a result, comparing outcomes of bleeding complications between studies and years is very challenging. Bleeding complications in the past twenty years have been decreasing, mostly in surgical site and cannulation site bleeding. Overall, bleeding complications were more frequent in V-A ECLS cases (30.0%) compared to V-V (21.9%) and the

mortality was higher in patients with bleeding complications. To analyze the trends of bleeding complications, we used data of the Extracorporeal Life Support Organization (ELSO) registry. The registry uses a common definition for bleeding complications, in contrast to individual published studies. Due to the data source and the pre-identified definitions, the outcomes of the study are applicable in general and gives us a good insight of the improvements of bleeding complications during ECLS runs over the world. A limitation of the use of the registry are the missing data, especially data on anticoagulation strategies, amount of blood loss and laboratory values. The interpretation of why the bleeding complications showed a decreasing trend is therefore difficult to interpret. (Chapter 3)

Despite decreasing trends, bleeding complication rate remains high and there is a need for further research on anticoagulation agents, dosage and laboratory measurements. Multiple studies have been performed to compare different drugs, timing and monitoring protocols and several reviews have been written [105-116]. Original studies are often observational studies and of retrospective nature. The most beneficial management is not established yet and presumable patient specific. A lower or no anticoagulation protocol might be beneficial for patients at high risk for bleeding complications. Prediction models for bleeding complications during ECLS would be helpful in detecting high risk patients in research settings. However, there are no risk modifications tools available to predict the risk for bleeding events in settings with ECLS.

The development of risk models to predict the risk of bleeding complications would be extremely useful in the ECLS setting. Such a objective was pursued in both V-V and V-A ECLS configuration always using the ELSO Registry data. The HEROES V-V prediction model yielded an AUC of 0.633 (95% CI 0.623-0.642, $p<0.001$) with good calibration, and the HEROES V-A model showed an AUC of 0.660 (95% CI -.653-0.667, $p<0.001$). Both models had excellent calibration plots and internal validation showed small overfitting of the models with optimisms of the AUC of 0.004 and 0.002 for V-V and V-A respectively, meaning that these models would perform similar in external cohorts. (Chapter 4 and 5) We used a multivariable logistic regression analysis with backward wald stepwise elimination to build our prediction models. With this method, the least significant risk factors are excluded based on statistical evidence of significance. Since we used a database including over 20.000 patients for V-V ECLS and 25.000 for V-A ECLS, the accuracy of the statistical analyses is very high.

Often a prediction model is based on previous found risk factors. In the literature, there are broad differences in outcomes in studies investigating risk factors for bleeding complications in ECLS vary great. Only one risk score for bleeding complications is available, however this score does not differentiate the risks

between V-A ECLS and V-V ECLS and was based on a retrospective cohort of 112 patients [8]. Female sex, body weight, fungal pneumonia, interstitial lung disease, higher peak inspiratory pressure, rapid CO2 change at ECLS initiation, previous surgery, central cannulation and ECLS duration are reported risk factors for bleeding events [3, 9-12]. In terms of laboratory findings, elevated activated partial thromboplastin time (aPTT) and activated clotting times (ACT), lower prothrombin time (PT), low fibrinogen levels, increased creatinine levels and thrombocytopenia are associated with bleeding events [3, 10, 13-15]. These outcomes are often based on small cohort studies, with heterogeneity between them and different definitions of bleeding complications. Therefore, we decided not to base our prediction model on previous selected variables but to include all possible variables and exclude less significant variables based in statistical significance. Furthermore, we decided to develop specific prediction models for V-V and V-A ECLS separately, because of the great differences between underlying mechanisms between the patients undergoing V-V and V-A ECLS.

For now, the models presented can be used in research settings to differentiate patients at high or low risk for bleeding complications. The usefulness of these models in clinical settings require external validation first. With the suggested web-based calculators, the use would be easy. A well-known disadvantage of retrospective database studies, is the previously determined included variables. With the ELSO registry, a lot of data is collected, however for specific questions, some desired variables are not included. In retrospect, the use of a prospective database, including anticoagulation management and laboratory values and transfusion data would have been of superior value. On the other hand, these analyses presented can be a fundament for future prospective studies. We now know which variables are important to include, and in the future anticoagulation agents and laboratory data could be added in following studies. With further optimizing of these models, predicting and anticipating of hemorrhagic complications will be improved.

The changes and improvements of ECLS circuits and management that are currently happening to reduce the risk of bleeding and thrombotic complications have been also assessed. Therefore, a review with an overview of different types of anti-coagulation drugs and types of coatings for circuit tubing and components was performed. We conclude that there is no uniform protocol for anticoagulation management. Each center and even clinicians have their own preferences and experiences with anticoagulation management, including the type of drugs as well as the used targets for dosage changes. Also, bioactive and bio-passive coating compounds are improving over the years. (Chapter 6) We believe that the

improvements in the ECLS components and management, may have contributed to the decrease of bleeding complications in the past two decades. (Chapter 3)

A specific patient group at risk for bleeding complications are trauma patients. Bleeding complications increase risk for hypothermia and acidosis, and secondary coagulopathy, and, in addition, massive transfusion and fluid resuscitation may further deteriorate the patient critical condition. However, ECLS can correct the hypothermia and acidosis, which than will restore the hemostatic balance. We investigated the amount of complications and trends over the past 20 years about the ECLS use in trauma conditions. (Chapter 7) Renal complications and cardiovascular complications are the most frequent reported complications, followed by ECLS circuit failure and hemorrhage. There was no statistical decrease of complications or survival rate over the years. However, the ELSO registry does not include trauma-specific variables, including type of injuries and use and timing of anticoagulation. There are only small cohorts or case-series available investigating the use of ECLS in trauma populations. In chapter 8, we elaborate on the different type of thoracic emergencies, where ECLS could add value when conventional treatment is failing. We believe more research is needed to understand the specific risk factors for bleeding complications in the trauma patient on ECLS, to be able to reduce the complication rate. Therefore, we recommend the use of an addendum for the ELSO Registry, to include trauma-related characteristics which will help to collect data for further investigations.

Future perspectives

Further research regarding hemostasis during ECLS should be focused on risk stratification and patient specific anticoagulation management. Individual and patient specific anticoagulation importance will increase. Therefore, identifying high-risk patients for bleeding-related complications will be of great value. The prediction models presented in Chapter 4 and 5 could be further improved by prospective cohort studies collecting the variables used in that analysis, but with additional variables such as platelet count, fibrinogen levels, red blood cell count, hematocrit, time of anticoagulation administration, type of agents and targets and transfusion data. An updated version of the prediction models would be easy to use if the web-based models could be implemented. With this online calculator, research on different timing and dosage on anticoagulation management could be facilitated.

Furthermore, future studies could include research on platelet function during ECLS. Coagulopathy in ECLS is often explained by the use of heparin. In addition, contact activation due to blood/foreign surface contact with the ECLS circuit and hemodilution due to fluid administration and priming volume, can lead to a reduction of available clotting factors and platelets [16]. Aside from the medical

induced coagulopathy and the relative decrease of available platelets, the function of the platelets can also be altered by the exposure to ECLS itself. A study in pediatric patients showed a correlation between duration of ECLS and platelet function. A decrease of fibrinogen receptors and platelet response was found. and a decrease platelet fibrinogen receptor expression during ECLS, which can possibly result in decreased ability of activation and aggregation of platelets [17]. Same results are found in adult population, where decreased platelet activation and reduced platelet aggregation are reported [18]. With in-depth research on the activation and aggregation of platelet in different scenarios, specific pathways might be found that are associated with bleeding complications. Interference with this pathway could possibly lead to a solution to reduce the risk of bleeding but also thrombotic events.

With more insight of bleeding tendency causes and possible solutions, research in high-risk patients could be broadened. Hypothermic patients or trauma patients or patient with pre-existent bleeding-related predisposition can potentially benefit much from ECLS in terms of temperature regulation, acidosis correction and fluid restoration, next to the conventional cardiopulmonary support the ECLS provides. With improved knowledge of the risk factors for bleeding and thrombosis, the initiation of ECLS in high-risk patients' group could become more accessible. Pre-hospital use of ECLS has been reported in ECPR settings, however the experience use in pre-hospital settings is small [19-21]. In the future, the use of ECLS in pre-hospital settings could be broadened to non-ECPR cases. However, this is hypothetical since there are still capability gaps to overcome. For instance, in combat settings, the lack of knowledge of ECLS indications, experience in low pulse cannulation and the lack of high-level facilities in establishing it are opposing factors [22].

In addition, research on optimizing materials of ECLS circuits should continue as well. Low-dose systemic heparin does not maintain adequate antithrombotic activity, and high-dose heparin results in direct cell activation instead of anticoagulation and anti-inflammatory effects [23]. There is a need for a modified ECLS surface, addressing the inflammation reaction and coagulation reaction at the same time, with permanent effect to ensure efficacy during long-term ECLS runs. Within the animal kingdom, different animals have special skin adaptations with embossing for optimal aerodynamics and friction [24]. Adapting solutions used in wildlife, could be helpful in finding an answer to our challenges.

Another scientific approach could be finding a surface that mimicking the human endothelium, to diminishing the activation of platelets, the inflammatory system and coagulation system and reduce the need for anticoagulation.

To find the solution to bleeding tendencies and thrombotic events during ECLS, and eventually achieve homeostasis in the hemostasis, research should be continued in materials, surface patters, risk stratification and anticoagulation management.

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10

Impact and valorization

In this dissertation, the amount of bleeding complications in extracorporeal life support (ECLS) and the balance of hemostasis and risk factors were investigated. Furthermore, the possibilities and challenges of application of ECLS in high-risk trauma patients were reviewed and discussed.

The dissertation presents substantial knowledge of bleeding-related complications in the use of ECLS based on the extracorporeal life support organization (ELSO) registry data and available literature. The trend of bleeding complications was thought to be decreasing, however the absolute decrease analysis was previously not performed due to the heterogenous characteristics between studies and lack of uniform complication definitions. This manuscript presents the first study with trend calculations on bleeding complications over a twenty-year period including international data with more than 50 000 patients.

Furthermore, this thesis presents the development of the prediction models for bleeding complications in veno-venous (V-V) and veno-arterial (V-A) ECLS based on the multi-international ELSO database including a high number of patients and using a standardized definition of bleeding complications. Prior to these studies, only one prediction model for bleeding ocmplications during ECLS was available. However, this model did not separate V-V and V-A ECLS, so underlying differences of pathophysiology were not considered in these analyses. Additionally, the development of the presented models is based on high number of patients and the analytical methods ensured a robust model development.

Researchers could benefit from models and the presented odds ratios. The odds ratios for all variables provide insight of the risk factors contributing to bleeding complications. The prediction models presented can be used in research settings to differentiate low and high-risk patients for bleeding complications. This can be implemented in studies assessing different types of anticoagulation managements such as low-dose anticoagulation or an anticoagulation-free period during ECLS. Prevention of bleeding complications in the future seems increasingly realistic and subsequently can contribute in anticipating on bleeding complications with altered anticoagulation methods.

In the future, improving the prediction models with additional factors such as anticoagulation use and laboraty findings, will have major impact on working towards personalized medicine.

Also, we present a great overview of improvement of the circuit and anticoagulation management during ECLS, where the collaboration between clinical and basic scientists is clarified to be essential to enable research from bench to bedside.

In addition, the dissertation focusses on high-risk trauma patients supported on ECLS.
In the presented analysis, almost 280 trauma patients were included, one of the largest cohorts presented in ECLS investigation focussed on trauma patients. In this analysis, a decrease of complications was found with the increase of use of ECLS in trauma patients, emphasizing the need for further investigation in this subgroup of patients. Moreover, in the following review we provided a great synopsis of the applications of ECLS in different types of trauma.

With the outcomes presented in this dissertation the ECLS society, including intensivist, surgeons, cardiologists, pulmonologists, perfusionists and other clinicians working with ECLS, should be encouraged to continue the use of ECLS in challenging cases with bleeding risks and contribute research in ECLS settings. The increase of ECLS use with decreasing mortality and bleeding complications should strengthen the believe in effectiveness of ECLS. Furthermore, the ECLS society should be inspired to improve the ELSO database by including a trauma addendum and possibly anticoagulation and laboratory data in the future to improve research in the future.

11

Summary | Samenvatting

English summary

In this dissertation, the use of extracorporeal life support (ECLS) is addressed in the context of bleeding complications. Bleeding complications remain the most frequent complications during the use of ECLS. With expanding indications and the growing numbers of patients supported with ECLS, preventing bleeding complications is fundamental. With preventing bleeding complications, mortality, morbidity and health care costs can be minimized as well.

Part I Bleeding complications in extracorporeal life support

Chapter 2 is a systematic overview of patients with pre-existent hemorrhagic conditions submitted to ECLS. We found 181 patients in total, with 82.3% survival and 26% bleeding complications. Causes of death included mostly multiorgan failure and shock. Only five patients died due to further bleeding. Most complications were found in patients without anticoagulation in the initial period of ECLS. Protocols to control bleeding included damage control surgery, tracheal clamping and stenting. Furthermore, no anticoagulation or anticoagulation free period during ECLS was frequently reported to reduce the risk of further bleeding. With multiple solutions to prevent further bleeding, ECLS could serve as a bridge to hemorrhagic control treatment in pre-existent hemorrhagic conditions in patients.

The overall incidence of bleeding complications varies widely between studies. Also, due to different definitions for bleeding complications, comparing the outcomes and investigating the trends over the years is nearly impossible. In chapter 3 we investigated the trends of bleeding complications in the past twenty years and trends of mortality of patients submitted to ECLS with the use of the ELSO registry. We included 53.664 patients, with almost 20.000 patients submitted to V-V ECLS and 30.000 to V-A ECLS. In the past 20 years, we found a decrease in bleeding complications in both V-V and V-A ECLS, mainly in surgical and cannula-site related bleeding complications. Bleeding complications were associated with a higher mortality, however there was no decreasing trend in mortality found.

Part II Prediction of bleeding complications in extracorporeal life support

In chapter 4 and 5, the development of prediction models for hemorrhagic complications in patients submitted to V-V and V-A ECLS subsequently is reported. In the prediction model for bleeding complications focused on V-V ECLS patients, the AUC was 0.63. Pre-ECLS arrest, surgical cannulation, lactate, pO2, HCO3, ventilation rate, mean airway pressure, pre-ECLS cardiopulmonary bypass or renal

replacement therapy, pre-ECLS surgical interventions, and different types of diagnosis were included in the prediction model. The prediction model for bleeding complications during V-A ECLS yielded 0.66, and included sex, BMI, surgical cannulation, pre-ECLS respiratory and hemodynamic variables, pre-ECLS support and interventions and different type of diagnosis as predictive factors. Further research may improve the model by identifying and adding other important predictors such as anticoagulation management and laboratory values. External validation is needed to implement the model in clinical settings; however, the model might already be used for research purposes and crude estimates in bleeding risk.

Part III Developments in extracorporeal life support and applicability of extracorporeal life support in trauma settings.

In chapter 6 we investigate the developments and trends of anticoagulation management and coatings of ECLS circuit to reduce bleeding complications. De interaction between the human body, blood and artificial materials can be reduced with anticoagulation agents, biomimetic and biopassive surfaces. The goal is to find the balance between clotting and bleeding risks. In the future, endothelialization of the ECLS circuits and the use of bio-compatible materials could eliminate the need for systemic anticoagulation, but intense efforts are still required to fulfill this purpose.

Chapter 7 assesses the main complications in the high-risk subgroup of trauma patients submitted to ECLS. We found a high rate of complications of 80%. Renal complications were the most frequent complications and were reported in 44%, followed by hemorrhagic complications and ECLS mechanical failure (both 30%). The analysis showed a high survival of ECLS of 70.3% and 60.6% of hospital survival.

Chapter 8 presents the possibilities of ECLS in thoracic emergency situations. It presents the type of injuries that have been successfully supported by ECLS. This includes tracheobronchial emergencies, blunt and penetrating chest injuries, aortic injuries, cardiac trauma and cardiac arrests, multiple trauma injuries, blast and burn injuries and combat injuries. It elaborates on this wide variety of circumstances where ECLS could be of great value, where previously ECLS was not even considered.

In conclusion, this thesis presents investigations in bleeding complications during ECLS with possible solutions and trends over the years. Thereafter, the development and internal validation of two prediction models for bleeding complications in V-V

and V-A ECLS are presented. Further, we elaborate on the progress of anticoagulation managements and circuit coating development. Lastly, we report the analysis of the trends of complications in a high-risk trauma patient and present a wide variety of different type of high-risk injuries that could benefit from ECLS.

Further studies are warranted to improve in the prediction of bleeding complications and to find the perfect balance between coagulation and bleeding tendencies with further development of anticoagulation management and circuit materials and coatings.

Nederlandse samenvatting

In dit proefschrift wordt onderzoek gepresenteerd met de focus op bloedingscomplicaties tijdens het gebruik van een artificiële hart-long-machine; extracorporele life support (ECLS).
Bloedingscomplicaties blijven de meest voorkomende complicaties tijdens het gebruik van ECLS. Met toenemende indicaties en het groeiende aantal patiënten dat wordt ondersteund met ECLS, is het voorkomen van bloedingscomplicaties van fundamenteel belang. Door bloedingscomplicaties te voorkomen, kunnen ook mortaliteit, morbiditeit en gezondheidszorgkosten worden geminimaliseerd.

Sectie I Bloedings complicaties in extracorporele life support

Hoofdstuk 2 presenteert een systematisch onderzoek van patiënten met pre-existente bloedingen, die werden ondersteund door ECLS. We vonden in totaal 181 patiënten, met 82,3% overleving en 26% bloedingscomplicaties. Doodsoorzaken waren voornamelijk multi-orgaanfalen en shock. Slechts vijf patiënten stierven ten gevolge van verdere bloedingen. De meeste complicaties werden gevonden bij patiënten zonder antistolling in de beginperiode van ECLS. Protocollen om bloedingen onder controle te houden waren onder meer spoedoperaties, tracheale afklemming en stentplaatsing. Daarnaast werd geen antistolling of een antistollingsvrije periode tijdens ECLS gemeld als optie om het risico op verdere bloedingen te verminderen. Met verschillende opties om verdere bloedingen te voorkomen, zou ECLS kunnen dienen als een overbrugging naar de behandeling van hemorragische controle bij reeds bestaande bloedingen bij patiënten.

De totale incidentie van bloedingscomplicaties varieert sterk tussen gepubliceerde studies. Ook vanwege verschillende definities voor bloedingscomplicaties is het bijna onmogelijk om de uitkomsten van studies te vergelijken en de trends door de jaren heen te onderzoeken. In hoofdstuk 3 onderzochten we de trends van bloedingscomplicaties in de afgelopen twintig jaar en trends in sterfte van patiënten die werden ingediend bij ECLS met behulp van de ELSO-registratie. We includeerden 53.664 patiënten, van wie bijna 20.000 patiënten werden ondersteund door veno-veneus (V-V) ECLS en 30.000 door veno-arterieel (V-A) ECLS. In de afgelopen 20 jaar vonden we een afname van bloedingscomplicaties in zowel V-V als V-A ECLS, voornamelijk in chirurgische en canule-gerelateerde bloedingscomplicaties. Bloedingscomplicaties waren geassocieerd met een hogere sterfte, maar er werd geen dalende trend in sterfte gevonden.

Sectie II Voorspelling van bloedingsomplicaties in extracorporele life support

In hoofdstuk 4 en 5 wordt de ontwikkeling van voorspellingsmodellen voor bloedingen bij patiënten die worden ondersteund door V-V en V-A ECLS vervolgens beschreven. In het voorspellingsmodel voor bloedingscomplicaties gericht op V-V ECLS-patiënten was de AUC 0,63. Een hartstilstand vóór ECLS, chirurgische canulatie, verhoogd lactaat, pO2, HCO3, ventilatiesnelheid, gemiddelde luchtwegdruk, pre-ECLS cardiopulmonale bypass of niervervangende therapie, chirurgische ingrepen vóór de start van ECLS en verschillende soorten diagnoses werden opgenomen in het voorspellingsmodel. Het voorspellingsmodel voor bloedingscomplicaties tijdens V-A ECLS leverde een AUC van 0,66 op en voorspellingsfactoren waren; geslacht, BMI, chirurgische canulatie, pre-ECLS respiratoire en hemodynamische variabelen, pre-ECLS-ondersteuning en interventies en verschillende soorten diagnoses als voorspellende factoren. Verder onderzoek kan het model verbeteren door andere belangrijke voorspellers te identificeren en toe te voegen, zoals antistollingsbehandeling en laboratoriumwaarden. Externe validatie is nodig om het model in de kliniek te implementeren; het model kan al wel worden gebruikt voor onderzoeksdoeleinden en ruwe schattingen van het bloedingsrisico.

Sectie III Ontwikkelingen in extracorporele life support en toepasbaarheid van extracorporele life support in trauma settings

In hoofdstuk 6 onderzoeken we de ontwikkelingen van antistollingsbehandeling en coatings van het ECLS-circuit om bloedingscomplicaties te verminderen. De interactie tussen het menselijk lichaam, bloed en kunstmatige materialen kan worden verminderd met antistollingsmiddelen, biomimetische en biopassieve oppervlakken. Het doel is om de balans te vinden tussen stollings- en bloedingsrisico's. In de toekomst zou endothelialisatie van de ECLS-circuits en het gebruik van biocompatibele materialen de noodzaak van systemische antistolling kunnen elimineren, maar er zijn nog steeds intense inspanningen nodig om dit doel te bereiken.

Hoofdstuk 7 bestudeerd de belangrijkste complicaties in de hoog-risico subgroep van traumapatiënten die aan ECLS werden onderworpen. We vonden een hoog percentage complicaties van 80%. Nierproblemen waren de meest voorkomende complicaties en werden gemeld bij 44%, gevolgd door bloedingscomplicaties en mechanisch falen van de ECLS (beide 30%). De analyse

toonde een hoge overleving van ECLS van 70,3% en een ziekenhuisoverleving van 60,6%.

Hoofdstuk 8 presenteert de mogelijkheden van ECLS in thoracale noodsituaties. In dit hoofdstuk worden de type letsels behandeld waarbij ECLS mogelijk kan ondersteunen indien conventionele behandeling onvoldoende blijkt. Deze letsels zijn onder andere; tracheobronchiale letsels, stompe en doordringende borstletsels, aortaletsels, hartkneuzingen en hartstilstand, meervoudig traumaletsel, ontploffings-, brand- en gevechtsverwondingen. Dit hoofdstuk gaat dieper in op deze verschillende omstandigheden waarin ECLS van grote waarde zou kunnen zijn, waar dit voorheen vaak niet werd overwogen.

Concluderend presenteert dit proefschrift onderzoeken naar bloedingscomplicaties tijdens ECLS met mogelijke oplossingen en trends door de jaren heen. Daarna worden de ontwikkeling en interne validatie van twee voorspellingsmodellen voor bloedingscomplicaties in V-V en V-A ECLS gepresenteerd. Verder gaan we dieper in op de voortgang van antistollingsbehandelingen en de ontwikkeling van circuitcoating. Ten slotte rapporteren we de analyse van de trends van complicaties bij hoog risico trauma patiënten.

Verdere studies zijn nodig om de voorspelling van bloedingscomplicaties te verbeteren en om de perfecte balans te vinden tussen coagulatie en bloedingsneigingen met verdere ontwikkeling van antistollingsbeheer en circuitmaterialen en coatings.