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Longitudinal trends in bleeding complications on Extracorporeal Life Support (ECLS) over the past two decades – ELSO Registry Analysis

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Authors' contributions:

AW, JS, RL and JET conceived of the presented idea. HB, ZM, HtC, SM and SvK verified the methods. All authors devised the project, the main conceptual ideas and proof outline. AW and SvK performed the statistical calculations. RL, SM and JET verified the results. AW and JS wrote the manuscript. All authors discussed the results and contributed to the final manuscript.

Conflict of interest:

Prof. Dr. Lorusso is a consultant for Medtronic, Getinge and LivaNova and medical advisory board member for EUROSETS, all unrelated to this work; all honoraria to the university for research funding.

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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 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.

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Abstract

Objective: Data about in-hospital 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 (ELSO) Registry.

Patients: Data of 53.644 adult patients (≥18 years 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, 19.748 cannulated for V-V ECLS and 30.696 for 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 to V-V (30.0% versus 21.9%, p<0.001). Hospital survival in those who developed bleeding complications was lower in both V-V ECLS (49.6% versus 66.6%, p<0.001) and V-A ECLS (33.9 versus 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, in V-A ECLS: female gender, ECLS duration, pre-ECLS arrest or bridge to transplant, therapeutic hypothermia, and surgical cannulation.

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 central nervous system, have remained stable and overall bleeding remains associated with a persistent increase in mortality.

Keywords

ECLS; ECMO; bleeding complications; anticoagulation; 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 incidence 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 incidence 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 incidence and risk factors in bleeding complications over the past 20 years in patients undergoing ECLS in veno-venous and veno-arterial mode (V-V ECLS and V-A ECLS, respectively) across the world. The authors hypothesized decreasing rates of bleeding complications in ECLS, attributable to improvements in equipment development e.g. 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 (≥18 years old) supported with ECLS between 01.01.2000 and 31.03.2020 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-samples t-test were used. Pearson’s chi-square test was used to compare categorical data and, the Fisher’s Exact test in case of expected count was less than 5 cells in 20% of the cells. Significance was set at a two-sided p-value of less than 0.05. Uni- and multivariable logistic regression were performed in the V-V and V-A ECLS group to evaluate predictive factors for bleeding. Associations were quantified as odds ratio (OR) including 95% confidence interval (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 decade to see

whether there was a substantial difference in the last decade, since techniques have been changed in this time. Analyses were performed with SPSS statistical software (Version 26.0, IBM, Armonk, New York, USA).

Outcomes and co-variates

ELSO registry data definitions were used for data assessment with error and validity checks. Reported mortality was in-hospital 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 red blood cell transfusion (PRBCs) of >20ml/kg/24hrs or >3 Units/24hrs, endoscopic interventions for bleeding, CT-, ultrasound- or MRI-imaging for gastro-intestinal, cannulation site, surgical site, central nervous system, and pulmonary bleeding complications.

Secondary outcomes were different types of bleeding complications, including gastro-intestinal, pulmonary, central nervous system, 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 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.

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 (±SD 15.9) years and 64.5% were male. Mean weight was 85.4 kg (±SD 25.6) and height 170.7 cm (±SD 11.0), with a calculated BMI of 29.7 (±SD 10.5). Overall, mean duration of ECLS was 8.2 ±SD 11.5) days. V-V ECLS patients were younger, had a higher BMI and were supported longer and their in-hospital survival was significantly higher compared to V-A ECLS group (Supplemental Table 1).

Overall bleeding complications were reported in 27.6% and occurred more often in V-A ECLS (30.0%) compared to V-V (21.9%) ($p<0.001$). However, central nervous system 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%), $p<0.001$. (Supplemental 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 1). 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 2).

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%), $p<0.001$ (Supplemental Table 2). 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 2, Supplemental Table 4). 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 2, Supplemental Table 2, 3).

Subtypes of bleeding complications

Cannulation site and surgical site bleeding were the most common bleeding complications, but markedly declined in the last two decades (Supplemental Table 2, 3). In contrast, central nervous system, gastrointestinal bleeding, and bleeding tamponade, all less frequent than the former bleeding complications reached a stable rate between 2008–2010 (Figure 1). 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 (Supplemental 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 2, Supplemental Table 2, 3).

Other complications and survival 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 1). 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 1).

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 post-cardiotomy setting yielded the pooled rates of surgery due to bleeding complications of 42.9% and 50%, respectively (7, 11).

While comparing the first and second decade, the decrease of bleeding complications was most significant in the last 10 years (Figure 2). Finally, higher mortality was found in patients with bleeding complications during ECLS compared to patients without bleeding. Furthermore, we found a difference in subtypes of bleeding between V-V and V-A groups. Cannulation site, surgical site and tamponade bleeding occurred more often in V-A whereas gastro-intestinal, pulmonary hemorrhage, and brain hemorrhage were more observed in V-V ECLS. Also, these differences deserve ad hoc investigations, particularly with regards to cerebral bleeding.

The incidence of bleeding complications in V-A was higher than in V-V ECLS, even though V-V support and exposure to artificial surfaces was longer. This may be explained by a possibly higher risk for bleeding in arterial cannulation and more frequent pre-ECLS cardiac surgical procedures. Other groups found in V-V ECLS, that bleeding occurred more frequently than thromboembolism, and bleeding was associated with decreased survival (1, 18, 28, 30, 31, 40–42). 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 promote thrombosis. Anticoagulation is typically needed to maintain patency of the extracorporeal circuit, to achieve a hemostatic balance during ECLS (43). Although decreasing, hemocompatibility-related adverse events remain common during V-A ECLS and have a cumulative association with survival (36). Also, 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. Also, the venous site cannulation might play a role, as observed in the

V-V group. Paden et al found cannulation bleeding complications in 17.2% and 20.9% of V-V and V-A ECLS, retrospectively (19). Higher rates of bleeding complications in V-V ECLS were found in the EOLIA trial (53%) (17) and of 22% in the ANZ-ECMO study (20). Thus, cannulation site bleeding has been reported as high incidence bleeding site, but literature is non-conclusive 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 incidence in central cannulation compared to peripheral cannulation (51.9% vs 32.9%) in post-cardiotomy patients (21).

In the annual ELSO Registry report of 2012 a surgical site bleeding percentages of 16.7% and 25% were observed in adults undergoing V-V and V-A ECLS respectively (19) which is similar to our findings in terms of bleeding distribution between V-V and V-A ECLS. Cheng et al. conducted a meta-analysis of 1866 adults and found a range of re-thoracotomy due to bleeding or tamponade between 16.1% and 86.7% in V-A ECLS (8). 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 gastro-intestinal bleeding complications in ECLS varies considerably. Our data shows gastrointestinal bleeding in 4.0%, and 4.9% in V-A and V-V ECLS. Percentages of this bleeding complications can vary due to underdiagnoses and different definitions of gastro-intestinal bleeding. In the literature, Otani et al. reported an incidence of 24% after extracorporeal life support resuscitation (ECPR) (9). In post-cardiotomy shock or cardiogenic shock and V-A support an incidence of 0.9% was found (22). Reported incidence of gastrointestinal bleeding in V-V ECLS ranges between 6.2% and 14% (20, 23–25) and may be causative for significant longer ECLS support and higher mortality (26, 27).

Previous ELSO registry analysis reported intracranial hemorrhage rates of 1.8% and 3.6% in V-A and V-V ECLS, respectively (28, 29), 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 (17). Other authors reported an incidence of 9% up to 14.4% (20, 23). Fletcher-Sandersjöo et al reported pre-existing anticoagulation as an additional risk factor for intracranial hemorrhage in a cohort of 253 adults supported with V-V and V-A ECLS (30). The same authors performed a systematic review on the incidence, 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 (31). Compared to other bleeding sources, no significant decrease over the last two decades was recorded in gastro-intestinal bleeding or cerebral bleeding (32). The reasons behind the variance in incidence between V-V and V-A ECLS are presumably due to differences in risk factors, and in the underlying clinical condition and comorbidities (31). In V-A groups, factors related to cardiogenic shock (low cerebral

blood flow, hypoxia, acidosis, 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, 33) and the use of shorter circuit tubes for decreased surface contact to reduce the risk of thromboembolic events may have a protective effect reducing bleeding risk. Also, 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, thus 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, 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 (34, 35). 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. (36). Also, Sy at al evaluated the effect of anticoagulation in V-A ECLS on outcomes reporting the prevalence of 27% for major bleeding and for in-hospital mortality of 59% (95% CI, 52%−67%; I^2=78%) (37). Nakasato et al. found thrombocytopenia, post-cardiotomy extracorporeal support, pneumonia, previous antithrombotic therapy, platelet count decline, and age to be risk factors for bleeding complications (38).

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. 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 >1 to >5 units. ‘Surgery requirement’, ‘gastroscopy’ or ‘bleeding on cannulation or surgical site’ referred to bleeding complications (39).

Previous studies have largely been metanalyses of single center studies. This manuscript provides a clear overview in the development of bleeding complications during ECLS in the past twenty 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, 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 world-wide adds significant validity, not only to the approach of this study but moreover and importantly to the findings, respectively.

Limitations

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 two 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 unfractioned heparin (or a similar antithrombotic agent) is administered as an initial bolus of 50–100 units/kg and a continue dose of 20–50 units/kg/h to ensure an activated clotting time (ACT) range of 180–220 seconds (16). 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. Also, 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 an indirect outcome derived from treatment and diagnostic proxies (number of packed red blood cells 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 bleeding. 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 central nervous system, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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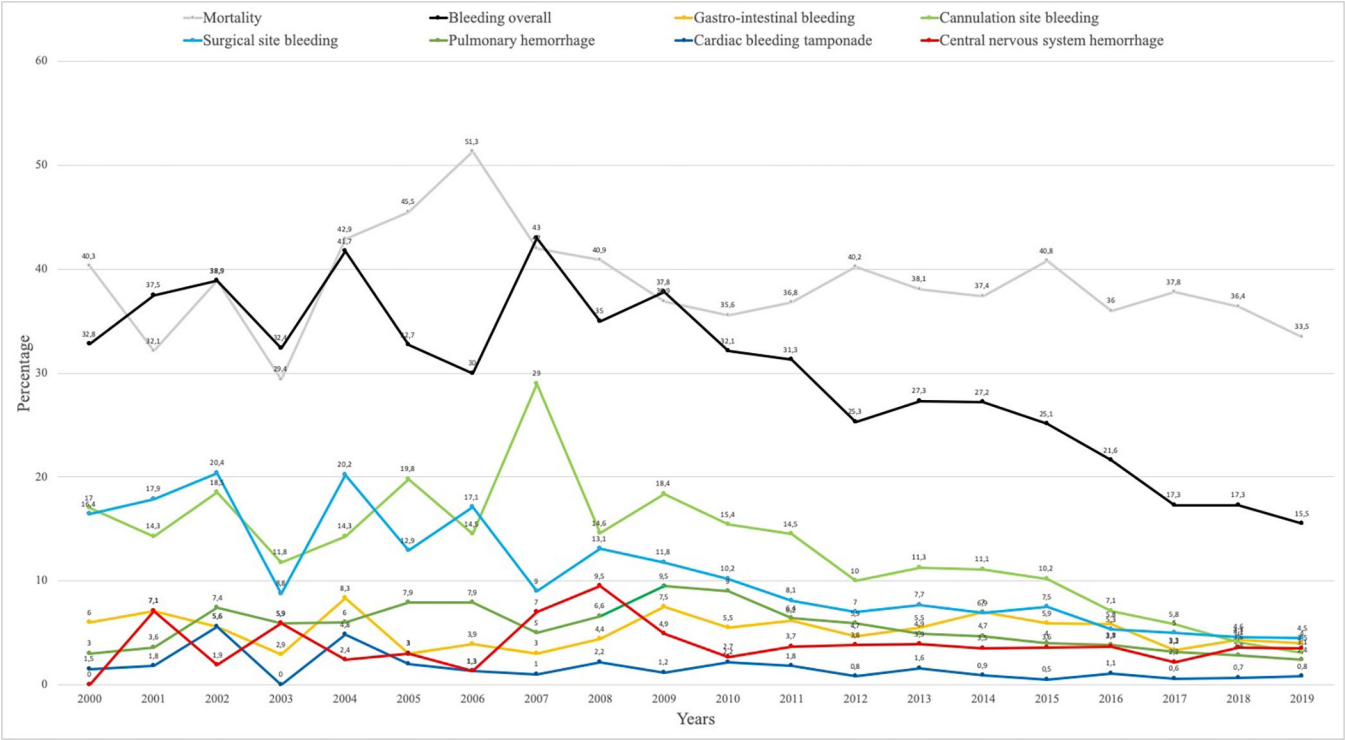

Figure 1.
Bleeding complications trends in the past two decades in the overall cohort

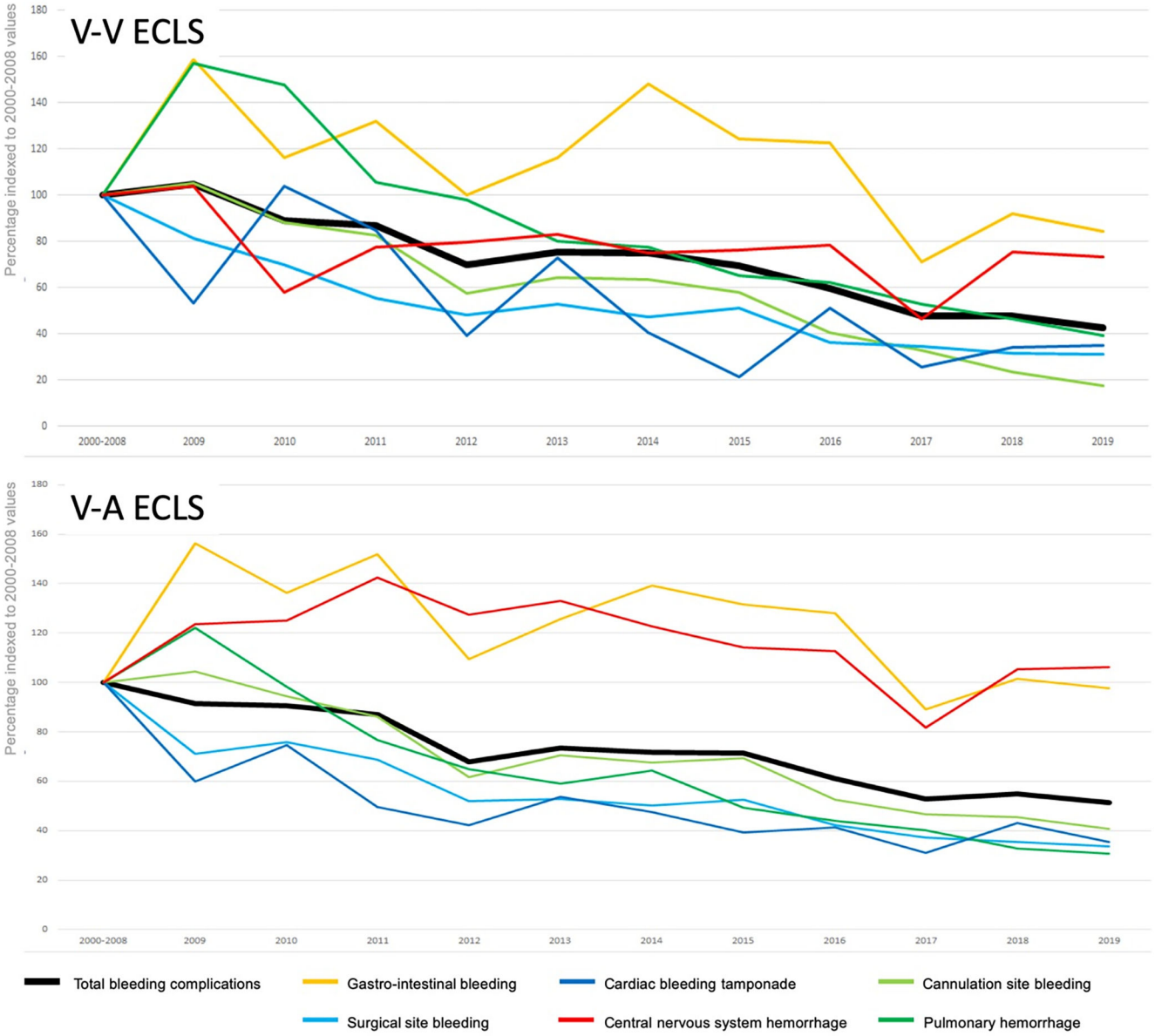

Figure 2.

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

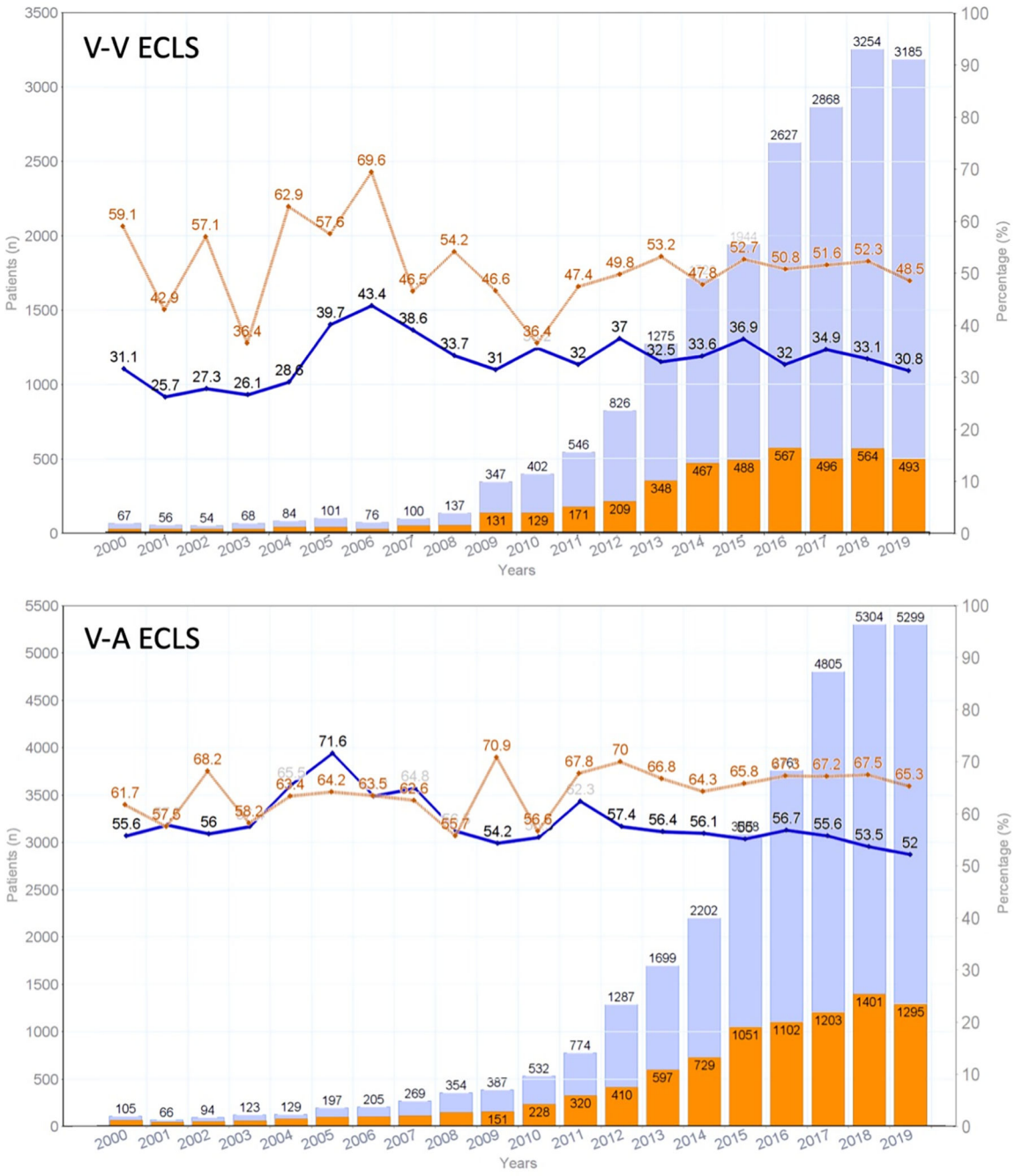

Figure 3.

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

Table 1

Characteristics and outcomes of patients supported on extracorporeal life support

Patient characteristics Pre-ECLS interventions Outcomes	*Veno - venous ECLS*			*Veno - arterial ECLS*		
	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 (23.1)	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 years	5362 (34.8)	1602 (37.0)	-	4137 (19.2)	1806 (19.6)	-
40.1–60 years	6397 (41.5)	1824 (42.1)	-	8512 (39.6)	3498 (38.0)	-
60.1–80 years	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						
CPB n (%)	430 (2.8)	149 (3.4)	0.025	2619 (12.2)	2234 (24.3)	<0.001
VADs 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*
BiVAD n (%)	*25 (0.2)*	*11 (0.3)*	*0.211*	*37 (0.2)*	*27 (0.3)*	*0.037*
LVAD n (%)	*124 (0.8)*	*51 (1.2)*	*0.021*	*722 (3.4)*	*433 (4.7)*	<0.001
RVAD n (%)	*92 (0.6)*	*25 (0.6)*	*0.881*	*115 (0.5)*	*56 (0.6)*	*0.453*
PVAD n (%)	*44 (0.3)*	*10 (0.2)*	*0.543*	*727 (3.4)*	*338 (3.7)*	*0.207*
IABP 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
RRT 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 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, 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

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

Veno - venous ECLS						
Variables	**Univariable**			**Multivariable**		
	OR	CI 95%	P value	OR	CI 95%	P value
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 betablokkage	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						
Variables	**Univariable**			**Multivariable**		
	OR	CI 95%	P value	OR	CI 95%	P value
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 betablokkage	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

OR - odds ratio, CI - confidence interval 95%, ECLS - extracorporeal life support