Clinical Features and Risk Factors Analysis for Hemorrhage in Adults on ECMO

Wenwen Hu[1], Meifang Wang[2], Lin Chai[3], Wei Chen[4], Leung Lai-han Elaine [5], Yijun Tang[2]*

[1] Postgraduate Training Basement of Jinzhou Medical University, Taihe Hospital, Hubei University of Medicine, Shiyan, China

[2] Department of Respiratory and Critical Care Medicine, Taihe Hospital, Shiyan, China

[3] Department of Emergency Medicine, Taihe Hospital, Shiyan, China

[4] Department of Critical Care Medicine, Taihe Hospital, Shiyan, China

[5] State Key Laboratory of Quality Research in Chinese Medicine, Macau Institute for Applied Research in Medicine and Health, Macau University of Science and Technology, Macau, China

*Corresponding author: Yijun Tang, Department of Respiratory and Critical Care Medicine, Taihe Hospital, 32 Renmin South Road, Shiyan 442000, China.
Email: tangyijun_799@163.com
Tel: 0719-8801545

ABSTRACT

Background: The use of extracorporeal membrane oxygenation (ECMO) to support critically ill patients with cardiorespiratory dysfunction is increasing over the last decades. However, hemorrhagic complications remain occurring frequently during ECMO support, which have a significant impact on morbidity and mortality.

Methods: A retrospective study was performed on the 60 patients, who were admitted to the Taihe hospital in Shiyan City, Hubei Province from February 2017 to October 2020. All those were rescued with ECMO. Including 18 patients developed hemorrhage complications and 42 patients did not. Demographic, laboratory tests, clinical manifestations prior to ECMO were collected to analysis the clinical features. Univariable and multivariable logistic analysis methods were used in our study to explore the risk factors for hemorrhage in adults on ECMO.

Results: There were significant differences between the hemorrhage group and no-hemorrhage group in duration of ECMO support, mode of ECMO, red blood cell count, hemoglobin, platelet count, serum creatinine. Particularly, multivariate logistic analysis showed that the longer duration of ECMO support and the higher activated partial thromboplastin time (APTT) prior to ECMO were independent factors for hemorrhage in adults on ECMO. In addition, we found that the mortality of hemorrhagic patients was higher than no-hemorrhagic patients. Cannula site was the most common bleeding site. Most bleeding events occurred within the first three days of ECMO therapy.

Conclusions: Clinicians should evaluate the risk of hemorrhage based on patients' coagulation function, underlying disease as well as the duration of ECMO support.

Especially in the first three days during ECMO support. Attempting to wean from ECMO early whenever feasible is also effective to reduce the occurrence of hemorrhage. Special attention should be given on cannula site, mucosal, dermal and digestive tract to alert hemorrhage.
Key words Extracorporeal membrane oxygenation, Hemorrhage, Bleeding, Complication

1. Introduction

Extracorporeal membrane oxygenation (ECMO) is an advanced life support technique used to provide respiratory and cardiac support. During the period of A/H1N1 flu and corona virus disease 2019 (COVID-19), ECMO has saved the lives of many critical patients as a rescue and irreplaceable therapy[1, 2]. However, it remains invasive and is associated with critical complications historically. Hemorrhage is the most common and serious complication in patients with ECMO support, which cause a significant increase in mortality risk[3].

The activation of procoagulant and anticoagulant factors when a cannula makes contact with the endothelial surface of the blood vessels caused the potential risk of thrombosis. The Extracorporeal Life Support Organization (ELSO) anticoagulation guideline recommends the use of antithrombotic therapy during ECMO. However, bleeding events can result from the anticoagulation. Therefore, predicting the potential bleeding risk of patients is significant for the prognosis in adults on ECMO.

2. Materials and methods

2.1 Patients and data collection

Sixty cases admitted to the Taihe Hospital in Shiyan City, Hubei Province from February 2020 to October 2020 were collected in a retrospective study. The demography, chronic medical histories, cause of ECMO therapy, acute physiology and chronic health evaluation II (APACHE II) score, duration of ECMO support, mode of ECMO, laboratory values, prognosis, hemorrhage sites and time from ECMO operated to hemorrhage were collected. According to the patients with or without hemorrhage, sixty cases were divided into two groups. No- hemorrhage patients were set as the control group (n = 42). Hemorrhage patients were set as the study group (n = 18). All patients studied were treated by a therapeutic regimen adhering to standardized management guidelines in accordance with the current recommendations of the ELSO or the respective medical society. All bleeding events documented within the clinical data management system were retrospectively analyzed in a total of 60 patients. Hemorrhage complications were further subdivided into different categories according to the locations of the bleeding sites. Including cannulation sites, surgical wounds, mucosal or dermal bleeding, gastrointestinal bleeding, respiratory tract bleeding, intracranial bleeding, intra-abdominal bleeding or bleeding from other organs.

2.2 Statistical analysis

Continuous variables were expressed as mean ± standard deviation if they were normally distributed or median (IQR) if they were not. We compared means for continuous variables by using independent group T-tests when the data were normally

distributed; otherwise, we used the Mann-Whitney U test. Categorical variables were expressed as numbers (%). We compared proportions for unordered categorical variables by using the χ^2-test or Fisher' s exact test. We compared proportions for ordered categorical variables by using the Wilcoxon rank-sum test. To explore the risk factors for hemorrhage in adults on ECMO, univariable and multivariable logistic regression models were used. Considering the total number (n=60) in our study and to avoid multicollinearity in the model, three variables were chosen for multivariable analysis based on the previous findings and clinical constraints. For unadjusted comparisons, a two-sided α of less than 0.05 was considered statistically significant. Statistical analyses were done using the SPSS software, version 24.0.

3. Results

3.1 Demographics characteristics

The demography and clinical characteristics of 60 patients with ECMO support were shown in Table 1. Eighteen patients (30.0%) had hemorrhagic complications. The mean age of hemorrhage patients was 48.7±10.4 years, including 12 (66.7%) male patients and 6 (33.3%) female patients. The mean age of no-hemorrhage group was 48.2±12.8 years, the number of males was 34 (81.0%), and the number of females was 8 (19.0%). There was no significant difference between the two groups in the age and gender distribution. More than half of the 60 patients had comorbidities. For the hemorrhage group, 13 (72.2%) had comorbidities, including 9(50.0%) patients had hypertension, 2(11.1%) patients had diabetes, 3(16.7%) patients had chronic obstructive pulmonary disease (CDPD), 8(44.4%) patients had preexisting cardiac disorder, 2(11.1%) patients had chronic kidney diseases (CKD) and 1(5.6%) patient had cancer. For the no-hemorrhage group, 13(40.1%) patients had hypertension, 2(4.8%) patients had diabetes, 1(2.4%) patient had CDPD, 12(28.6%) had preexisting cardiac disorder,1(2.4%) had cancer and no one had CKD. There were no significant differences between the two groups on comorbidities.

3.2 Clinical characteristics

For the cause of ECMO therapy, the majority of patients 32(53.3%) suffered from cardiogenic shock. As a consequence, 54(90%) of the patients received V-A ECMO support, whereas 6(10%) underwent V-V ECMO therapy due to respiratory failure. Other causes included traumatic shock 7(11.7%), aortic dissection (6.7%), electrical injury 2(3.3%), intoxication 1(1.7%). Eight (44.4%) hemorrhage patients received external cardiopulmonary resuscitation (ECPR). 19 (45.2%) no-hemorrhage patients received ECPR. For acute physiology and chronic health evaluation (APACH) II, the median of it in hemorrhage group (27.8±6.9) is higher than no-hemorrhage group (24.0±9.1). We found the mortality (77.8%) in hemorrhage group was higher than no-hemorrhage group (66.7%). There were no significant differences between two groups. However, it had significant difference between hemorrhage group (120.0 (72.0~288.0)) and no-hemorrhage group (27.3 (8.8~96.0) on the duration of ECMO support (P=0.001).

Table 1. Demographics and clinical characteristics of patients.

Variable	Hemorrhage Group (n=18)	No-hemorrhage Group (n=42)	P-value

Age, years	48.5±11.7	48.0±14.6	0.899
Gender			0.231
Male	12 (66.7%)	34 (81.0%)	
Female	6 (33.3%)	8 (19.0%)	
Comorbidities			
Hypertension	9 (50.0%)	13 (40.1%)	0.161
Diabetes	2 (11.1%)	2 (4.8%)	0.576
Preexisting Cardiac Disorder	8(44.4%)	12 (28.6%)	0.232
COPD	3 (16.7%)	1 (2.4%)	0.077
CKD	2 (11.1%)	0 (0)	0.086
Cancer	1 (5.6%)	1 (2.4)	0.514
Cause of ECMO Therapy			
Cardiogenic Shock	7 (38.9%)	25 (59.5%)	0.142
Respiratory failure	4(22.2%)	2 (4.8%)	0.060
Infectious shock	3 (16.7%)	1(2.4%)	0.077
Traumatic shock	2 (11.1%)	5 (11.9%)	1.000
Electrical injury	0 (0)	2 (4.8%)	1.000
Intoxication	0 (0%)	1 (2.4%)	1.000
Aortic dissection	1 (5.6%)	3 (7.1%)	1.000
Others	1 (5.6%)	3 (7.1%)	1.000
ECPR	8 (44.4%)	19 (45.2%)	0.955
APACHE II	26.2±7.1	24.9±10.2	0.621
Duration of ECMO support, h	141.3 (72.0~288.0)	27.3 (8.8~87.5)	0.001*
Mode			0.008*
V-V ECMO	5 (27.8%)	1 (2.4%)	
V-A ECMO	13 (72.2%)	41 (97.6%)	
Outcome			0.389
Mortality	14 (77.8%)	28 (66.7%)	
Discharge	4 (22.2%)	14 (33.3%)	

Data are mean ± standard, median (IQR), n (%). P values were calculated by Mann-Whitney U test, χ^2 test, or Fisher' s exact test, as appropriate. COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease; ECPR: External Cardiopulmonary Resuscitation; APACHE: Acute Physiological and Chronic Health Evaluation.

3.3 Laboratory characteristics

All laboratory test results on patients pre-ECMO were collected (Table 2). There were significant differences between two groups on red blood cell count, hemoglobin, platelet count, serum creatinine. For hemorrhage group, the median of platelet count was 140.3×10^9/L. It was lower than no-hemorrhage group (180.7×10^9/L). Red blood cell count in hemorrhage group (4.19 (3.86~4.75) $\times10^{12}$/L) was lower than in no-hemorrhage group (4.43 (4.21~4.93) $\times10^{12}$/L). Hemoglobin in hemorrhage group (125.0 (113.5~137.0) g/L) was also lower than in no-hemorrhage group (144.0 (135.8~161.8) g/L). However, serum creatinine in hemorrhage group (198.7μ mol/L)

were higher than no-hemorrhage group (111.6μ mol/L). There were significant differences between the two groups on platelet count and serum creatinine ($P < 0.05$).

Table 2. Laboratory characteristics of patients.

Variable	Hemorrhage Group (n=18)	No-hemorrhage Group (n=42)	P-value
White blood cell count, $\times 10^9$/L	15.5(13.1~21.2)	12.0(8.8~18.3)	0.084
Neutrophil count, $\times 10^9$/L	11.8(10.9~15.1)	11.0(7.4~14.1)	0.283
Lymphocyte count, $\times 10^9$/L	2.0(1.4~3.8)	1.7(0.8~3.1)	0.545
Red blood cell count, $\times 10^{12}$/L	4.19 (3.86~4.75)	4.43 (4.21~4.93)	0.019*
Hemoglobin, g/L	125.0 (113.5~137.0)	144.0 (135.8~161.8)	0.092
Platelet count, $\times 10^9$/L	148.2±57.3	183.1±71.5	0.072
ESR, mm/h	34.5(23.3~68.0)	8.0(3.3~42.4)	0.013
Alanine aminotransferase, IU/L	118.0(46.5~256.3)	36.5(14.5~201.5)	0.045*
Aspartate aminotransferase, IU/L	181.5(62.0~388.8)	114.0(51.8~565.5)	0.821
Serum creatinine, μ mol/L	198.7(145.9~239.4)	111.6(89.4~158.3)	0.191
Lactate dehydrogenase, IU/L	675.5(279.8~1380.5)	595(404.8~1340.5)	0.463
Creatine kinase, IU/L	1201.5(329.5~1659.3)	998.0(356~2325.5)	0.634
α-HBDH	357.0(222.5~900.8)	332.5(214.8~655.0)	0.711
Albumin, g/L	28.5(24.0~31.2)	32.1(25.5~36.8)	0.223
APTT, s	71.3(44.1~105.9)	39.9 (29.7~58.8)	0.015*
PT, s	25.9(18.7~29.2)	12.1(9.3~15.5)	0.578
D-Dimer, μ g/ml	4.0(0.7~10.5)	1.8(0.8~14.7)	0.503
Fibrinogen, g/L	3.1(2.6~4.7)	2.9(2.2~3.6)	0.242
PH	7.34(7.28~7.38)	7.35(7.30~7.38)	0.187
PaO_2	62.5(25.0~108.5)	63.0(37.0~98.0)	0.296
$PaCO_2$	40.5(19.0~69.8)	39.5(13.5~87.6)	0.197

Data are mean ± standard, median (IQR), n (%). P values were calculated by Mann-Whitney U test, χ^2 test, or Fisher' s exact test, as appropriate. α-HBDH: Alpha-hydroxybutyric Dehydrogenase. APTT: Activated Partial Thromboplastin Time. PT: Prothrombin Time.

3.4 Logistic regression

We included 60 patients with complete data for all variables in the binary logistic regression model by stepwise regression method (Table 3). We found that duration of ECMO support (OR =1.026, 95% CI: 1.010~1.042, P = 0.001) and activated partial thromboplastin time (APTT) (OR = 1.044, 95% CI: 1.009~1.079, P = 0.013) were independently associated with hemorrhagic complications in adults on ECMO.

Table 3. Logistic regression analysis for the related factors predicting hemorrhage.

Variable	B	S.E.	Wals	OR	95%CI	P-value

Duration of ECMO support, h	0.026	0.008	10.611	1.026	1.010~1.042	0.001
APTT, s	0.043	0.017	6.153	1.044	1.009~1.079	0.013

3.5 Hemorrhagic sites and time from ECMO operated to hemorrhage

Ten of hemorrhage patients (55.6%) had more than one hemorrhagic site (Table 4 & Figure 1). The most prevalent hemorrhagic complication was cannula site bleeding (11(61.1%)), as is showen in Figure 2. Mucosal or dermal hemorrhage (10(55.6%)) and gastrointestinal hemorrhage (9(50%)) were also common. The mean time from ECMO operated to hemorrhage was 2.1±0.96 days. Any hemorrhage sites may cause the high mortality of patients on ECMO.

Table 4. Hemorrhage sites and time from ECMO operated to hemorrhage.

Variable	Total (n=18)
Hemorrhage sites	
Cannula site	11 (61.1%)
Mucosal or dermal hemorrhage	10 (55.6%)
Gastrointestinal hemorrhage	9 (50.0%)
Respiratory hemorrhage	3 (16.7%)
Cerebral hemorrhage	1 (5.6%)
More than one site	10 (55.6%)
Time from ECMO operated to hemorrhage, days	2.1±0.96

Data are mean ± standard and n (%).

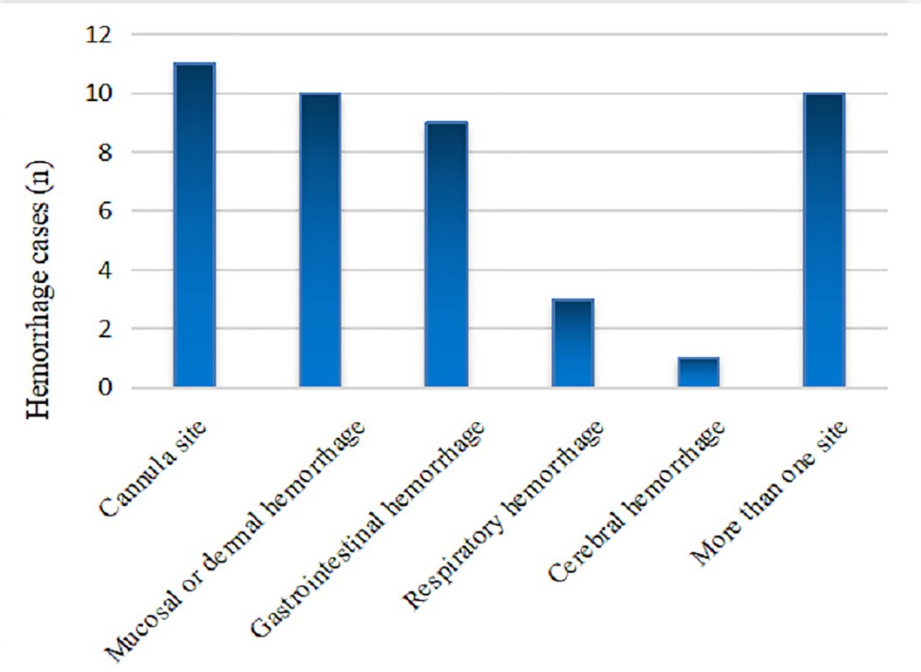

Figure 1. Hemorrhage sites.

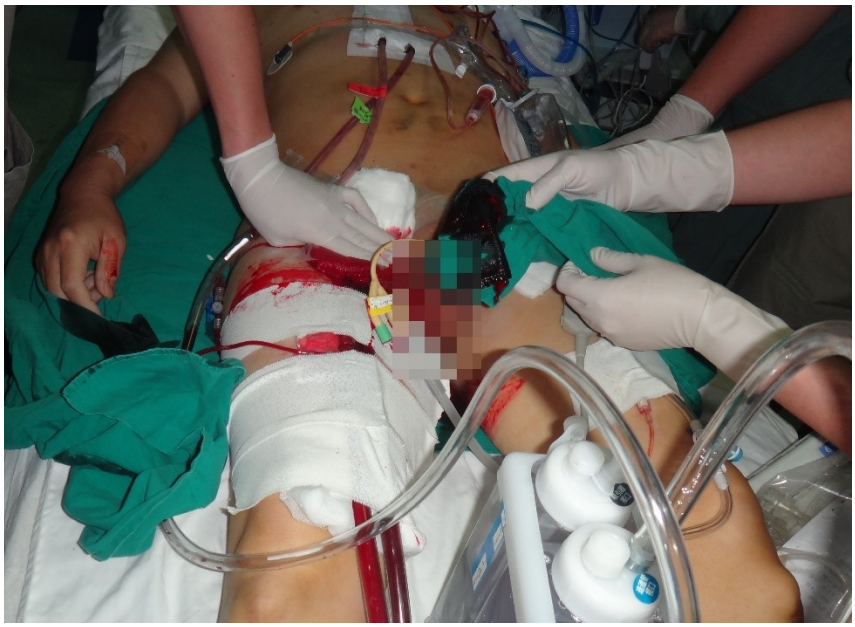

Figure 2. Cannula site hemorrhage in a patient' right femoral artery on ECMO.

4. Discussion

The use of ECMO is a proven life-saving treatment for patients with respiratory and cardiac failure. However, there are still high mortality rate during the ECMO support. Hemorrhagic complications are frequent and act as an important factor not only limiting therapeutic efficiency, but also survival of the patients. In several studies of adult patients on ECMO the incidence for hemorrhagic complications varied between 15 and 63%[4-6]. In a study on anticoagulation in V-V ECMO (n = 646) the overall rate of hemorrhagic complication was 29% while major bleeding across all studies was 10–16%[7, 8]. The necessity of anticoagulants and complicated pathophysiological changes of the coagulation cascade in critical patients present a substantial challenge in reducing the incidence of bleeding events. Clinicians should consider potential risk factors of hemorrhage prior to ECMO initiation.

We confirmed two risk factors for hemorrhage in adults on ECMO. In particular, the longer duration of ECMO support and the higher APTT on the time prior to ECMO were independently associated with higher incidence of hemorrhage. APTT is the time (in seconds) in which calcium-free plasma clots in response to a fibrin activating reagent combined with calcium. APTT was primarily used to monitor and titrate heparin dosing. ELSO guidelines (2014) recommended that patients at low bleeding risk should be maintained ACT 180 ~200 s or APTT 60 ~80 s (or 1.5 times the basal value). Patients at high bleeding risk should be maintained flow greater than 3 L/min, ACT 160 s or APTT 45-60 s. Patients with active bleeding should be maintained flow greater than 3 L/min, withhold heparin anticoagulation, and closely monitor ACT, APTT, membranopulmonary and ductal thrombosis, and patient thrombogenesis. Thromboelastography should be monitored daily to assess the risk of coagulation[9]. Our findings are in line with a retrospective study of 164 patients, supported by ECMO, in which the highest APTT quartile on the day prior to the bleeding event was shown to be an independent risk factor[10]. Administration of

heparin as reflected by the level of anticoagulation (APTT target) is modifiable. A higher APTT was associated with the occurrence of hemorrhagic complications. A study from university of Miami, Miller School of Medicine showed that ECMO duration in patients with intracranial hemorrhage (ICH) was approximately double with those without ICH and was an independent risk for ICH occurring during ECMO support[11]. This is probably related to the longer exposure to anticoagulant medications, which are crucial for all patients on ECMO. The current study shows that duration of ECMO support is an independent risk for hemorrhage in adults on ECMO. Longer ECMO duration means longer exposure to anticoagulant medications. Therefore, there is a higher chance of exposure to supratherapeutic levels of anticoagulants. We recommend more frequent monitoring of coagulation indicators (especially ACT and APTT) in patients who remain on ECMO for longer duration and to attempt earlier rather than later weaning from ECMO whenever feasible to avoid risk of bleeding.

Several other factors have been confirmed to be associated with the occurrence of hemorrhagic complications during ECMO support, including renal failure, higher APACHE III score at admission, post-surgical ECMO, fungal pneumonia and acquired von-Willebrand's disease[12]. Uremic bleeding is a well-recognized complication in patients with renal failure[13]. Von Willebrand factor (vWF) is a large glycoprotein produced by vascular endothelial cells and platelets. It is a carrier of factor VIII and is involved in promoting platelet adhesion. Platelet plasma membrane glycoprotein (GPIb) is a receptor for vWF. The affinity of GPIB receptor is decreased in patients with renal failure. The interaction between vWF and GPIB receptor is weakened. And the function of coagulation factor VIII is also weakened. Prostacyclin (PGI2), cyclic guanosine monophosphate (cGMP) and NO are platelet aggregation inhibitors[14, 15]. The high expression of them in patients with renal failure leads to an increased risk of hemorrhage[13]. Serum creatinine is an important indicator for the diagnosis of renal failure. Therfore, high serum creatinine levels before ECMO support was significant predictor of increased incidence rate for patients with hemorrhage on ECMO. Patients with chronic renal failure or acute renal injury should be paid more attention to avoid bleeding complication on ECMO support. Lower level of platelet count is a well-recognized risk factor in patients. The use of anticoagulants is essential during the cardiopulmonary bypass. The contact between blood and non-physiological channels can lead to decreased platelet count and impaired platelet function. And some others with CHD or atrial fibrillation may have prior use of antithrombotic therapy. All of the above result in low level of platelet count may increase the risk of bleeding on ECMO. In addition, heparin-induced thromobocytopenia (HIT) is an infrequent but important factor of low level of platelet count. The estimated incidence of HIT ranges from 0.4 to 5% of heparin-exposed patients[16-18]. HIT was associated with a greater risk of further haemorrhages and thromboembolic events, along with a greater rate of mortality[19]. Due to the lack of HIT antibody detection, there is no data about HIT in our center. Once HIT was suspected, heparin should be stopped immediately and replacement anticoagulants should be given. In our study univariable analysis finds that the level of serum

creatinine in hemorrhage group was higher than no-hemorrhage group and the level of platelet count was the opposite of serum creatinine. But there was no significance in multivariable logistic analysis. This difference may be caused by our limited sample size. Our central has been developing this technology for almost three years. Therefore, a large number of patients on ECMO are needed to be enrolled and a further prospective study is needed to be carried out.

Bleeding sites may include cannula insertion sites, recent surgical incisions, dermal or mucosal, lung, gastrointestinal tract, and brain[20]. The guidelines ELSO reported that cannulation site is the most common site of bleeding, particularly if access has been gained by direct cutdown[3]. It was the same as our study. The most prevalent hemorrhagic complications in our study was cannula site bleeding (11(61.1%)). The proportion of mucosal or dermal hemorrhage was 55.6%. The proportion of gastrointestinal hemorrhage was 50.0%. Damage to vascular and skin caused by cannula cannot be avoided. Usually cannula site bleeding is slow oozing related to disruption of small vessels in the skin or subcutaneous tissue. Topical pressure will often control the bleeding events in these areas. When the body is in the stress state of ischemia and hypoxia, the blood redistributes. Then stress ulcer occurs in gastrointestinal tract due to insufficient blood supply. This may be the main cause of gastrointestinal bleeding. Some patients have gastritis or peptic ulcer, which may increase the risk of gastrointestinal hemorrhage[21]. ICH and respiratory hemorrhage were rare in our study up to now, but both of them are serious and cannot be ignored. However, as ECMO patients are commonly moderately-to-deeply coma, it may be challenging to diagnose ICH early[22]. Clinical manifestations of ICH vary greatly, depending on the cerebral structures affected. It may present with focal sensorimotor deficits, seizures, pupillary abnormalities, coma or brain death. It is of great importance to physical examination and CT examination. Small amounts of upper respiratory hemorrhage may be due to endotracheal intubation and tracheal suction. Proper operation may avoid the occurrence of it. Pulmonary alveolar hemorrhage may cause acute respiratory distress syndrome (ARDS) in patients which was a major clinical conundrum to be solved[23]. Severe bleeding events may force the cessation of anticoagulation and increase thromboembolic risk. Thus, balancing the risk of thrombosis and bleeding in the management of such patients is both crucial and challenging. The mean time from ECMO operated to hemorrhage is 2.1±0.96 days. It showed that prevent bleeding events in the first three days was of great importance.

5. Conclusion

Patients receiving ECMO support with hemorrhage complications are subject to risks from their coagulation function, underlying disease as well as the duration of ECMO support. For patients with high level of APTT and serum creatinine, low level of platelet count, we should pay more attention to avoid the hemorrhage complication. Cannula sites and gastrointestinal hemorrhage should be prevented mostly. In addition, weaning from ECMO support timely and monitoring of coagulation indicators frequently in the first three days on ECMO are sensible and crucial.

Our study has several limitations. First, this is a single-center retrospective study. Our hospital has not yet enough patients on ECMO to conduct a large-scale clinical study. Thus, we can only explore the association between risk factors and hemorrhagic complications. Second, we do not routinely use thromboela-stogram (TEG), platelet function and anti-Xa factor analysis in our hospital, which are important anticoagulation indicators and might have provided additional information. A larger prospective study considering separately fatal bleeding as an outcome will also be meaningful to perform.

Funding

This work was supported by the the National Natural Science Foundation of China (81270092).

Acknowledgments

We acknowledge all health-care workers involved in the treatment of patients.

Ethical approval and consent to participate

This study was approved by the Human Ethics Committee and the Research Ethics Committee of Taihe Hospital, Hubei, China. Data records were deidentified and completely anonymous, so informed consent was waived.

Author contributions

Wenwen Hu: Data curation, Formal analysis, Writing- original draft preparation. Meifang Wang: Methodology. Wei Chen & Elaine Lai-Han Leung: Writing - review & editing. Lin Chai: Formal analysis, Software. Yijun Tang: Supervision, Project administration, Funding acquisition.

Competing Interest

The authors declare that there are no competing interests.

Data availability statement

The data that supports the findings of this study are available in the article and supplementary materials. Further inquiries can be directed to the corresponding

authors.

References:

[1] Hong X, Xiong J, Feng Z, et al. Extracorporeal membrane oxygenation (ECMO): does it have a role in the treatment of severe COVID-19?[J]. Int J Infect Dis, 2020,94:78-80.DOI:10.1016/j.ijid.2020.03.058.

[2] Davies A, Jones D, Bailey M, et al. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome[J]. JAMA, 2009,302(17):1888-1895.DOI:10.1001/jama.2009.1535.

[3] Organization T E L S, ELSO. Extracorporeal Life Support Organization (ELSO) General Guidelines for all ECLS Cases [R].2013.

[4] Sy E, Sklar M C, Lequier L, et al. Anticoagulation practices and the prevalence of major bleeding, thromboembolic events, and mortality in venoarterial extracorporeal membrane oxygenation: A systematic review and meta-analysis[J]. Journal of critical care, 2017,39:87-96.DOI:10.1016/j.jcrc.2017.02.014.

[5] Aubron C, Cheng A C, Pilcher D, et al. Factors associated with outcomes of patients on extracorporeal membrane oxygenation support: a 5-year cohort study[J]. Crit Care, 2013,17(2):R73.DOI:10.1186/cc12681.

[6] Cheng R, Hachamovitch R, Kittleson M, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients[J]. Ann Thorac Surg, 2014,97(2):610-616.DOI:10.1016/j.athoracsur.2013.09.008.

[7] Sklar M C, Sy E, Lequier L, et al. Anticoagulation Practices during Venovenous Extracorporeal Membrane Oxygenation for Respiratory Failure. A Systematic Review[J]. Ann Am Thorac Soc, 2016,13(12):2242-2250.DOI:10.1513/AnnalsATS.201605-364SR.

[8] Vaquer S, de Haro C, Peruga P, et al. Systematic review and meta-analysis of complications and mortality of veno-venous extracorporeal membrane oxygenation for refractory acute respiratory distress syndrome[J]. Ann Intensive Care, 2017,7(1):51.DOI:10.1186/s13613-017-0275-4.

[9] Extracorporeal Life Support Organization (ELSO) General Guidelines for all ECLS Cases August, 2017.[EB/OL].https://www.elso.org/Portals/0/ELSO%20Guidelines%20General%20All%20ECLS%20Version%201_4.pdf.

[10] Oude L A, de Vries A J, Droogh J M, et al. Hemorrhagic complications during extracorporeal membrane oxygenation - The role of anticoagulation and platelets[J]. J Crit Care, 2019,54:239-243.DOI:10.1016/j.jcrc.2019.09.013.

[11] Omar H R, Mirsaeidi M, Mangar D, et al. Duration of ECMO Is an Independent Predictor of Intracranial Hemorrhage Occurring During ECMO Support[J]. ASAIO J, 2016,62(5):634-636.DOI:10.1097/MAT.0000000000000368.

[12] Aubron C, DePuydt J, Belon F, et al. Predictive factors of bleeding events in adults undergoing extracorporeal membrane oxygenation[J]. Ann Intensive Care, 2016,6(1):97.DOI:10.1186/s13613-016-0196-7.

[13] Hooper J S, Hedges S J, Dehoney S B, et al. Evidence-based treatment recommendations for uremic bleeding[J]. Nature Clinical Practice Nephrology, 2007,3(3):138-153.DOI:10.1038/ncpneph0421.

[14] Bladowski M, Gawrys J, Gajecki D, et al. Role of the Platelets and Nitric Oxide

Biotransformation in Ischemic Stroke: A Translative Review from Bench to Bedside[J]. Oxid Med Cell Longev, 2020,2020:2979260.DOI:10.1155/2020/2979260.

[15] Reddoch K M, Montgomery R K, Rodriguez A C, et al. Endothelium-Derived Inhibitors Efficiently Attenuate the Aggregation and Adhesion Responses of Refrigerated Platelets [J]. Shock, 2016,45(2):220-227.DOI:10.1097/SHK.0000000000000493.

[16] Giorgia Colarossi H S A T. Prognostic factors for patients with heparin-induced thrombocytopenia: a systematic review[J]. International journal of clinical pharmacy, 2020.DOI:10.1007/s11096-020-01166-2.

[17] Seigerman M, Cavallaro P, Itagaki S, et al. Incidence and Outcomes of Heparin-Induced Thrombocytopenia in Patients Undergoing Cardiac Surgery in North America: An Analysis of the Nationwide Inpatient Sample[J]. Journal of cardiothoracic and vascular anesthesia, 2014,28(1):98-102.DOI:10.1053/j.jvca.2013.07.021.

[18] Chaudhry R, Wegner R, Zaki J F, et al. Incidence and Outcomes of Heparin-Induced Thrombocytopenia in Patients Undergoing Vascular Surgery[J]. Journal of cardiothoracic and vascular anesthesia, 2017,31(5):1751-1757.DOI:10.1053/j.jvca.2017.05.024.

[19] Pishko A, Lefler D, Gimotty P, et al. The Risk of Major Bleeding in Patients with Suspected Heparin-Induced Thrombocytopenia (HIT)[J]. Blood, 2018,132(Supplement 1):377.DOI:10.1182/blood-2018-99-112200.

[20] Thomas J, Kostousov V, Teruya J. Bleeding and Thrombotic Complications in the Use of Extracorporeal Membrane Oxygenation[J]. Seminars in thrombosis and hemostasis, 2018,44(1):20.

[21] Wang Y, Ge L, Ye Z, et al. Efficacy and safety of gastrointestinal bleeding prophylaxis in critically ill patients: an updated systematic review and network meta-analysis of randomized trials[J]. Intensive care medicine, 2020.DOI:10.1007/s00134-020-06209-w.

[22] Cavayas Y A, Del S L, Fan E. Intracranial hemorrhage in adults on ECMO[J]. Perfusion, 2018,33(1_suppl):42-50.DOI:10.1177/0267659118766435.

[23] Wang A L, Hittesdorf E, Takeda K, et al. Pulmonary alveolar hemorrhage in a patient with a temporary external ventricular assist device and extracorporeal membrane oxygenation[J]. J Card Surg, 2019,34(10):1110-1113.DOI:10.1111/jocs.14161.