Safety of heparin-free after 3000IU heparin loaded in veno-venous ECMO supported acute respiratory failure patients with hemorrage risk

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Abstract

Background: The anti-coagulation protocol of patients with hemorrhage risk primary disease who need extracorporeal membrane oxygenation (ECMO) supported is controversial. This study evaluated the safety of heparin-free after 3000IU heparin loaded in veno-venous ECMO (VV ECMO) supported acute respiratory failure patients with hemorrhage risk.

Methods: A retrospective study was performed in a series of hemorrhage risk patients supported with VV ECMO at the First Affiliated Hospital of Zhengzhou University, between June 2012 to Sept 2020. A total of 70 patients received a low heparin bolus of 3000 units for cannulation but without subsequent, ongoing heparin administration. Patients were divided into survival (n=25) and non-survival group (n=45). Data of coagulation, hemolysis and membrane lung function were calculated and analyzed. The complications of patients were recorded. Finally, the binary Logistic regression was conducted.

Results: The longest heparin-free time was 216 hours, and the mean heparin-free time was 102 hours. The percentage of thrombosis complications was 54.3% (38/70) including 3 oxygenator changed but there was no significant difference of complications in survival and non-survival groups ($p>0.05$). Compared with survivors, the non-survivors were showed higher baseline SOFA score and lower platelet counts in 0.5 hour, 24 hours, 48 hours and 96 hours after ECMO applied. However, there was no significant differences between survivors and non-survivors in ACT, APTT, INR, D-dimer, fibrinogen, LDH, blood flow rate, Δp and $P_{post\text{-}ML}O_2$ (all $p<0.05$) of all different time point. Moreover, only the baseline SOFA score was significantly associated with mortality ($p<0.001$, OR(95%CI): 2.754 (1.486-5.103)) while the baseline levels of ACT, APTT, INR, platelet, D-dimer, fibrinogen and LDH have no association with mortality.

Conclusions: The anticoagulation protocol that no heparin after a 3000 units heparin bolus in VV ECMO supported acute respiratory failure patients with hemorrhage risk is safe.

1. Introduction

Venovenous extracorporeal membrane oxygenation (VV ECMO) implementation is a rescue strategy to severe reversible refractory respiratory failure patients [1], and the application of VV ECMO is increased as people recognized its benefits. However, the complications especially bleeding and thromboembolic events are potentially life-threatening during ECMO support [2,3]. Activated partial thromboplastin time (APTT) and activated clotting time (ACT) are usually used clinically to adjust the dosage of unfractionated heparin (UFH) in order to reduce the incidence of complications. The current guidelines recommend an ACT-guided approach aiming at 1.5 fold increase of normal [4], instead of maintaining ACT within 120-180 seconds and APTT between 40-80 seconds [5]. Despite clinical strictly compliance with the heparin anticoagulation regimen guided by ACT, the incidence of bleeding complications still exceeds 50% [3]. The alternative anticoagulatory strategies with lower risk of bleeding and thromboembolism is extremely needed.

Polytrauma and after-surgery patients with acute respiratory failure and acute respiratory failure patients accompanied with a history of gastrointestinal or airway hemorrhage were existed the risk of severe bleeding or re-hemorrhage. The incidence of bleeding complications during VV ECMO supported was obviously higher in patients with high hemorrhage risk than others. The anticoagulatory strategies aim to high hemorrhage risk patients is needed. Previous case reports found heparin-free to be generally safe in critical ill patients but conclusions are limited [6,7].

Our study applied a heparin-free regimen after 3000 units of heparin loaded to hemorrhage risk patients supported by VV ECMO for the first time. We hypothesized that the strategy is safe and the indicators of coagulation, hemolysis and membrane lung function have no relationship with ICU mortality.

2. Materials And Methods

2.1 Study design and patients

The present study retrospectively enrolled 70 severe acute respiratory failure patients receiving VV ECMO with hemorrhage risk in the First Affiliated Hospital of Zhengzhou University immediately from June 2012 to Sept 2020. 70 enrolled patients were divided into survival group (n=25) and non-survival group (n=45) (Figure 1). In this study, the low heparin protocol was defined as 3000 units of heparin intravenously at the time of ECMO initiation and no ongoing heparin administration, as long as Δp were kept below 30mmHg and $P_{post\text{-}ML}O_2$ were over 200mmHg. ECMO system used was BE-PLS 2050 (Maquet, Rastatt, Germany). The cannulation of femoral vein and jugular vein were 17-25 French (Fr) cannulas.

Inclusion criteria were: 1) VV-ECMO support longer than 24h; 2) potentially hemorrhage risk (trauma, history of gastrointestinal or airway hemorrhage, and after surgery). The exclusion criteria were as follows: 1) aged<18 years old; 2) pregnancy; 3) irreversible multiple organ failure; 4) uncontrolled metastatic malignancy; 5) severe craniocerebral injury; 6) active bleeding; 7) preexisting indication for therapeutic anticoagulation; 8) contraindication to heparin; 9) missing informed consent.

ACT was measured at the initiation(0h), 0.5h, 1h, 2hs, 4hs, 8hs, 16hs, 24hs, 48hs, 72hs, 96hs, 120hs, 144hs, 168hs, 192hs and 216hs after ECMO running. APTT, international normalized ratio (INR), D-dimer and Fibrinogen were measured at 0h, 0.5h, 8hs, 16hs, 24hs, 48hs, 72hs, 96hs, 120hs, 144hs, 168hs, 192hs and 216hs. The levels of platelet and lactate dehydrogenase (LDH) were measured at 0h, 0.5h, 24hs, 48hs, 72hs, 96hs, 120hs, 144hs, 168hs, 192hs and 216hs. The blood flow rate, the Δp and $P_{post\text{-}ML}O_2$ of membrane lung were recorded at 0.5h, 1h, 2hs, 4hs, 8hs, 16hs, 24hs, 48hs, 72hs, 96hs, 120hs, 144hs, 168hs, 192hs and 216hs. The time of ECMO assisted, mechanical ventilation and intensive care unit (ICU) stay were collected. The severity of the illness was assessed based on the sepsis-related organ failure assessment (SOFA) score before ECMO initiation. Finally, the complications were recorded.

2.2 Endpoints

The primary endpoint was 30-day ICU mortality. Secondary endpoints were symptomatic thromboembolic events, ECMO oxygenator change and severe bleeding complications. The severe bleeding was defined as need for intervention or ≥10 red blood cell transfusions.

Routine threshold for platelet transfusion was < 50×10^9/L but could be individualized depending on the clinical situations. Fibrinogen or cryoprecipitate could be infused when the level of blood fibrinogen was less than 2g/L. When the level of D-dimer was too high, tranexamic acid could be used in combination with the condition.

Oxygenator change was considered in the following situations: 1) decreasing $P_{post\text{-}ML}O_2$<200 mmHg with increasing transmembrane pressure gradient or Δp (=$P_{pre\text{-}ML}$- $P_{post\text{-}ML}$) >30mmHg; 2) increasing $P_{post\text{-}ML}CO_2$>40 mmHg and $P_{pre\text{-}ML}CO_2$- $P_{post\text{-}ML}CO_2$ <10mmHg; 3) apparent circuit thrombosis with thrombi>5 mm; 3) rising D-dimers with progressive thrombocytopenia and hyperfbrinolysis with increasing transmembrane pressure gradient and 4) unexplained haemolysis with increasing transmembrane pressure gradient [8].

2.3 Statistical analysis

All collected data were statistically analyzed using SPSS 21.0 (Armonk, NY: IBM Corp.). Measurement data were expressed by the mean±standard deviation (SD), and the two groups compared by analysis of variance. Count data were expressed by frequency (composition ratio), and comparison between groups was by χ^2 test or Fisher's exact test. P<0.05 indicates that the difference is statistically significant. The binary Logistic regression was conducted to analyze whether coagulation and hemolysis indicators have relationships with ICU mortality.

3. Results

3.1 Baseline characteristics of VV ECMO patients

The characteristics of 70 enrolled patients are shown in Table 1. The longest heparin-free time was 216 hours, and the mean heparin-free time was 102 hours. Compared with survivors, the non-survivors were showed higher baseline SOFA score (8 (6.5-11) vs. 5 (4-6), p=0.001, Table 1), longer time in ICU (17.16±9.95d vs. 23.15±10.72d, p=0.022, Table 1) and lower platelet counts in 0 hour, 0.5 hour, 24 hours, 48 hours and 96 hours after ECMO applied (0h: 131.6±47.50×10^9/L vs. 163.2±47.49×10^9/L, p=0.010; 0.5h: 109.16±46.55×10^9/L vs. 139.88±48.56×10^9/L, p=0.011; 24h: 100.24±45.45×10^9/L vs. 131.16±45.61×10^9/L, p=0.008; 48h: 94.14±48.12×10^9/L vs. 119.96±48.20×10^9/L, p=0.043; 96h: 72.42±42.78×10^9/L vs. 107.69±49.25×10^9/L, p=0.039; Table1, Figure 2; respectively). However, there was no significant differences between survivors and non-survivors in ACT, APTT, INR, D-dimer, Fibrinogen, LDH, blood flow rate, Δp and $P_{post\text{-}ML}O_2$ of all different time point (all p<0.05; Table1, Figure 2 and Figure 3).

3.2 Description and comparison of complications of VV ECMO

The percentage of thrombosis complications was 54.3% (38/70) including 3 oxygenator changed but there was no significant difference of complications in survival and non-survival groups (all p>0.05, Table 2). In detail, the survivors were suffered 5 cases of membrane lung thrombosis, 4 cases of lower extremity venous thrombosis, 4 cases of venous cannula thrombosis, 1 case of ECMO circuit thrombosis and 1 case of oxygenator change. The non-survivors were appeared 11 cases of membrane lung thrombosis, 7 cases of lower extremity venous thrombosis, 3 cases of venous cannula thrombosis and 2 cases of oxygenator change. However, there was no bleeding complication occurred.

3.3. Explanations of oxygenator changed cases

The capacity of oxygen uptake was calculated as $P_{post}O_2$, the capacity of carbon dioxide removal was showed as $P_{pre}CO_2$-$P_{post}CO_2$, and the blood flow obstruction was described as Δp ($P_{pre\text{-}ML}$- $P_{post\text{-}ML}$). The oxygenator changed case 1: BFR=3.7L/min (BFR of the last day was 4.3 L/min at the same rotating speed), $S_{post}O_2$=89.2%, $P_{post}O_2$ = 61 mmHg (**<200 mmHg**), $P_{post}CO_2$ = 49mmHg, $P_{pre}CO_2$ = 40.2 mmHg, $P_{pre}CO_2$ -$P_{post}CO_2$ = 8.8 mmHg (**<10 mmHg**), Δp = 51 mmHg (**>30 mmHg**). The oxygenator changed case 2: BFR=3.8 L/min (BFR of the last day was 4.2 L/min at the same rotating speed), $S_{post}O_2$ = 98%, $P_{post}O_2$ = 82 mmHg (**<200 mmHg**), $P_{post}CO_2$ = 30.7 mmHg, $P_{pre}CO_2$ = 36 mmHg, $P_{pre}CO_2$ -$P_{post}CO_2$ = 5.3 mmHg (**<10 mmHg**), Δp = 39 mmHg (**>30 mmHg**). The oxygenator changed case 3: BFR=3.9 L/min (BFR of the last day was 4.2 L/min at the same rotating speed), $S_{post}O_2$ = 96.2%, $P_{post}O_2$ = 63 mmHg (**<200 mmHg**), $P_{post}CO_2$ = 31 mmHg, $P_{pre}CO_2$ = 37 mmHg, $P_{pre}CO_2$ -$P_{post}CO_2$ = 6 mmHg (**<10 mmHg**), Δp = 34 mmHg (**>30 mmHg**).

3.4. The relationship between indicators and ICU mortality

The baseline levels of ACT, APTT, INR, platelet, D-dimer, Fibrinogen, LDH and SOFA score were choose as variables for the binary Logistic regression analysis of VV ECMO supported patients' ICU mortality. As shown in Figure 4, only the baseline SOFA score was significantly associated with ICU mortality (2.754 (1.486-5.103), p<0.001, Figure 4).

4. Discussion

The retrospective study enrolled 70 VV ECMO patients using a new anticoagulation protocol, found there was no significance difference of coagulation indexes except palate counts in some time points and complications between the survivors and non-survivors, showed SOFA score but not coagulation indexes was associated with ICU mortality, and pointed that 3000 units of heparin intravenously at the time of ECMO initiation and no ongoing heparin administration was safe in hemorrhage risk patients.

In recent years, due to improvements in technology and deepens in cognition gradually, ECMO has faced a dramatic growth spurt and resurgence and played an increasingly important role in saving critically ill patients. However, ECMO has been associated with a number of complications including bleeding

complications, thrombo-embolic events and even end-organ dysfunction [9]. There are various anticoagulation strategy for ECMO supported patients in different centers, particularly for those receiving VV ECMO [10, 11]. The ELSO Anticoagulation Guideline recommends using systemic heparinization to run ACT of 180 and 220 seconds in non-bleeding patients [4]. However, the optimal anticoagulation regime to prevent thrombosis while minimizing bleeding is unclear.

Many studies have been conducted on low-intensity anticoagulation during ECMO supporting. Part et al demonstrated the safety of low dose heparin anti-coagulation regime during ECMO support for acute respiratory distress syndrome in conscious sheep [12]. A small randomized, controlled study enrolled 32 patients showed that a low heparin dose during the ECMO run was safe [13]. Recent years many studies had emerged which foucus on the comparison of different heparin anticoagulation protocols usually low and standard ones [6,7,14]. For special patients, studies on anticoagulation without heparin were carried out. As early as the year 2011, doctors found that using peripheral heparin-bonded cardiopulmonary bypass circuits without systemic heparinization reduced bleeding complications in re-operative cardiac surgery patients [15]. Heparin free during VA ECMO supported lung transplantation was also reported [16]. Moreover, postcardiotomy patients and patients with traumatic brain injury or pulmonary hemorrhage using heparin-free ECMO support were reported feasible by case series and smaller retrospective studies [17-20]. However, those studies still does not provide evidence on the optimal anticoagulation protocol for patients undergoing ECMO. Our present study also believed in the safety and feasible of heparin free therapy with a innovation of 3000IU heparin loaded at the ECMO initiation.

Most research was aimed at VA ECMO patients. A recent analysis showed that a minimal heparin strategy may be protective of major bleeding complications in VA-ECMO specially [21]. Patients on VA ECMO often have indications for therapeutic anticoagulation due to their underlying conditions, (e.g., atrial fibrillation, deep venous thrombosis, pulmonary emboli, intracardiac thrombus). Another study compared therapeutic anticoagulation (target APTT between 50 and 70s) with lower dose heparin (aiming for APTT< 45s) and found that in patients undergoing VA ECMO, there was no significant difference in the daily heparin doses between two groups (geometric daily mean dose of heparin 15,293 IU vs. 19,260 IU; p = 0.39) [22]. Our study focused on VV ECMO supported hemorrhage risk patients including polytrauma, post surgery, history of respiratory tract or gastrointestinal hemorrhage ones, and longitudinally compared the ACT, APTT, INR, D-dimer, fibrinogen, platelet, LDH, blood flow rate, Δp and $P_{post\text{-}ML}O_2$ of all different time point between the survivors and non-survivors. There was no bleeding complication occurred in our study, but the most common complication was thrombosis. The percentage of thrombosis complications was 54.3% (38/70) including 3 oxygenator changed.

The major problems of low-dose or no heparin anticoagulation are thromboembolic events and ECMO oxygenator change. Based on the pathophysiology of the membrane lung, ECMO oxygenator change may be required if there is an associated hematologic abnormality, an increasing obstruction to blood flow, or inadequate gas exchange [8]. Membrane lung dysfunction is associated with considerable morbidity [23]. The functions of membrane lung are carbon dioxide removal and oxygen uptake. The non-biologic surface of the membrane lung is responsible of membrane lung dysfunction, through activates

inflammatory and coagulation pathways with leukocyte activation, fibrinolysis, and thrombus formation [24,25]. Activation of coagulation and fibrinolysis might result in systemic coagulopathy or hemolysis, while clot deposition can obstruct blood flow [26, 27]. The hematologic abnormalities, mechanical obstruction, and inadequate gas exchange effects alone or together eventually lead to membrane pulmonary dysfunction [28, 29]. In our present study, there were 3 patients manifested membrane lung dysfunction and changed the ECMO oxgyenator finally because the increased obstruction to blood flow or inadequate gas exchange.

This is a retrospective study of our single-center and the sample size is small, and the future verified by multi-center, large-sample, prospective randomized controlled study is needed. This study selected VV ECMO supported acute respiratory failure patients with hemorrhage risk. For patients with no bleeding risk or severe bleeding and VA ECMO supported patients, the effect of the anticoagulant regimen is unknown. The last but not least, the indicators selected in this study are not comprehensive enough, and some new indicators, such as anti-Xa, can be added in the future.

5. Conclusion

The anticoagulation protocol for hemorrhage risk patients supported by VV ECMO without heparin after a load of 3000 IU of heparin is safe. There was no bleeding complication occurred in our study, but the most common complication was thrombosis. The ACT, APTT, INR, D-dimer, fibrinogen, LDH, blood flow rate, Δp and $P_{post\text{-}ML}O_2$ of all different time point and the occurrences of complications have no significant difference between the survivors and non-survivors. Although the counts of platelet at some points showed significantly differences, only the SOFA score was associated with the ICU mortality in the present study.

6. Declarations

6.1 Ethical Approval and Consent to participate

The present study fully complied with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China (no. 2020-KY-429). Informed consent was waived because of the retrospective nature of the analysis.

6.2 Consent for publication

Not applicable.

6.3 Availability of supporting data

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

6.4 Competing interests

The authors declare that they have no competing interests.

6.5 Funding

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6.6 Authors' contributions

YCZ and XZ: Designed the study and wrote the first draft of the manuscript. GWF, MJH, SLW, YBK and JL: Verified data extraction, data analysis, and reviewed the manuscript. WTM, QFX, QLL, HBL, XXL and QQS: Supervised the data acquisition, data analysis and interpretation. All authors read and approved the final manuscript.

6.7 Acknowledgments

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Tables

Table 1. Baseline characteristics of acute respiratory failure

	Total (n=70)	**Survival Group** (n=25)	**Non-survival Group** (n=45)	**P**-value
Male gender, (n%)	43 (61.4)	14 (56)	29 (64.4)	0.487
Age (y)	43.51±13.31	40.36±13.43	45.27±13.07	0.141
BMI (Kg/M^2)	24.49±2.91	24.04±2.21	24.74±3.23	0.333
SOFA score	7 (5-9.25)	5 (4-6)	8 (6.5-11)	**0.001**
Primary disease or comorbidities, (n%)				0.565
Polytrauma	26 (37.1)	9 (36)	17 (37.8)	
Respiratory tract hemorrhage	10 (14.3)	3 (12)	7 (15.6)	
Gastrointestinal hemorrhage	20 (28.6)	6 (24)	14 (31.1)	
Cardiovascular surgery	8 (11.4)	3 (12)	5 (11.1)	
Non-cardiovascular surgery	6 (8.6)	4 (16)	2 (4.4)	
Heparin free time, (min)	102.34±43.70	104.92±48.01	100.91±41.62	0.720
ECMO assisted time, (h)	190.80±88.95	188.60±78.34	192.02±95.17	0.880
Ventilation time, (h)	279 (214.75-432)	360 (144-480)	268 (220-354.5)	0.730
tracheotomy, (n%)	28 (40)	12 (48)	16 (35.6)	0.323
Time in ICU, (d)	19.30±10.56	23.15±10.72	17.16±9.95	**0.022**
CRRT, (n%)	36 (51.2)	13 (52)	23 (51.1)	0.943
PaO_2/FiO_2	49.00±7.17	54.01±5.66	46.21±6.41	**<0.001**
Baseline laboratory examinations				
Creatine, (umol/L)	86.7 (66.95-112.75)	79 (59.5-88.5)	94 (74.5-130)	**0.002**
Platelet count, (10^9/L)	142.89±49.56	163.2±47.49	131.6±47.50	**0.010**
Total bilirubin, (umol/L)	13.85 (8.78-25.13)	12 (8.9-22.5)	14 (8.55-27)	0.060
ACT, (s)	101.51±12.76	98.64±12.08	103.11±12.98	0.162
APTT, (s)	34.08±6.30	34.57±8.13	33.8 ±5.10	0.627

INR	1.19±0.32	1.15±0.32	1.20±0.32	0.513
D-dimer, (mg/L)	2.65 (0.88-5.42)	1.59 (0.45-4.81)	3.18 (1.04-5.77)	0.422
Fibrinogen, (g/L)	4.09±1.57	4.01±1.44	4.14±1.65	0.734
LDH, (U/L)	820.63±527.62	751.8±455.17	858.87±565.12	0.420

*****The data was shown as the mean ± SD, median (interquartile 25-75) or n (percentage). Bold values indicate statistical significance. VV-ECMO= veno-venous extracorporeal membrane oxygenation; BMI= body mass index; SOFA= sepsis-related organ failure assessment; ICU=intensive care unit; CRRT= continuous renal replacement therapy; ACT= activated clotting time; APTT= activated partial thromboplastin time; INR= international normalized ratio; LDH= lactate dehydrogenase.

Table 2. Comparison of the complications of the survivors and non-survivors of acute respiratory failure patients assisted with VV-ECMO

	Total (n=70)	**Survivors** (n=25)	**Non-survivors** (n=45)	***P*-value**
Lower extremity venous thrombosis	11 (15.7)	4 (16)	7 (15.6)	0.961
Membrane lung thrombosis	16 (22.9)	5 (20)	11 (24.4)	0.671
ECMO circuit thrombosis	1 (1.4)	1 (4)	0 (0)	0.177
Venous cannula thrombosis	7 (10)	4 (16)	3 (6.7)	0.212
Oxygenator change	3 (4.3)	1 (4)	2 (4.4)	0.930

*****The data was shown as n (percentage). Bold values indicate statistical significance. VV-ECMO= veno-venous extracorporeal membrane oxygenation.

Figures

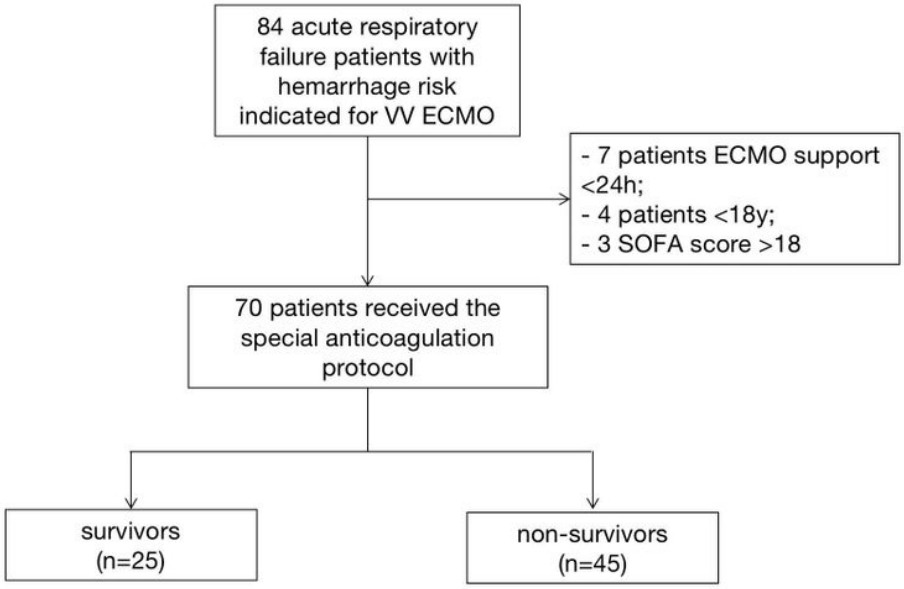

Figure 1

The flow chart.

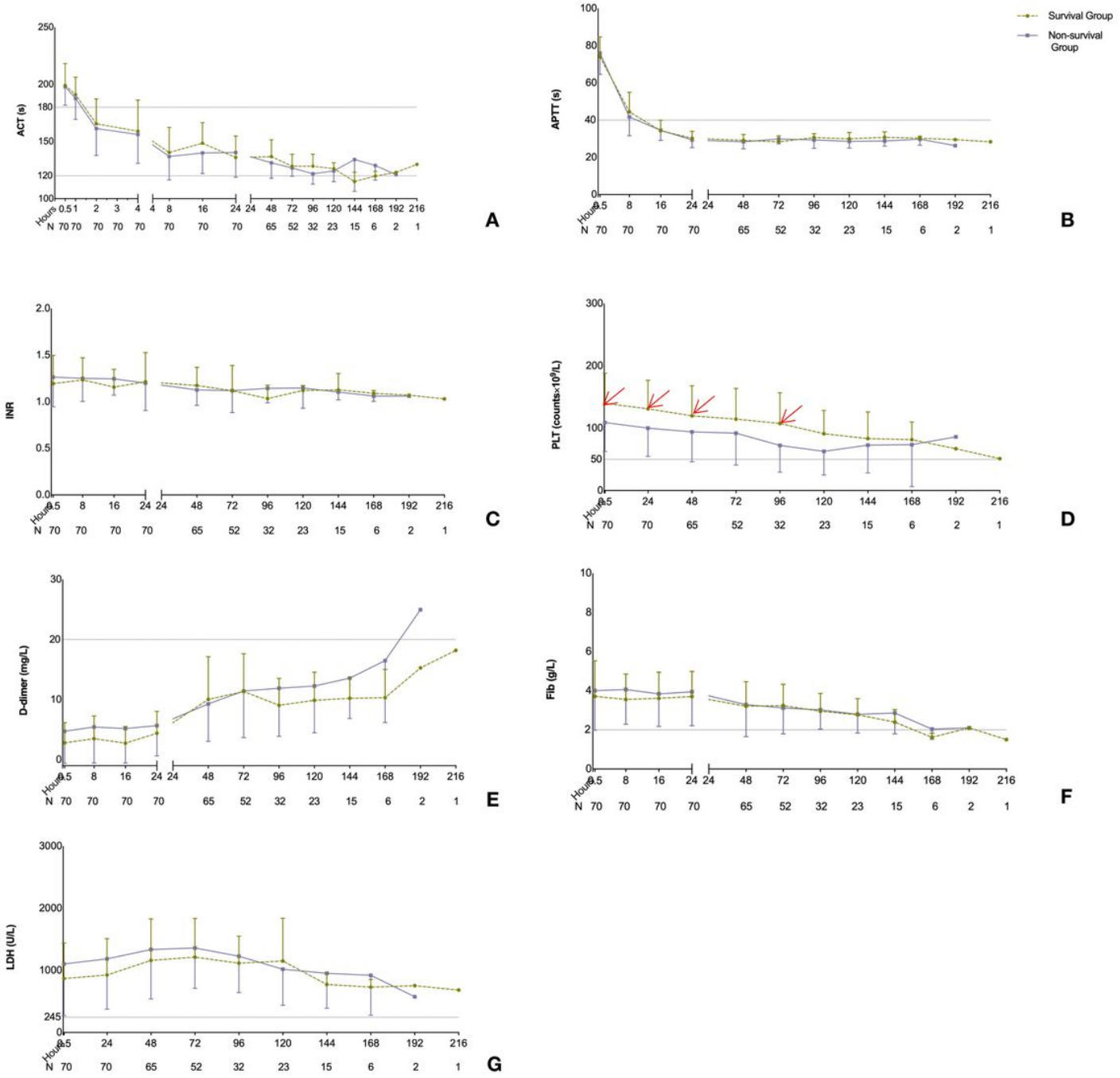

Figure 2

Compared of coagulation indicators in different time points between survivors and non-survivors. **2(A):** ACT; **2(B):** APTT; **2(C):** INR; **2(D):** Platelet; **2(E):** D-dimer; **2(F):** Fibrinogen; **2(G):** LDH. The red arrows indicate statistical significance.

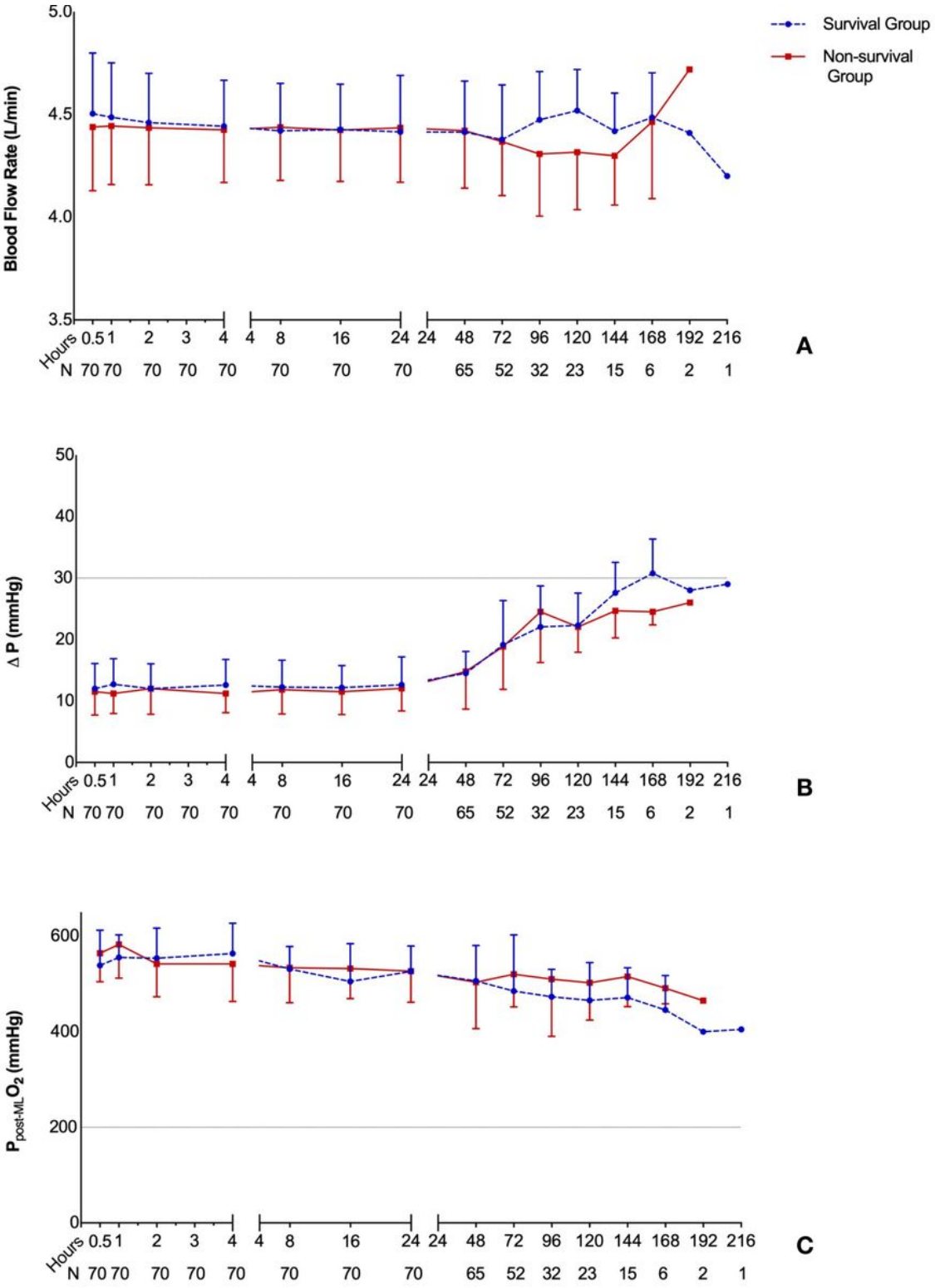

Figure 3

Compared of ECMO-related indicators in different time points between survivors and non-survivors. **3(A):** blood flow rate; **3(B):** Δp; **3(C):** $P_{post\text{-}ML}O_2$.

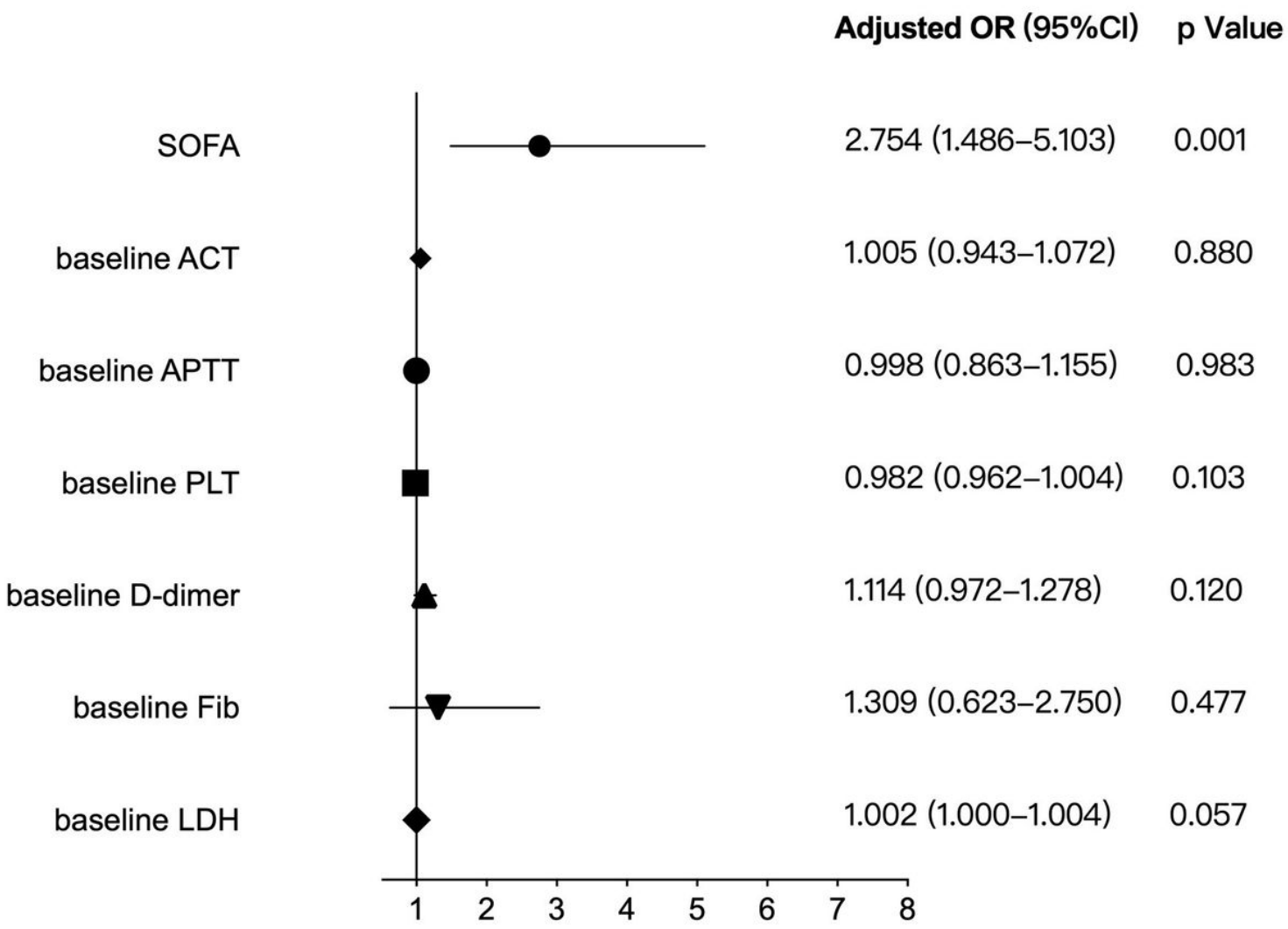

Figure 4

The binary Logistic regression analysis of mortality.