Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Prognostic value of endothelial biomarker in refractory cardiogenic shock with ECLS: a prospective monocentric study

Tsung-Yu Tsai
Chang Gung Memorial Hospital Linkou Branch
Kun-Hua Tu
Chang Gung Memorial Hospital Linkou Branch
Feng-Chun Tsai
Chang Gung Memorial Hospital Linkou Branch
Yu-Yun Nan
Chang Gung Memorial Hospital Linkou Branch
Pei-Chun Fan
Chang Gung Memorial Hospital Linkou Branch
Chih-Hsiang Chang
Chang Gung Memorial Hospital Linkou Branch
Ya-Chung Tian
Chang Gung Memorial Hospital Linkou Branch
Ji-Tseng Fang
Chang Gung Memorial Hospital Linkou Branch
Chih-Wei Yang
Chang Gung Memorial Hospital Linkou Branch
Yung-Chang Chen (cyc2356@gmail.com)
Chang Gung Memorial Hospital Linkou Branch https://orcid.org/0000-0002-6614-5427

Research article

Keywords:

Posted Date: April 19th, 2019

DOI: https://doi.org/10.21203/rs.2.43/v3

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Version of Record: A version of this preprint was published on May 15th, 2019. See the published version at https://doi.org/10.1186/s12871-019-0747-1.

Abstract

Background Extracorporeal membrane oxygenation (ECMO) is often used in critical patients with severe myocardial failure. However, patients on ECMO often have high mortality rate. Recent studies suggest that endothelial activation with subsequent vascular barrier breakdown is a critical pathogenic mechanism in organ damage and related to the outcome in critical illness. This study aimed to determine whether the endothelial biomarkers could serve as prognostic factors for the outcome of patients on ECMO. Methods This prospective study enrolled total 23 critically ill patients on veno-arterial ECMO in the intensive care units of a tertiary care hospital between March 2014 and February 2015. Serum samples were tested for thrombomodulin, angiopoietin (Ang)-1, Ang-2, and vascular endothelial growth factor (VEGF). Demographic, clinical, and laboratory data were also collected. Results The overall mortality rate was 56.5%. The combination of Ang-2 at the time of ECMO support (day 0) and VEGF at day 2 had the ability of discriminating mortality (area under receiver operating characteristic curve [AUROC], 0.854; 95% confidence interval: 0.645-0.965). Conclusions In this study, we found that the combination of Ang-2 at day 0 and VEGF at day 2 was a modest model for mortality discrimination in this group of patients.

Introduction

Extracorporeal membrane oxygenation (ECMO) is often used in critical patients with severe myocardial failure (e.g., cardiogenic shock or myocarditis). It provides these patients with temporary circulatory support and has been utilized as a bridging therapy for further treatment. However, patients on ECMO still have high mortality rate though the technique and post-operation care of ECMO supplement has progressed much in recent decades.1-4

Previous studies showed that several intensive care unit (ICU) scoring systems have good ability in outcome prediction for patients on ECMO.1,5,6 However, these scoring systems usually consist of many laboratory data and physiological measurements, and sometimes need complex calculation. Recently, several biomarkers are applied in predicting renal and neurologic outcomes in patients on ECMO7,8, but no particular biomarker is associated with mortality in this patient group.

Recent studies suggest that endothelial activation with subsequent vascular barrier breakdown is a critical pathogenic mechanism in organ damage and related to the outcome in critical illness.9-12 Thrombomodulin (TM) is a transmembranous glycoprotein found on the vascular endothelium.13 It enhances thrombin-induced activation of protein C and has roles in inflammation, coagulation, and fibrinolysis.14 Soluble thrombomodulin levels are associated with mortality in patients with disseminated intravascular coagulation, sepsis, or acute respiratory distress syndrome.12,15,16 Angiopoietin (Ang)-1, Ang-2, and vascular endothelial growth factor (VEGF) are proteins associated with angiogenesis. Ang-1 has an anti-inflammatory effect with limiting endothelium activation, while Ang-2 triggers an inflammatory response by activating the endothelium. Besides, Ang-1 downregulates VEGF expression and reduces thrombin-induced permeability.17-19 In recent studies, lower Ang-1 concentration and high

Ang-2 concentration are associated with increased mortality of patients with sepsis.10,20-22 However, the relationship between VEGF level and mortality is discordant in different studies.12,23,24

Although endothelial activation and injury are involved in organ damage and associated with the prognosis in critical illness, these has been no associated study on patients on ECMO. Therefore, this study aimed to determine whether the serum biomarkers of endothelial injury and activation could serve as prognostic factors for the outcome of patients on ECMO.

Materials And Methods

Study population and data collection

The local Institutional Review Board of Chang Gung Memorial Hospital approved the study protocol (Institutional Review Board No. 103-1569C). The study was performed in the ICUs of a tertiary care hospital in Taiwan between March 2014 and February 2015. Patients who met the inclusion criteria were invited to participate in the study on the first day of ECMO support. Written informed consent was obtained from the next-of-kin of the patients before their participation. The following patients were excluded: pediatric patients younger than 18 years old, patients with end stage renal disease undergoing regular renal replacement therapy, and patients whose next-of-kin declined study enrollment. Besides, patients with veno-venous (V-V) ECMO support were also excluded due to different pathophysiologic changes between veno-arterial (V-A) and V-V ECMO. For patients with repeated ECMO support during hospitalization, we only collected the data on the first ECMO support. 66 patients were screened during the study period, but next-of-kin of 43 patients refused the study due to the critical condition of the patients. Finally, total 23 patients were enrolled.

The following data were prospectively collected: demographic data, indications for ECMO support, and outcomes. Physiological calculations utilized the worst physiological values on the day of ECMO support. The primary study outcome was 30-day in-hospital mortality. Follow-up at 6 months after hospital discharge was performed via chart records or telephone interviews if necessary.

Sampling and quantifying serum biomarkers

Ten milliliters of blood were collected from each patient with routine blood tests performed at the time of ECMO support (day 0), the morning of the first post-ECMO day (day 1), and the morning of the second post-ECMO day (day 2). The blood samples were centrifuged at 1000 g for 5 minutes, and the supernatants were stored at -80°C. Serum biomarkers (Ang-1, Ang-2, VEGF, and TM) were quantified by an enzyme-linked immunosorbent assay (R&D system, Minneapolis, MN, USA) according to manufacturer instructions.

Clinical management

The ECMO device (Medtronic, Inc., Anaheim, CA) was composed of a centrifugal pump and a hollow-fiber microporous membrane oxygenator with an integrated heater. All ECMO circuits had a heparin-bound

Carmeda bioactive surface. A silicone oxygenator (Medtronics, Minneapolis, MN, USA) was incorporated into the ECMO circuit. A 17–19 Fr percutaneous arterial (outflow) cannula and a 19–21 Fr percutaneous venous (inflow) cannula (DLP; Medtronic Inc., Minneapolis, MN) were chosen according to patients' body size. Percutaneous access through the common femoral vein (inflow) and the common femoral artery (outflow) was preferred for V-A ECMO. If cyanosis was noted on the cannulated limb, an 8 Fr distal perfusion catheter would be implanted into the ipsilateral superficial femoral artery.

Statistical analysis

There was no sufficient power to test normality of continuous variables due to the small sample size of this study. Therefore, all statistical tests were done using nonparametric statistics. Descriptive statistics of continuous variables were expressed as median with interquartile range. Data between the survivors and non-survivors were compared using Mann-Whitney U test for continuous variables or Fisher's exact test for categorical variables. The performance of discriminating mortality by those biomarkers at day 0, day 1, and day 2 of ECMO support was assessed using receiver operating characteristic (ROC) curve analysis. All statistical tests were two-tailed, and a value of $P < 0.05$ was considered statistically significant. No adjustment for multiple testing (multiplicity) was made in this study. Statistics analysis was conducted using SPSS 22 software (IBM SPSS, Armonk, NY: IBM Corp).

Results

Between March 2014 and February 2015, 23 patients on ECMO support at the ICU were enrolled. The average age was 57 years and 19 (82.6%) were male. The in-hospital mortality rate was 56.5% (13/23). Table 1 presents the patients' demographic data and clinical characteristics. Non-survivors had higher vasopressor/inotrope dose and higher Sequential Organ Failure Assessment (SOFA) score than survivors at the day of ECMO supplement. Table 2 shows the concentration changes of biomarkers at day 0, day 1, and day 2 of ECMO support. TM and Ang-1 concentrations showed no significant difference between survivors and non-survivors during the first two days. The Ang-2/Ang-1 ratio increased gradually in both groups and was higher in non-survivors. Noticeably, decreased Ang-2 level at day 0 (median: 15.7 vs. 24.4 ng/mL, $P = 0.035$) and tremendously increased VEGF level at day 2 (median: 119.9 vs. 24.2 pg/mL, $P = 0.005$) were observed in the survivors as compared to non-survivors (Figure 1). Figure 2 depicts the ROC curves of the four biomarkers in discriminating mortality at day 0, day 1, and day 2 of ECMO support. We found that the combined predicted probability of Ang-2 at day 0 and VEGF at day 2 had the ability of discriminating mortality (area under the ROC curve, 0.854; 95% confidence interval [CI], 0.645-0.965; as shown in Figure 2D).

Discussion

This study is the first one investigating the relationship between endothelial biomarkers and mortality in patients on ECMO. In this study, we noticed an increased Ang-2 level in non-survivors compared with survivors. Besides, we also observed that the combination of Ang-2 at day 0 and VEGF at day 2 showed a modest performance on mortality discrimination in patients on ECMO.

The initiation of ECMO brings an immediate and complex inflammatory reaction in patients, as seen in systemic inflammatory response syndrome. The inflammatory reaction then results in the widespread activation of the endothelium and induces pro-inflammatory cytokines secretion.25 Moreover, active diseases that require ECMO support may be associated with endothelial inflammation, such as cardiotomy surgery and acute myocardial infarction. Non-pulsatile flow during aortic cross-cramping during cardiotomy is associated with diminished endothelial shear stress with reduction in endothelial nitrogen oxide production, while intra-aortic balloon pump support provides steady pulsatile flow, which induces a steady shear stress on the endothelial cells, reducing endothelial activation and inflammatory response.26,27 Acute kidney injury following ECMO support is also related to endothelial injury.28 Therefore, endothelial injury is an important issue in patients on ECMO.

Previous studies showed that Ang-2 level was associated with mortality in critically-ill patients.29-32 Ang-2, a competitive antagonist of Ang-1, reacts with Tie2 receptor to keep vascular stabilization. Upon inflammatory stimulus, Ang-2 is released from the Weibel-Palade bodies, causing capillary leakage and facilitating leukocyte migration.33 In patients on ECMO, Ang-2 increased in response to early endothelial activation. Although it didn't reveal a close relationship with acute kidney injury in our study, it still provided a potential marker for mortality prediction in patients on ECMO. Besides, Ang-2/Ang-1 ratio increased during capillary endothelial damage, and high Ang-2/Ang-1 ratio was related to poor outcome in patients with sepsis20,21. In our study, the Ang-2/Ang-1 ratio increased gradually in both groups and was higher in non-survivors, which may implicate more severe endothelial damage in non-survivor group.

VEGF is considered as an endothelial survival factor that prevents microvascular apoptotic cell loss in vitro.34 Both low and high VEGF concentrations have been reported in critically-ill patients24,30,35, and the significance of which is not fully understood. In our study, the VEGF concentration in the survivor group continued to increase over the first 72 hours and was higher than the non-survivor group, which was similar to previous studies.24 VEGF modulates the effect of Ang-2 in a context-dependent fashion: Ang-2 promotes basal lamina remodeling and endothelial cell proliferation at high VEGF concentration, but causes endothelial cell death and vessel regression if VEGF is inhibited.36 In our study, we observed that survivors had significantly higher 72-hour VEGF concentration compared to non-survivors. Higher VEGF concentration may modulate the Ang-2 effect and help endothelial cell proliferation and neovascularization, but the detailed relationship with mortality needs further studies to evaluate and confirm.

There are some limitations in our study. First, our study was performed in a tertiary care center with a small sample size. Although it was a prospective study, many next-of-kin of the patients declined to join the study at the time of ECMO support due to the critical condition of the patients. Large-scale studies at multiple centers should be performed to confirm these findings. Second, although we excluded patients on V-V ECMO support and only collected patients on V-A ECMO support, the diversity of the diseases indicated for ECMO support may still affect the results, and further subgroup investigations are needed to explore the relationship between specific diseases and endothelial biomarkers. Third, we did not compare the differences in the endothelial biomarkers levels with a control group because we could not find a group of patients with the same disease severity but without ECMO support.

In summary, we presented the relationship between endothelial biomarkers change and mortality in patients on V-A ECMO. The combination of Ang-2 at day 0 and VEGF at day 2 was a modest model for mortality discrimination in this group of patients. However, further larger studies are warranted due to the small sample size at a single tertiary-care medical center in this study.

Abbreviations

ECMO, Extracorporeal membrane oxygenation; Ang, angiopoietin; VEGF, vascular endothelial growth factor; AUROC, area under receiver operating characteristic curve; ICU, intensive care unit; TM, Thrombomodulin; V-V, veno-venous; V-A, veno-arterial; ROC, receiver operating characteristic; SOFA, sequential organ failure assessment; CI, confidence interval.

Declarations

Ethics approval and consent to participate:

Written informed consent was obtained from the next-of-kin of the patients before their participation. The study was approved by the local Institutional Review Board of Chang Gung Memorial Hospital approved the study protocol (Institutional Review Board No. 103-1569C).

Consent for publication:

Not applicable.

Availability of data and material:

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

Funding:

No funding was received.

Authors' contributions:

TYT contributed to collecting data and manuscript drafting. KHT and CHC revised the manuscript and conducted the statistical analysis. FCT and YYN helped with acquisition and interpretation of data. PCF conducted the statistical analysis. YCT, JTF, and CWY contributed to provide intellectual content of the work and involved in editing the manuscript. YCC contributed to the conception, design, and interpretation

of data. All authors critically revised the manuscript. All authors have seen and approved the final draft of the manuscript.

Acknowledgements:

The authors thank the staff of the Chang Gung Kidney Research Center and

Chang Gung Memorial Hospital ICUs for their assistance.

Reference

1. Lin CY, Tsai FC, Tian YC, et al. Evaluation of outcome scoring systems for patients on extracorporeal membrane oxygenation. Ann Thorac Surg 2007;84:1256–62.

2. Chen YC, Tsai FC, Chang CH, et al. Prognosis of patients on extracorporeal membrane oxygenation: the impact of acute kidney injury on mortality. Ann Thorac Surg 2011;91:137–42.

3. Aubron C, Cheng AC, Pilcher D, et al. Factors associated with outcomes of patients on extracorporeal membrane oxygenation support: a 5-year cohort study. Crit Care 2013;17:R73.

4. Zangrillo A, Landoni G, Biondi-Zoccai G, et al. A meta-analysis of complications and mortality of extracorporeal membrane oxygenation. Crit Care Resusc 2013;15:172–8.

5. Tsai TY, Tsai FC, Chang CH, et al. Prognosis of patients on extracorporeal membrane oxygenation plus continuous arteriovenous hemofiltration. Chang Gung Med J. 2011;34:636-43.

6. D'Arrigo S, Cacciola S, Dennis M, et al. Predictors of favourable outcome after in-hospital cardiac arrest treated with extracorporeal cardiopulmonary resuscitation: A systematic review and meta-analysis. Resuscitation. 2017;121:62-70.

7. Zwiers AJ, Cransberg K, de Rijke YB, van Rosmalen J, Tibboel D, de Wildt SN. Urinary neutrophil gelatinase-associated lipocalin predicts renal injury following extracorporeal membrane oxygenation. Pediatr Crit Care Med. 2015;16:663-70.

8. Bembea MM, Rizkalla N, Freedy J, et al. Plasma biomarkers of brain injury as diagnostic tools and outcome predictors after extracorporeal membrane oxygenation. Crit Care Med. 2015;43:2202-11.

9. Aird WC. Vascular bed-specific hemostasis: role of endothelium in sepsis pathogenesis. Crit Care Med. 2001;29(7 Suppl):S28-34.

10. Mikacenic C, Hahn WO, Price BL, et al. Biomarkers of endothelial activation are associated with poor outcome in critical illness. PLoS One. 2015;10:e0141251.

11. Robinson-Cohen C, Katz R, Price BL, et al. Association of markers of endothelial dysregulation Ang1 and Ang2 with acute kidney injury in critically ill patients. Crit Care. 2016;20:207.

12. Hou PC, Filbin MR, Wang H, et al. Endothelial permeability and hemostasis in septic shock: results from the ProCESS trial. Chest. 2017;152:22-31.

13. Maruyama I, Bell CE, Majerus PW. Thrombomodulin is found on endothelium of arteries, veins, capillaries, and lymphatics, and on syncytiotrophoblast of human placenta. J Cell Biol. 1985;101:363-71.

14. Conway EM. Thrombomodulin and its role in inflammation. Semin Immunopathol. 2012;34:107-25.

15. Lin SM, Wang YM, Lin HC, et al. Serum thrombomodulin level relates to the clinical course of disseminated intravascular coagulation, multiorgan dysfunction syndrome, and mortality in patients with sepsis. Crit Care Med. 2008;36:683-9.

16. Sapru A, Calfee CS, Liu KD, et al. Plasma soluble thrombomodulin levels are associated with mortality in the acute respiratory distress syndrome. Intensive Care Med. 2015;41:470-8.

17. Asahara T, Chen D, Takahashi T, et al. Tie2 receptor ligands, angiopoietin-1 and angiopoietin-2, modulate VEGF-induced postnatal neovascularization. Circ Res. 1998;83:233-40.

18. Lemieux C, Maliba R, Favier J, Theoret JF, Merhi Y, Sirois MG. Angiopoietins can directly activate endothelial cells and neutrophils to promote proinflammatory responses. Blood. 2005;105:1523-30.

19. Liu KL, Lee KT, Chang CH, Chen YC, Lin SM, Chu PH. Elevated plasma thrombomodulin and angiopoietin-2 predict the development of acute kidney injury in patients with acute myocardial infarction. Crit Care. 2014;18:R100.

20. Ricciuto DR, dos Santos CC, Hawkes M, et al. Angiopoietin-1 and angiopoietin-2 as clinically informative prognostic biomarkers of morbidity and mortality in severe sepsis. Crit Care Med. 2011;39:702-10.

21. Fang Y, Li C, Shao R, Yu H, Zhang Q, Zhao L. Prognostic significance of the angiopoietin-2/angiopoietin-1 and angiopoietin-1/Tie-2 ratios for early sepsis in an emergency department. Crit Care. 2015;19:367.

22. Fisher J, Douglas JJ, Linder A, Boyd JH, Walley KR, Russell JA. Elevated plasma angiopoietin-2 levels are associated with fluid overload, organ dysfunction, and mortality in human septic shock. Crit Care Med. 2016;44:2018-27.

23. van der Flier M, van Leeuwen HJ, van Kessel KP, Kimpen JL, Hoepelman AI, Geelen SP. Plasma vascular endothelial growth factor in severe sepsis. Shock. 2005;23:35-8.

24. Karlsson S, Pettilä V, Tenhunen J, et al. Vascular endothelial growth factor in severe sepsis and septic shock. Anesth Analg. 2008;106:1820-6.

25. Millar JE, Fanning JP, McDonald CI, McAuley DF, Fraser JF. The inflammatory response to extracorporeal membrane oxygenation (ECMO): a review of the pathophysiology. Crit Care. 2016;20:387.

26. Macha M, Yamazaki K, Gordon LM, et al. The vasoregulatory role of endothelium derived nitric oxide during pulsatile cardiopulmonary bypass. ASAIO J. 1996;42:M800-4.

27. Onorati F, Santarpino G, Tangredi G, et al. Intra-aortic balloon pump induced pulsatile perfusion reduces endothelial activation and inflammatory response following cardiopulmonary bypass. Eur J Cardiothorac Surg. 2009;35:1012-9.

28. Basile DP. The endothelial cell in ischemic acute kidney injury: implications for acute and chronic function. Kidney Int. 2007;72:151-6.

29. Gallagher DC, Parikh SM, Balonov K, et al. Circulating angiopoietin 2 correlates with mortality in a surgical population with acute lung injury/adult respiratory distress syndrome. Shock. 2008;29:656-61.

30. Kümpers P, Lukasz A, David S, et al. Excess circulating angiopoietin-2 is a strong predictor of mortality in critically ill medical patients. Crit Care. 2008;12:R147.

31. Siner JM, Bhandari V, Engle KM, Elias JA, Siegel MD. Elevated serum angiopoietin 2 levels are associated with increased mortality in sepsis. Shock. 2009;31:348-53.

32. van der Heijden M, Pickkers P, van Nieuw Amerongen GP, et al. Circulating angiopoietin-2 levels in the course of septic shock: relation with fluid balance, pulmonary dysfunction and mortality. Intensive Care Med. 2009;35:1567-74.

33. van Meurs M, Kümpers P, Ligtenberg JJ, Meertens JH, Molema G, Zijlstra JG. Bench-to-bedside review: Angiopoietin signalling in critical illness - a future target? Crit Care. 2009;13:207.

34. Gerber HP, McMurtrey A, Kowalski J, et al. Vascular endothelial growth factor regulates endothelial cell survival through the phosphatidylinositol 3'-kinase/Akt signal transduction pathway. Requirement for Flk-1/KDR activation. J Biol Chem. 1998;273:30336-43.

35. van der Heijden M, van Nieuw Amerongen GP, Koolwijk P, van Hinsbergh VW, Groeneveld AB. Angiopoietin-2, permeability oedema, occurrence and severity of ALI/ARDS in septic and non-septic critically ill patients. Thorax. 2008;63:903-9.

36. Lobov IB, Brooks PC, Lang RA. Angiopoietin-2 displays VEGF-dependent modulation of capillary structure and endothelial cell survival in vivo. Proc Natl Acad Sci USA. 2002;99:11205-10.

Tables

Table 1. Patients' demographic data and clinical characteristics

Variable	All Patients (*n* = 23)	Non-Survivors (*n* = 10)	Survivors (*n* = 13)	*P* value
Age (years)	57 (19)	55 (7)	58 (20)	0.250
Male sex, n (%)	19 (82.6)	7 (70)	12 (92.3)	0.281
Diabetes mellitus, n (%)	4 (17.4)	1 (10)	3 (23.1)	0.604
Coronary artery disease, n (%)	15 (65.2)	5 (50)	10 (76.9)	0.221
Duration of ECMO support (days)	5 (5)	7 (11)	4 (1)	0.483
Duration of ICU stay (days)	11 (10)	8 (11)	17 (38)	0.020
Mechanical ventilation (days)	8 (8)	8 (11)	8 (8)	0.454
IABP, n (%)	18 (78.3)	8 (80)	10 (76.9)	1.000
Myocardial failure during operation	10 (55.6)	6 (75)	4 (40)	0.188
Cardiogenic shock	8 (44.4)	2 (25)	6 (60)	0.188
Indication for ECMO, n (%)				0.119
Postcardiotomy	12 (52.2)	5 (50)	7 (53.8)	
Myocarditis	1 (4.3)	1 (10)	0 (0)	
Acute myocardial infarction	6 (26.1)	1 (10)	5 (38.5)	
Heart transplantation	1 (4.3)	1 (10)	0 (0)	
Profound shock with desaturation	2 (8.7)	2 (20)	0 (0)	
VT with cardiogenic shock	1 (4.3)	0 (0)	1 (7.7)	
Complication of ECMO, n (%)				
Lower extremity ischemia	2 (8.7)	1 (10)	1 (7.7)	1.000
Stroke	1 (4.3)	1 (10)	0 (0)	0.435
Coma or brain hypoxia	4 (17.4)	4 (40)	0 (0)	0.024
Significant bleeding	8 (34.8)	4 (40)	4 (30.8)	0.685
Rethoractomy for bleeding	5 (21.7)	2 (20)	3 (23.1)	1.000
Vasopressor/inotrope on ECMO 1st day				
Dopamine (μg/kg/min)	0.0 (9.5)	0.0 (4.7)	0.0 (10.7)	0.538
Norepinephrine (μg/kg/min)	0.1 (0.2)	0.1 (0.3)	0.0 (0.2)	0.324
Dobutamine (μg/kg/min)	0.0 (6.3)	5.0 (5.0)	0.0 (0.0)	0.032

Epinephrine (μg/kg/min)	0.1 (0.4)	0.4 (0.4)	0.0 (0.2)	0.027
Biochemistry data on ECMO 1st day				
MAP (mmHg)	58 (19)	55 (21)	59 (14)	0.306
Diuresis(ml/kg/hr)	0.9 (1.1)	1.2 (1.0)	0.9 (1.0)	0.495
SCr (mg/dL)	1.4 (0.8)	1.3 (0.5)	1.5 (0.9)	0.321
WBC count (cu/mm) x 1000	16.0 (17.8)	16.9 (12.3)	15.7 (17.8)	0.756
Hemoglobin (g/dL)	9.2 (1.5)	9.1 (1.1)	9.4 (2.0)	0.710
Platelets (x109/L)	9.7 (8.6)	9.0 (7.9)	10.2 (10.9)	0.535
Sodium (mEq/L)	143 (18)	147 (20)	143 (11)	0.456
Potassium (mEq/L)	3.2 (1.8)	3.2 (2.0)	3.6 (1.5)	0.926
Albumin (g/L)	2.7 (0.7)	2.8 (0.2)	2.7 (1.1)	1.000
Lactate (mmol/L)	79.4 (48.9)	83.2 (75.2)	75.3 (15.2)	0.710
PaO2/FiO2	384 (235)	187 (411)	395 (99)	0.193
AaDO2	237 (163)	388 (382)	235 (87)	0.172
APACHE II score	23 (10)	26 (10)	23 (8)	0.153
SOFA score	10 (5)	11 (5)	9 (2)	0.026
Acute kidney injury, n (%)	18 (78.3)	8 (80)	10 (76.9)	1.000
KDIGO criteria (Stage 0/1/2/3)	5/10/4/4	2/4/3/1	3/6/1/3	0.572
Renal replacement therapy, n (%)	10 (43.5)	4 (40)	6 (46.2)	1.000

Continuous data were presented median (interquartile);

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IABP, intraaortic balloon pumping; VT, ventricular tachycardia; MAP, mean arterial pressure; SCr, serum creatinine; WBC, white blood cell; PaO2, partial pressure of oxygen; FiO2, fraction of inspired oxygen; AaDO2, alveolar-arterial oxygen tension difference; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; KDIGO, kidney disease improving global outcomes.

Table 2. Patients' endothelial biomarkers in the first 3 days

Biomarker	All Patients (*n* = 23)	Non-Survivors (*n* = 10)	Survivors (*n* = 13)	*P* value
Thrombomodulin (ng/mL)				
Day 0	5.9 (2.4)	6.3 (1.9)	5.6 (1.8)	0.420
Day 1	6.3 (1.9)	6.0 (1.9)	6.7 (1.6)	0.535
Day 2	7.5 (2.7)	6.8 (3.0)	7.5 (2.2)	0.215
Angiopoietin-1 (ng/mL)				
Day 0	29.0 (16.1)	30.8 (13.0)	22.1 (18.7)	0.203
Day 1	24.9 (17.1)	24.2 (8.8)	26.2 (15.8)	0.107
Day 2	20.7 (13.8)	20.1 (6.6)	22.2 (9.5)	0.172
Angiopoietin-2 (ng/mL)				
Day 0	19.2 (24.8)	24.4 (58.2)	15.7 (23.2)	0.035
Day 1	24.7 (35.3)	25.6 (29.0)	17.7 (26.6)	0.137
Day 2	22.7 (15.4)	23.7 (14.7)	20.3 (9.2)	0.577
VEGF (pg/mL)				
Day 0	8.5 (13.7)	15.3 (32.4)	7.9 (2.1)	0.071
Day 1	33.0 (65.0)	24.2 (37.6)	35.6 (58.1)	0.438
Day 2	62.1 (119.2)	24.2 (33.9)	119.9 (105.8)	0.005
Ang-2/Ang-1 ratio				
Day 0	0.82 (1.82)	0.90 (1.53)	0.71 (2.20)	0.470
Day 1	1.01 (1.74)	1.01 (3.67)	0.79 (1.95)	0.342
Day 2	1.09 (0.64)	1.10 (0.21)	1.02 (1.54)	0.763

Data were presented median (interquartile); VEGF, vascular endothelial growth factor; Ang, angiopoietin.

Figures

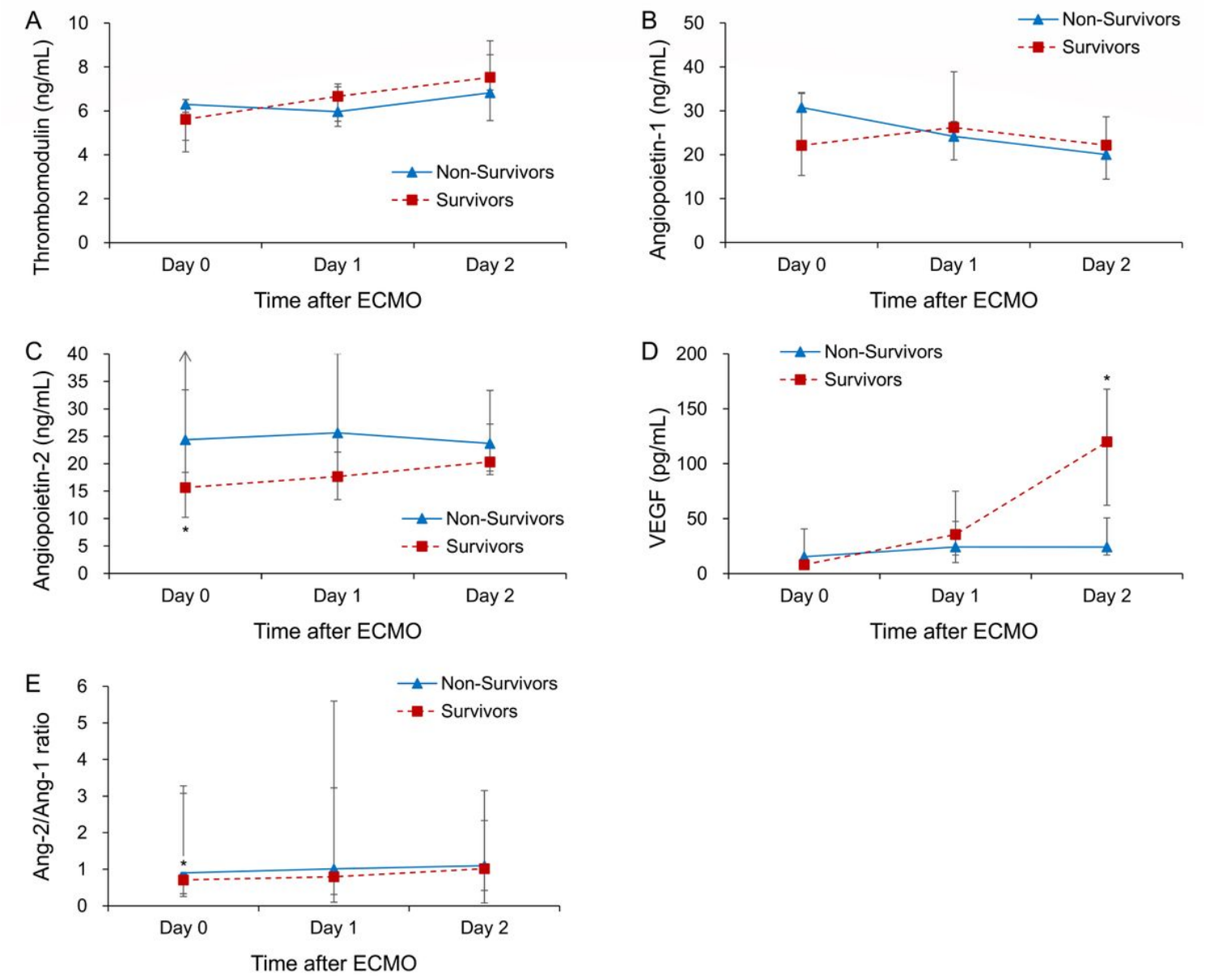


Figure 1

Median values (lower limit of bar represents 25th percentile and upper limit of bar represents 75th percentile) of endothelial biomarkers in the non-survivors and survivors. * indicates $P < 0.05$ between non-survivors and survivors. ECMO, extracorporeal membrane oxygenation; VEGF, vascular endothelial growth factor.

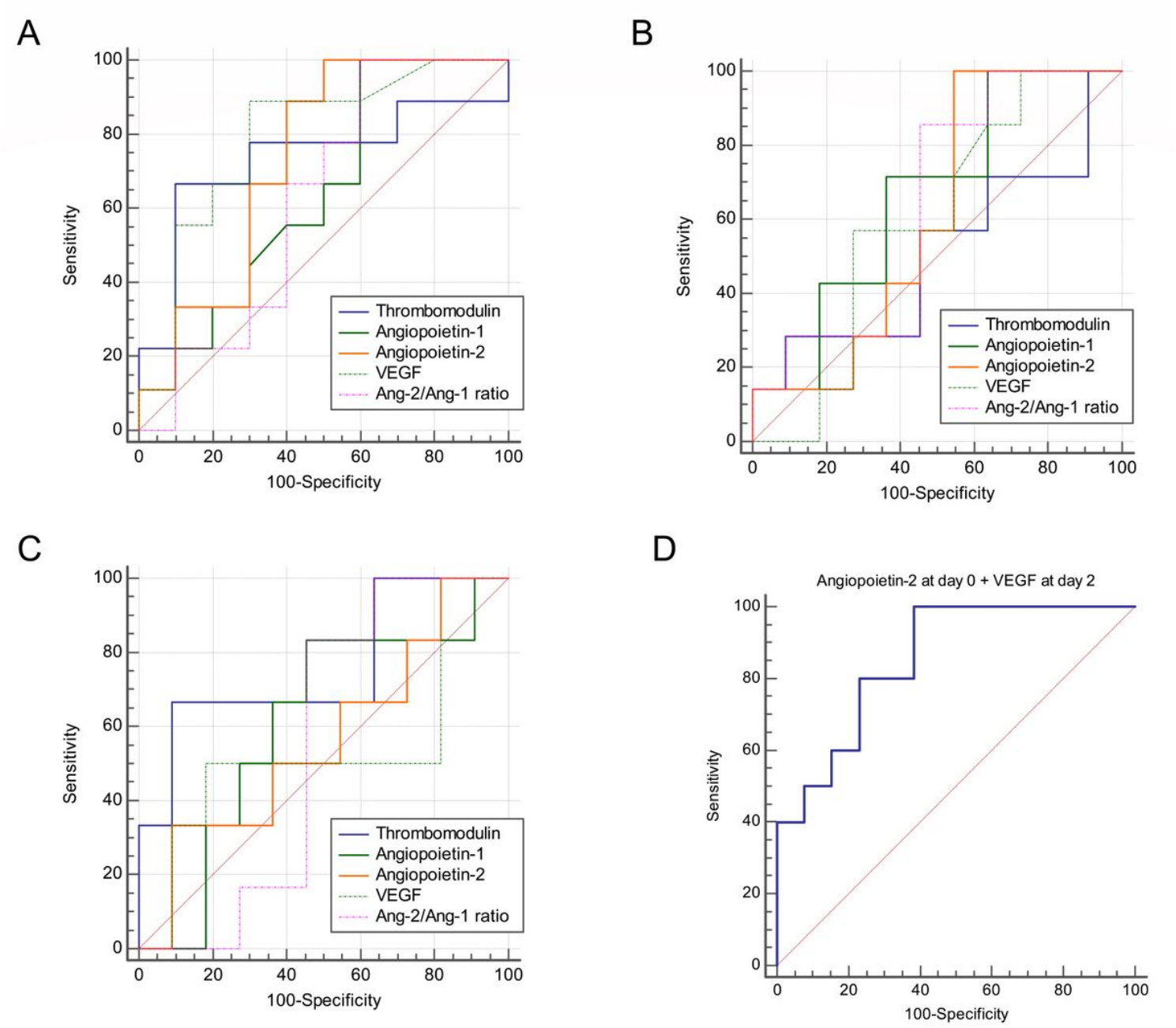


Figure 2

Receiver operating characteristic curves (ROC) of discriminating mortality for (A) at day 0, (B) at day 1, (C) at day 2, and (D) combination of angiopoietin-2 at day 0 and VEGF at day 2. The area under ROC of angiopoietin-2 at day 0 + VEGF at day 2 was 0.854 (95% confidence interval: 0.645 to 0.965). VEGF, vascular endothelial growth factor; Ang, angiopoietin.