Clinical factors associated with successful venoarterial extracorporeal membrane oxygenation weaning: A single-center retrospective cohort study

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Abstract

***Objective*: To investigate and identify factors associated with successful venoarterial extracorporeal membrane oxygenation (VA-ECMO) while initiating, during, and before VA-ECMO weaning.**

***Design*: A single-center retrospective cohort study.**

***Setting*: A 510-bed tertiary hospital.**

***Patients and participants*: We consecutively enrolled 51 patients treated with VA-ECMO at our center between April 2010 and March 2016. Patients who received venovenous ECMO, backup VA-ECMO, and post-cardiotomy VA-ECMO were excluded.**

***Interventions*: VA-ECMO for cardiopulmonary arrest (CPA) or cardiogenic shock. Successful VA-ECMO weaning was defined as survival for more than 24 hours after discontinuation without requiring reintroduction.**

***Measurements and results*: Factors associated with VA-ECMO were collected at initiation, during, and before weaning. These were then compared between the successful and unsuccessful VA-ECMO weaning groups. We included 41 patients after 10 exclusions; 17 (41.5%) and 24 (58.5%) were weaned successfully and unsuccessfully, respectively. Among the factors measured at initiation and prior to weaning, higher blood pressure (BP) and pH and lower serum potassium and creatinine were associated with successful weaning. In addition, lower white blood cell counts at initiation, lower lactate levels, and higher pulse pressure before weaning were also associated with successful weaning. Moreover, among the factors analyzed at initiation, successful weaning was associated with CPA during catheterization, percutaneous coronary intervention (PCI), and a shorter CPA-ECMO time. Among the factors studied before weaning, patients successfully weaned from VA-ECMO had lower Kidney Disease: Improving Global Outcomes (KDIGO) urine output stages and intra-aortic balloon pump (IABP) use.**

***Conclusion*: BP and anaerobic condition-related factors, such as pH or lactate, can be important predictors for successful VA-ECMO weaning. Other clinical factors may also influence VA-ECMO weaning, such as CPA during catheterization, PCI performance, IABP use, the CPA-ECMO time, and renal function markers such as the KDIGO urine output stage and serum creatine and potassium levels.**

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Introduction

The general interest in venoarterial extracorporeal membrane oxygenation (VA-ECMO) has increased as the importance of VA-ECMO becomes more apparent. Consequently, evidence continues to grow regarding the indications for VA-ECMO, in-hospital and long-term prognoses, and neurological outcomes after VA-ECMO weaning. (1) However, clinical factors associated with successful VA-ECMO weaning have yet to be fully elucidated. Lüsebrink et al. suggested separately evaluating VA-ECMO weaning and survival after VA-ECMO withdrawal. (2) Therefore, this study evaluated the clinical factors associated with successful VA-ECMO weaning in our institution.

Materials and methods

Study design and population

This single-center retrospective cohort study evaluated the clinical factors associated with successful VA-ECMO weaning at the National Hospital Organization Yokohama Medical Center in Japan. We enrolled consecutive patients treated with VA-ECMO between April 2010 and March 2016. Patients who received venovenous ECMO, VA-ECMO for backup percutaneous coronary intervention (PCI), and those who underwent open heart cardiovascular surgery were excluded (**Figure 1**). The medical team was responsible for deciding the indications for VA-ECMO, managing the patients on VA-ECMO, and deciding when to wean. The study outcome was a successful VA-ECMO weaning. Patients were followed up until discharge.

Data collection

We collected the following clinical data from medical records: (1) at initiation and prior to VA-ECMO weaning: systolic and diastolic blood pressure (BP); mean BP; pulse pressure; pH; white blood cell (WBC) and platelet counts; and lactate, brain natriuretic peptide, hemoglobin, total bilirubin, serum potassium, and creatinine levels; (2) at VA-ECMO initiation: age, sex, height, weight, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, cardiogenic cardiopulmonary arrest (CPA), out-of-hospital cardiac arrest, in-hospital cardiac arrest, CPA during catheterization, PCI performance, cardiopulmonary resuscitation (CPR), bystander CPR, witnessed CPA, the return of spontaneous circulation, and CPA-ECMO time; (3) during or prior to VA-ECMO weaning: VA-ECMO duration, intra-aortic balloon pump (IABP) usage, and continuous hemodialysis filtration use; acute kidney injury (AKI), the maximum Kidney Disease: Improving Global Outcomes (KDIGO) classification, maximum KDIGO serum creatinine stage, maximum KDIGO urine output stage, bacteremia, serious bleeding, and serious limb ischemia.

Definitions

Successful VA-ECMO weaning was defined as survival for more than 24 hours after VA-ECMO withdrawal without requiring reintroduction. Serious bleeding was defined as a Bleeding Academic Research Consortium type 3-5. (3) Serious limb ischemia was defined as VA-ECMO canulation-induced limb ischemia requiring withdrawal. Good and poor neurological outcomes were defined as Cerebral Performance Category (CPC) classifications 1-2 and 3-5, respectively. (4)

Statistical analyses

For data comparisons, we divided patients into two groups (successful and unsuccessful VA-ECMO weaning). The student's t-test was used for parametric continuous variables, the Mann-Whitney test for non-parametric continuous variables, and the χ^2 test for categorical variables. Continuous variables were presented as means±standard deviations. Categorical variables were presented as numbers and percentages. Missing variables were treated as missing variables without imputation. A p-value <0.05 was considered statistically significant. Patient prognoses were based on the in-hospital survival rate at discharge among successfully weaned patients. Neurological outcomes were determined based on the rate of good and poor neurological outcomes at discharge among successfully weaned patients. JMP software for Windows version 16.2 (SAS Institute, Cary, NC) was used for the statistical analyses.

Results

Study population

We registered 51 patients and included 41 in the analyses. Ten patients were excluded due to the usage of venovenous ECMO (n=1), VA-ECMO for backup PCI (n=1), and open-heart cardiovascular surgery (n=8). Overall, 17 (41.5%) and 24 (58.5%) patients were successfully and unsuccessfully weaned from VA-ECMO, respectively (**Figure 1**).

Clinical factors both at initiation and prior to VA-ECMO weaning

Systolic BP (95.1±40.7 mmHg vs 62.6±54.1 mmHg, p=0.0429), diastolic BP (61.5±28.7 mmHg vs 35.7±34.6 mmHg, p=0.0161), mean BP (72.7±32.2 mmHg vs 44.7±40.5 mmHg, p=0.0229), WBC count (9129±3810/mm^3 vs 12708±6207/mm^3, p=0.0415), serum potassium (4.3±0.6 mmol/l vs 5.0±1.1 mmol/l, p=0.0315), and

pH (7.31±0.21 vs 7.09±0.25, p=0.0177) levels at VA-ECMO initiation significantly differed between the two groups. Systolic BP (122.5±24.5 mmHg vs 79.1±41.9 mmHg, p=0.0005), diastolic BP (62.4±17.0 mmHg vs 43.9±26.2 mmHg, p=0.0149), mean BP (82.4±18.0 mmHg vs 55.6±30.7 mmHg, p=0.0026), pulse pressure (60.1±17.6 mmHg vs 35.2±21.0 mmHg, p=0.0003), creatinine levels (1.27±0.78 mg/dl vs 2.25±1.36 mg/dl, p=0.0237), pH (7.44±0.08 vs 7.11±0.20, p<0.0001), and lactate (1.9±1.2 mmol/l vs 13.1±7.4 mmol/l, p<0.0001) levels before weaning significantly differed between the two groups (**Table 1**).

Differences in clinical factors at VA-ECMO initiation between the two groups

CPA during catheterization (9/17 [52.9%] vs 5/24 [20.8%], p=0.0327), PCI performance (12/17 [70.6%] vs 9/24 [37.5%], p=0.0368), and the CPA-ECMO time (26.8±21.0 minutes vs 54.5±30.3 minutes, p=0.0024) significantly differed between the two groups. All other factors at VA-ECMO initiation did not differ between the two groups (**Table 2**).

Differences in clinical factors during or before VA-ECMO weaning between patients successfully and unsuccessfully weaned

IABP usage (16/17 [94.1%] vs 15/24 [62.5%], p=0.0202) and the KDIGO urine output stage (0.9±1.4 vs 2.0±1.4, p=0.0250) significantly differed between the two groups. All other factors during VA-ECMO did not differ between the two groups (**Table 3**).

In-hospital survival and neurological outcomes in successfully weaned patients

Of the 17 successfully weaned patients, 13 (76.5%) survived and were discharged. Unfortunately, four patients died, one due to a cardiovascular event and the remaining three from other causes (two from infectious causes and one from multiple system organ failures) (**Figures 2 A, B**). Of the 13 surviving patients, 9 (69.2%) and 4 (30.8%) had good neurological outcomes (CPC classification 1 or 2) and poor prognoses (CPC classification 3 or 4), respectively (**Figure 3**).

Discussion

We observed clinical factors that significantly differed between patients successfully and unsuccessfully weaned from VA-ECMO.

First, we assessed factors measured at initiation and before VA-ECMO weaning. In our study, the pH at initiation and before weaning and lactate levels before weaning were associated with successful weaning, as previously reported. (5-8) Ellouze et al. demonstrated that the veno-arterial difference in the PCO2 (Da-vCO2), a direct indicator of tissue anaerobic condition, (9) could be a clinical factor related to successful VA-ECMO weaning and 72-hour survival. (10) Our study findings and previous reports supported the importance of anaerobic-related factors (e.g., pH, lactate, and the Da-vCO2) in VA-ECMO weaning. (5-8,10) Similarly, BP values both at initiation and before weaning and pulse pressure before weaning were found to be significant factors in our study. Interestingly, previous studies have demonstrated a relationship between BP or pulse pressure only in the stages before and after successful weaning. (11-13) These findings highlight the importance of BP and related pulse pressure, especially before VA-ECMO weaning.

Regarding laboratory investigations, serum creatinine and potassium both at initiation and before weaning were found to be significant factors in our study, suggesting the importance of renal function, as reported previously. (6) On the other hand, although a lower WBC count at initiation was found in the successful weaning group in our study, we were unable to find similar results in the literature. Therefore, we considered that laboratory markers, except for markers of renal function, may have limited importance. However, further evaluation was needed to validate the use of laboratory markers as prognostic indicators.

Second, we assessed factors significantly different between the two groups at VA-ECMO initiation. In our study, the factors that significantly differed were CPA during catheterization, PCI performance, and the CPA-ECMO time. Although the CPA-ECMO time and PCI performance on VA-ECMO weaning have been well studied as predictive factors for survival or neurological outcomes, (14-16) the same cannot be said of their predictive ability for successful VA-ECMO weaning. A short CPA-ECMO time and revascularization by PCI are important for faster cardiac recovery. CPA during catheterization is the best approach to combine short CPA-ECMO time and PCI performance; hence, the significance of this factor in this study is consistent. Therefore, we considered that these factors contributed to a successful VA-ECMO weaning. On the other hand, age and CPR performance did not differ significantly between the successful and unsuccessful VA-ECMO groups in our study. There are conflicting reports regarding the influence of age on VA-ECMO weaning. (5,17) Concerning CPR, an episode of cardiac arrest or receiving CPR or ECPR were associated with unsuccessful VA-ECMO

weaning. (5,18) In our study, CPR was more frequent in the unsuccessful weaning group, although the difference was not statistically significant. Since our results could be due to a small sample size, the effects of age, CPA occurrence, or CPR on VA-ECMO weaning require further investigation.

Finally, we assessed the clinical factors measured during VA-ECMO or before VA-ECMO weaning. In our study, the factors during VA-ECMO that significantly differed between the successful and unsuccessful VA-ECMO weaning groups were IABP usage and the KDIGO urine output stage. Regarding IABP usage, there are several reports that demonstrate a positive relationship with successful weaning. (19-21) Furthermore, a meta-analysis of IABP in VA-ECMO reported that IABP was associated with successful VA-ECMO weaning but was not related to in-hospital survival. (19) These findings and our study suggested that IABP use may be associated with successful weaning. In addition, AKI indicators, such as the risk, injury, failure, loss, ESRD [end-stage renal disease] (RIFLE) score, and its association with VA-ECMO weaning, have been reported. (7) Interestingly, among the AKI-related factors in our study, only the KDIGO urine output stage and creatinine levels before VA-ECMO weaning significantly differed between the successful and unsuccessful weaning groups. Surprisingly, continuous hemodialysis filtration use, AKI occurrence, and the KDIGO stage did not differ between the two groups. Together, these results suggest that AKI itself has a weaker association with VA-ECMO weaning than urine output in the subacute phase and the serum creatinine during AKI recovery.

Limitations

This was a single-center, retrospective cohort study without statistical power calculations. Consequently, the limitations are: (1) there was an institutional and patient selection bias; (2) we had a small sample size and no sample size calculation; (3) there was an attending doctor's bias on heterogeneous data acquisition and ECMO management; (4) there was no confounding bias assessment; (5) the study was performed before the coronavirus disease 2019 pandemic; and (6) there was no assessment of echocardiographic factors. Well-designed studies are needed to identify the clinical factors associated with successful ECMO weaning definitively.

Conclusions

Among the clinical factors investigated, BP and anaerobic-related factors, such as pH or lactate levels, may be important clinical factors for successful VA-ECMO weaning. In addition, other factors may also be associated with successful VA-ECMO weaning and are interesting targets for future studies, such as CPA during catheterization, PCI performance, the CPA-ECMO time, IABP use, the KDIGO urine output stage, and the serum creatine and potassium levels.

Declarations

Conflicts of interest

The authors declare there were no conflicts of interest.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the National Hospital Organization Yokohama Medical Center (reference number 2020-14) and has been conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its subsequent amendments.

As this was a retrospective study, written informed consent was waived. This study was conducted using the opt-out method, in which the study's information was announced on the hospital homepage, and all participants or their guardians were allowed to decline the use of their medical records.

Data availability

The data that support the findings of this study were available from the corresponding author upon reasonable request.

Table 1. Successful and unsuccessful VA-ECMO weaning based on patient clinical factors both at initiation and before VA-ECMO weaning

	Successful (n=17)	Unsuccessful (n=24)	p-value
BP systole at induction (mmHg)	95.1±40.7	62.6±54.1	0.0429
BP systole before weaning (mmHg)	122.5±24.5	79.1±41.9	0.0005
BP diastole at induction (mmHg)	61.5±28.7	35.7±34.6	0.0161
BP diastole before weaning (mmHg)	62.4±17.0	43.9±26.2	0.0149
BP mean at induction (mmHg)	72.7±32.2	44.7±40.5	0.0229
BP mean before weaning (mmHg)	82.4±18.0	55.6±30.7	0.0026
Pulse pressure at induction (mmHg)	33.6±17.2	26.9±24.2	0.3294
Pulse pressure before weaning (mmHg)	60.1±17.6	35.2±21.0	0.0003
pH at induction	7.31±0.21	7.09±0.25	0.0177
pH before weaning	7.44±0.08	7.11±0.20	<0.0001
Lactate at induction (mmol/l)	7.6±5.5	11.6±4.6	0.0808
Lactate before weaning (mmol/l)	1.9±1.2	13.1±7.4	<0.0001
Brain natriuretic peptide at induction (pg/ml)	510.6±522.6	464.0±539.0	0.8251
Brain natriuretic peptide before weaning (pg/ml)	311.1±173.9	423.7±127.6	0.6079
White blood cell count at induction (/mm^3)	9129±3810	12708±6207	0.0415
White blood cell count before weaning (/mm^3)	11118±5846	13970±6902	0.1768
Hemoglobin at induction (g/dl)	12.0±2.0	12.3±2.8	0.6375
Hemoglobin before weaning (g/dl)	10.7±2.0	9.8±3.5	0.3100
Platelet count at induction (x10^4/mm^3)	21.9±7.7	17.3±9.0	0.0924
Platelet count before weaning (x10^4/mm^3)	9.2±6.0	12.5±9.7	0.2164
Total bilirubin at induction (mg/dl)	0.7±0.4	0.9±1.1	0.4015
Total bilirubin before weaning (mg/dl)	3.2±3.2	5.9±7.5	0.2202
Potassium at induction (mmol/l)	4.3±0.6	5.0±1.1	0.0315
Potassium before weaning (mmol/l)	4.1±0.3	4.8±0.2	0.0394
Creatinine at induction (mg/dl)	0.99±0.36	1.43±0.65	0.0172
Creatinine before weaning (mg/dl)	1.27±0.78	2.25±1.36	0.0237

Legend: VA-ECMO=venoarterial extracorporeal membrane oxygenation; BP=blood pressure. Statistics are presented as mean±standard deviation.

Table 2. Successful and unsuccessful VA-ECMO weaning based on patient clinical factors at VA-ECMO initiation

	Successful (n=17)	Unsuccessful (n=24)	p-value
Age (years)	70.6±13.2	68.0±14.5	0.5486
Male, n (%)	12/17 (70.6%)	17/24 (70.8%)	0.9864
Height (cm)	161.3±8.3	161.1±7.1	0.9344
Weight (kg)	60.5±17.1	69.3±17.8	0.1381
Hypertension, n (%)	11/17 (64.7%)	11/24 (45.8%)	0.2325
Dyslipidemia, n (%)	6/17 (35.3%)	4/24 (16.7%)	0.1712
Diabetes mellitus, n (%)	7/17 (41.2%)	8/24 (33.3%)	0.6075
CKD, n (%)	5/17 (29.4%)	4/23 (17.4%)	0.3681
Cardiogenic CPA, n (%)	14/17 (82.4%)	18/24 (75.0%)	0.5752
Out-of-hospital cardiac arrest, n (%)	1/17 (5.9%)	7/24 (29.2%)	0.0638
In-hospital cardiac arrest, n (%)	8/17 (47.1%)	13/24 (54.2%)	0.6537
CPA during catheterization, n (%)	9/17 (52.9%)	5/24 (20.8%)	0.0327
CPR, n (%)	14/17 (82.4%)	22/24 (91.7%)	0.3693
Bystander CPR, n (%)	13/17 (76.5%)	20/24 (83.3%)	0.5849
Witnessed CPA, n (%)	14/17 (82.4%)	19/24 (79.2%)	0.7998
Return of spontaneous circulation, n (%)	2/17 (11.8%)	6/24 (25.0%)	0.2921
Percutaneous coronary intervention, n (%)	12/17 (70.6%)	9/24 (37.5%)	0.0368
CPA-ECMO time (min)	26.8±21.0	54.5±30.3	0.0024

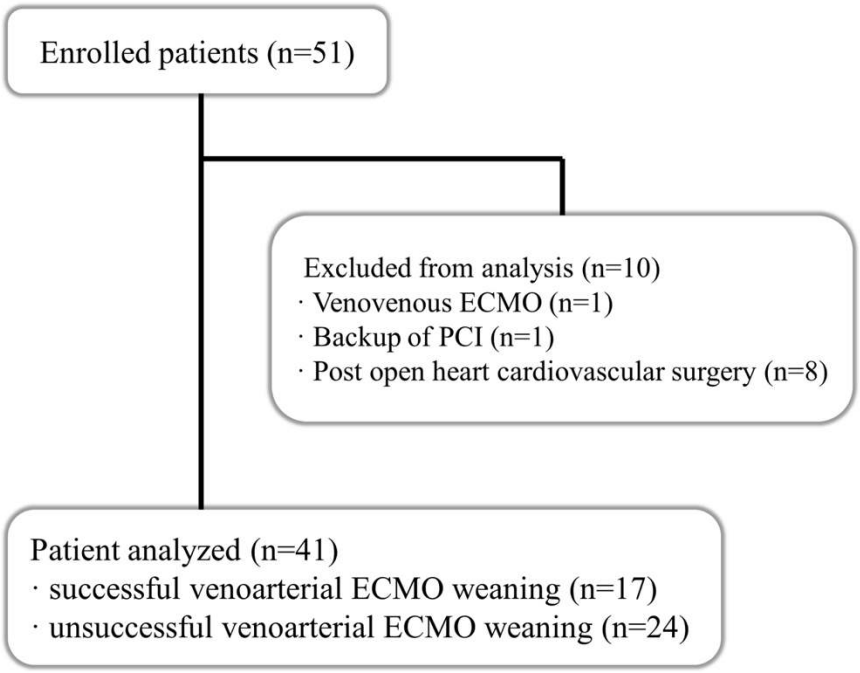
Legend: VA-ECMO=venoarterial extracorporeal membrane oxygenation; CKD=chronic kidney disease; CPA=cardiopulmonary arrest; CPR=cardiopulmonary resuscitation. Statistics are presented as mean±standard deviation for continuous variables and as numbers and percentages for categorical variables. Since data on CKD was absent in one participant of the unsuccessful group, the statistic was calculated with the CKD parameter of 23 in the unsuccessful group.

Table 3. Successful and unsuccessful VA-ECMO weaning based on patient characteristics during the process of VA-ECMO or prior to weaning

	Successful (n=17)	Unsuccessful (n=24)	p-value
ECMO duration (days)	3.4±2.1	3.5±4.1	0.8941
Bacteremia during VA-ECMO, n (%)	1/17 (5.9%)	1/24 (4.2%)	0.8016
Serious bleeding during VA-ECMO, n (%)	3/17 (17.7%)	6/24 (25.0%)	0.5752
Serious limb ischemia during VA-ECMO, n (%)	2/17 (11.8%)	1/24 (4.2%)	0.3574
Intra-aortic balloon pump usage, n (%)	16/17 (94.1%)	15/24 (62.5%)	0.0202
Continuous hemodialysis filtration, n (%)	5/17 (29.4%)	7/24 (29.2%)	0.9864
Acute kidney injury during VA-ECMO, n (%)	6/17 (35.3%)	6/24 (25.0%)	0.4754
KDIGO classification	1.4±1.3	2.1±1.3	0.0882
KDIGO serum creatinine staging	1.2±1.4	1.7±1.4	0.3369
KDIGO urine output staging	0.9±1.4	2.0±1.4	0.0250

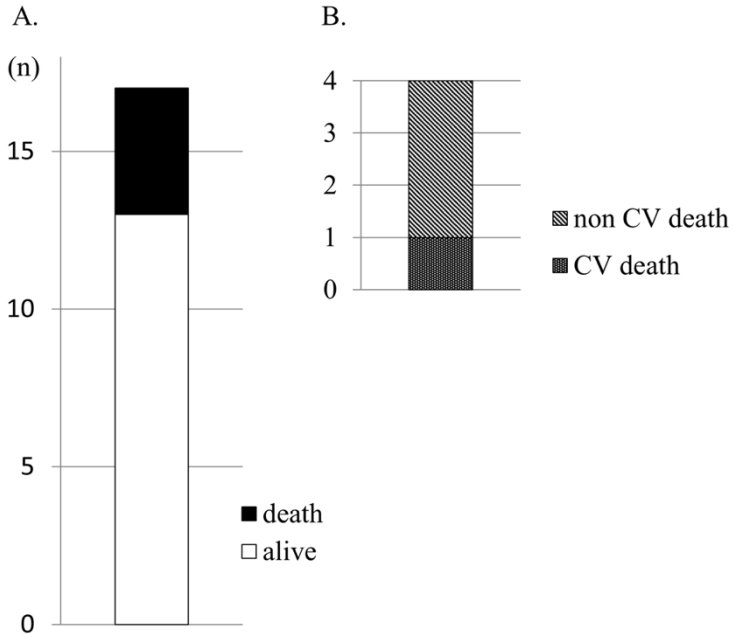
Legend: VA-ECMO=venoarterial extracorporeal membrane oxygenation; KDIGO=Kidney Disease: Improving Global Outcomes. Statistics are presented as mean±standard deviation for continuous variables and as numbers and percentages for categorical variables.

Figure 1. Study flow chart



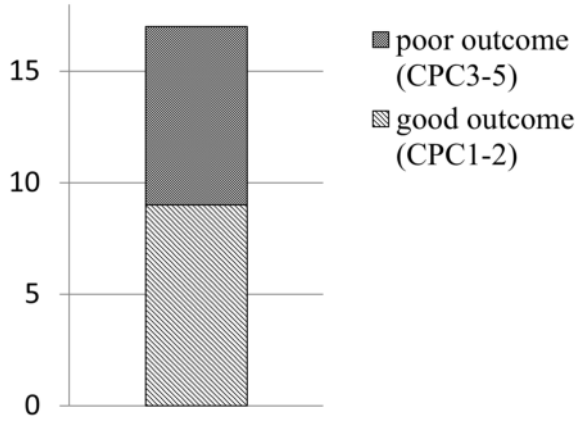
Legend: ECMO=extracorporeal membrane oxygenation; PCI=percutaneous coronary intervention.

Figure 2. In-hospital survival in patients with successful VA-ECMO weaning



Legend: VA-ECMO=venoarterial extracorporeal membrane oxygenation; CV=cardiovascular.
A. In-hospital survival.
B. Cause of death.

Figure 3. The neurological outcomes at discharge in patients with successful VA-ECMO weaning



Legend: VA-ECMO=venoarterial extracorporeal membrane oxygenation; CPC=cerebral performance category.

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