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Survival After Endocarditis Surgery Needing Venoarterial Extracorporeal Membrane Oxygenation Support: Results from the Netherlands Heart Registration

Running title: VA-ECMO Support after Endocarditis Surgery

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ABSTRACT

The incidence of venoarterial extracorporeal membrane oxygenation (VA-ECMO) support after cardiac surgery ranges from 0.4% - 3.7%, with in-hospital mortality rates reported at 60%. While the incidence of VA-ECMO after endocarditis (IE) surgery is unknown, these patients may face an even greater mortality risk due to additional IE-related complications. The primary objective of this study is to investigate the incidence and mortality rates of postoperative VA-ECMO following endocarditis surgery. The secondary objective is to compare clinical outcomes and to identify factors associated with in-hospital mortality in patients requiring and not requiring VA-ECMO support. Data were retrieved from the Netherlands Heart Registration. Of 3468 IE surgeries performed between 2013 and 2022, 49 patients (1.4%) received postoperative VA-ECMO. The in-hospital mortality rate was 49% and the one-year mortality rate was 60.9%. As expected, this was significantly higher compared to patients not requiring VA-ECMO support (49.0% versus 9.8% and 60.9% versus 15.2% respectively; $p < 0.001$). At baseline, VA-ECMO patients had statistically higher rates of previous valve surgery, peripheral vascular disease and pulmonary hypertension, as well as lower renal and left ventricular functions compared to than patients not requiring VA-ECMO support. In addition, VA-ECMO patients more frequently underwent emergency surgeries and required aortic root surgery and coronary artery bypass grafting more often. While several comorbidities were associated with in-hospital mortality in patients not requiring VA-ECMO, no such associations were observed in VA-ECMO patients. In conclusion, while the incidence of VA-ECMO support after IE surgery is low, it comes with high mortality rates. However, mortality rates do not seem to differ from those reported for non-IE postcardiotomy VA-ECMO patients in current literature, and mortality after VA-ECMO support remains difficult to predict. Based on our data, postcardiotomy VA-ECMO should not be withheld from IE patients because of high-anticipated mortality risk.

KEYWORDS

Infective endocarditis; extracorporeal membrane oxygenation; cardiac surgery

INTRODUCTION

The incidence of cardiogenic shock after cardiac surgery is approximately 3-9% [1]. Managing postcardiotomy cardiogenic shock is challenging due to the complexities of postoperative fluid management and the administration of inotropic agents and vasopressors. In cases where patients fail to wean from cardiopulmonary bypass, venoarterial extracorporeal membrane oxygenation (VA-ECMO) therapy may be indicated [2]. The incidence of postcardiotomy VA-ECMO is estimated to range from 0.5% to 3.7%, with mortality rates reported as high as 60% [3].

It is conceivable that the incidence as well as mortality rates of postoperative VA-ECMO are increased following endocarditis surgery since infective endocarditis (IE) patients often suffer from preoperative heart failure and systemic complications, with a higher risk of postoperative cardiogenic shock. Moreover, postoperative vasoplegic shock syndrome has been reported in up to a third of patients undergoing cardiac surgery for IE [4].

Moreover IE surgeries frequently involve complex anatomical repairs, with prolonged aortic cross-clamp and cardiopulmonary bypass times, further heightening the risk of failure to wean from cardiopulmonary bypass and subsequent VA-ECMO initiation [5].

The current ESC guideline suggests poor outcomes after VA-ECMO therapy following IE surgery. However, it remains questionable whether these outcomes significantly differ from non-IE postcardiotomy ECMO patients because data is limited to small single center case series that reported mortality rates up to 77% [6,7]. In daily practice, VA-ECMO is often denied to IE patients because of high-anticipated mortality rates. Therefore, the aim of this study is to investigate the incidence and mortality rates of postoperative VA-ECMO following endocarditis surgery, based on a large nationwide prospective cohort. The secondary objectives was to compare clinical outcomes and to identify factors associated with in-hospital mortality in patients requiring and not requiring VA-ECMO support.

METHODS

We used data from the Netherlands Heart Registration (NHR) [8]. The NHR is a national prospective registry collecting patient characteristics, procedural data and clinical outcomes of all cardiac surgeries and interventions in the Netherlands. Data is collected by the 15 heart centers (8 secondary hospitals, 7 university hospitals). For this study, all IE patients who underwent cardiac surgery in the Netherlands between 2013 and 2022 were retrieved from the NHR database and the incidence of postoperative VA-ECMO support (initiated intraoperatively) was assessed. Cases were excluded if the in-hospital mortality was unknown. One-year survival was displayed with Kaplan Meier curves. Baseline characteristics were stratified by both ECMO and in-hospital mortality status. Clinical outcomes included mortality rates up to one year, vascular complications and renal failure. Analyses were performed in R studio, version 4.3.2. Normally distributed variables were reported as mean (standard deviation (SD)) and non-normally distributed variables are displayed as median (interquartile range (IQR)). Baseline characteristics were displayed as a percentage of the total cohort, in which missing values were excluded from the calculation. To assess differences in categorical variables, chi-squared tests were performed. For assessing differences in continuous data, independent 2-tailed Student's t-tests and Mann– Whitney U tests were performed for normally and non-normally distributed variables. Since this study uses de-identified data, the Dutch Medical Ethics Review Committee waived the need for informed consent.

RESULTS

INCIDENCE AND MORTALITY OF VA-ECMO SUPPORT AFTER ENDOCARDITIS SURGERY

Between 2013 and 2022, 3468 IE valve surgeries were performed in 3338 patients. In-hospital mortality status was available for all patients. Postoperative VA-ECMO support was initiated in 49 patients (1.4%). One patient was lost to follow-up after in-hospital survival. The median age of the total cohort was 64.0 years (IQR 54.0– 71.0) and 76.1% was male (n = 2540). 37.5% of cases had a history of cardiac surgery (n = 1299) of which 1125 cases had previous valvular surgery. The in-hospital mortality rate of ECMO patients was 49.0% and the one-year mortality rate was 60.9%.

COMPARISON OF CLINICAL OUTCOMES BETWEEN ECMO AND NON-ECMO ENDOCARDITIS PATIENTS

The in-hospital mortality rate was significantly higher in IE patients needing ECMO support than in patients not needing ECMO support (49.0% versus 9.8%; $p < 0.001$). In ECMO patients, 83.3% of deaths occurred in the intensive care unit (n = 20) and one (2.1%) in the operating room. The location of mortality was unknown for three ECMO patients. The one-year mortality rate was also significantly higher in ECMO patients than in non-ECMO patients (60.9% versus 15.2%; log rank $p < 0.001$). The Kaplan Meier curves for one-year survival for patients with and without ECMO support are presented in figure 1. During admission, ECMO patients experienced significantly higher rates of renal failure and vascular complications than non-ECMO patients (55.3% versus 11.9% and 12.5% versus 0.6% respectively; $p < 0.001$). Moreover, rethoracotomy for cardiac tamponade was performed more frequently in ECMO patients than in non-ECMO patients (38.1% versus 12.7%; $p < 0.001$). There was no difference in postoperative stroke between ECMO and non-ECMO patients (4.3% versus 3.8%; $p = 0.834$).

FACTORS ASSOCIATED WITH IN-HOSPITAL MORTALITY

In patients not requiring ECMO support, several factors were associated with in-hospital mortality, such as older age, female sex, a history of cardiac surgery and the presence of several comorbidities such as chronic pulmonary disease, peripheral vascular disease, and impaired left ventricular- and renal functions. In contrast, no baseline characteristics or comorbidities were associated with in-hospital mortality in patients receiving ECMO support. In addition, the performed surgical treatments as well as AoX and CPB times did not statistically differ between survivors and non-survivors in the ECMO group. Baseline characteristics, surgical treatments and clinical outcomes according to survival status for both ECMO and non-ECMO cases are presented in table 1.

BASELINE CHARACTERISTICS ASSOCIATED WITH VA-ECMO SUPPORT

Preoperatively, IE patients who eventually received ECMO support had significantly more comorbid conditions in comparison to those not requiring ECMO support. These included poorer renal function (median estimated glomerular filtration rate (eGFR) 57.0 ml/min/1.73m^2 (IQR 38.3 – 69.1) versus 70.2 ml/min/1.73m^2 (IQR 49.0 – 90.3) in non-ECMO patients; $p < 0.001$), a higher EuroSCORE II (median 32.0 (IQR 20.8 – 48.5) versus 8.3 (IQR 3.5 – 19.4) in non-ECMO patients; $p < 0.001$), impaired left ventricular function (61.2% versus 34.0%; $p < 0.001$), pulmonary hypertension (38.8 versus 16.3%; $p < 0.001$)) and peripheral vascular disease (18.4% versus 8.3%; $p < 0.001$). Moreover, patients eventually requiring ECMO support were more frequently in a critical preoperative state (40.8% versus 14.7%; $p < 0.001$), and required emergency surgery more often (30.6% versus 16.5%; $p < 0.027$) . Regarding surgical procedures, IE patients receiving ECMO support had a higher rate of previous cardiac surgeries (69.4% versus 37.0%; $p < 0.001$), and underwent aortic root surgery and concomitant coronary artery bypass grafting more often (61.2% versus 20.6%; $p < 0.001$ and 30.6% versus 10.5%; $p < 0.001$ respectively). Aortic cross clamp (AoX) and cardiopulmonary bypass (CPB) times were prolonged in patients subsequently receiving ECMO support (median AoX 207 minutes (IQR 128 – 284) versus 105 minutes (IQR 73 – 149); $p < 0.001$ and median CPB 373 minutes (IQR 273 – 446) versus 151 minutes (IQR 109 – 217); $p < 0.001$ respectively).

DISCUSSION

To date, this is the largest cohort study examining clinical outcomes following VA-ECMO after IE surgery. Between 2013 and 2022, 49 patients out of 3468 surgeries received VA-ECMO support following IE surgery, resulting in an incidence of 1.4%. We observed an in-hospital mortality rate after VA-ECMO support of 49.0%. Mortality rates stabilize three months after surgery and we observed a one-year mortality rate of 60.9%. While several factors seem associated with in-hospital mortality after IE surgery, no such associations were identified for patients requiring VA-ECMO support. These findings highlight the difficulty in predicting mortality after VA-ECMO support, as traditional risk factors fail to explain survival differences in this high-risk patient population.

Only one study including 13 patients previously examined clinical outcomes after VA-ECMO support following IE surgery, and reported an in-hospital mortality rate of 77% [6]. In that single center cohort, most patients underwent Bentall procedures, similar to our nationwide cohort in which 60.4% of patients underwent aortic root surgery with or without concomitant procedures. We believe this can be explained by prolonged aortic cross clamp and cardiopulmonary bypass times in these procedures; increasing the risk of postoperative cardiogenic shock. The current ESC guideline on infective endocarditis states that outcome after VA-ECMO following IE surgery is poor [7]. Although this statement is true, mortality rates do not seem to differ from non-IE postcardiotomy VA-ECMO patients based on the current literature [3]. We hypothesize that, although IE patients often experience systemic inflammatory reactions with a distributive shock component, generally prolonged preoperative antibiotic therapy inhibits these reactions. In our cohort, the majority of patients underwent urgent surgery (68.8%) (defined as procedures performed during the current hospital admission, but not within 24 hours), suggesting adequate preoperative antibiotic therapy. Unfortunately, preoperative antibiotic therapy is not registered in the NHR. Important to note is that ECMO therapy increases the volume of distribution, while drug clearance and half-lives may decrease. These alterations in pharmacokinetics require extensive drug monitoring since antibiotic therapy may become suboptimal or supratherapeutic, causing side effects [9].

STRENGTHS AND LIMITATIONS

The main strength of this study is the comprehensiveness of the nationwide, prospectively collected data provided by the NHR. The mandatory registration of postoperative VA-ECMO (initiated intraoperatively) and in-hospital mortality enabled accurate analyses of the incidence and survival after IE surgery requiring VA-ECMO support.

The first limitation of our study is that ECMO-specific data, such as the indication, duration of support and weaning protocols are not registered in the NHR. This prohibits gaining a deeper understanding of management strategies employed in this complex patient population. Secondly, the NHR does not include the cause of death. As a result, we cannot determine whether death

resulted from failure to wean from VA-ECMO or due to other causes after successful weaning. Lastly, IE-specific risk factors for postoperative VA-ECMO and in-hospital mortality could not be identified because they are currently not registered in the NHR.

CONCLUSION

VA-ECMO support after IE surgery is occasionally required and comes with high in-hospital mortality rates. However, mortality rates do not seem to differ from those reported for non-IE postcardiotomy VA-ECMO patients in current literature and mortality after VA-ECMO support seems difficult to predict. Based on our data, postcardiotomy VA-ECMO should not be withheld from IE patients because of high-anticipated mortality risk.

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None declared

CONFLICT OF INTEREST

The authors report no relationships that could be construed as a conflict of interest

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author and the Netherlands Heart Registration.

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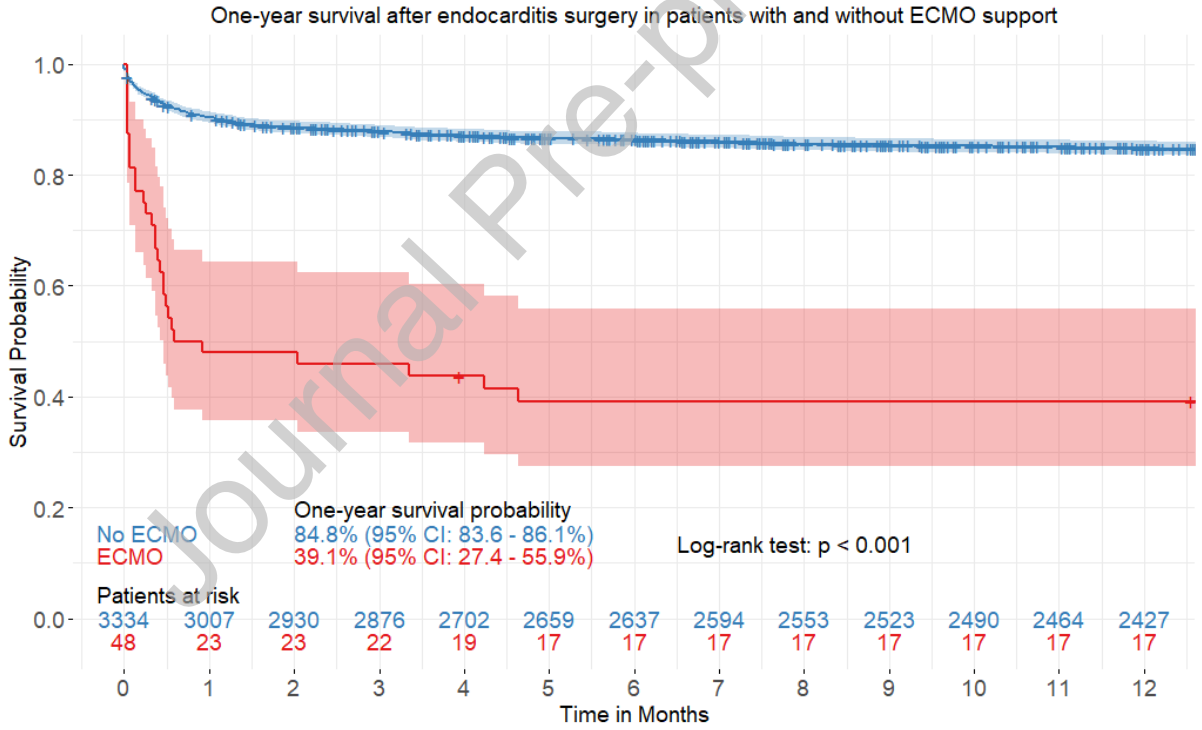

figure 1 is "One-year survival after endocarditis surgery in patients with and without ECMO support

	No ECMO (n = 3419)			ECMO (n = 49)		
Variables[a]	Survival (n = 3084)	In-hospital mortality (n = 335)	p-value	Survival (n = 25)	In-hospital mortality (n = 24)	p-value
Sex – male, n (%)	2382 (77.2)	(220 (65.7)	<0.001	20 (80.0)	19 (79.2)	0.942
Age (median, IQR)	64.0 (53.0 – 71.0)	69.0 (63.0 – 74.0)	<0.001	66.0 (52.0– 72.5)	66.0 (54.8 – 70.8)	0.944
Previous cardiac surgery, n (%)	1104 (35.8)	161 (48.1)	<0.001	19 (76.0)	15 (62.5)	0.305
Previous valve surgery, n (%)	949 (31.2)	145 (44.1)	<0.001	16 (66.7)	15 (62.5)	0.763
Chronic pulmonary disease, n (%)	275 (8.9)	60 (17.9)	<0.001	3 (12.0)	4 (16.7)	0.641
Peripheral vascular disease, n (%)	226 (7.3)	57 (17.0)	<0.001	4 (16.0)	5 (20.8)	0.662
Previous stroke, n (%)	432 (16.9)	61 (20.5)	0.124	3 (14.3)	4 (18.2)	0.729
Diabetes Mellitus, n (%)	433 (14.7)	84 (26.3)	<0.001	4 (16.7)	4 (16.7)	1.000
eGFR (median, IQR)	72.4 (51.4 – 92.0)	52.5 (33.4 – 70.7)	<0.001	57.4 (38.9 - 70.8)	55.5 (37.1 – 67.1)	0.483
Functional class			<0.001			0.150
NYHA I, n (%)	574 (22.5)	31 (12.0)		3 (14.3)	3 (16.7)	
NYHA II, n (%)	778 (30.4)	54 (20.8)		7 (33.3)	2 (11.1)	
NYHA III, n (%)	837 (32.7)	105 (40.5)		4 (19.0)	9 (50.0)	
NYHA IV, n (%)	367 (14.4)	69 (26.6)		7 (33.3)	4 (22.2)	
Left ventricular function			<0.001			0.760
Good (LVEF > 50%), n (%)	2069 (67.1)	186 (55.5)		11 (44.0)	8 (33.3)	
Moderate (LVEF 31 – 50%), n (%)	810 (26.3)	120 (35.8)		10 (40.0)	12 (50.0)	
Poor (LVEF 21 – 30%), n (%)	78 (2.5)	13 (3.9)		3 (12.0)	2 (8.3)	
Very poor (LVEF ≤ 20 %), n (%)	127 (4.1)	16 (4.8)		1 (4.0)	2 (8.3)	
Pulmonary hypertension			0.010			0.425
No pulmonary hypertension (PA systolic pressure ≤30 mmHg), n (%)	2602 (84.4)	261 (77.9)		16 (64.0)	14 (58.3)	
Moderate (PA systolic pressure 31 – 55 mmHg), n (%)	374 (12.1)	57 (17.0)		6 (24.0)	9 (37.5)	
Severe (PA systolic pressure >55 mmHg), n (%)	108 (3.5)	17 (5.1)		3 (12.0)	1 (4.2)	
Urgency			<0.001			0.349
Elective, n (%)	434 (14.8)	26 (8.0)				
Urgent, n (%)	2033 (69.1)	208 (64.2)		16 (66.7)	17 (70.8)	
Emergency, n (%)	440 (15.0)	80 (24.7)		6 (25.0)	7 (29.2)	
Salvage, n (%)	34 (1.2)	10 (3.1)		2 (8.3)	0 (0.0)	
Critical preoperative state, n (%)	387 (12.5)	114 (34.0)	<0.001	13 (52.0)	7 (29.2)	0.104
EuroSCORE II (median, IQR)	7.5 (3.2 – 17.1)	20.4 (9.8 – 39.8)	<0.001	35.1 (23.5 – 55.6)	27.3 (18.9 – 46.0)	0.307
Surgical treatment, n (%)						
Aortic root replacement +- concomitant procedures	608 (19.7)	95 (28.4)	<0.001	16 (64.0)	14 (58.3)	0.684
Isolated aortic valve replacement	883 (28.6)	51 (15.2)	<0.001	2 (8.0)	0 (0.0)	0.157
Isolated mitral valve replacement	445 (14.4)	58 (17.3)	0.157	2 (8.0)	1 (4.2)	0.576
Isolated mitral valve plasty	234 (7.6)	11 (3.3)	0.004	0 (0.0)	(0.0)	N.A.
Concomitant coronary artery bypass grafting	300 (9.7)	66 (19.7)	<0.001	8 (32.0)	7 (29.2)	0.830
Aortic cross-clamp time, minutes (median, IQR)	103.0 (72.0 – 146.0)	124.0 (81 – 184)	<0.001	194.0 (112.0 – 286.0)	212 (153.5 – 284.0)	0.595
Cardiopulmonary bypass time, minutes (median, IQR)	148.0 (108 – 210)	214 (137 – 314)	<0.001	356.0 (266.0 – 413.0)	386.0 (273.5 – 456.8)	0.533
Clinical outcomes						
Postoperative length of stay, days (median, IQR)	14.0 (8.0 – 25.0)	6.0 (2.0 – 17.0)	<0.001	33.5 (16.5 – 48.0)	8.0 (2.0 – 14.0)	<0.001
Renal failure, n (%)	307 (10.0)	96 (28.9)	<0.001	12 (52.2)	14 (58.3)	0.671
Vascular complications, n (%)	13 (0.4)	8 (2.7)	<0.001	4 (20.0)	1 (5.0)	0.459
Rethoracotomy for cardiac tamponade, n (%)	303 (11.5)	69 (23.8)	<0.001	8 (38.1)	8 (38.1)	0.884

Table 1. Baseline characteristics, surgical treatments and clinical outcomes of IE patients with and without VA-ECMO support according to survival status. eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; N.A., not applicable; NYHA, New York Heart Association ; PA, Pulmonary Artery.

[a] Numbers are presented as a valid percentage, excluding missing values.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: