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David Vandroux, Hugo Kerambrun, Cyril Ferdynus, Nicolas Allou, Jérôme Allyn, et al.. Postpandemic Influenza Mortality of Venovenous Extracorporeal Membrane Oxygenation–Treated Patients in Reunion Island: A Retrospective Single Center Study. *Journal of Cardiothoracic and Vascular Anesthesia*, WB Saunders, 2020, 34 (6), pp.1426-1430. 10.1053/j.jvca.2019.12.043 . hal-03404404

HAL Id: hal-03404404

<https://hal-unilim.archives-ouvertes.fr/hal-03404404>

Submitted on 22 Aug 2022

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Title. Postpandemic Influenza Mortality of veno-venous ECMO-treated patients in Reunion Island: a retrospective single center study.

Classification. Original article.

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COI. The authors declare no conflict of interest.

Financial support: none.

Funding: The authors received no financial support for the research, authorship and/or publication of this article.

Acknowledgments: The authors wish to thank Ms. Jessica Vanderwal for her translation skills.

Postpandemic Influenza Mortality in Venovenous ECMO-Treated Patients in Reunion Island: a Retrospective Single Center Study

Introduction

In 2009, a new pandemic of H1N1 variant Influenza started in Mexico and quickly spread to other countries, leading to many admissions in ICU for severe Acute Respiratory Distress Syndrome (ARDS). In Australia and New Zealand, regional referral centers supported young patients presenting with severe ARDS with Venovenous Extracorporeal Membrane Oxygenation (VV-ECMO), cutting the mortality down to 21%.¹ Originally, the mortality of patients with Influenza and requiring ECMO was lower than that of patients with ARDS of other causes. **Since then, influenza is considered a favored reason for the use of VV-ECMO in severe ARDS.**² In the following years, **various experiences report an improved outcome when the patient is ECMO-treated**³ and many patients received ECMO treatment for Influenza or other causes of ARDS. Data suggest that survival differs when the cause of ARDS is considered and AH1N1 is associated with lower mortality⁴⁻⁵. **However, the weight of the pandemic period is important in these studies**⁵ and mortality could be higher in the post pandemic period.⁶ In many countries, specific care networks were developed and patients with severe ARDS were grouped in tertiary hospitals that were experts in this technique. Nevertheless, it is very difficult to show the benefit of ECMO in the management of severe ARDS.⁷⁻⁸

Reunion Island is a French overseas territory located in the South-West Indian Ocean. Our ICU is the largest on the island (23 beds) and has developed a network of care with a mobile circulatory support unit.⁹ This team also coordinates the implementation of ECMO in other French hospitals in the Indian Ocean as well as the evacuation to mainland Paris for patients requiring heart or lung transplant. For many years, influenza has been considered a preferred indication for ECMO based

on studies conducted during the pandemic. Thus, the decision to implant an ECMO was more innate for influenza than for other conditions of ARDS. Our initial hypothesis was that influenza responded better to ECMO than other causes of ARDS during the post-pandemic period. Thus, the objective of this study was to assess the mortality of patients treated with ECMO for influenza by comparing it to other ECMO patients.

Methods

Participants

We conducted a retrospective study from January 2013 to December 2017 on all patients diagnosed with Influenza, admitted in the adult ICU of the University Teaching Hospital Félix Guyon and under ECMO. Influenza cases were defined as positive Polymerase Chain Reaction (PCR) in nasopharyngeal or respiratory tract samples [(Xpert flu/VRS^R (GeneXpert) and the multiplex kit FTD-Respiratory pathogens 21^R (Fast-Track Diagnostic)]. We started the data collection in 2013, four years after the beginning of the pandemic. During this period, PCR was consistently and routinely available.

The following data were collected: age, gender, body mass index, medical history, vaccination against flu, time between ICU admission and ECMO, virus type, routine biological data, severity scores (Simplified Acute Physiology Score [SAPS II] made out of the most abnormal parameters within 24 hours of admission; Sequential Organ Failure Assessment [SOFA] score at admission and before ECMO, Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score [RespScore]), duration of conventional mechanical ventilation (CMV), use of nitric oxide, continuous renal replacement therapy (CRRT). A superinfection was defined by the microorganisms detected on the samples during the first 48 hours. Bacteria were cultured from tracheal aspiration, broncho-alveolar lavage, protected distal sampling, or blood culture. The presence of ARDS was defined according the Berlin ARDS criteria. A regional protocol (supplementary data 1: S1) helped

in the decision of treatment with ECMO.

Design

The primary objective of this study was to compare the mortality of patients under ECMO for Influenza with the mortality of other patients on ECMO. Given the fact that the veno-venous ECMO (VV-ECMO) was the most frequently used technique, we used the RespScore⁷ and we determined the expected mortality using a Standardized Mortality Ratio (SMR) approach based on the quartiles of the Resp-score. A calculation of the Resp-score of patients on VV-ECMO hospitalized during the same period and in the same ICU was performed in order to define a population reference.

According to French law (L.1121-1 paragraph 1 and R1121-3 Public Health Code), neither informed consent nor approval by an ethics committee is necessary for the extraction of anonymous data or for the analysis of patients' medical files. Nonetheless, this study was ancillary to a cohort of all patients admitted for influenza that had been approved by the French Ethics Committee for Research in Anesthesia and Intensive Care (IRB00010254-2018-045, *CESAR, Société Française d'anesthésie et de Réanimation*).

Statistical analysis

Qualitative variables were expressed as frequency and percentages. Quantitative variables were expressed as median and 1st and 3rd quartiles. Percentages were compared using the chi-square test or the Fisher's exact test, as appropriate. Quantitative variables were compared using the Mann Whitney test. SMR with 95% confidence intervals (CI 95%) was calculated from Resp-score quartiles of the reference population of hospitalized patients with VV-ECMO. To calculate the SMR, patients with influenza should have been included in the reference population. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

A total of 127 patients exhibiting Influenza were hospitalized in our ICU between January 1, 2013 and December 31, 2017. Twenty-four patients underwent ECMO including 18 patients with femoral-atrial VV-ECMO, 6 patients with veno-arterial ECMO (VA-ECMO). Seven ECMO were implanted outside our hospital by our Mobile Circulatory Assist Unit and mortality of these patients was not different from those implanted in-house. The characteristics of all patients on ECMO are presented in **Table 1**.

Among the 18 patients on VV-ECMO, half were women, including two pregnant women. Viral strains defined by PCR (**figure 1-A**) were AH1N1 (12 patients, 67%), A not H1N1 (5 patients, 28%) and B (one patient, 6%). Prone ventilation has been performed before ECMO for 11 (61%) patients. One patient (survivor) required a second ECMO after first weaning and for two patients, VV-ECMO were switched to VA-ECMO. ECMO was associated with mortality (RR 2.35 [1.16-4.74]). In the same period, 234 patients on ECMO were hospitalized in our ICU including 72 with VV-ECMO. For 60 cases of VV-ECMO, the data allowed the calculation of RespScore (**figure 2**). **Tables 2 and 3** present the baseline characteristics of the reference population and specify the characteristics of influenza patients.

Mortality of patients on VV-ECMO

The overall mortality rate of influenza patients on VV-ECMO was 61% vs 46% for non-influenza patients. However, SAPSII was higher for patients with influenza whereas RespScores seemed similar (Risk class II). To refine the mortality comparison to the severity of the patients, we perform a calculation of the SMR from 60 cases of ECMO implantations including 16 cases of influenza. The SMR per quartile of RespScore was 1.28 (CI95%: 0.61-2.35).

Three deaths occurred early (**Days 1, 1, 4**) after multiple organ failure with proven septic shock

(Two MSSA, one leptospirosis). Three patients died of hemorrhagic complications: one due to technical complications during cannulation (Day 1), two due to cerebral hemorrhage. Three late deaths (Days 25, 32, 33) were related to a process of withholding or withdrawing life-sustaining treatment for pulmonary fibrosis. Two of these patients had received corticosteroid therapy, one with cyclophosphamide (Figure 1-B).

Mortality of patients on VV-ECMO or VA-ECMO

This subgroup of 24 patients (Table 1) had a mortality rate of 62% for a SAPSII2 of 65 [47-76]. The subgroup was compared to a population of 234 patients with ECMO in our department during the same period. Patients requiring an ECMO for influenza had a higher mortality than in other indications with an odds ratio of 1.63 [0.69- 3.84]. The SMR per Quartile of SAPSII of the ECMO subgroup was 1.24 (CI:0.68-2.08).

Discussion

In our cohort, influenza does not appear to be a factor of better outcome than the other indications of VV-ECMO. The severity of influenza is well illustrated by the higher mortality rate and a SMR as high as 1.28. Determining the expected mortality using a SMR approach based on the quartiles of the RespScore allowed us to compare mortality according to the severity of the patients. We did not use the ECMO-net score to compare the outcomes between patients with influenza and without influenza because it was developed using data from Influenza A(H1N1)-associated respiratory failure. We have chosen the RespScore as a standardization variable because this score, developed from a large population of 2355 patients¹⁰, integrates many variables: age, immunodeficiency, length of mechanical ventilation prior initiation of ECMO, etiology of pulmonary failure, cerebral dysfunction, associated infection, use of neuromuscular blockade agents, nitric oxide or bicarbonate infusion, cardiac arrest before ECMO, hypercapnia and peak inspiratory pressure. However, in our

study, RespScore had two defects:(i) the use of peak inspiratory pressure rather than driving pressure or plateau increased the missing data exclusions in this retrospective study;(ii) in cases of viral pneumonia, such as influenza, the RespScore is increased by +3 and the expected survival is better. It is therefore possible that the RespScores of the influenza cohort have been overestimated compared to other patients. For this reason, we realized an SMR by changing the standardization variable. Using the SAPSII score, and applying it to all ECMO patients, we found a similar result. Higher mortality for influenza in patients with ECMO could be explained by the severity of influenza in tropical areas. We also found an excess mortality of influenza patients in hospitalized patients in intensive care unit for pneumonia.¹¹ It is also possible that the influx of patients during periods of influenza epidemic can lead to a saturation of intensive care admission capacities and delay the care of patients. Finally, another explanation could be that other causes of ARDS in tropical environments, such as leptospirosis, have a better prognosis and create a bias.¹²

The mortality of our cohort of patients on ECMO for influenza remains high (61% vs 24% for Risk Class II of RespScore¹⁰). Several explanations can be advocated: higher ICU mortality of patients infected with Influenza during post-pandemic period than during the 2009 pandemic period⁶; high rate of coinfection with higher mortality¹³, delayed ECMO initiation despite inter-hospital care network. The group of early deaths (**Figure 1-B**) corresponded to a multiorgan failure with a large hemodynamic involvement. These patients have high severity scores (SAPSII > 70). It is likely that in prospective and randomized studies, they were excluded as moribund status. All these patients, but one, died of septic shock with detection of MSSA. Indeed, Reunion is an emergent area of Panton-Valentine leukocidin-producing *Staphylococcus aureus*.¹⁴ A second group of late deaths was related to lung fibrosis. Early corticotherapy is not indicated for influenza patients¹⁵ and corticotherapy in ARDS still lacks the support of rigorous evidence. It is possible that a prognostic improvement pathway may arise from new studies on the use of corticosteroids for influenza patients on ECMO.

In conclusion, Influenza is a serious disease despite the progress of the past decade. Our results do not support the postulate that the mortality of patients with Influenza and requiring ECMO is lower than that of patients with ARDS of others causes. ECMO remains a reference treatment for ARDS in influenza but its benefit should be evaluated on larger samples in the post-pandemic period.

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FIGURE LEGENDS

Figure 1.

Viral strain and VV-ECMO duration for 18 patients treated for influenza.

On the y-axis: number of cases; in black, the number of deceased cases. **A. Viral strain** defined by Polymerase Chain Reaction. There is no significant difference between the viral strains. **B. ECMO duration** for 18 VV-ECMO-treated patients. The majority of survivors have ECMO duration between 2 and 21 days. Early mortality from hypovolemic shock and late mortality from pulmonary fibrosis are observed.

Figure 2.

Flow diagram describing the selection of eligible patients for analysis of Standardized Mortality Ratio. VV-ECMO : veno-venous ExtraCorporeal Membrane Oxygenation. VA-ECMO : veno-arterial ExtraCorporeal Membrane Oxygenation.

SUPPLEMENTAL DATA

S1. Regional ECMO protocol.

ECMO : Extra Corporeal Membrane Oxygenation, CMV : Mechanical ventilation, PEEP : Positive End Expiratory Pressure, ARDS : Acute respiratory Distress Syndrome, NO : nitric oxide, FiO₂ : Fraction of inspired oxygen, PBW : Predicted Body Weight

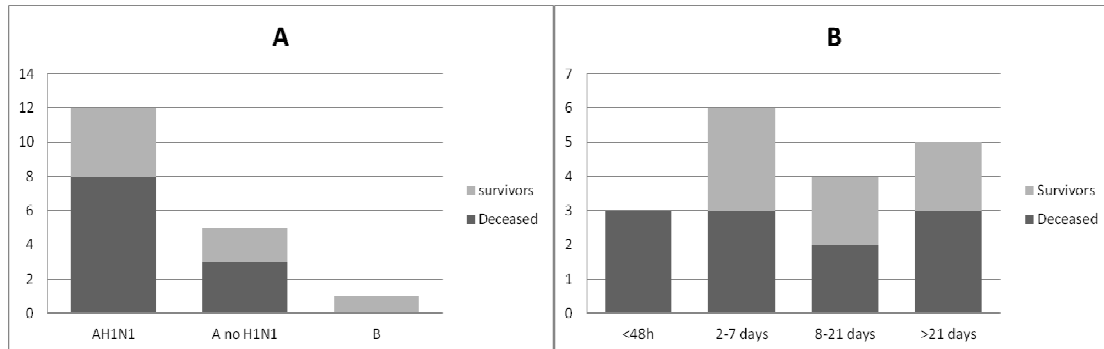
S2. Summary of ECMO-treated Patients with Influenza.

VV-ECMO: veno-venous ExtraCorporeal Membrane Oxygenation. VA-ECMO: veno-arterial ExtraCorporeal Membrane Oxygenation. SAPS II: Simplified Acute Physiology Score II.

S3. Mortality by year (2013-17).

On the y-axis: number of cases; in black, the number of deceased cases.

Figure 1. Viral strain and VV-ECMO duration for 18 patients treated for influenza.



On the y-axis: number of cases; in black, the number of deceased cases. **A. Viral strain** defined by Polymerase Chain Reaction. There is no significant difference between the viral strains. **B. ECMO duration** for 18 VV-ECMO-treated patients. The majority of survivors have ECMO duration between 2 and 21 days. Early mortality from hypovolemic shock and late mortality from pulmonary fibrosis are observed.

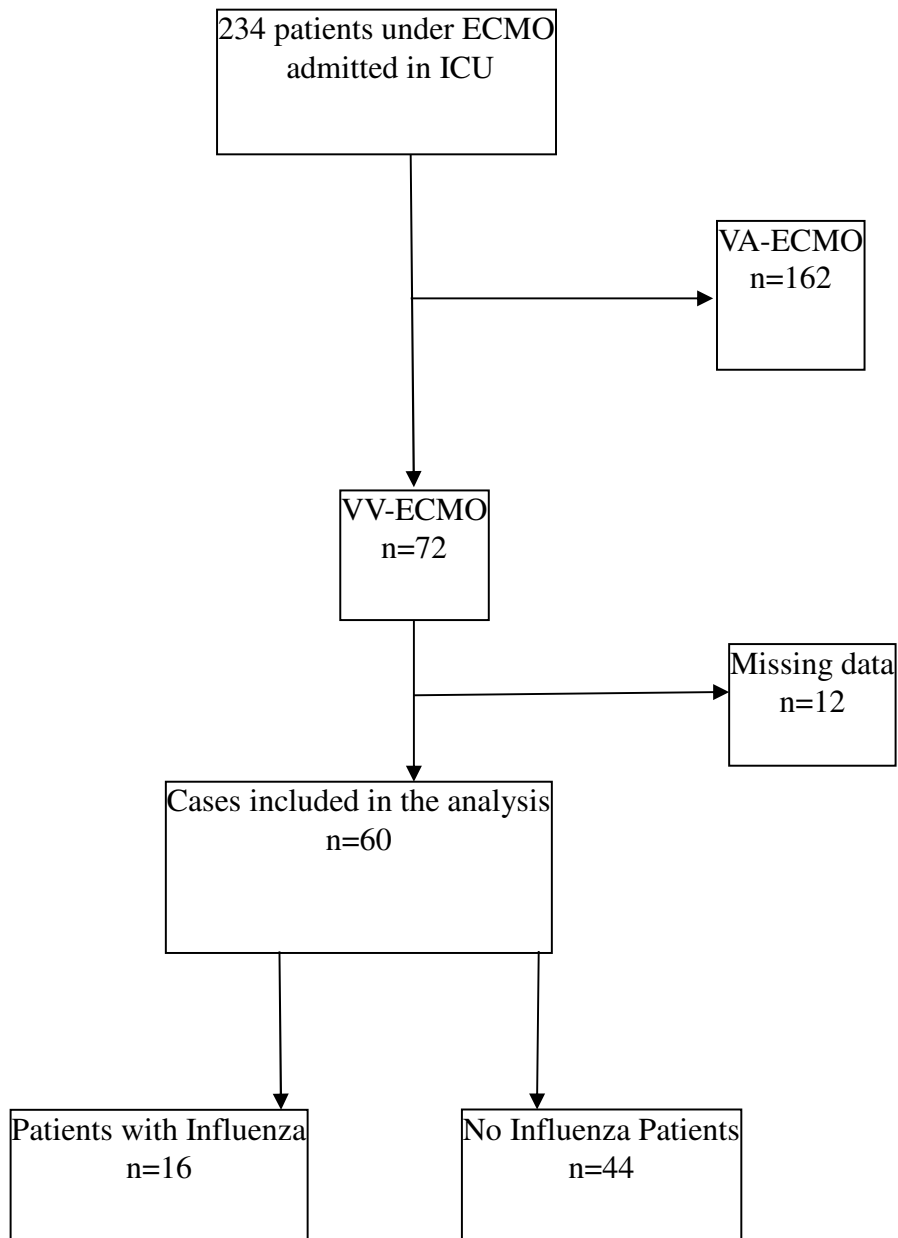


Fig 2. Flow diagram describing the selection of eligible patients for analysis of Standardized Mortality Ratio. VV-ECMO : veno-venous ExtraCorporeal Membrane Oxygenation. VA-ECMO :

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Table 1. Baseline characteristics and outcomes in 24 patients with influenza treated with ECMO.

Characteristics	Total (n=24)	Non survivors (n=15)	Survivors (n = 9)	p
	Median (IQ1;IQ3) or n(%)			
Age	46 [39-54]	47 [42-54]	46 [31-53]	0.30
BMI	26 [21-32]	28 [21-31]	26 [23-32]	0.68
SAPS II	66 [46-77]	69 [54-83]	61 [34-66]	0.15
SOFA	10 [7-13]	10 [8-13]	9 [4-10]	0.09
Time between ICU admission and ECMO implantation > 1 days	9(37)	7(29)	2(8)	0.45
Length of ECMO	6 [3-15]	6 [1-11]	6 [4-21]	0.44
VV ECMO	18(75)	11(46)	7(29)	1
VA ECMO	6(25)	4(17)	2(8)	1
ICU Length of stay	14 [4-29]	6 [3-23]	22 [13-31]	0.04
Duration of mechanical ventilation	13.5 [4-29]	6 [3-26]	21 [12-28]	0.08
Superinfection at admission	11(46)	8 (34)	3(12)	0.35
Renal replacement therapy	15(63)	12(50)	3(12)	0.03
ECMO implanted by mobil team	7(29)	3(12)	4(17)	0.2
PreECMO pH	7.16 [7.12-7.27]	7.14 [7.12-7.30]	7.18 [7.16-7.21]	0.87
PreECMO PaO ₂ /FiO ₂ ratio	62 [52-113]	62 [51-104]	73 [57-127]	0.76
PreECMO PaCO ₂	49 [39-60]	42 [37-61]	52 [43-60]	0.55
PreECMO SOFA	10 [8-13]	11.5 [9-13]	9 [4-10]	0.03

BMI, body mass index; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; ICU, Intensive Care Unit; ECMO, ExtraCorporeal Membrane Oxygenation; VV ECMO, veno-venous ECMO; VA ECMO, veno-arterial ECMO; PreECMO, last data before implantation.

Table 2. Baseline characteristics in 60 patients on veno-venous ECMO

Characteristics	Influenza n= 16	No Influenza n= 44	P
	Median [IQ-IQ3] or n(%)		
Age	46 [39-54]	50 [40-60]	0.42
Male gender	8 (50)	31 (73)	0.15
SAPS II	63 [34-77]	49 [35-69]	0.45
Resp Score	3.5 [0-4.25]	3 [1-4.5]	0.84
Time of mechanical ventilation before ECMO	3 [1-4]	1 [1-3.5]	0.40
NO before ECMO	9 (56)	28 (65)	0.73
Pre-ECMO PaO ₂ /FiO ₂ ratio	62.5 [60-87]	75 [61-100]	0.28
Pre-ECMO PaCO ₂	54 [44-63]	53 [45-67]	0.71
Duration of ECMO	7 [3-12]	9 [4-16]	0.41
Mortality	10 (62)	20 (46)	0.28

Quantitative variables were expressed as median and 1st and 3rd quartiles; Qualitative variables were expressed as frequency and percentages; SAPS II, Simplified Acute Physiology Score II; ICU, Intensive Care Unit; ECMO, Extra Corporeal Membrane Oxygenation; NO, nitric oxide.

Table 3. Acute respiratory failure diagnostic groups for reference population.

Diagnoses	All patients	Dead n(%)
Influenza	16	10 (63)
No Influenza viral or bacterial pneumonia	20	8 (40)
Immunocompromised	6	4 (67)
After cardiac surgery	2	1 (50)
Leptospirosis	1	0
Asthma	4	0
Trauma	5	1 (20)
Aspiration pneumonitis	1	1
Others acute respiratory diagnoses	14	10 (71)
TRALI	3	3
Pancreatitis	1	0
Aspergillosis	1	1
Malignancy	1	1
Pneumothorax	1	1
Others ARDS	7	4 (57)

Immunocompromised is defined as human deficiency virus, hematologic malignancies, solid tumor organ transplantation or cirrhosis. TRALI : Transfusion-related acute lung injury.