



Intérêt du dosage des D-dimères chez les patients sous ECMO : étude rétrospective

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pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

ANESTHÉSIE - RÉANIMATION

par

Vincent LE NESTOUR

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**Intérêt du dosage des D-dimères chez les patients sous ECMO :
étude retrospective.**

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ABSTRACT

Objective: Patients undergoing extracorporeal membrane oxygenation (ECMO) have modified hemostasis due to several factors. Thrombosis, occurring on the membrane oxygenator (MO) or being a systemic event, might cause morbidity or mortality. In this study, we evaluated the association between D-dimer level and MO-related outcomes and thrombotic events in a cohort of ECMO patients.

Design: We conducted a monocentric retrospective study from March 2019 to August 2021 with patients undergoing ECMO for at least 72 hours with daily D-dimer measurement. Primary outcomes were the occurrence of at least one MO exchange, and MO impairment defined by at least one post-oxygenator partial pressure in oxygen / delivered fractional oxygen percentage on ECMO. Secondary outcomes were incidental venous or arterial thrombotic events and survival at ICU discharge.

Main results: 97 patients were included in our study. A significant difference in maximum D-dimer level was found between patients without or with at least one MO exchange (respectively 31889 vs. 57552 ng/L, $p = 0,002$), and between patients without and with MO impairment (respectively 36197 vs. 67626 ng/L, $p = 0,006$). No significant difference was observed for secondary outcomes. In our cohort, a D-dimer cut-off point at 25988 ng/L had a sensitivity of 0.70, a specificity of 0.84, a positive predictive value of 0.39, and a negative predictive value of 0.95 for the happening of an MO exchange.

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D-dimer monitoring in patients undergoing ECMO: a retrospective study.

INTRODUCTION

BACKGROUND

The use of extracorporeal membrane oxygenation (ECMO) to support patients with cardiac or respiratory failure refractory to conventional treatment has grown over the last years [1].

During a five-year period (2016 - 2021), the Extracorporeal Life Support Organization (ELSO) registered 10,393 ECMO runs in Europe for adult patients; the overall survival was 53% (63% in pulmonary indication, 47% in cardiac indication, 33% in ECPR) [2]. Although the prognosis of patients under ECMO mainly depends on the primary disease, adverse events occurring during extracorporeal circulation significantly increase morbidity and mortality [3] [4] [5] [6].

Once ECMO is running, besides providing patients with specific treatment of the disease, the main challenge is preventing, detecting, and treating complications of extracorporeal circulation if needed. In addition to close clinical monitoring, several biological assays were proposed to help the attending physician to detect infra-clinic complications such as hemolysis or clotting events [7] [8] [9]. Nevertheless, numerous events occurring like surgical stress, massive transfusion, biological trauma, and its associated systemic inflammatory response often lead to unspecific biologic abnormalities with unclear meaning. As a result, the detection of complications (including thrombosis) through a combination of several parameters is often delayed, which can worsen the prognosis.

Systemic anticoagulation is indicated during the ECMO run [10]. Despite technical improvements in biocompatibility [11], ECMO is pro-inflammatory and interferes with coagulation by contacting the patient's blood and the non-endothelialized surface of the circuit, resulting in the activation of the contact system [12]. The long-term durability of membrane oxygenator (MO) is limited due to fibrous and cellular accumulations on the gas exchange surface, which can increase resistance to blood flow and diffusion path [13]. Therefore, MO may need to be exchanged; this procedure is sometimes poorly tolerated since the circuit needs to be disconnected from the patient for a short time. There are no precise guidelines regarding the timing of MO exchange, but ELSO suggests that the outlet PO₂ on the ECMO should be over 300 mmHg.

PRELIMINARY ANALYSIS

A preliminary study was conducted on 50 patients undergoing any type of ECMO for at least three days from April 2015 to July 2016 (IRB 00010254–2016-038) in our intensive care unit (ICU) in Nantes Laennec University Hospital. In the univariate analysis, several factors were associated with mortality in the ICU: higher delivered fractional oxygen percentage on ECMO (FdO₂), longer time on ECMO, MO exchanges, any cause of thrombosis (including ECMO thrombosis), higher immature platelet fraction (IPF) ([Appendix 1](#)). Despite being multifactorial, those factors were likely to be related to the degradation or impairment of the MO.

INTEREST IN D-DIMER ASSAY

D-dimer is a biomarker of fibrin formation and degradation that can be measured in whole blood or plasma. Healthy individuals have low levels of circulating D-dimer, whereas elevated levels are found in conditions associated with thrombosis. D-dimer has been extensively investigated for the diagnosis of venous thromboembolism (VTE) and is used routinely for this indication [14]. Nevertheless, elevated D-dimer may be found in various physiological or pathological states other than VTE [15] [16].

D-dimer has been little explored in ECMO patients. Studying 13 membrane oxygenator (MO) exchanges, Dornia et al. found a significant increase in clot volume inside MO in patients with high D-dimer levels (> 35 mg/L) for at least two days [17]. Lubnow et al. found a significant difference between D-dimer levels before and after MO change in 19 out of 35 patients undergoing veno-venous ECMO [18]. No significant association was set between D-dimer level and MO impairment.

At the time of our preliminary analysis, our hospital laboratory used to measure D-dimer by enzyme-linked immunosorbent assay (ELISA); this technique was not routinely available in ICU patients' hemostasis daily assessments, and therefore D-dimer was not evaluated in this preliminary study. Since 2019, our hospital laboratory has updated our daily hemostasis assessment by embedding an automated latex agglutination assay using an immunoturbidometric technique to detect D-dimer to antibody-coated latex beads. As with the ELISA, this method is known to be extremely sensitive for diagnosing VTE and has an excellent negative predictive value in this indication [19].

OBJECTIVE

In the present study, we retrospectively analyzed biological and clinical data of a population of patients undergoing ECMO to search for a potential association between D-dimer measurement and MO-related outcomes.

MATERIAL AND METHOD

STUDY DESIGN AND SETTING

This study took place in the ICU of Nantes Laennec University Hospital, a reference center for adults with ECMO, total artificial heart, ventricle assist device, or heart and lung transplantation. The technical and institutional aspects of ECMO in this center follow international recommendations.

As part of a healthcare quality improvement program trying to reduce blood sampling and the number of tests, this study relies on a standardized biological monitoring used since February 2014 with all patients undergoing ECMO in Nantes Laennec University Hospital.

We included every patient undergoing ECMO for at least three days in Nantes Laennec University Hospital ICU from March 2019 to August 2021, aged 18 or more. Combined assistance device (i.e., balloon intra-aortic pump or Impella) was possible. Patients were excluded if they were pregnant, if they underwent surgery with cardiopulmonary bypass once already under ECMO, if they had already been assisted by ECMO during the study period, if an accidental decannulation occurred, if a power failure occurred.

STANDARD OF CARE FOR ECMO PATIENTS

Extracorporeal membrane oxygenation circuits and settings

All the circuits were composed of polyvinyl chloride tubing. Membrane oxygenators were Hilite 7000 LT (Medos-Xenios AG, Heilbronn Germany), Quadrox Bioline (Maquet, Orléans, France), or Eos ECMO (Sorin, Milano, Italy). The membrane oxygenator was ventilated by an oxygen-air blender (Sechrist Industries, Anaheim, Calif). Centrifugal pump used either Biomedicus (Medtronic, Boulogne-Billancourt, France), Rotaflow (Maquet), IBC FloPump (International biophysic, Austin, Texas), or Deltastream DP3 (Medos-Xenios AG). Cannulae were Biomedicus (Medtronic) or Edwards (Lifesciences, Irvine, Calif).

The insertion of the cannulae was either percutaneous or surgical. Veno-venous ECMO was performed for acute respiratory distress syndrome or primary graft dysfunction after lung transplantation via femoro-jugular catheterization. Veno-arterial ECMO for cardiogenic shock was either central (right atrium and aortic cannulation) or peripheral (femoro-femoral cannulation with an optional reperfusion cannula in the femoral artery to prevent inferior limb ischemia).

Blood tests

Standard blood tests (blood cell count, blood electrolytes, coagulation test) were conducted at least once a day for every patient as part as their general care. A specific range of other assays including partial pressure of oxygen (PO₂) before and after MO, haptoglobin, lactate dehydrogenase (LDH), schistocyte, AT III were conducted every day as part as the standardized monitoring used in our ICU since 2014 for our patients undergoing ECMO.

In addition, D-dimer were quantified once a day by automated latex agglutination assays using immunoturbidometric technique.

Management of patients under ECMO

The multimodal monitoring program included a daily inspection by a perfusionist looking for clotting of the oxygenation membrane or the circuit, kinking of the cannula, or chattering of the lines. The warmth, the coloration of the limbs, and hemolysis-related dark-colored urine were controlled daily. The heparin therapy was adjusted according to the ELSO recommendation and could be withdrawn for bleeding issues. Supplemental antithrombin III (AT III) could be used.

Patients were transfused to maintain hemoglobin level over 8,0 g/dL, prothrombin rate over 50%, and platelet count over 50 G/L. Fibrin was maintained over 2 g/L. Patients could be supplemented with erythropoietin or erythropoietin during ICU stay.

The perfusionist or the attending physician could replace the MO for one of the following conditions: a significant amount of fibrin deposition on the membrane, hemolysis, thrombocythemia, or decline of the post-oxygenator PO₂ / FdO₂ ratio (P/F) measured with FdO₂ equal to 1. No systematic replacement of the circuit was advised unless one of these conditions.

OUTCOMES

Primary outcomes

Two primary outcomes were recorded: MO exchanges and MO impairment. MO impairment was defined as the measurement of at least one P/F under 300 mmHg during ECMO run to fit with the ELSO suggested operative range.

Secondary outcomes

Venous thrombosis events were identified as incidental pulmonary embolism or deep vein thrombosis identified by computed tomography (CT) scan or doppler sonography, which theoretically requires systemic anticoagulation. Arterial thrombosis events were defined as incidental stroke, other organ infarction, or limb ischemia identified by a CT scan or magnetic resonance imaging (MRI). Survival at ICU discharge was also recorded.

DATA COLLECTION AND STATISTICAL ANALYSIS

Clinical and biological data were collected from Powerchart (Cerner, USA). Blood transfusion data were collected from HEMO Service (Inlog, Limonest, France). For every day under ECMO, the most pejorative value was retained for each biological variable.

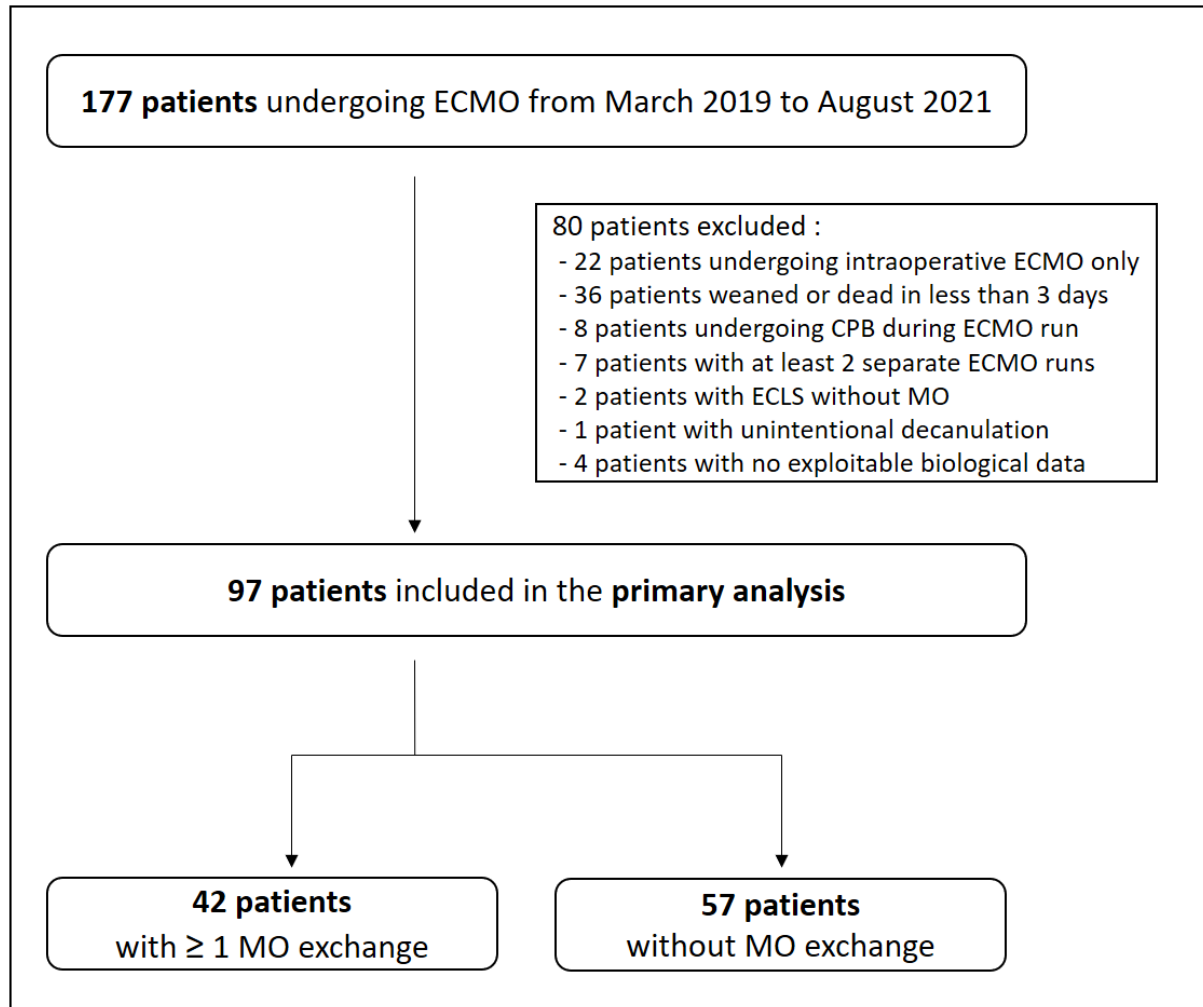
Demographic and clinical variables were evaluated descriptively using proportions with percentages or means with standard deviations (SDs) as appropriate. Means were compared with paired Student's t-tests. A two-sided alpha of .05 was considered to be statistically significant. All analyses were conducted in R software (version 4.1.3).

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Consent was waived for retrospective data collection. However, all patients and their families received oral and written information before surgery regarding clinical research in the Intensive Care Unit.

RESULTS

Figure 1: Flow-chart.



ECMO: extracorporeal membrane oxygenation, CPB: cardiopulmonary bypass, ECLS: extracorporeal life support, MO: membrane oxygenator.

PRIMARY ANALYSIS

From March 2019 to August 2021, 177 patients were assisted by ECMO in the Intensive Care Unit of Nantes Laennec; 97 met the inclusion criteria and were retained for the primary analysis (Figure 1). Among them, ECMO indication was primary graft dysfunction after cardiac transplantation ($n = 20$, 20,6%), cardiogenic shock after cardiac arrest and terminal cardiomyopathy ($n = 31$, 32,0%), postcardiotomy cardiac dysfunction ($n = 33$, 34,0%), acute respiratory distress syndrome ($n = 5$, 5,1%); other indications ($n = 8$, 8,3%) included myocarditis, pulmonary embolism and intoxication with cardiotoxic drugs. Thus, a majority of ECMO were veno-arterial ($n = 91$, 93,8%). Mean duration of ECMO was 8,2 (SD 5,9) days. Detailed patients' characteristics are listed in Table 1. No patient suffered heparin induced thrombocytopenia.

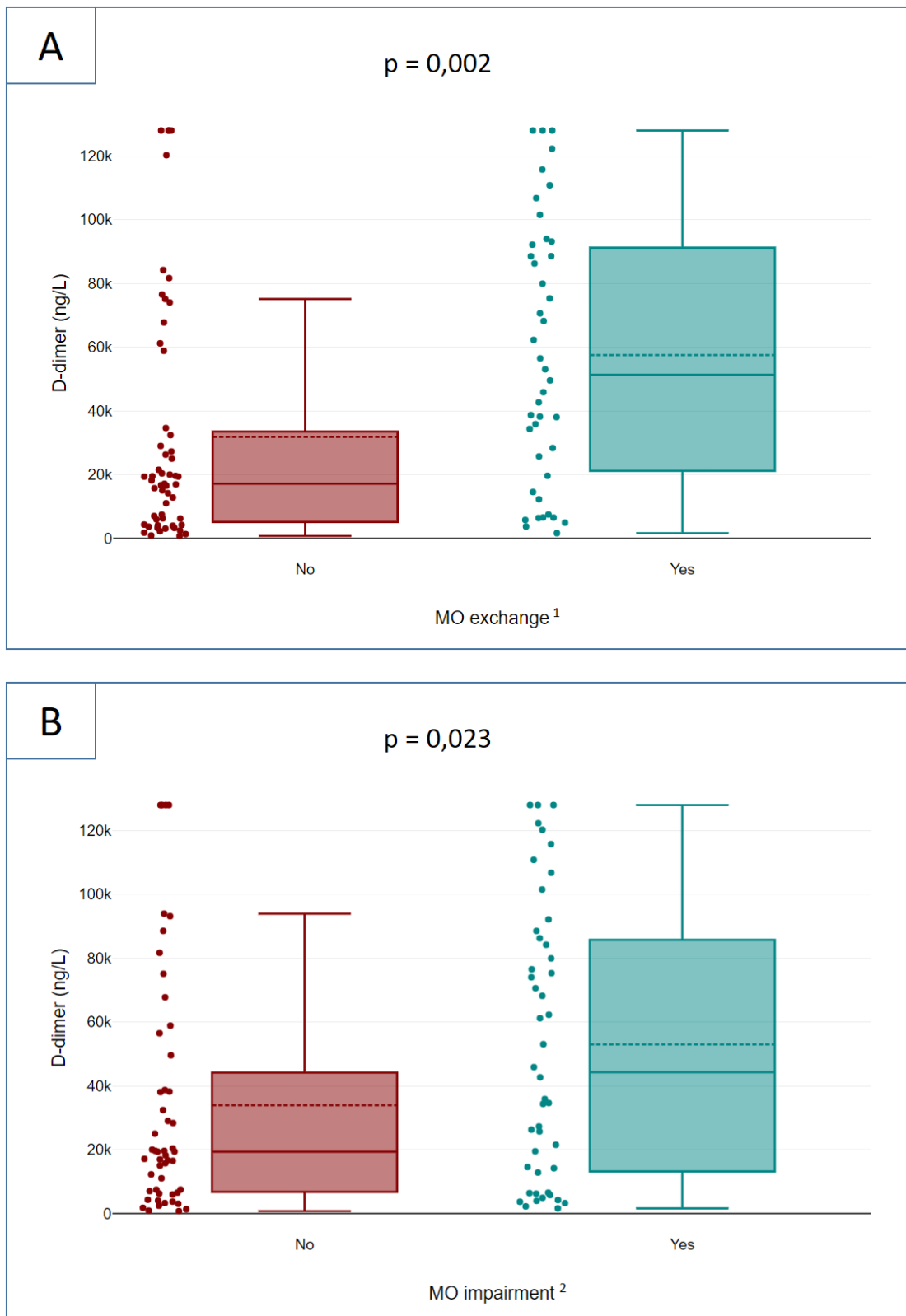
Table 1: Patients' characteristics (n = 97).

age – year	54 (+/- 15)
male sex – no. (%)	76 (78%)
SAPS II score ¹	58 (+/- 14)
BMI ² – kg/m ²	25,2 (+/- 5,7)
ECMO ³ duration – days	8,2 (+/- 5,9)
type of cannulation – no. (%) :	
- veno-arterial	91 (93,8%)
- veno-venous	6 (6,2%)
- central	32 (33,0%)
- peripheral	65 (67,0%)
ECMO indication – no. (%) :	
- primary graft dysfunction after heart transplant	20 (20,6%)
- cardiogenic shock after cardiac arrest and terminal cardiomyopathy	31 (32,0%)
- post-cardiotomy	33 (34,0%)
- ARDS ⁴	5 (5,1%)
- other	8 (8,3%)
RRT ⁵ during ECMO – no. (%)	37 (38,1%)
antiplatelet medication during ECMO – no. (%) :	
- no antiplatelet drug	52 (53,6%)
- one antiplatelet drug	28 (28,9%)
- two antiplatelet drugs	17 (17,5%)
proportion of days without effective anticoagulation during ECMO ⁶	38% (+/-24)
labile blood products transfusion per day during ECMO – units :	
- red blood cells concentrate	1,3 (+/- 1,0)
- fresh frozen plasma	0,8 (+/-1,3)
- platelet	0,5 (+/- 0,4)

¹Simplified Acute Physiology Score II, ²body mass index, ³extracorporeal membrane oxygenation, ⁴acute respiratory distress syndrome, ⁵renal replacement therapy, ⁶number of days with at least one anti-Xa factor assay below 0,20 UI/mL, divided by the number of days of ECMO for each patient.

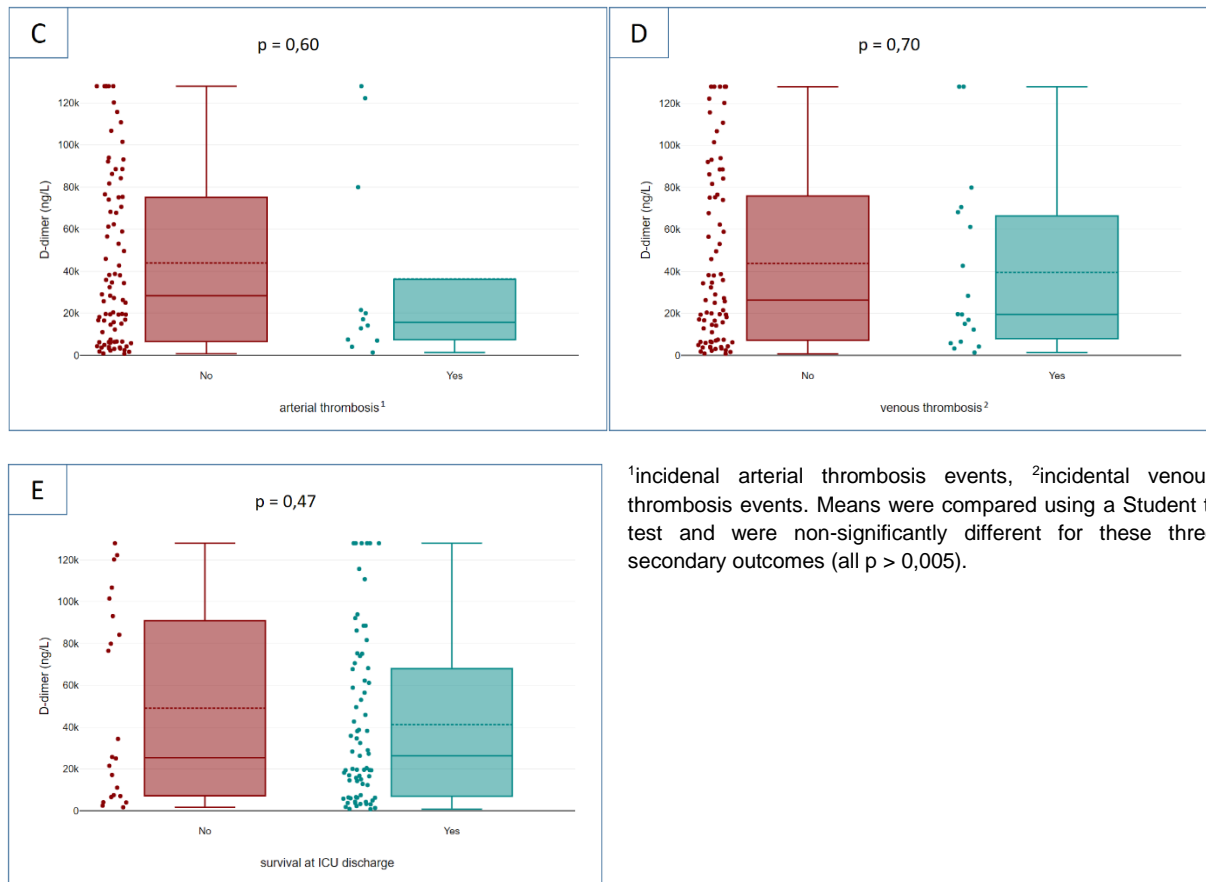
A significant difference in maximum D-dimer value was found between patients without and with at least one MO exchange (respectively 31889 vs. 57552 ng/L, p = 0,002), and between patients without and with MO impairment (respectively 36197 vs. 67626 ng/L, p = 0,006) (Figure 2).

Figure 2: Boxplots showing mean differences in maximum D-dimer values depending on the primary outcomes: MO exchange (A), MO impairment (B). Events are shown on X-axis (red = no event; green = event), maximum D-dimer level during ECMO are shown on Y-axis (n = 97).



¹MO exchange: at least one MO exchange during ECMO run, ²MO impairment: at least one post-oxygenator partial pressure of oxygen / delivered fractional oxygen ratio inferior to 300 mmHg during ECMO run. Means were compared using a Student t-test and were significantly different for both primary outcomes (both p < 0,005).

Figure 3: Boxplots showing mean differences in maximum D-dimer values depending on the secondary outcomes: arterial thrombosis (C), venous thrombosis (D), survival at ICU discharge (E). Events are shown on X-axis (red = no event; green = event), maximum D-dimer level during ECMO are shown on Y-axis (n = 97).



¹incidental arterial thrombosis events, ²incidental venous thrombosis events. Means were compared using a Student t-test and were non-significantly different for these three secondary outcomes (all p > 0,005).

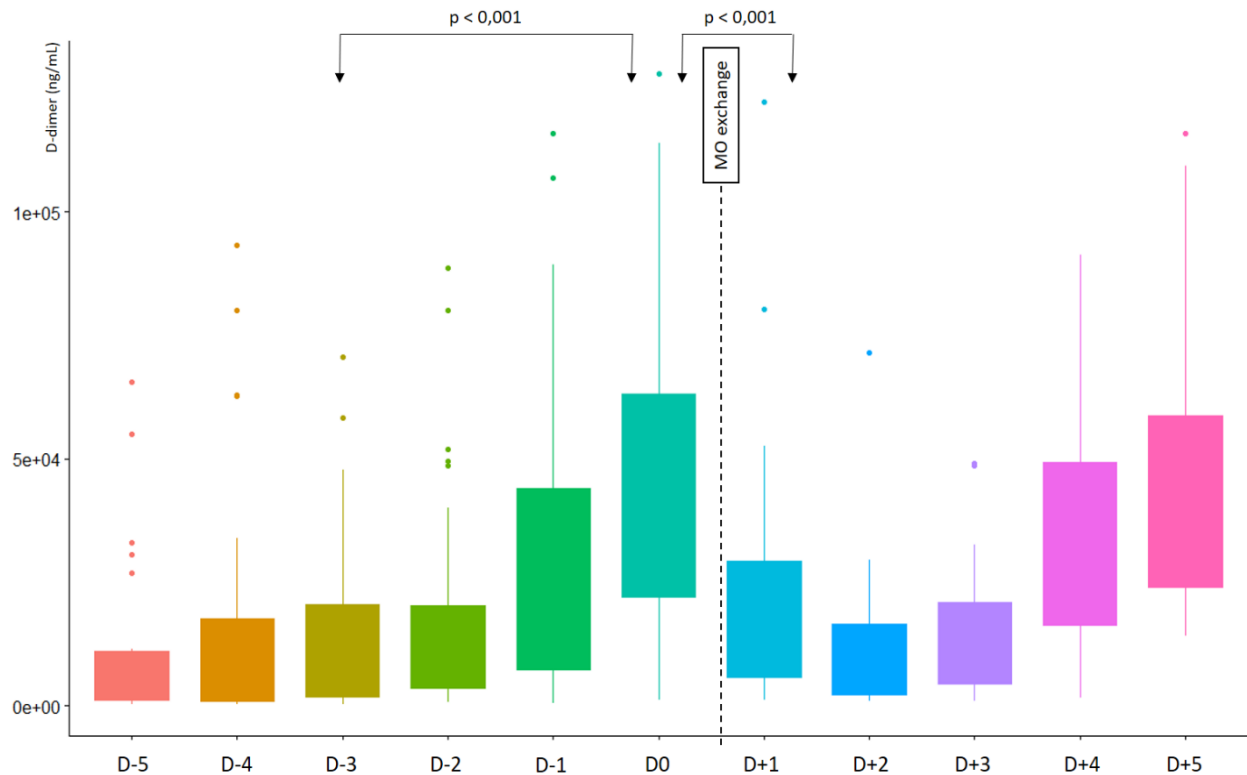
This difference was non-significant between patients without and with incidental arterial thrombosis (respectively 36339 vs. 43942 ng/L, p = 0,60), between patients without and with incidental venous thrombosis (respectively 43787 vs. 39551 ng/L, p = 0,70), and between non-survivors and survivors at ICU discharge (respectively 49136 vs. 41201 ng/L, p = 0,47) (Figure 3).

SUBGROUP ANALYSIS WITH MO EXCHANGE PROCEDURES

A subgroup analysis was conducted with data from the 42 patients who required at least one MO exchange to determine the D-dimer trend before and after the procedure. Patient characteristics in this subgroup were similar to the whole cohort and are listed in Appendix 3. A total of 53 MO exchange procedures were recorded and treated as separate events. MOs were exchanged after a mean time of 5,4 (+/- 2,4) days.

A difference was observed in D-dimer levels with a significant increase before MO exchange (13032 ng/L three days before exchange "D-3", 45650 ng/L the day of exchange "D0", p < 0,001) and a significant decrease after MO exchange (45650 ng/L at D0, 20131 ng/L one day after exchange "D1", p < 0,001) (Figure 4).

Figure 4: Boxplots showing D-dimer and post-oxygenator PaO₂ / FdO₂ ratio evolution from 5 days before (D-5) to 5 days after (D+5) MO exchange (n = 53).



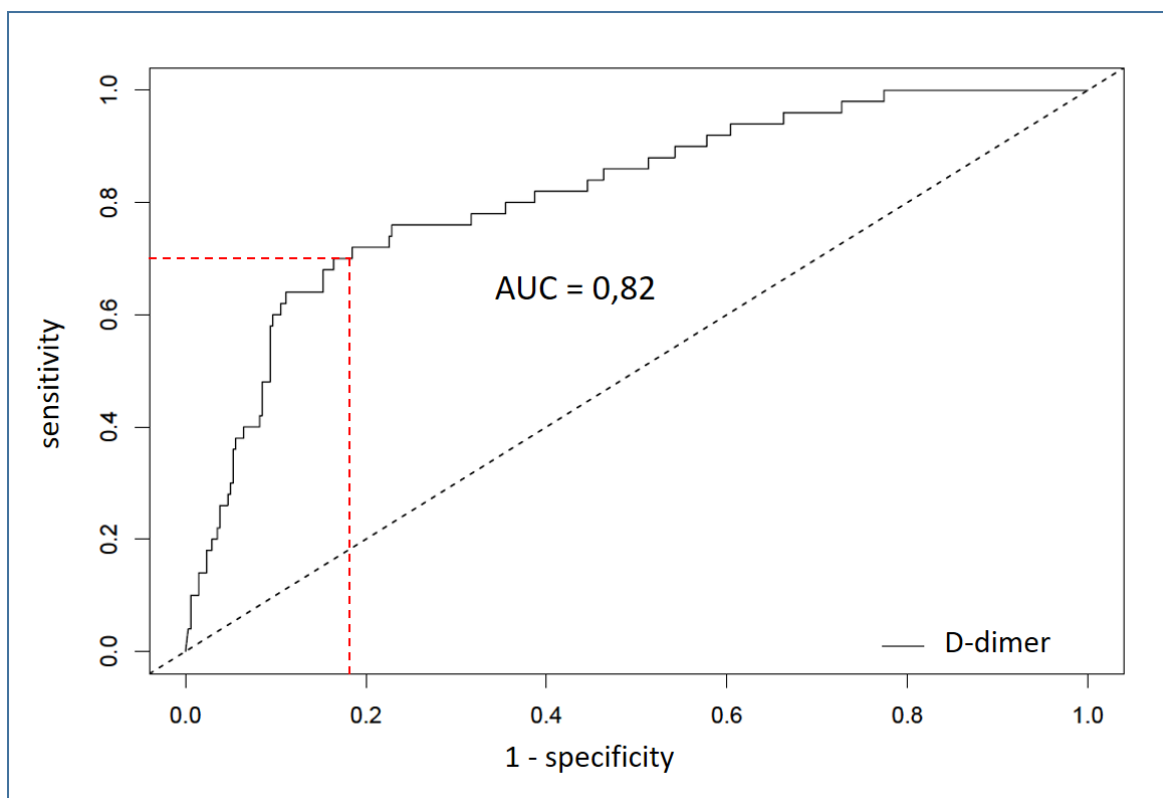
MO: membrane oxygenator. Arrows show significant difference between D-3 and D0, and D0 and D+1 (both $p < 0,001$, T-test).

D-DIMER THRESHOLD FOR MO EXCHANGE

An a posteriori was modeled to assess the performance of the D-dimer assay for the requirement of MO exchange. It was realized using up to the five daily D-dimer values from patients from the whole cohort ($n = 97$), paired with the daily decision to change or not the MO. Values from days of death or ECMO weaning were excluded. A total of 391 values were used to model a receiver operating characteristics (ROC) curve with an area under the curve (AUC) of 0.82 (Figure 5). The optimal cut-off point determined by the Youden method was set at 25988 ng/L for a sensitivity of 0.70, a specificity of 0.84, a positive predictive value of 0.39, and a negative predictive value of 0.95.

In comparison, when using data from the same 391 days, MO impairment, as defined in our study, had a slightly lower Youden index with a sensitivity of 0.64, a specificity of 0.81, a positive predictive value of 0.28, and a negative predictive value of 0.95.

Figure 5: ROC curve modeling 391 daily paired data to determine the D-dimer threshold linked with an MO exchange decision.



AUC: area under the curve. The dotted lines show the optimal D-dimer cut-off point (25988 ng/L) for the happening of an MO exchange with a sensitivity of 0.70, a specificity of 0.84, a positive predictive value of 0.39, and a negative predictive value of 0.95.

DISCUSSION

In this study, several outcomes happening with ECMO patients were explored and related to D-dimer measurement.

As observed in other studies, D-dimer is a highly sensitive marker regardless of the assay used. The values observed in our critical ICU population, already carrying basal conditions known to increase D-dimer concentration (i.e., infection, recent surgery), vary on a large range. Nonetheless, as observed in several studies, D-dimer might be a potential marker to assess for MO exchange. Our D-dimer threshold was coherent with values associated with a significantly higher MO clot formation in Dornia's study [17] [18] [20]. Taking into account that physicians were not blinded to the data used in our analysis, the predictive power of D-dimer for MO exchange was similar to the measurement of a post-oxygenator PO₂ / FdO₂ ratio lower than 300 mmHg, but its potential benefit seems to reside in its negative predictive value, as with VTE. In the end, MO exchange should remain a multifactorial decision.

D-dimer discriminated neither venous thrombosis in our population, nor arterial thrombosis; as mentioned, most of these events might contribute to only a relatively non-relevant small part

in already high D-dimer values. Nonetheless, it must be noted that some of these events might have been underdiagnosed since CT scans or doppler sonography were not systematic; they can be an underestimated cause of morbidity in this population [21].

D-dimer did not discriminate between survivors and non-survivors at ICU discharge; this could indirectly appear discordant with our preliminary analysis, which was based on mortality. However, higher FdO₂ observed in non-survivors back then might be explained by a respiratory failure rather than MO impairment, thrombosis definition was extensive (either systemic and ECMO-related), and MO replacement could not be considered independent from ECMO duration. Evolving practices might have permitted better management of patients undergoing prolonged ECMO in the four-year span between our analyses since the overall mortality at ICU discharge is not comparable.

An overall limitation was the recall bias. Although data were collected on institutional software, some were missing or misreported for some patients; several P/F values were not exploitable because of post-oxygenator PO₂ measured with a FdO₂ not equal to 1.

Nevertheless, this study was carried out with patients on ECMO for at least 72 hours, without selection according to the pathology or type of ECMO used, over a period of 30 months. They are a good reflection of the heterogeneous population requiring circulatory assistance at Nantes Laennec University Hospital. The important share of veno-arterial ECMO is explained by the fact that it is the reference center and the only ward in the area to receive that kind of assistance; instead, veno-venous ECMO is performed in other ICUs in Nantes. Nantes Laennec University Hospital was not a first-line ward during the Covid pandemic.

CONCLUSION

In conclusion, in a population of patients undergoing ECMO for at least three days, patients with MO impairment had significantly different maximum D-dimer values. Further studies are needed to explore D-dimers as predictors of MO exchange.

REFERENCES

- [1] Sauer CM, Yuh DD, Bonde P. Extracorporeal membrane oxygenation use has increased by 433% in adults in the United States from 2006 to 2011. *ASAIO J.* 2015 Jan-Feb;61(1):31-6. doi: 10.1097/MAT.000000000000160.
- [2] ELSO Live Registry Dashboard of ECMO Patient Data.
- [3] Combes A, Leprince P, Luyt C-E, et al. Outcomes and long-term quality-of-life of patients supported by extracorporeal membrane oxygenation for refractory cardiogenic shock. *Crit Care Med.* 2008;36(5):1404-1411. doi: 10.1097/CCM.0b013e31816f7cf7.
- [4] Rastan AJ, Dege A, Mohr M, et al. Early and late outcomes of 517 consecutive adult patients treated with extracorporeal membrane oxygenation for refractory postcardiotomy cardiogenic shock. *J Thorac Cardiovasc Surg.* 2010;139(2):302–11–311.e1. doi: 10.1016/j.jtcvs.2009.10.043.
- [5] 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(2):R73. doi: 10.1186/cc12681.
- [6] Dalton HJ, Garcia-Filion P, Holubkov R, et al. Association of bleeding and thrombosis with outcome in extracorporeal life support. *Pediatr Crit Care Med.* 2015;16(2):167-174. doi: 10.1097/PCC.0000000000000317.
- [7] Murphy DA, Hockings LE, Andrews RK, et al. Extracorporeal membrane oxygenation-hemostatic complications. *Transfus Med Rev.* 2015;29(2):90-101. doi: 10.1016/j.tmr.2014.12.001.
- [8] Lubnow M, Philipp A, Foltan M, Bull Enger T, Lunz D, Bein T, Haneya A, Schmid C, Riegger G, Müller T, Lehle K. Technical complications during veno-venous extracorporeal membrane oxygenation and their relevance predicting a system-exchange--retrospective analysis of 265 cases. *PLoS One.* 2014 Dec 2;9(12):e112316. doi: 10.1371/journal.pone.0112316.
- [9] Lehle K, Philipp A, Zeman F, et al. Technical-Induced Hemolysis in Patients with Respiratory Failure Supported with Veno-Venous ECMO - Prevalence and Risk Factors. Ahrens I, ed. *PLoS ONE.* 2015;10(11):e0143527. doi:10.1371/journal.pone.0143527.
- [10] ELSO Guidelines General v1.4, Aug 2017.
- [11] Betit P. Technical Advances in the Field of ECMO. *Respir Care.* 2018 Sep;63(9):1162-1173. doi: 10.4187/respcare.06320.
- [12] 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 Nov 28;20(1):387. doi: 10.1186/s13054-016-1570-4.
- [13] Lehle K, Philipp A, Gleich O, Holzamer A, Müller T, Bein T, Schmid C. Efficiency in extracorporeal membrane oxygenation-cellular deposits on polymethylpentene membranes increase resistance to blood flow and reduce gas exchange capacity. *ASAIO J.* 2008 Nov-Dec;54(6):612-7. doi: 10.1097/MAT.0b013e318186a807.
- [14] Weitz JI, Fredenburgh JC, Eikelboom JW. A Test in Context: D-Dimer. *J Am Coll Cardiol.* 2017 Nov 7;70(19):2411-2420. doi: 10.1016/j.jacc.2017.09.024.
- [15] Olson JD. D-dimer: An Overview of Hemostasis and Fibrinolysis, Assays, and Clinical Applications. *Adv Clin Chem.* 2015;69:1-46. doi: 10.1016/bs.acc.2014.12.001.
- [16] Tripodi A. D-dimer testing in laboratory practice. *Clin Chem.* 2011 Sep;57(9):1256-62. doi: 10.1373/clinchem.2011.166249.
- [17] Dornia C, Philipp A, Bauer S, Stroszczyński C, Schreyer AG, Müller T, Koehl GE, Lehle K. D-dimers Are a Predictor of Clot Volume Inside Membrane Oxygenators During Extracorporeal Membrane Oxygenation. *Artif Organs.* 2015 Sep;39(9):782-7. doi: 10.1111/aor.12460.

[18] Lubnow M, Philipp A, Dornia C, Schroll S, Bein T, Creutzenberg M, Diez C, Schmid C, Pfeifer M, Riegger G, Müller T, Lehle K. D-dimers as an early marker for oxygenator exchange in extracorporeal membrane oxygenation. *J Crit Care*. 2014 Jun;29(3):473.e1-5. doi: 10.1016/j.jcrc.2013.12.008.

[19] Anoop P, Chappell P, Kulkarni S, Shirley JA. Evaluation of an immunoturbidimetric D-dimer assay and pretest probability score for suspected venous thromboembolism in a district hospital setting. *Hematology*. 2009 Oct;14(5):305-10. doi: 10.1179/102453309X446162.

[20] Basken R, Cosgrove R, Malo J, Romero A, Patanwala A, Finger J, Kazui T, Khalpey Z, Mosier J. Predictors of Oxygenator Exchange in Patients Receiving Extracorporeal Membrane Oxygenation. *J Extra Corpor Technol*. 2019 Jun;51(2):61-66. PMID: 31239577; PMCID: PMC6586268.

[21] Rastan AJ, Lachmann N, Walther T, Doll N, Gradistanac T, Gommert JF, Lehmann S, Wittekind C, Mohr FW. Autopsy findings in patients on postcardiotomy extracorporeal membrane oxygenation (ECMO). *Int J Artif Organs*. 2006 Dec;29(12):1121-31. doi: 10.1177/039139880602901205.

APPENDIX

Appendix 1: Demographics, clinical and biological data in a preliminary cohort of patients on ECMO for at least 72 hours from April 2015 to July 2016 (n = 50).

variable	survivors (n = 29)	non survivors (n=21)	OR	95% CI	p-value
age – years	55 [42;61]	50 [41;59]	0.99	[0.96;1.03]	0.79
male sex – no (%)	22 (63%)	13 (37%)	0.52	[0.15;1.76]	0.29
SAPS II score ¹	52 [41;65]	56 [46;68]	0.98	[0.94;1.02]	0.27
BMI ² – kg/m ²	24.0 [21.3;27.0]	24.6 [22.9;28.7]	1.07	[0.94;1.22]	0.28
time on support - hours	168 [96;264]	317 [215;384]	1.01	[1.00;1.01]	0.004
heart or lung transplantation – no (%)	13 (45%)	6 (29%)	0.49	[0.15;1.63]	0.25
Thrombosis ³ – no (%)	5 (17.24%)	11 (52.38%)	5.28	[1.51;19.21]	0.01
FdO ₂ ⁴ – %	80 [70;100]	100.00 [100;100]	1.07	[1.01;1.14]	0.03
circuit replacement – no (%)	13 (45%)	16 (76%)	3.94	[1.14;13.64]	0.03
anti-Xa activity, min. – UI/mL	0.1 [0.1;0.1]	0.1 [0.1;0.1]	20.3	[1.00;1.54]	0.58
D-dimer max. – ng/L	14982 [7985;29705]	16692 [12438;40435]	1.0	[1.00;1.00]	0.14
schistocytes max. – /mm ³	5.0 [3.0;7.0]	6.5 [4.5;18.5]	1.1	[0.97;1.19]	0.18
PfHb ⁵ max – mg/L	26.0 [24.5;95.3]	76.0 [29.0;724.5]	1.0	[1.00;1.00]	0.09
IPF ⁶ max. – %	8.8 [6.4;13.1]	20.5 [9.9;26.5]	1.3	[1.05;1.47]	0.009
factor VIII min. – %	215 [146;245]	194 [121;260]	1.0	[0.99;1.01]	0.91
antithrombin min. – %	50 [37;58]	49.00 [38;74]	1.02	[0.98;1.05]	0.32
fibrinogen min. – g/L	2.4 [1.9;3.0]	2.1 [1.6;2.4]	0.9	[0.6;1.5]	0.78
fibrin degradation product - µg/mL	42.5 [10.0;120.0]	25.0 [10.0;60.0]	1.00	[0.98;1.01]	0.58
CPK ⁷ – UI/L	36.5 [21.0;42.6]	39.0 [3.6;129.8]	1	[1.00;1.01]	0.31
haptoglobin – µmol/L	0.10 [0.10;0.10]	0.10 [0.10;0.10]	0.03	[0.0;702.3]	0.49
prothrombin ratio min. – %	49 [41;56]	44 [36;54]	0.98	[0.94;1.02]	0.34
hemoglobin min. – g/dL	7.8 [7.5;8.0]	7.7 [7.2;8.1]	1.24	[0.47;3.25]	0.66
platelets min. – G/L	43 [35;46]	38 [33;51]	0.99	[0.94;1.04]	0.69

¹Simplified Acute Physiology Score II, ²body mass index, ³ECMO or patient thrombosis, ⁴fraction delivered in oxygen on ECMO, ⁵plasma free hemoglobin, ⁶immature platelet fraction, ⁷creatinine phosphokinase.

Appendix 2: Incidence of outcomes in the primary analysis and comparison of maximum D-dimer values.

outcome	patients not presenting outcome		patients presenting outcome		p-value ¹
	no (%)	maximum D-dimer – mean [95% Student CI]	no (%)	maximum D-dimer - mean [95% Student CI]	
MO impairment²	51 (52,6%)	33971 [23393; 44550]	46 (47,4%)	53012 [40304; 65721]	0.022
need for MO exchange	55 (56,7%)	31889 [21656; 42122]	42 (43,3%)	57552 [44782; 70322]	0.002
ECMO-related thrombosis	94 (96,9%)	41783 [33436; 50129]	3 (3,1%)	81168 [-14531; 176867]	0.215
arterial thrombosis	85 (87,6%)	43942 [35206; 52677]	12 (12,4%)	36339 [6949; 65728]	0.597
venous thrombosis	79 (81,4%)	43787 [34535; 53039]	18 (18,6%)	39551 [19167; 59935]	0.696
survival at ICU discharge	75 (77,3%)	49136 [28395; 69877]	22 (22,7%)	41201 [32136; 50267]	0.475

¹Student T-test (p values < 0,05 considered significant), ²at least one PO₂ / fiO₂ measurement < 300 mmHg on arterial cannulae

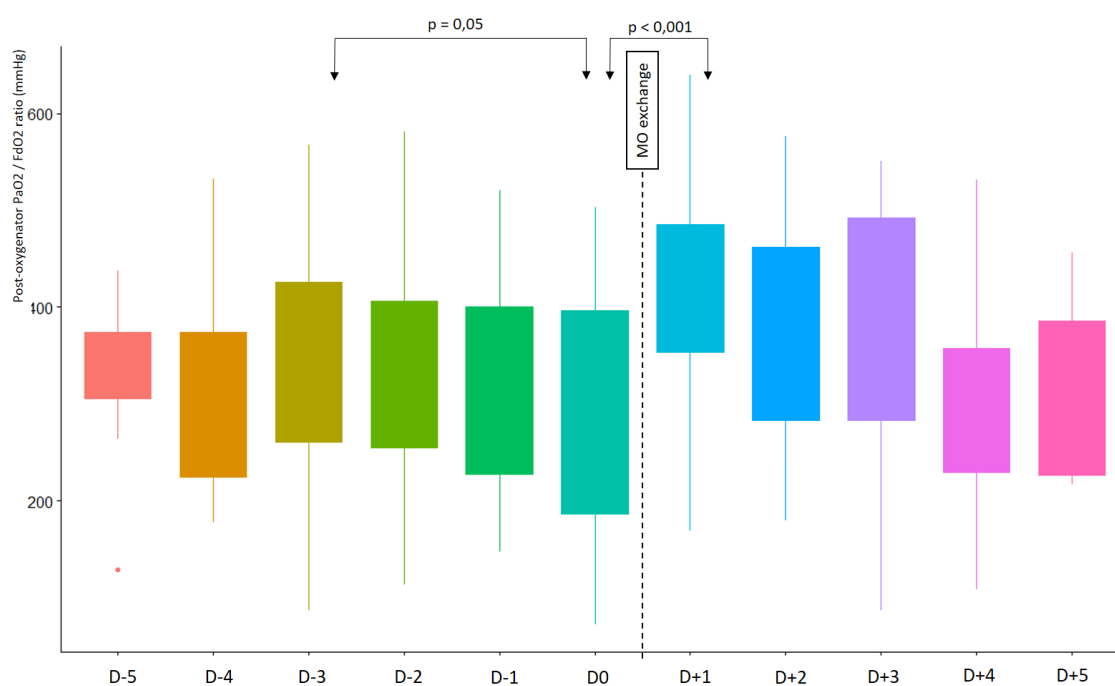
Appendix 3: Patients' characteristics in the secondary analysis (n = 42).

age – year	51,5 (+/- 16,6)
male sex – no.	37 (88,1%)
SAPS II score¹	52,1 (+/- 13,3)
BMI² – kg/m²	25,0 (+/- 5,7)
ECMO³ duration – days	11,3 (+/- 7,7)
type of cannulation – no (%) :	
- veno-arterial	39 (92,9%)
- veno-venous	3 (7,1%)
- central	12 (28,6%)
- peripheral	30 (71,4%)
ECMO indication – no (%) :	
- primary graft dysfunction after heart transplant	4 (9,5%)
- cardiogenic shock after cardiac arrest and terminal cardiomyopathy	17 (40,5%)
- post-cardiotomy	15 (35,8%)
- ARDS⁴	3 (7,1%)
- other	3 (7,1%)
RRT⁵ during ECMO – no (%)	15 (35,8%)
antiplatelet medication during ECMO – no (%) :	
- no antiplatelet drug	21 (50,0%)
- one antiplatelet drug	13 (31,0%)

- two antiplatelet drugs	8 (19,1%)
myelopoiesis stimulation – no (%) :	
- erythropoietin administration	19 (45,2%)
- thrombopoietin administration	13 (31,0%)
proportion of days without effective anticoagulation during ECMO ⁶	28,0% (+/-25,7)

¹Simplified Acute Physiology Score II, ²body mass index, ³extracorporeal membrane oxygenation, ⁴acute respiratory distress syndrome, ⁵renal replacement therapy, ⁶number of days with at least one anti-Xa factor assay below 0,20 UI/mL, divided by the number of days of ECMO for each patient.

Appendix 4: Boxplot showing post-oxygenator PO₂ / FdO₂ ratio evolution from 5 days before (D-5) to 5 days after (D+5) MO exchange (n = 53).



MO: membrane oxygenator. Arrows show non-significant difference between D-3 and D0 ($p = 0,0053$), and significant difference between D0 and D+1 ($p < 0,001$) (T-test).

Nom : LE NESTOUR Vincent. **Date de naissance :** 3 décembre 1993.

Titre de thèse : Intérêt du dosage des D-dimères chez les patients sous ECMO : étude rétrospective.

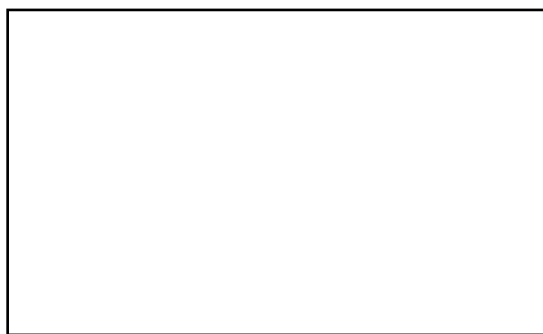
RÉSUMÉ :

Les patients assistés par oxygénation par membrane extracorporelle (ECMO, selon le sigle anglophone) présentent, pour des raisons multifactorielles, une hémostasie perturbée. Des phénomènes thrombotiques, potentiels sources de morbi-mortalité, sont susceptibles d'intervenir à la fois sur l'oxygénateur de l'ECMO, mais aussi de façon systémique. Dans cette étude, nous avons analysé un biomarqueur de la fibrinoformation et de la fibrinodégradation, le D-dimère, afin d'analyser son taux dans une cohorte de patients sous ECMO susceptibles de présenter ces phénomènes thrombotiques.

L'analyse a été conduite de façon rétrospective de mars 2019 à août 2021, chez des patients assistés plus de 72 heures par ECMO, qui avaient un dosage quotidien de D-dimères. Les critères de jugement principaux étaient d'une part le recours à un ou plusieurs changements d'oxygénateur, et d'autre part la dysfonction d'oxygénateur définie par la mesure d'au moins un ratio de pression partielle en oxygène / fraction délivrée en oxygène par l'ECMO inférieur à 300 mmHg.

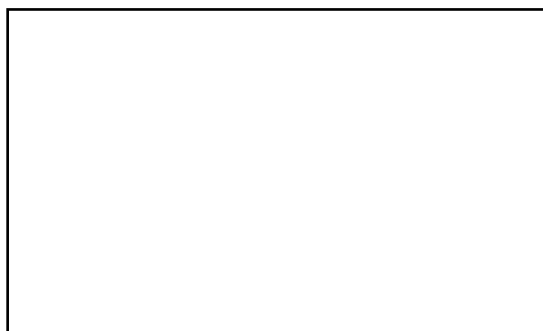
Quatre-vingt-dix-sept patients ont été inclus dans l'analyse. Une différence significative du maximum de D-dimères était observée d'une part entre les patients n'ayant pas et ayant eu au moins un changement d'oxygénateur (respectivement 31889 vs. 57552 ng/L, $p = 0,002$), et d'autre part entre les patients n'ayant pas eu et ayant eu une dysfonction d'oxygénateur (respectivement 36197 vs. 67626 ng/L, $p = 0,006$). Aucune différence significative n'était observée sur les critères de jugement secondaires.

Vu, le Président du jury



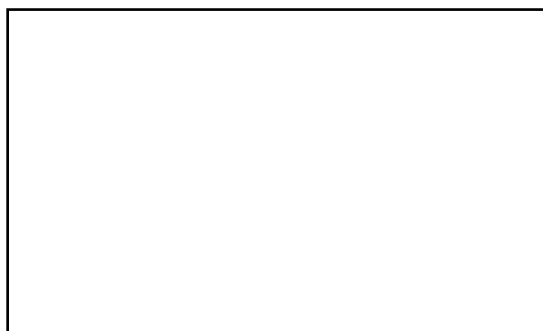
Pr B. ROZEC

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Dr M. VOURC'H

Vu, le Doyen de la Faculté



Pr P. JOLLIET