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Assistance respiratoire extra-corporelle veino-veineuse au cours du syndrome de détresse respiratoire aigu dû à la COVID-19 : Comparaison entre les premières et secondes vagues

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Abbreviation list

ΔP: Driving pressure

APRV: airway pressure release ventilation

aPTT: activated partial thromboplastin time.

ASAT: aspartate aminotransferase

ALAT: alanin aminotransferase

BMI: body mass index

CARDS: COVID-19-Acute Respiratory Distress Syndrome

COVID-19: Coronavirus disease 2019

Compliance RS: respiratory system compliance

ELSO: Extracorporeal Life Support Organization

EOLIA: ECMO to Rescue Lung Injury in Severe ARDS

FiO2: fraction of inspired oxygen

FmO2: fraction of membrane oxygen

MP: Mechanical Power

NO: Nitric oxide

Ppeak: Peak pressure

Pplat: plateau pressure

PEEP: positive end-expiratory pressure

RESP: Respiratory Extracorporeal Membrane Oxygenation Survival Prediction.

RR: respiratory rate

RPM: rate per minute

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SAPSII: Simplified Acute Physiology Score II

SOFA: Sequential Organ-Function Assessment

V-V ECMO: veno-venous extracorporeal membrane oxygenation

Vt: Tidal volume

Vt IBW: ideal body weight tidal volume

V-A ECMO: veno-arterial extracorporeal membrane oxygenation

Abréviations françaises

PAVM : pneumonie acquise sous ventilation mécanique

REVA : réseau européen de recherche en ventilation artificielle

SDRA : syndrome de détresse respiratoire aigu

SDRA COVID : syndrome de détresse respiratoire aigu lié à la COVID-19

Abstract

Background

During the two waves of COVID-19 pandemic, significant advance in intensive care management has emerged ranging from immunomodulatory therapies to ventilatory setting. We aimed to compare the characteristics and outcomes of patients under veno-venous extracorporeal membrane oxygenation (V-V ECMO) for COVID-19-Acute Respiratory Distress Syndrome (CARDS) between the first and the second wave.

Methods

The present study was a single-center retrospective observational cohort study from March 1st 2020, to November 30th 2020. All consecutive adult patients requiring V-V ECMO for severe CARDS were included. Patient demographics, pre-ECMO and Day 1, 3, 7 on-ECMO data and outcomes were collected.

Results

Fifty patients required a V-V ECMO support for CARDS. The overall 90-day mortality was 32/50 (64%). This mortality rate was 11% higher during the second wave [18/26 (69%)] compared to the first wave [14/24 (58%)], but without reaching statistical significance (p=0,423). During the second wave, all the patients were given steroids before ECMO implantation compared to 16.7% during the first wave (p<0.001). Second wave's patients had been on non-invasive ventilation support for a longer period than in the first wave, with a median time from ICU admission to ECMO implantation significantly higher [14 (11-20) vs. 7.7 (5-12) days; p<0.001]. Mechanical properties of the lung were worsened in second wave's CARDS patients before ECMO implantation [median static compliance 20 (16-26) vs. 29 (25-37) mL/cmH2O; p<0.001] and during ECMO day 1, 3, 7. More bacterial co-infections before implantation and under ECMO were documented in the second wave group.

Conclusion

ECMO provides a valuable support for patients developing CARDS, but despite a better evidence-driven critical care management, we depicted less encouraging outcomes during the second wave.

Résumé français

Introduction

Durant les deux vagues de la pandémie de COVID-19, des avancées significatives dans la prise en charge en médecine intensive réanimation ont émergé allant des thérapies immunomodulatrices aux adaptations des stratégies ventilatoires. L'objectif de notre étude était de comparer les caractéristiques et le devenir des patients placés sous assistance respiratoire extra-corporelle veino-veineuse de type *Extra Corporeal Membrane Oxygenation* (ECMO) pour syndrome de détresse respiratoire aigu lié à la COVID-19 (SDRA COVID) entre les premières et deuxièmes vagues épidémiques.

Méthode

Il s'agissait d'une étude de cohorte observationnelle, rétrospective, monocentrique réalisée du 1er mars au 30 novembre 2020. Tous les patients adultes consécutifs requérant une ECMO pour un SDRA COVID sévère étaient inclus. Les données démographiques, les données pré-ECMO et sous ECMO à J 1, 3 et 7 ainsi que le devenir des patients étaient collectés.

Résultats

Durant la période de l'étude, 50 patients étaient placés sous ECMO pour un SDRA COVID. La mortalité globale à J90 était de 32/50 (64%). Ce taux de mortalité était 11% plus élevé durant la seconde vague épidémique [18/26 (69%)] comparé à la première vague [14/24 (58%)], mais sans atteindre la significativité statistique (p=0,423). Durant la seconde vague, tous les patients étaient sous corticoïdes avant l'implantation de l'ECMO comparé à 16,7% durant la première vague (p<0.001). Les patients de la seconde vague étaient placés sous support ventilatoire non invasif durant une période plus longue que lors de la première vague avec un temps médian de l'admission en réanimation à l'implantation de l'ECMO significativement plus long [14 (11-20) vs. 7.7 (5-12) jours; p<0.001]. Les propriétés mécaniques du poumon étaient plus altérées durant la seconde vague des patients atteints de SDRA COVID avant implantation de l'ECMO [compliance statique médiane de 20 (16-26) vs. 29 (25-37) mL/cmH2O; p<0.001] et sous ECMO à J1, J3 et

J7. Des co-infections bactériennes étaient significativement plus documentées avant implantation et sous ECMO durant la seconde vague épidémique.

Conclusion

L'ECMO assure un traitement de support efficace pour les patients développant un SDRA COVID, mais malgré une amélioration de la prise en charge en réanimation basée sur des preuves scientifiques, nous décrivons des évolutions moins encourageantes durant la seconde vague.

Introduction (français)

La COVID-19 causée par le nouveau coronavirus SARS-CoV-2 peut conduire à des dysfonctions d'organe sévères. L'insuffisance respiratoire aiguë apparait être la principale indication d'admission en soins intensifs avec un taux d'admission en réanimation de 4,0 à 32% (1). Précocement au cours de l'épidémie actuelle, des controverses concernant les stratégies ventilatoires ont émergé (2-5). Certains experts et plusieurs recommandations internationales ont préconisé une intubation orotrachéale précoce plutôt qu'une prise en charge ventilatoire non invasive (6-11). Cette approche était motivée d'une part, par la prévention de contamination aérienne du personnel soignant et d'autre part, afin de diminuer le risque de lésions pulmonaires auto-induites par le patient, dénommées P-SILI (« Patient self-inflicted lung injury »), qui sont un facteur aggravant de l'insuffisance respiratoire (6-13). Durant la seconde vague de l'épidémie de COVID-19, une importante accumulation de preuves scientifiques ont influencé la stratégie globale de prise en charge. L'administration précoce d'une faible dose de corticoïdes a montré une diminution de la mortalité chez les patients atteints de la COVID-19 (14). Un nombre croissant de publication ont révélé que le syndrome de détresse respiratoire aigu lié à la COVID-19 (SDRA COVID) était similaire à un syndrome de détresse respiratoire aigu (SDRA) de cause classique (15-16). Ceci a conduit les médecins réanimateurs à être plus enclins à utiliser des stratégies ventilatoires non invasives. L'étude de cohorte prospective du réseau européen de recherche en ventilation artificielle (REVA) a mis en évidence une diminution progressive de la mortalité à J90 avec une plus forte proportion de patients sous stratégies ventilatoires non invasives durant la deuxième vague (17). Néanmoins, ces données sont contrastées par d'autres résultats concernant les patients sous ventilation mécanique invasive qui retrouvaient une augmentation de mortalité durant la seconde vague (18).

En cas de SDRA COVID réfractaires à une prise en charge ventilatoire optimale, l'assistance respiratoire extra-corporelle veino-veineuse de type *Extra Corporeal Membrane Oxygenation* (ECMO) apparait être un traitement de support efficace avec des critères conventionnels de

sélection des patients (19-22). La prévalence de patients atteints de COVID-19 placés sous ECMO veino-veineuse était de 6,4% (IC95%, 4,1-9,1) des admissions en réanimation (23) avec une incidence cumulée de mortalité à J90 de 38% (IC95%, 34,6-41,5) (20). Cependant, des résultats préliminaires du réseau européen de traitement de support extra-corporel (Euro-ELSO) retrouvaient une augmentation de mortalité entre les premières et deuxièmes vagues des patients atteints de COVID-19 sous ECMO veino-veineuse (24).

Finalement, peu de données sont disponibles sur l'impact des stratégies thérapeutiques combinées actuelles (stratégies ventilatoires et corticothérapie) sur les patients atteints de COVID-19 les plus sévères placés sous ECMO veino-veineuse sur une longue période d'étude. L'objectif de cette étude était de comparer les caractéristiques et l'évolution des patients placés sous ECMO veino-veineuse pour un SDRA COVID entre les premières et deuxièmes vagues de l'épidémie de COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can lead to severe organ dysfunction. Acute respiratory failure appears to be the main indication for critical care admission with a rate of ICU admission from 4.0% to 32%(1). Early in the ongoing pandemic, controversy regarding ventilatory management has emerged(2–5). Some expert physiologists and several international guidelines have endorsed early intubation over an initial non-invasive strategy(6–11). This approach was driven both by the prevention of further contamination and the lower risk of patient self-induced lung injury which has been incriminated to further worsen respiratory failure(6–13). During the second wave of the COVID-19 outbreak, cumulative evidence influenced the global strategy of care management. An early low dose of corticosteroids has been proven to decrease the mortality in COVID-19 patients(14). A growing body of reports revealed COVID-19-Acute Respiratory Distress Syndrome (CARDS) as being similar to classic ARDS(15, 16). Thus, physicians were less reluctant to use non-invasive ventilatory strategy. The prospective REVA network's cohort study captured a progressive decrease in 90-day mortality with a higher proportion of patients on non-invasive ventilatory management(17). Furthermore, other data concerning patients on invasive mechanical ventilation found an increase in mortality during the second wave(18).

In case of CARDS refractory to other management strategies, veno-venous extracorporeal membrane oxygenation (V-V ECMO) appears to provide a valuable support with conventional patient selection criteria(19–22). The pooled estimate of prevalence of COVID-19 patients placed on ECMO was 6.4% (95% CI, 4.1-9.1) of ICU cases(23) with a cumulative incidence of 90 day-mortality at 38% (95%CI, 34,6-41,5)(20). However, preliminary results of the European Extracorporeal Life Support Organization (ELSO) found an increase in mortality between the first and the second waves in COVID-19 patients under V-V ECMO(24). Finally, little is known about the impact of the current bundled treatment combination (ventilatory strategies and corticosteroids) on the most critically ill COVID-19 patients on V-V ECMO for a long study period.

The aim of this study was to describe the characteristics and outcomes of patients who received V-V ECMO for CARDS between the first and the second wave of the COVID-19 outbreak.

Materials and Methods

Study design and participants

The present study was a single-center retrospective observational study. From March 1st 2020, to November 30th 2020, all consecutive adult patients with laboratory confirmed SARS-CoV-2 infection, admitted in ICU to receive V-V ECMO for severe ARDS at the Lille University Hospital were included. Patients who received veno-arterial ECMO (V-A ECMO) were excluded. March 1st 2020 to May 31th 2020 defines the first wave, and September 1st 2020 to November 30th 2020 defines the second wave of the COVID-19 outbreak. All SARS-CoV-2 infections were documented by real-time RT-PCR on nasopharyngeal swabs and lower respiratory tract aspirates. Severe ARDS was defined according to Berlin's definition(25). Patients received V-V ECMO in case of refractory hypoxemia and/or hypercapnia despite ventilator optimization according to the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA)'s criteria (26).

French institutional authority for personal data protection (Committees for the Protection of Human Subjects, registration no DEC21-199) approved the study. Patient data were anonymized before analysis. According to French laws, only non-opposition of the patient or their legal representative for use of the data was obtained because this observational study did not modify existing diagnostic or therapeutic strategies.

Data Collection and Outcome Measures

Data was collected from our electronic health records (IntelliSpace Critical Care and Anesthesia (ICCA), Philips Healthcare®).

V-V ECMO cannulation was done percutaneously under ultrasonography guidance by an intensivist physician or a cardiovascular surgeon. Unless anatomic contraindication blood drainage with a large cannula (23–29 Fr) inserted into the common femoral vein and returned through the right internal jugular vein (17-21 Fr) was recommended. Pump speed was adjusted to obtain a blood-oxygen saturation of 90% or more. Cannula position was guided by ultrasonography and verified by chest x-ray. For highly unstable patients in a secondary hospital,

our mobile ECMO retrieval teams were sent to the patient's bedside for ECMO cannulation. Once ECMO had been implanted, patients were referred to our hospital. According to preliminary reports of high thrombotic complication during management in COVID-19 patients on ECMO(19, 20, 49), systemic anticoagulation was maintained using unfractioned heparin for a targeted anti-Xa activity of 0.3–0.5 UI/mL after an initial bolus of 50–100 IU/kg. This targeted anti-Xa activity was decreased in high risk of bleeding and hemorrhagic patients. Plasma-free haemoglobin, haptoglobin and schizocytosis concentrations were monitored daily. The haemoglobin threshold for red blood cell transfusion was 7–8 g/dL (or 10 g/dL when hypoxemia persisted); platelet transfusions were discouraged except for severe thrombocytopenia (<50 × 109 cells per L) or thrombocytopenia of more than 100 × 109 cells per L with bleeding. Ultraprotective mechanical ventilation targeting lower tidal volume (1-4 mL/kg of IBW), respiratory rate (< 20/min), and driving pressure (< 15 cmH2O) was recommended for the first days of V-V ECMO initiation. Prone positioning under ECMO and early spontaneous breathing using airway pressure release ventilation (APRV) or Spontaneous – Proportional Pressure Support were strongly recommended.

Driving pressure (ΔP) was calculated according to Amato et al.(27), as end-inspiratory plateau pressure minus PEEP. Mechanical Power (MP) was computed with surrogate formulas defined elsewhere(28, 29). Major bleeding was defined according to ELSO guidelines(19). Massive hemolysis was defined as plasma-free hemoglobin > 500 mg/L associated with clinical signs of hemolysis. Thrombotic complications included proven pulmonary embolism and deep venous thrombosis. Reasons for circuit change was clogged circuit, thrombocytopenia, hypofibrinogenemia, acquired Willebrand's disease, membrane lung failure (define to PaO2/FmO2 < 250), pump failure.

The primary objective of this study was to compare the overall 90-day mortality of CARDS patients on V-V ECMO between the first and the second waves of SARS-CoV-2's outbreak.

The secondary objective was to describe hospital mortality, ICU and hospital lengths of stay, duration of ECMO, mechanical ventilation, catecholamines and RRT, rate of ECMO weaning,

prognostic scores (SAPS II(30), Sequential Organ-Failure Assessment score(31), Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score(32)), demographic characteristics, clinical and biological parameters, respiratory support and mechanical data, adjunctive interventions, and adverse events (ischemic stroke, hemorrhagic stroke, major bleeding, thrombotic complications, massive hemolysis, circuit change, cardiac arrest, pneumothorax, ventilator associated pneumonia, bacteremia, and acute kidney injury defined as KDIGO III score) before ECMO and on ECMO at day 1, 3, 7 between the two phases of SARS-CoV-2's outbreak.

Data Analysis

Categorical and quantitative variables were reported as percentage (%) and medians (interquartile range) or means (standard deviation) as appropriate. We compared groups using $\chi 2$ or Fisher exact tests for categorical variables, and Mann-Whitney U or Unpaired t tests for continuous variables. All the analyses were computed at a two-sided α level of 5% with the software GraphPad Prism 9.1.2® and IBM SPSS Statistics 28.0.0.0®.

Results

From March 1st 2020, to November 30th 2020, 52 patients required a V-V ECMO assistance for CARDS. Two patients in the second wave group had a V-A ECMO support for cardiac arrest and were excluded from the analysis. The flow chart of the study is reported in **Figure 1**. The main indication for ECMO implantation was a PaO2/FiO2 < 80 mmHg for > 6 hours concerning 38/50 (76%) patients of the global cohort with no difference between the two groups, respectively 19/24 (79%) and 19/26 (73%) of patients. Other indications were refractory hypoxemia with PaO2/FiO2 < 50 mmHg for > 3 hours for two patients in each group, persistent hypercapnic acidosis with pH < 7.25 and PaCO2 > 60 mmHg for > 6h for six patients (2 in the first wave and 4 in the second wave), and other reasons not included in EOLIA trial inclusion criteria for one patient in each group. All V-V ECMO cannulation was done percutaneously. Fourteen percent (7/50) of V-V ECMO were placed in a secondary hospital by mobile ECMO retrieval teams.

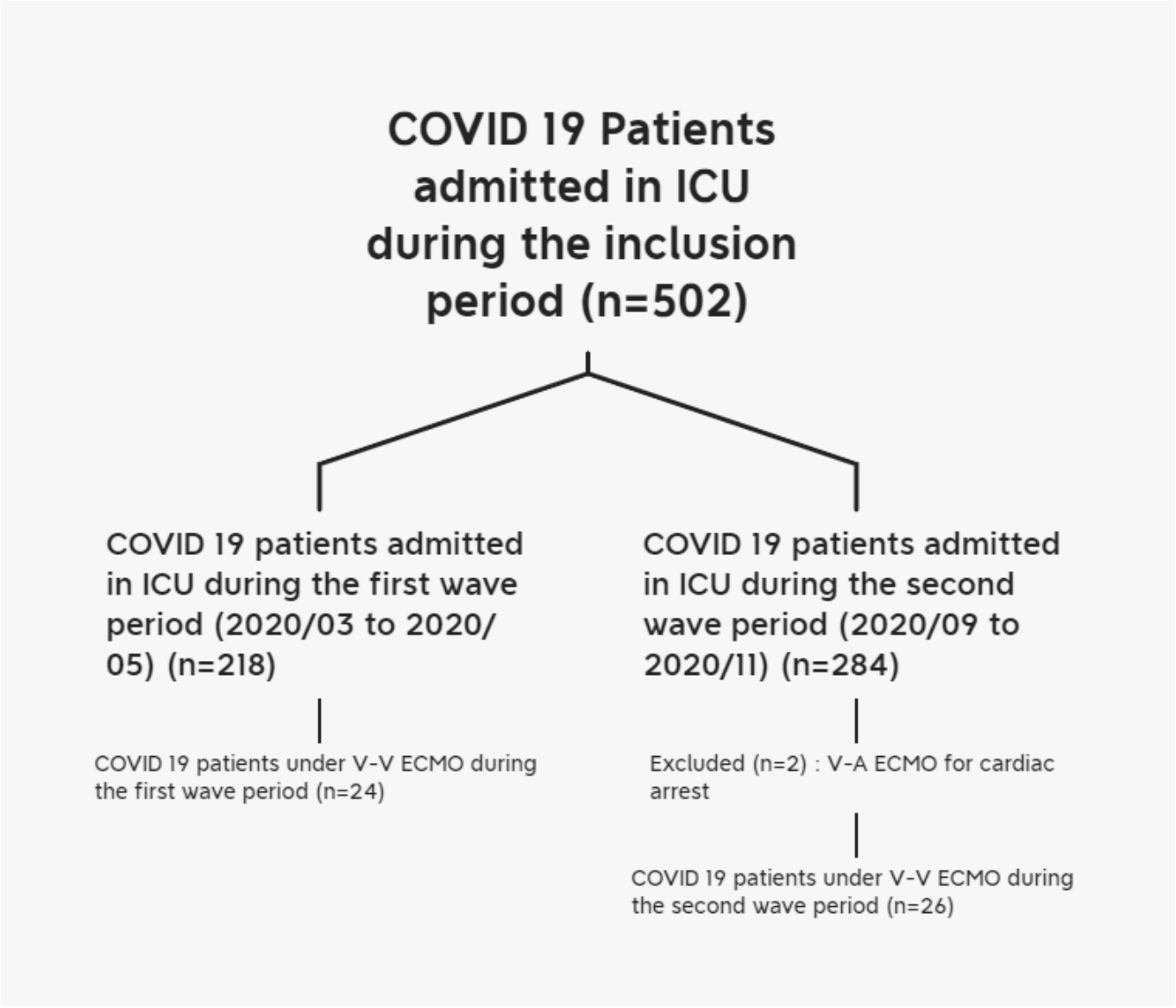

Figure 1*. Flow chart of the study. V-V ECMO : Veno-Venous Extracorporeal Membrane Oxygenation. V-A ECMO : Veno-Arterial Extracorporeal Membrane Oxygenation.*

Pre-ECMO characteristics are reported in **Table 1**. Demographic, prognostic scores, comorbidities between the first and second wave groups were not statistically different, except age and SOFA. The median times from first symptoms and ICU admission to ECMO were significantly higher in the second wave group due to a significantly longer time between ICU admission and intubation and the increased use of non-invasive respiratory support before intubation. Only 2/24 patients (8%) had at least 24-hours of High Flow Nasal Oxygen or non-invasive ventilation prior to intubation during the first wave compared to 21/26 patients (81%) during the second wave, $p<0.0001$. The median time from intubation to ECMO was similar between the first wave (7 (4-10) days) and the second wave groups (8 (3-12) days; $p=0.67$).

Table 1. Patients' Characteristics at Veno-venous Extracorporeal Membrane Oxygenation (V-V ECMO) Initiation in First and Second Wave Groups.

Characteristics at ECMO initiation	All patients (=50)	First Wave (=24)	Second Wave (=26)	P-value
Age (years)	61 (53-66)	58 (49-63)	63 (59-67)	**0.017**
Male	46 (92%)	21 (87.5%)	25 (96.2%)	0.34
BMI (kg/m²)	31 (28-36)	33 (29-38)	30 (27-35)	0.158
SAPSII	58 (34-67)	60 (42-69)	42 (32-67)	0.079
SOFA	10 (8-12)	11 (9-12)	9 (8-11)	**0.027**
RESP	-3 (-6,-1)	-2 (-4,-1)	-5 (-6.3,-1)	0.063
No Comorbidities	9 (18%)	6 (25%)	3 (11.5%)	0.216
HTA	27 (54%)	11 (46%)	16 (61.5%)	0.266
Diabetes	18 (36%)	9 (37.5%)	9 (34.6%)	0.832
Dyslipidemia	20 (40%)	7 (29.2%)	13 (50%)	0.133
Obesity (BMI > 30)	29 (58%)	16 (66.7%)	13 (50%)	0.233
Malignancy	1 (2%)	1 (4%)	0 (0%)	0.48
Other immunocompromised condition	6 (12%)	2 (8.3%)	4 (15.4%)	0.669
Time from first symptoms to ECMO (days)	16 (14-26)	15 (11-16)	19 (16-26)	**0.004**
Time from first symptoms to ICU (days)	7 (5-9)	7 (5-9)	6 (4-9)	0.33
Time from ICU admission to ECMO (days)	12 (6-15)	7.5 (5-12)	14 (11-20)	**<0.001**
Time from ICU admission to intubation (days)	1 (0-6)	0 (0-1)	5,5 (1-9)	**<0.001**

Data are median (IQR) or n (%). BMI=body mass index. SAPSII=Simplified Acute Physiology Score II. SOFA=Sequential Organ-Function Assessment. RESP=Respiratory Extracorporeal Membrane Oxygenation Survival Prediction. ECMO=extracorporeal membrane oxygenation.

Concerning biological parameters before ECMO, there was no significant difference between the two groups except for a much lower PaO2/FiO2 ratio in the second wave group (median 68 (57-75) mmHg compared to 73 (65-84) mmHg in first wave group, p=0.04), and lower inflammatory biomarkers (respectively, 7.1 (5.9-8.1) g/L for fibrinogen compared to 8 (7.2-9.3) g/L in first wave group, p=0.009 and 0.51 (0.23-1.6) ng/L for PCT compared to 1.8 (0.55-7.1) in first wave group, p =0.016). For more details, refer to **Supplementary Table 1.**

Details about respiratory support, adjuvant treatment, COVID-19 therapies, and complications pre-ECMO are reported in **Table 2**. Briefly, the whole cohort was placed on mechanical ventilation with an assist control ventilation mode before ECMO implantation. The median static compliance was significantly lower and the median driving pressure was significantly higher in second wave group. No difference was observed regarding adjuvant treatment for ARDS pre-ECMO between the two groups. In the second wave group, all patients received glucocorticoids with a median time to ECMO of 13 (11-19) days while only 16.7% patients of the first wave group with a median time to ECMO of 7.5 (5.3-9) days (p=0.015). Antiviral treatments were significantly more regularly administered in the first wave group in comparison to the second wave group. Regarding complication before ECMO implantation, we reported much higher pneumothorax and secondary bacterial infection in the second wave group. These infections were mainly documented bacterial ventilator associated pneumonia with respectively 5/24 (21%) in the first wave group and 13/26 (50%) in the second wave group (p=0.032). No difference regarding bacteremia was reported between the two wave groups, respectively 3/24 (12.5%) and 5/26 (19.2%).

Table 2. Respiratory support, Adjuvant Treatments, COVID-19 therapies, and Complications pre-ECMO in First and Second Wave Groups.

Pre-ECMO characteristics	All patients (=50)	First Wave (=24)	Second Wave (=26)	P-value
Respiratory Support				
FIO2	100 (100-100)	100 (100-100)	100 (88-100)	0.082
Vt (mL)	420 (380-460)	425 (393-480)	410 (380-440)	0.08
Vt IBW (mL/kg)	6,1 (5,7-6,6)	6,5 (5,7-7)	6 (5,3-6,2)	**0.009**
RR (bpm)	30 (26-31)	30 (26-30)	30 (30-32)	0.159
Ppeak (cmH2O)	40 (36-45)	43 (38-47)	38 (35-42)	0.068
Pplat (cmH2O)	30 (28-32)	30 (27-32)	31 (30-32)	0.402
PEEP (cmH2O)	12 (7.5-15)	14 (12-16)	10 (5-14)	**<0.001**
Driving Pressure (cmH2O)	17 (14-22)	15 (12-17)	21 (17-24)	**<0.001**
Static Compliance (mL/cm H2O)	25 (18-29)	29 (25-37)	20 (16-26)	**<0.001**
Mechanical Power (J/min)	35 (30-47)	43 (34-52)	32 (28-39)	**0.004**
Adjuvant treatment				
Prone Positioning (PP)	48 (96%)	24 (100%)	24 (92%)	0.491
Number of PP before ECMO	3 (2-5)	3 (2-5)	3 (2-5)	0.979
Neuromuscular Blockade	50 (100%)	24 (100%)	26 (100%)	1
Inhaled nitric oxide	44 (88%)	21 (87.5%)	23 (88.5%)	1
Almitrine	29 (58%)	11 (45.8%)	18 (69%)	0.094
COVID-19 therapies				
Glucocorticoids	30 (60%)	4 (16.7%)	26 (100%)	**<0.001**
Antiviral	14 (28%)	11 (45.8%)	3 (11.5%)	**0.007**
Complications pre-ECMO				
Renal replacement therapy	8 (16%)	5 (21%)	3 (11.5%)	0.456
Pulmonary embolism	15 (30%)	7 (29%)	8 (31%)	0.902
Pneumothorax	5 (10%)	0 (0%)	5 (19.2%)	**0.051**
Documented bacterial co-infection	21 (42%)	5 (21%)	16 (61.5%)	**0.004**

Data are median (IQR) or n (%). Antiviral therapies were Lopinavir-Ritonavir, Chloroquine, Remdesivir. FiO2=fraction of inspired oxygen. Vt=Tidal volume. Vt IBW=ideal body weight tidal volume. RR=respiratory rate. Ppeak=Peak pressure. Pplat=plateau pressure. PEEP=positive end-expiratory pressure.

ECMO, ventilation, and biological parameters, and SOFA score at day 1, 3, 7 under V-V ECMO between first wave and second wave groups are reported in **Table 3, supplementary Table 2 and 3**. The SOFA score was not statistically different between the first (12 (10-14)) and the second wave groups (11 (9.5-13); p=0.07) at Day 1 under V-V ECMO. During the ECMO course, 44/50 (88%) patients received glucocorticoids, respectively 22/24 (91.7%) in first wave group and 22/26 (84.6%) in second wave group, p=0.669. The inflammatory biomarkers remained lower at ECMO day 1,3,7 in the second wave group.

Table 3. ECMO, ventilation, and biological parameters at Veno-venous Extracorporeal Membrane Oxygenation (V-V ECMO) Day 1 in First and Second Wave Groups.

Day 1 Characteristics	Parameters	All patients (=50)	First Wave Group (=24)	Second Wave Group (=26)	P-value
ECMO parameters	FmO2 (%)α	100 (80-100)	100 (80-100)	95 (79-100)	0.648
	RPMβ	3600 (3300-4033)	3500 (3200-4065)	3600 (3375-4025)	0.705
	ECMO blood flow (L/min)γ	5.5 (5-6)	5.9 (5.5-6.1)	5.1 (4.8-5.5)	**0.025**
	Sweep gaz flow (L/min)δ	5 (4.3-6)	6 (4-6)	5 (4.4-6.3)	0.336
Ventilation parameters	FiO2 (%)φ	50 (40-50)	50 (40-60)	50 (40-60)	0.674
	Vt (mL)χ	250 (180-295)	280 (240-300)	230 (180-250)	0.197
	Vt IBW (mL/kg)ε	3.6 (2.7-4.3)	4 (3.5-4.8)	3.4 (2.4-3.9)	0.223
	RR (cpm)†	17 (13-20)	16 (14-20)	17 (12-21)	0.82
	Pplat (cmH2O)#	24 (20-26)	25 (22-27)	23 (20-25)	**0.034**
	PEEP (cmH2O)‡	12 (10-14)	14 (10-16)	10 (10-12)	**0.007**
	Driving Pressure (cmH2O)¶	12 (10-14)	11 (10-15)	12 (10-14)	0.376
	Compliance RS (mL/cm H2O)¥	21 (14-30)	23 (17-31)	19 (12-26)	0.273
	Mechanical Power (J/min)¤	9.4 (6.6-15)	12 (9-17)	7.4 (4.4-10)	**0.01**
Biological parameters	pH	7.4 (7.3-7.5)	7.4 (7.3-7.5)	7.4 (7.3-7.5)	0.836
	PaO2 (mmHg)	75 (65-85)	76 (67-87)	73 (65-84)	0.299
	PaCO2 (mmHg)	47 (42-55)	44 (40-50)	52 (44-59)	**0.016**
	Bicarbonates (mmol/L)	30 (26-34)	28 (24-32)	30 (27-35)	0.089
	Hemoglobin (g/dL)	8.7 (7.9-9.8)	8.5 (8-9.7)	8.7 (7.6-10)	0.841
	Platelets (10^9/L)	234 (162-301)	245 (178-326)	202 (156-267)	0.163
	Fibrinogen (g/L)	7.1 (5.4-8.2)	7.9 (6.6-8.7)	6.1 (4.6-7.6)	**0.002**
	aPTT (ratio)	1.5 (1.2-1.8)	1.5 (1.2-1.8)	1.5 (1.2-1.7)	0.662
	CRP (mg/L)d	148 (92-252)	178 (104-329)	107 (79-176)	**0.025**
	PCT (ng/mL)e	1 (0.3-3.2)	2.3 (0.6-4.8)	0.48 (0.2-1.8)	**0.048**

Values are number (%) or median (interquartile range). FmO2=fraction of membrane oxygen. RPM=rate per minute. FiO2=fraction of inspired oxygen. Vt=Tidal volume. Vt IBW=ideal body weight tidal volume. RR=respiratory rate. Ppeak=Peak pressure. Pplat=plateau pressure. PEEP=positive end-expiratory pressure. Compliance RS =

respiratory system compliance. aPTT=activated partial thromboplastin time. ASAT=aspartate aminotransferase. ALAT= alanin aminotransferase.

[α]1 missing value in first wave group, [β]1 missing value in first wave group, [γ]1 missing value in first wave group, [δ]1 missing value in first wave group, [φ]1 missing value in first wave group, [χ] 1 missing value in first wave group, 1 missing value in second wave group, [ε]1 missing value in second wave group, †1 missing value in first wave group, 1 missing value in second wave group, #1 missing value in first wave group, 1 missing value in second wave group, ‡1 missing value in first wave group, 1 missing value in second wave group, ¶1 missing value in first wave group, 1 missing value in second wave group, ¥1 missing value in first wave group, 1 missing value in second wave group, ¤1 missing value in first wave group, 1 missing value in second wave group, [d]1 missing value in first wave group, [e]2 missing values in first wave group.

Concerning ARDS adjuvant treatments, 34/50 (68%) patients were prone positioning in the whole cohort, with 13/24 (54.2%) in the first wave group and 21/26 (80.8%) in the second wave group (p=0.044). No significant difference between groups was noted concerning the use of inhaled nitric oxide and almitrine. Ninety-eight percent patients received red cells transfusion under ECMO with median 8.5 (5-14) packed red blood cells, 34% received platelets, 28% received fresh frozen plasma, and 14% received fibrinogen concentrate under ECMO with no difference between the two groups. For more details, refer to **Supplementary Table 4**.

Outcomes and complications under ECMO are reported in **Table 4**. The overall 90-day mortality of COVID-19 patients under V-V ECMO was 32/50 (64%) in our cohort. This mortality rate was higher during the second wave 18/26 (69%) compared to first wave 14/24 (58%), but without reaching statistical significance (p=0.423). Renal replacement therapy was used during ECMO support in nearly half of the whole cohort (22 (44%) patients) and significantly more frequently during the first wave.

Table 4. Outcomes and complications under ECMO in First and Second Wave Groups.

Outcomes and Complications under ECMO	All patients (=50)	First Wave (=24)	Second Wave (=26)	P-value
Outcomes				
Lenght of stay ICU (days)	33 (20-60)	25 (17-42)	35 (26-71)	0.055
Lenght of stay Hospital (days)	33 (21-64)	26 (19-53)	40 (26-97)	**0.021**
Length of Catecholamines (days)	14 (7-17)	8 (6-16)	15 (9-27)	**0.049**
Length of RRT (days)	0 (0-10)	5 (0-13)	0 (0-6.3)	**0.045**
Length of Mechanical ventilation (days)	23 (16-45)	21 (15-38)	29 (19-61)	0.097
ECMO weaning	20 (40%)	11 (46%)	9 (35%)	0.419
ECMO duration (days)	12 (7-16)	11 (6-13)	14 (8.8-25)	**0.013**
Tracheotomy	16 (32%)	6 (25%)	10 (38%)	0.308
Hospital mortality	31 (62%)	14 (58%)	17 (65%)	0.608
Complications				
Ischemic stroke	2 (4%)	2 (8.3%)	0 (0%)	0.225
Hemorrhagic stroke	6 (12%)	4 (16.6%)	2 (7.7%)	0.409
RRT	22 (44%)	15 (62.5%)	7 (26.9%)	**0.011**
Hemorrhagic - Site canulation	32 (64%)	12 (50%)	20 (76.9%)	**0.048**
Hemorrhagic - Other	33 (66%)	14 (58.3%)	19 (73.1%)	0.272
Thrombotic	8 (16%)	5 (20.8%)	3 (11.5%)	0.456
Circuit change	20 (40%)	8 (33.3%)	12 (46.2%)	0.355
Massive Hemolysis	11 (22.9%)	8 (33.3%)	3 (12.5%)	0.086
Cardiac arrest	3 (6%)	2 (8.3%)	1 (3.8%)	0.602
Pneumothorax	7 (14%)	3 (12.5%)	4 (15.4%)	1
Antibiotic-treated blood stream infection	30 (60%)	11 (45.8%)	19 (73%)	**0.049**
Antibiotic-treated VAP	33 (66%)	15 (62.5%)	18 (69.2%)	0.616

Values are number (%) or median (interquartile range). RRT : Renal replacement therapy ; VAP : Ventilator associated pneumonia; other sites of hemorrhage: urinary tract, pulmonary tract, gastrointestinal tract, ear, nose and throat.

Discussion

We report here a retrospective single institution study regarding the impact of the current bundled treatment combination (ventilatory setting management and corticosteroids) on the most critically ill COVID-19 patients under V-V ECMO for a long study period. The main finding of our study was a 11% higher 90-day mortality during the second wave, however without reaching statistical significance maybe due to the small size of the cohort.

The overall 90-day mortality rate of CARDS patients on V-V ECMO in our study was 32/50 (64%). Data from high-volume centers with retrospective design show that ECMO therapy was associated with a lower in-hospital mortality rate ranging from 36-54%(33–35). Data from the international ELSO Registry captures a 52.4% in-hospital mortality in 1531 treated patients as of September 14th 2020(36). Barbaro et al. reported in the subset of CARDS patients receiving V-V ECMO an estimated cumulative incidence of in-hospital mortality 90 days after the initiation of ECMO of 38.0% (95% CI 34.6–41.5)(20). A recent multinational meta-analysis confirmed a lower pooled in-hospital mortality of 37.1% (95% CI 32.3–42.0%) of COVID-19 patients receiving ECMO (22 studies, 1896 patients)(37). However, all of these studies took place solely during the first wave of COVID-19's pandemic. In contrast, other studies reported a comparable high mortality such as a recent multicenter study in Germany involving a total of 768 COVID-19 ECMO patients admitted to hospitals between February and December 2020 with a 73% in-hospital mortality (38). The reasons for the high in-hospital mortality in our cohort might be the higher mean age of 58 (±10) years in the whole cohort. This is comparable to the mean age of 57.7 (±11.4) years in Karagiannidis et al. study (38) but significantly higher than previous studies with mean age ranged from 48(±11) to 55.4(±9.3) years(20, 34–36). Increasing age is one of important pre-ECMO variables associated with a worse outcome as demonstrated by many studies (20, 34, 38, 39). Another factor, contributing to the higher mortality rates in our cohort, may be the median SAPSII [58 (34-67)] higher than the ones reported by Schmidt et al.(35) (median 45 (29–56)) and by

Lebreton et al. (median 40 (31–56))(34). Although not characterized to COVID-19 ARDS, the RESP score(32) reported by Schmidt et al.(35) was 4 (2–5) and 3 (1–5) by Diaz et al.(33), which is significantly higher than in our cohort with median -3 (-6,-1) and an estimated survival probability of 33 %.

Regarding specific COVID-19 therapies during the second wave, several treatment options have been established since then, such as the systematic use of corticosteroids in our second wave patients' group in light of the RECOVERY trial(14) rather than only 4 (16.7%) patients during the late first wave. Due to extent inclusion in international clinical trials, antiviral treatments were significantly more administered in the first wave group rather than in the second wave group, respectively 11/24 (45.8%) and 3/26 (11.5%) ; p=0.007), in light of recent trials demonstrating that none of these treatments are efficient in treating COVID-19(40, 41), including patients requiring mechanical ventilation(42–44). Regarding non-invasive respiratory support strategies, there is a paucity of high-quality evidence in COVID-19 resulting in marked variation in international practice(45). Interestingly, a recent report providing data from the EuroELSO survey indicate a trend to less favorable outcomes during the second wave. Including deaths reported after successful weaning, survival was 53% in the first wave and 44% in the second wave (p<0.0001)(24). In the same way, we found an 11% higher 90-day mortality during the second wave in our study. Several hypotheses might be considered.

First, the second wave patients were significantly older than those from the first wave (p<0.017). As already discussed previously, age is a well-established risk factor for worse outcomes. Comorbidities were not different between the two wave groups and similar to other large cohort studies (20, 34–36, 38, 46). Otherwise, the patients during the second wave were prone to manifest higher severity of pulmonary involvement even if they had less extra-pulmonary organ dysfunction. Indeed, we reported a trend to lower SAPSII score, a statistically significant lower total SOFA score and a trend to worsen RESP score in the second wave group. We may speculate that the more frequent use of corticosteroids during the second wave had mitigated the

cytokine release syndrome observed in severe COVID 19 (47) and the extrapulmonary organ dysfunctions.

Secondly, the longer delay between ICU admission and intubation due to a more frequent use of non-invasive respiratory support during the second wave was responsible of a longer time from ICU admission to ECMO. This could participate to the worsen respiratory phenotype at ECMO implantation. Indeed, the static compliance of respiratory system was significantly lower with a significantly higher driving pressure in the second wave group. Biological parameters corroborate this data with a significantly lower PaO2/FiO2 ratio than in the first wave group and a trend to hypercapnic acidosis with an equilibrated pH due to significantly higher alkaline reserve. To note, no significant difference in adjuvant treatment (Prone Positioning, neuromuscular blockade, inhaled nitric oxide) before ECMO implantation was noticed between the two groups. Thus, the more severe respiratory phenotype during the second wave may be due to 1) an ECMO initiation at a more advanced stage of the disease, and 2) patient self-inflicted lung injury secondary to vigorous respiratory drive during non-invasive support as already described in other reports(3, 13). As such, we observe much more pneumothorax before ECMO canulation in the second wave group. Finally, the same trend to a more severe respiratory phenotype persisted under ECMO at day 1, 3 and 7 in the second wave group.

Thirdly, the relative immunodepression related to systematic use of corticosteroid, as could be suggested by the lymphopenia significantly lower on ECMO day 7 during the second wave, might contribute to less favorable outcomes. On the one hand, we documented significantly more bacterial co-infection before ECMO implantation in our study with 61.5% patients during the second wave period compared to 21% in the first wave period (p=0.004) with a predominance of bacterial ventilator-associated pneumonia, that could participate to the worsen respiratory phenotype at ECMO implantation. On the other hand, we reported much higher antibiotic blood stream infections under ECMO during the second wave, that could partly explain the higher length of ECMO, catecholamines, ICU and hospital stay.

Several limits must be highlighted in our study. First, the limited size of our cohort and the retrospective and monocentric design which exposed the study to confounders may have resulted in underpowered analyses. Nevertheless, as all ECMO patients were referred to our tertiary center, patient management during the two periods of the study were homogenous and allowed to make relevant comparison. Moreover, the changes in patient care between the two waves were especially evidence-driven and thus not preclude to extent these results to other centers(48). Second, the statistically significant difference of age during the second wave group is a major limitation and only assumptions can be made about the meaning of other pre-ECMO variables associated with a worse outcome during the second wave. Data from larger multicentric comparative studies are needed to confirm this trend.

Conclusions

Our study describes the impact of the current bundled treatment combination (ventilatory setting management and corticosteroids) on the most critically ill COVID-19 patients on V-V ECMO during the two waves of COVID-19 outbreak and reveals that the clinical picture is less encouraging during the second wave with a trend of an increase in 90-day mortality. Further data analysis is expected to support our preliminary results and provide valuable data on ECMO management strategies for these patients.

Discussion et Conclusion (français)

Nous rapportons ici une étude rétrospective monocentrique d'un centre hospitalier tertiaire évaluant l'impact de l'actuelle stratégie thérapeutique combinée (associant stratégies ventilatoires multimodales et corticothérapie) sur les patients atteints de COVID-19 les plus critiques placés sous ECMO veino-veineuse sur une longue période d'étude. Le résultat principal de notre étude était une surmortalité à 90 jours de 11% durant la seconde vague épidémique sans atteindre néanmoins la significativité statistique du fait du faible effectif de notre cohorte.

La mortalité globale à 90 jours des patients SDRA COVID placés sous ECMO était, dans notre étude, de 32/50 (64%). Les données issues de larges cohortes rétrospectives retrouvaient une plus faible mortalité hospitalière allant de 36 à 54% (33-35). Les données issues du registre international de l'ELSO sur 1531 patients traités au 14 septembre 2020 mettaient en évidence une mortalité hospitalière de 52,4% (36). Barbaro et al. rapportaient dans le sous-groupe de patients atteints de SDRA COVID et recevant une ECMO veino-veineuse une incidence cumulée de mortalité hospitalière à 90 jours de 38% (IC95%, 34,6-41,5) (20). Une méta-analyse internationale récente confirmait une moindre mortalité hospitalière de 37,1% (IC95% 32,3-42%) chez des patients atteints de COVID-19 sous ECMO veino-veineuse (22 études, 1896 patients) (37). Cependant, toutes ces études ont été conduites durant la première vague épidémique uniquement. A contrario, d'autres publications ont rapporté une mortalité similaire à notre cohorte comme cette étude récente multicentrique conduite en Allemagne et impliquant un total de 768 patients COVID-19 placés sous ECMO admis à l'hôpital entre février et décembre 2020 avec une mortalité hospitalière globale de 73% (38). L'une des raisons de cette mortalité plus élevée dans notre cohorte pourrait être l'âge moyen de 58 (+/- 10) ans de notre population globale. Ceci est comparable à l'âge moyen de 57,7 (+/- 11,4) ans de l'étude de Karagiannidis et al. (38) mais significativement plus élevé que les études précédentes avec un âge moyen allant de 48 (+/-11) ans à 55,4 (+/- 9,3) ans (20,34-36). L'augmentation de l'âge est une des variables pré-ECMO les plus déterminantes dans l'aggravation du pronostic global comme démontré par de nombreuses

études (20,34,38,39). Un autre facteur, contribuant à la mortalité plus élevée dans notre cohorte, pourrait être le score SAPSII médian de 58 (34-67), plus élevé que celui rapporté par Schmidt et al. (35) avec un score médian de 45 (29-56) et par Lebreton et al. avec un score médian de 40 (31-56) (34). Enfin, le score RESP médian (32) décrit par Schmidt et al. (35) était de 4 (2-5) et 3 (1-5) par Diaz et al. (33), ce qui est significativement plus élevé et donc associé à un meilleur pronostic que celui de notre cohorte avec une médiane à -3 (-6, -1) et une probabilité de survie estimée à 33%.

En ce qui concerne les thérapies spécifiques de la COVID-19 et à la lumière des résultats de l'essai RECOVERY (14), tous nos patients de la seconde vague ont reçu l'administration précoce systématique de corticoïdes alors que seulement 4 (16,7%) patients ont reçu des corticoïdes durant la première vague. Dû à l'inclusion soutenue dans les essais cliniques internationaux, les traitements antiviraux étaient, en revanche, significativement plus administrés durant la première vague que la seconde, respectivement 11/24 (45,8%) et 3/26 (11,5%) ; p=0,007). En effet, des essais récents démontraient qu'aucun de ces traitements n'étaient efficaces dans la prise en charge des patients atteints de la COVID-19 (40,41), incluant les patients requérant une ventilation mécanique invasive (42-44). Concernant la prise en charge ventilatoire et notamment le recours à la ventilation non-invasive, peu de preuves scientifiques de bonne qualité dans la COVID-19 sont actuellement disponibles conduisant à de grandes variations de pratiques internationales (45). De façon intéressante, une publication récente provenant de données du registre international Euro-ELSO indiquait une tendance à une évolution moins favorable des patients sous ECMO durant la seconde vague. En incluant les décès rapportés après succès du sevrage de l'ECMO, la survie était de 53% durant la première vague et 44% durant la seconde vague (p<0,0001) (24). De la même manière, nous retrouvons une augmentation de 11% de la mortalité à 90 jours durant la seconde vague dans notre étude. A la lumière de nos résultats, plusieurs hypothèses peuvent être considérées.

Premièrement, les patients issus de la deuxième vague étaient significativement plus âgés que ceux issus de la première vague (p<0,017). Comme précédemment discuté, l'âge est un facteur de risque bien établi d'évolution défavorable. Pour autant, les comorbidités n'étaient pas différentes entre les groupes issus des deux vagues et similaires à celles décrites dans d'autres études (20,34-36,38,46). Ensuite, les patients issus de la deuxième vague présentaient un phénotype respiratoire plus sévère avant la mise sous ECMO même s'ils avaient moins de dysfonctions d'organes extra-respiratoires. En effet, nous rapportons une tendance à un score SAPSII plus faible, un score SOFA significativement plus faible et une tendance à un score RESP plus sévère dans le groupe issu de la deuxième vague. L'utilisation systématique de corticoïdes durant la seconde vague aurait pu diminuer l'intensité du syndrome de relargage cytokinique observé chez les patients atteints de COVID-19 sévères (47) et ainsi contribuer à diminuer les dysfonctions d'organes extra-pulmonaires.

Deuxièmement, le délai plus long entre l'admission en réanimation et l'intubation orotrachéale dû à l'utilisation plus fréquente de supports ventilatoires non invasifs durant la seconde vague était responsable d'une implantation plus tardive de l'ECMO. Ceci pourrait participer au phénotype respiratoire plus sévère à l'implantation de l'ECMO. En effet, la compliance statique du système respiratoire était significativement plus basse avec une pression motrice significativement plus élevée dans le groupe issu de la seconde vague. Les paramètres biologiques corroboraient ces données avec un rapport PaO2/FiO2 plus bas que lors de la première vague et une tendance à l'acidose hypercapnique avec un pH équilibré du fait d'une augmentation significative de la réserve alcaline. A noter qu'aucune différence en termes de traitements adjuvants (décubitus ventral, utilisation de curares, utilisation de NO inhalé) avant implantation de l'ECMO n'était rapportée entre les deux groupes. Ainsi, le phénotype respiratoire plus sévère durant la seconde vague pourrait être dû à 1) une initiation de l'ECMO à un stade plus avancé de la maladie, et 2) à des lésions pulmonaires auto-induites par le patient (P-SILI) secondaires à des efforts inspiratoires excessifs durant la ventilation non-invasive comme déjà rapportés dans d'autres publications (3, 13). A ce titre, nous avons observé plus de pneumothorax avant l'implantation de

l'ECMO durant la seconde vague. Enfin, la même tendance à un phénotype respiratoire plus sévère persistait sous ECMO à J1, J3 et J7 pour le groupe issu de la seconde vague.
Troisièmement, l'immunodépression relative à l'utilisation systématique des corticoïdes, comme suggéré par la lymphopénie significativement plus basse sous ECMO à J7 durant la seconde vague, pourrait contribuer à une évolution moins favorable. D'une part, nous avons documenté significativement plus de co-infections bactériennes avant l'implantation de l'ECMO dans notre étude avec 61,5% de patients durant la seconde vague en comparaison à 21% durant la première vague (p=0,004). Parmi ces co-infections, on notait une prédominance de pneumonies acquises sous ventilation mécanique (PAVM), qui pourrait également participer au phénotype respiratoire plus sévère à l'implantation de l'ECMO. D'autre part, nous avons rapporté plus de bactériémies sous ECMO durant la seconde vague, ce qui pourrait, en partie, expliquer l'augmentation significative de la durée d'ECMO, de traitements par catécholamines, de durée de séjour en réanimation et à l'hôpital.

Plusieurs limites peuvent être soulignées dans notre étude. Premièrement, la taille limitée de notre cohorte et le design rétrospectif et monocentrique exposent à de nombreux facteurs de confusion et résultent en un manque de puissance statistique dans nos analyses. Néanmoins, comme tous les patients sous ECMO étaient adressés dans notre centre tertiaire, la prise en charge des patients durant les vagues épidémiques de la période d'étude était homogène et autorise des comparaisons pertinentes. De plus, les changements de pratique dans la prise en charge des patients entre les deux vagues épidémiques étaient essentiellement guidés par des données issues de preuves scientifiques et donc n'altèrent pas la généralisation de ces résultats à d'autres centres (48). Deuxièmement, la différence statistiquement significative d'âge durant la seconde vague épidémique est une limite majeure de notre travail et seules des assomptions peuvent être faites concernant l'association d'autres variables pré-ECMO sur le pronostic défavorable durant la seconde vague. Les données issues de plus larges études comparatives multicentriques sont nécessaires pour confirmer cette tendance.

En conclusion, notre étude décrit l'impact de la stratégie actuelle de traitements combinés (associant stratégies ventilatoires multimodales et corticothérapie) sur les patients atteints de COVID-19 les plus critiques et placés sous assistance respiratoire extra-corporelle veino-veineuse durant les deux premières vagues épidémiques. Nos données révèlent que la situation est malgré tout moins favorable durant la deuxième vague avec une tendance à l'augmentation de la mortalité à 90 jours. Des données supplémentaires sont attendues pour soutenir ces résultats préliminaires et fournir des éléments fiables sur les stratégies de prise en charge de ces patients sous ECMO.

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Annexes

Supplementary Table 1. Biological parameters before ECMO.

Biological parameters before ECMO	All patients (=50)	First Wave (=24)	Second Wave (=26)	P-value
pH	7.4 (7.3-7.4)	7.4 (7.3-7.4)	7.4 (7.3-7.4)	0.327
PaO2/FiO2, mmHg	70 (62-79)	73 (65-84)	68 (57-75)	**0.04**
PaCO2, mmHg	54 (46-63)	52 (42-62)	56 (49-66)	0.067
Bicarbonates, mmol/L	29 (25-36)	29 (23-31)	31 (29-39)	**0.009**
Lactate, mmol/L	1.5 (1.1-1.9)	1.3 (1.1-1.7)	1.6 (1.1-1.9)	0.252
Urea, g/L	0.60 (0.40-0.93)	0.7 (0.3-0.98)	0.6 (0.4-0.93)	0.494
Creatinine, mg/L	8 (6-21)	10 (7-32)	6 (6-17)	0.082
Bilirubin, mg/L	6 (4-9.8)	6 (5-16)	6 (4-8.3)	0.363
WBC, 10^9/L	11 (9.4-15)	11 (8.9-14)	11 (10-16)	0.315
Lymphocyte count*, 10^9/L	0.7 (0.45-1.1)	0.7 (0.5-1.2)	0.7 (0.4-0.95)	0.209
Hemoglobin, g/dL	9.7 (8.4-10)	9.7 (9.1-11)	9 (8.1- 10)	0.217
Hematocrit, %	30 (26-33)	30 (28-33)	29 (25-33)	0.128
Platelets, 10^9/L	258 (199-351)	280 (243-359)	236 (187-314)	0.085
aPTT, ratio	1.5 (1.3-1.8)	1.5 (1.2-2)	1.6 (1.2-1.8)	0.995
PT, %	75 (68-84)	74 (65-81)	78 (70-85)	0.163
D-Dimères‡, µg/mL	3.9 (2.3-6.5)	4 (2.3-14)	3.5 (2.3-4)	0.178
Fibrinogen, g/L	7.6 (6.6-8.7)	8 (7.2-9.3)	7.1 (5.9-8.1)	**0.009**
CRP, mg/L	250 (107-330)	280 (138-336)	149 (89-313)	0.081
PCT, ng/mL	1.1 (0.35-3.3)	1.8 (0.55-7.1)	0.51 (0.23-1.6)	**0.016**
Ferritine#, ng/mL	1328 (789-2436)	1716 (875-3048)	1281 (638-1893)	0.349

Values are number (%) or median (interquartile range). aPTT : activated partial thromboplastin time.

†1 missing value in first wave group. *1 missing value in first wave group. ‡1 missing value in first wave group and 1 missing value in second wave group. #3 missing values in first wave group and 1 missing value in second wave group.

Supplementary Table 2. ECMO, ventilation, biological parameters and SOFA score at Veno-venous Extracorporeal Membrane Oxygenation (V-V ECMO) Day 3 in First and Second Wave Groups.

Day 3 Characteristics	Parameters	All patients (=49)	First Wave Group (=23)	Second Wave Group (=26)	P-value
ECMO parameters	FmO2 (%)α	83 (70-100)	88 (70-100)	80 (68-100)	0.615
	RPMβ	3800 (3325-4041)	3800 (3225-4350)	3750 (3350-4000)	0.513
	ECMO blood flow (L/min)γ	5.4 (4.7-6)	5.9 (5-6.2)	5.1 (4.6-5.6)	**0.012**
	Sweep gaz flow(L/min)δ	6 (5-7)	6 (5-7.3)	6 (4.9-7)	0.562
Ventilation parameters	ACV = 1 / APRV = 2 / PSV = 3 / SB = 4ζ	1=14 2 = 21 3=11 4=2	1=10 2=5 3=7	1=4 2=16 3=4 4=2	
	FiO2 (%)φ	50 (40-70)	50 (40-70)	50 (40-80)	0.151
	Vt (mL)χ	230 (180-340)	280 (210-355)	205 (153-310)	0.058
	Vt IBW (mL/kg)ε	3.4 (2.7-5)	4.1 (3.2-5.3)	3 (2.4-4.6)	0.074
	RR (cpm)†	20 (18-23)	20 (15-23)	20 (19-24)	0.405
	Pplat (cmH2O)#	24 (21-26)	25 (22-28)	24 (20-26)	0.083
	PEP (cmH2O)‡	12 (10-15)	14 (10-17)	12 (10-12)	0.096
	Driving Pressure (cmH2O)¶	12 (9-14)	12 (8-14)	12 (10-14)	0.709
	Compliance RS (mL/cm H2O)¥	20 (13-32)	23 (20-40)	14 (11-29)	**0.026**
	Mechanical Power (J/min)¤	11 (7,1-14)	13 (9,7-19)	8,4 (5,4-12)	**0.001**
Biological parameters	pH	7.4 (7.4-7.5)	7.4 (7.4-7.5)	7.4 (7.4-7.5)	0.85
	PaO2 (mmHg)	76 (66-88)	77 (70-89)	72 (64-79)	0.133
	PaCO2 (mmHg)	43 (40-48)	41 (38-44)	47 (42-52)	**0.014**
	Bicarbonates (mmol/L)	28 (24-33)	26 (24-29)	31 (27-34)	**0.033**
	Lactate (mmol/L)	1.3 (0.9-2)	1.2 (0.9-2)	1.3 (0.8-1.8)	0.944
	WBC (10^9/L)	14 (11-18)	15 (11-18)	12 (11-17)	0.394

	Lymphocyte count (10^9/L)[z]	0.8 (0.4-1.3)	0.75 (0.4-1.3)	0.8 (0.4-1.3)	0.686
	Hemoglobin (g/dL)	8.3 (7.7-9)	7.9 (6.9-8.8)	8.8 (7.9-9.2)	**0.011**
	Platelets (10^9/L)[ϑ]	173 (106-250)	216 (113-301)	162 (101-201)	0.133
	D-Dimères (µg/mL)[w]	4 (3.6-12)	3.9 (3.3-10)	7.8 (4-22)	0.145
	Fibrinogen (g/L)	6.2 (4.3-7.4)	6.6 (5.5-8.4)	5.3 (4.2-6.5)	0.117
	aPTT (ratio)	1.7 (1.3-2.5)	1.7 (1.3-2.6)	1.5 (1.3-2.2)	0.367
	Creatinine (mg/L)	9 (6-25)	14 (7-37)	6.5 (5-17)	**0.009**
	Bilirubin (mg/L)	7 (5-17)	17 (6-24)	6 (5-7)	**0.002**
	ASAT (UI/L)	62 (47-132)	73 (52-167)	55 (40-114)	0.058
	ALAT (UI/L)	51 (34-85)	44 (34-79)	54 (33-102)	0.703
	CRP (mg/L)	86 (58-170)	145 (58-191)	83 (52-104)	0.094
	PCT (ng/mL)	0.91 (0.26-2.3)	1.7 (0.65-2.9)	0.43 (0.24-1.2)	**0.021**
SOFA Day 3		11 (9-14)	13 (11-15)	10 (7.8-13)	0.057

Values are number (%) or median (interquartile range). FmO2=fraction of membrane oxygen. RPM=rate per minute. FiO2=fraction of inspired oxygen. ACV=assist-control ventilation. APRV=airway pressure release ventilation. PSV=pressure support ventilation. SB=spontaneous breathing. Vt=Tidal volume. Vt IBW=ideal body weight tidal volume. RR=respiratory rate. Ppeak=Peak pressure. Pplat=plateau pressure. PEEP=positive end-expiratory pressure. Compliance RS = respiratory system compliance. aPTT=activated partial thromboplastin time. ASAT=aspartate aminotransferase. ALAT= alanin aminotransferase.

[α]1 missing value in first wave group, [β]1 missing value in first wave group, [γ]1 missing value in first wave group, [δ]1 missing value in first wave group, [ζ]2 missing values in first wave group, [φ]1 missing value in first wave group, [χ]1 missing value in first wave group, 2 missing values in second wave group, [ε]2 missing values in second wave group, †1 missing value in first wave group, 2 missing values in second wave group, #1 missing value in first wave group, 2 missing values in second wave group, ‡1 missing value in first wave group, 2 missing values in second wave group, ¶2 missing values in first wave group, 1 missing value in second wave group, ¥1 missing value in first wave group, 2 missing values in second wave group, ¤ 1 missing value in first wave group, 2 missing values in second wave group, [z]1 missing value in first wave group, [ϑ]1 missing value in first wave group, [w]1 missing value in first wave group, 3 missing values in second wave group.

Supplementary Table 3. ECMO, ventilation, biological parameters and SOFA score at Veno-venous Extracorporeal Membrane Oxygenation (V-V ECMO) Day 7 in First and Second Wave Groups.

Day 7 Characteristics	Parameters	All patients (=41)	First Wave Group (=17)	Second Wave Group (=24)	P-value
ECMO parameters	FmO2 (%)	80 (65-100)	80 (70-100)	75 (60-100)	0.693
	RPM	3600 (3100-4038)	4000 (2850-4400)	3500 (3200-3950)	0.233
	ECMO blood flow (L/min)	5.3 (4.5-6)	5.9 (4.5-6.9)	5.1 (4.4-5.5)	**0.048**
	Sweep gaz flow (L/min)	7 (4.5-8)	6 (5-8.5)	7 (4-8)	0.974
Ventilation parameters	ACV = 1 / APRV = 2 / PSV = 3 / SB = 4	1=10 2 =19 3=11 4=1	1=6 2=6 3=5	1=4 2=13 3=6 4=1	
	FiO2 (%)	50 (40-65)	50 (45-65)	55 (40-68)	0.626
	Vt (mL)ˣ	225 (153-375)	270 (210-395)	180 (130-360)	**0.045**
	Vt IBW (mL/kg)ᵋ	3.4 (2.3-5.1)	4 (3.3-5.6)	2.7 (1.9-5.1)	**0.02**
	RR (cpm)†	22 (17-28)	22 (17-28)	24 (15-26)	0.844
	Pplat (cmH2O)#	25 (24-29)	28 (25-30)	24 (23-26)	**0.031**
	PEEP (cmH2O)‡	12 (10-14)	12 (10-17)	10 (10-12)	0.134
	Driving Pressure (cmH2O)¶	14 (11-15)	14 (11-16)	14 (11-15)	0.551
	Compliance RS (mL/cm H2O)¥	18 (10-28)	20 (15-28)	16 (8.7-28)	0.165
	Mechanical Power (J/min)¤	11 (6.6-25)	19 (9-30)	7.4 (5.6-22)	**0.02**
Biological parameters	pH	7.4 (7.4-7.5)	7.4 (7.4-7.4)	7.4 (7.4-7.5)	0.552
	PaO2 (mmHg)	70 (61-85)	78 (73-94)	65 (58-75)	**0.005**
	PaCO2 (mmHg)	44 (40-50)	41 (39-47)	45 (41-52)	0.112
	Bicarbonates (mmol/L)	29 (24-31)	25 (23-31)	30 (27-32)	0.064
	Lactate (mmol/L)	1.2 (0.95-1.6)	1.2 (0.8-1.6)	1.2 (1.1-1.6)	0.338
	WBC (10^9/L)	15 (11-21)	18 (14-21)	12 (8.5-18)	**0.014**

	Lymphocyte count (10^9/L)	0.9 (0.5-1.6)	1.5 (1-2)	0.8 (0.43-1.1)	**0.001**
	Hemoglobin (g/dL)	8.3 (7.6-8.8)	7.9 (7.3-8.3)	8.5 (7.7-9)	0.075
	Platelets (10^9/L)	112 (75-169)	135 (89-185)	92 (64-141)	**0.05**
	D-Dimères (µg/mL)[w]	4 (3.7-16)	8.1 (3.3-16)	4 (3.9-29)	0.798
	Fibrinogen (g/L)	4.4 (2.8-6)	6 (3.8-7.9)	4 (2.7-5.2)	**0.005**
	aPTT (ratio)	1.7 (1.3-2.4)	1.5 (1.3-2.1)	1.8 (1.2-2.6)	0.382
	Creatinine (mg/L)	9 (5-17)	16 (7.5-25)	7 (4.3-14)	**0.007**
	Bilirubin (mg/L)	7 (5-14)	9 (6-45)	6 (5-7)	**0.007**
	ASAT (UI/L)	49 (41-87)	61 (40-129)	48 (42-70)	0.239
	ALAT (UI/L)	46 (31-72)	42 (30-63)	49 (34-84)	0.209
	CRP (mg/L)	85 (32-220)	153 (22-306)	78 (33-189)	0.56
	PCT (ng/mL)	0.57 (0.24-2.5)	1,3 (0.6-7.9)	0.44 (0.22-1.2)	**0.018**
SOFA Day 7		11 (8-16)	14 (8.5-18)	10 (8-14)	0.201

Values are number (%) or median (interquartile range). FmO2=fraction of membrane oxygen. RPM=rate per minute. FiO2=fraction of inspired oxygen. ACV=assist-control ventilation. APRV=airway pressure release ventilation. PSV=pressure support ventilation. SB=spontaneous breathing. Vt=Tidal volume. Vt IBW=ideal body weight tidal volume. RR=respiratory rate. Ppeak=Peak pressure. Pplat=plateau pressure. PEEP=positive end-expiratory pressure. Compliance RS = respiratory system compliance. aPTT=activated partial thromboplastin time. ASAT=aspartate aminotransferase. ALAT= alanin aminotransferase.

[x]1 missing value in second wave group, [ε]1 missing value in second wave group, †1 missing value in second wave group, #1 missing value in second wave group, ‡1 missing value in second wave group, ¶1 missing value in second wave group, ¥1 missing value in second wave group, ¤1 missing value in second wave group, [w]4 missing values in second wave group.

Supplementary Table 4. Treatments under ECMO

Treatments under ECMO	All patients (=50)	First Wave (=24)	Second Wave (=26)	P-value
Adjuvant ARDS treatment				
Prone Positioning	34 (68%)	13 (54.2%)	21 (80.8%)	**0.044**
Inhaled nitric oxide	33 (66%)	13 (54.2%)	20 (76.9%)	0.09
Almitrine	14 (28%)	5 (20.8%)	9 (34.6%)	0.278
COVID-19 therapies				
Glucocorticoids	44/50 (88%)	22/24 (91.7%)	22/26 (84.6%)	0.669
Antiviral	1 (2%)	1 (4.2%)	0 (0%)	0.48
Immunomodulators	2/50 (4%)	2/24 (8.3%)	0/26 (0%)	0.225
Renal replacement therapy	22 (44%)	15 (62.5%)	7 (26.9%)	**0.011**
Blood-product transfusion				
Red cells transfusion	49 (98%)	24 (100%)	25 (96.2%)	1
Platelets transfusion	17 (34%)	6 (25%)	11 (42.3%)	0.197
Fresh frozen plasma	14 (28%)	5 (20.8%)	9 (34.6%)	0.278
Fibrinogen concentrate	7 (14%)	2 (8.3%)	5 (19.2%)	0.42

Values are number (%). Antiviral therapies were Lopinavir-Ritonavir, Chloroquine, Remdesivir. Immunomodulators were intravenous immunoglobulin, anti-cytokine, JAK inhibitors.

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Date de soutenance : 07 octobre 2021

Titre de la thèse : Assistance respiratoire extra-corporelle veino-veineuse au cours du syndrome de détresse respiratoire aigu dû à la COVID-19 : Comparaison entre les premières et secondes vagues

Thèse - Médecine - Lille « 2021 »

Cadre de classement : *Médecine Intensive Réanimation*

DES + spécialité : *Médecine Interne + Médecine Intensive Réanimation*

Mots-clés : syndrome de détresse respiratoire aigu ; ECMO ; COVID-19

Résumé : ***Introduction*** : Durant les deux vagues de la pandémie de COVID-19, des avancées significatives dans la prise en charge en médecine intensive réanimation ont émergé allant des thérapies immunomodulatrices aux adaptations des stratégies ventilatoires. L'objectif de notre étude était de comparer les caractéristiques et le devenir des patients placés sous assistance respiratoire extra-corporelle veino-veineuse de type Extra Corporeal Membrane Oxygenation (ECMO) pour syndrome de détresse respiratoire aigu lié à la COVID-19 (SDRA COVID) entre les premières et deuxièmes vagues épidémiques.

Méthode : Il s'agissait d'une étude de cohorte observationnelle, rétrospective, monocentrique réalisée du 1er mars au 30 novembre 2020. Tous les patients adultes consécutifs requérant une ECMO pour un SDRA COVID sévère étaient inclus. Les données démographiques, les données pré-ECMO et sous ECMO à J 1, 3 et 7 ainsi que le devenir des patients étaient collectés.

Résultats : Durant la période de l'étude, 50 patients étaient placés sous ECMO pour un SDRA COVID. La mortalité globale à J90 était de 32/50 (64%). Ce taux de mortalité était 11% plus élevé durant la seconde vague épidémique [18/26 (69%)] comparé à la première vague [14/24 (58%)], mais sans atteindre la significativité statistique (p=0,423). Durant la seconde vague, tous les patients étaient sous corticoïdes avant l'implantation de l'ECMO comparé à 16,7% durant la première vague (p<0.001). Les patients de la seconde vague étaient placés sous support ventilatoire non invasif durant une période plus longue que lors de la première vague avec un temps médian de l'admission en réanimation à l'implantation de l'ECMO significativement plus long [14 (11-20) vs. 7.7 (5-12) jours ; p<0.001]. Les propriétés mécaniques du poumon étaient plus altérées durant la seconde vague des patients atteints de SDRA COVID avant implantation de l'ECMO [compliance statique médiane de 20 (16-26) vs. 29 (25-37) mL/cmH2O ; p<0.001] et sous ECMO à J1, J3 et J7. Des co-infections bactériennes étaient significativement plus documentées avant implantation et sous ECMO durant la seconde vague épidémique.

Conclusion : L'ECMO assure un traitement de support efficace pour les patients développant un SDRA COVID, mais malgré une amélioration de la prise en charge en réanimation basée sur des preuves scientifiques, nous décrivons des évolutions moins encourageantes durant la seconde vague.

Composition du Jury :

Président : Professeur Marc LAMBERT

Assesseurs : Professeur Éric KIPNIS, Professeur Julien POISSY

Directeur de thèse : Docteur Thibault DUBURCQ