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Assistance respiratoire extra-corporelle veino-veineuse au cours du syndrome de détresse respiratoire aigu dû à la COVID-19 : Evaluation du devenir des patients selon une stratification par l'âge

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Le candidat à la thèse et le directeur de thèse ne déclarent aucun lien d'intérêt avec le travail présenté.

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Abbreviations list

APRV : Airway Pressure Release Ventilation

ARDS : Acute Respiratory Distress Syndrome

AUC : Area Under the Curve

CARDS : COVID-19 related Acute Respiratory Distress Syndrome

COVID-19 : Coronavirus disease 2019

ELSO : Extracorporeal Life Support Organization

EOLIA : ECMO to rescue Lung Injury in severe ARDS

FiO_2 : Fraction of inspired oxygen

FmO_2 : Fraction of membrane oxygen

ICU : Intensive Care Unit

PEEP : Positive End-Expiratory Pressure

Ppeak : Peak pressure

Pplat : Plateau pressure

PRESERVE score : PRedicting dEath for SEvere ARDS on V-V ECMO score

PRESET score : PREdiction on Survival on ECMO-Therapy score

RESP score : Respiratory Extracorporeal membrane oxygenation Survival Prediction score

RT-PCR : Reverse Transcriptase Polymerase Chain Reaction

SAPS II : Simplified Acute Physiology Score II

SARS-CoV-2 : Severe Acute Respiratory Syndrome CoronaVirus 2

SOFA score : Sequential Organ Function Assessment score

V-A ECMO : Veno-Arterial ExtraCorporeal Membrane Oxygenation

V-V ECMO : Veno-Venous ExtraCorporeal Membrane Oxygenation

Liste des abréviations

COVID-19 : Coronavirus Disease 2019

ECMO V-A : Membrane d'oxygénation extra-corporelle Véno-Artérielle

ECMO V-V : Membrane d'oxygénation extra-corporelle Véno-Veineuse

ELSO : Extracorporeal Life Support Organization

FiO_2 : Fraction inspirée en oxygène

PEP : Pression Expiratoire Positive

(Score) PRESERVE : PRedicting dEath for SEvere ARDS on V-V ECMO

(Score) RESP : Respiratory Extracorporeal membrane oxygenation Survival Prediction

SARS-CoV-2 : Severe Acute Respiratory Syndrome CoronaVirus 2

SDRA : Syndrome de Détresse Respiratoire Aigüe

Abstract

Introduction

V-V ECMO has been used extensively worldwide for the treatment of refractory severe CARDS. Although the ELSO recommended that age ≥ 65 years became a relative contraindication during the pandemic, there is not to date a consensual age cutoff. Moreover, limited data are available concerning elderly patients under ECMO. We aimed to describe the impact of age on survival for patients under V-V ECMO for CARDS.

Methods

This study was conducted on a single-center retrospective observational cohort from March 1st 2020 to January 1st 2022. All patients requiring V-V ECMO for severe CARDS were included. Patients' characteristics, outcomes and complications under ECMO were collected. Hospital survival was described between the 18-49y, 50-59y and ≥ 60y groups (classification of the RESP-score) and the <50y and ≥ 50y groups by the Kaplan–Meier approach.

Results

A total of 105 patients were included in the study. The overall survival rate was 36.2% at day 180. The survival analysis revealed a trend to higher survival in the 18-49y group than in the 50-59y and ≥ 60y groups (55.2% vs. 34.4% and 25% respectively, p=0.1). The secondary survival analysis found a significantly lower survival in the ≥ 50y compared to the 18-49y (28.9% vs. 55.2%, p=0.035). The hospital-survival in the ≥ 65y was 25% without loss of autonomy one year after hospital discharge.

Conclusion

In our study of CARDS under V-V ECMO, survival to hospital discharge was significantly lower in patients ≥ 50y. But one fourth of elderly patient's ≥ 65y was still discharged home with a good autonomy. These results confirm that age is a major prognosis factor for COVID-19 patients receiving V-V ECMO, but should not be an absolute contraindication alone.

Introduction (Anglais)

The Coronavirus Disease 2019 (COVID-19) is now deeply rooted in the current medical landscape. It is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a novel member of the coronavirus family, which already caused in the past severe epidemic occurrences, and now the pandemic we know since December 2019 [1,2].

The COVID-19 is characterized by a various possibility of organ damages, with a particular tropism to the lungs and the possibility of acute lung injury, that can evolve to Acute Respiratory Distress Syndrome (ARDS) in the more severe cases [3]. The prevalence of ARDS was 85 % in ICU admissions, according to a large systematic review during the first wave [4]. The timing of invasive ventilation initiation is still debated. Indeed, the use of non-invasive ventilation strategy [5], especially combined with vigil prone positioning seems promising [6], but the effect on mortality is still to be proven. Actually, the management of CARDS (COVID-19-associated Acute Respiratory Distress Syndrome) is still based on 1) the standard of care of patients with ARDS, meaning protective invasive ventilation (tidal volumes of 4-6mL/kg of Ideal Body Weight, targeting Plateau Pressure < 30cmH_2O, and titrating FiO_2 and Positive End Expiratory Pressure (PEEP) [7,8]), and prone positioning [9–11]; 2) the use of immunomodulators such as glucocorticoids [12], and Interleukine-6 antagonists [13] or Baricitinib [14].

For the most severe CARDS refractory to conventional treatment, Veno-Venous Extracorporeal Membrane Oxygenation (V-V ECMO) has been used extensively worldwide. The prevalence of V-V ECMO during the first wave was 8 % in the international REVA Network cohort [15]. Concerns about the use of V-V ECMO were originally emitted, in front of the high mortality rate reported in the first case series of CARDS patients treated with ECMO [16]. Afterwards, subsequent observational studies examining patients who received ECMO for CARDS reported similar outcomes to previous observations in ECMO patients with acute respiratory failure from other causes [17,18]. However,

mortality in this population may be increasing over time. A systematic review and meta-analysis comprising 18,211 CARDS patients receiving ECMO reported a pooled mortality rate at 48.8%. This mortality rate increased as the pandemic progressed from 40.8% in 1st half 2020 to 62% in the 1st half 2021. Interestingly, a high variability of mortality rate was observed across the studies in each time period (ranging from 11.1% to 74.3% in 2nd half 2020 for example) [19]. Although several factors related to the use of immunomodulators, to the virulence of SARS-CoV-2 variants, and to the ECMO centers experience could explained this variability, the differences of median age between these cohorts seemed predominant. Indeed, the age is well known to be a main prognostic factor in non-COVID ARDS patients under ECMO [20,21]. Moreover, a recent analysis of more than 7 000 CARDS patients receiving V-V ECMO reported that age was the single most important predictor of death [22].

To date, the ELSO did not establish an age cutoff for V-V ECMO, and only indicated that "increased age increases the risk of death". In the context of the COVID pandemic and the risk of shortage of equipment and trained medical teams, the ELSO recommended that selection criteria become more stringent and age ≥ 65 years become a relative contraindication [23]. Moreover, in a recent registry based cohort study of 7,345 adults with COVID-19 associated acute respiratory failure, ECMO was less effective in patients aged > 65 years [24].

In order to help physicians at the bedside with decisions about the use of V-V ECMO in patients with COVID-19, we aimed to describe the impact of age on outcome in patients receiving V-V ECMO for CARDS during the two years of the COVID-19 outbreak in our tertiary teaching center.

Introduction (Français)

La COVID-19 (Coronavirus Disease 2019) est maintenant enracinée dans le paysage médical. Cette maladie est causée par le Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), un nouveau membre de la famille des coronavirus. Cette famille de virus a déjà causé des épidémies sévères par le passé, et maintenant la pandémie que nous connaissons depuis Décembre 2019 [1,2]

La COVID-19 peut entraîner des atteintes d'organe variées, avec un tropisme particulier pour les poumons, et la possibilité d'atteinte respiratoire aigüe pouvant évoluer jusqu'à un Syndrome de Détresse Respiratoire Aigüe (SDRA) dans les cas les plus sévères [3]. La prévalence du SDRA était de 85% dans les admissions en soins intensifs dans une large revue épidémiologique au cours de la 1ère vague [4]. Le timing de l'initiation de la ventilation mécanique chez ces patients est encore débattu. En effet, l'utilisation d'une approche non-invasive [5], notamment combinée à du décubitus ventral vigile [6] semble prometteuse, mais un bénéfice sur la mortalité reste à prouver. A ce jour, la prise en charge des SDRA repose sur 1) la prise en charge standard du SDRA, c'est-à-dire la ventilation invasive protectrice (volume courant à 4-6 mL/kg de poids idéal théorique, visant une Pression de Plateau < 30 cmH_20, ainsi que la titration de la Pression Expiratoire Positive (PEP) et de la FiO_2 [7,8]), et le décubitus ventral [9–11] ; 2) l'utilisation d'immunomodulateurs tels que les glucocorticoïdes [12], les antagonistes de l'interleukine-6 [13] ou le Baricitinib [14].

Pour les SDRA dû au COVID les plus sévères, réfractaires au traitement conventionnel, l'ECMO V-V (Membrane d'oxygénation extra-corporelle Véno-Veineuse) a beaucoup été utilisée dans le monde entier. La prévalence d'ECMO V-V durant la première vague était de 8% dans la cohorte internationale REVA Network [15]. Des doutes ont initialement été émis à propos de l'utilisation de l'ECMO V-V devant un taux de mortalité élevé sur les premières séries de cas de patients avec un SDRA dû à la COVID placés sous ECMO [16]. Par la suite, d'autres études observationnelles concernant cette population ont retrouvé des résultats similaires à ceux, antérieurs au COVID-19, sur

les patients sous ECMO avec une défaillance respiratoire [17,18]. Cependant, la mortalité dans cette population semble augmenter avec le temps. Une revue systématique de la littérature avec méta-analyse comprenant 18 211 SDRA dû au COVID sous ECMO V-V rapporte une mortalité globale à 48,8%. Ce taux de mortalité a augmenté avec l'avancement de la pandémie, de 40,8% lors du 1er semestre 2020 à 62% lors du 1er semestre 2021. A noter, une variabilité importante de la mortalité était observée dans les études incluses à chaque période (allant de 11,1% à 74,3% pour le 2ème semestre 2020 par exemple) [19]. Bien que plusieurs facteurs puissent expliquer cette variation, comme l'introduction de l'utilisation des immunomodulateurs, la virulence différente des variants de SARS-CoV-2, ou l'expérience des centres d'ECMO, c'est la différence d'âge entre les cohortes qui semble peser le plus. En effet, l'âge est un facteur pronostique reconnu et important dans les SDRA non-COVID sous ECMO [20,21]. De plus, une analyse récente sur plus de 7 000 SDRA dû au COVID sous ECMO V-V a retrouvé que l'âge était le meilleur prédicteur de mortalité dans cette population [22].

A ce jour, l'ELSO n'a pas établi d'âge limite pour l'indication d'ECMO V-V, et a seulement indiqué "increased age increases the risk of death", c'est-à-dire qu'une augmentation de l'âge augmente le risque de décès. Dans le contexte de la pandémie COVID, avec le risque de pénurie d'équipements et d'équipes médicales expérimentées, l'ELSO a recommandé que les critères de sélection deviennent plus stricts, et que l'âge ≥ 65 ans deviennent une contre-indication relative [23]. Par ailleurs, dans une étude récente basée sur une cohorte de 7 345 patients avec une défaillance respiratoire liée au COVID-19, l'ECMO était moins efficace chez les patients ≥ 65 ans [24].

Afin d'aider les cliniciens dans leurs décisions à propos de l'utilisation de l'ECMO V-V chez les patients COVID-19, notre étude vise à décrire l'impact de l'âge sur le devenir des patients avec un SDRA dû à la COVID qui ont requis cette technique durant les deux ans de pandémie COVID-19 dans notre centre tertiaire universitaire.

Methods

Study settings

The present study was observational, retrospective and single-centered. We included all the patients in the Lille University Hospital with a laboratory confirmed SARS-CoV-2 infection who presented a severe ARDS that required V-V ECMO from 1 March 2020 to 1 January 2022. This time lapse represented patients from the first COVID-19 wave to the fourth one. SARS-CoV-2 infection was confirmed by a real time RT-PCR from nasopharyngeal swab or lower respiratory tract aspirate. ARDS was definite along the Berlin definition [25].

The French Institutional Authority for Personal Data Protection (Committees for the Protection of Human Subjects, registration no DEC22-217) 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 since this observational study did not modify existing diagnostic or therapeutic strategies.

ECMO indication and management

Patients received V-V ECMO in case of severe ARDS with refractory hypoxemia and/or hypercapnia according to the ECMO to Rescue Lung Injury in Severe ARDS's criteria [26] and despite optimization of the ventilatory settings with low tidal volume lung-protective ventilation and high level of PEEP, prone positioning, and neuromuscular blockade according to the latest French recommendations [27].

The cannulation was done percutaneously under ultrasonography guidance. A large admission cannula (23 to 29 Fr) in the common femoral vein, and a returned one in the right internal jugular

vein (17 to 21 Fr) was recommended unless anatomic contraindication. The cannula position was checked using ultrasonography and chest radiography. For highly unstable patients in secondary hospital, the V-V ECMO cannulation was performed by a mobile ECMO retrieval team on place, and then the patients were referred to our hospital.

ECMO's pump speed and fraction of membrane oxygen (FmO_2) was adjusted to obtain a blood oxygen saturation of 90 % or more, and sweep gas flow to slowly achieve an adequate partial pressure of carbon dioxide (PCO_2). Ventilator settings under V-V ECMO were settled to achieve an ultraprotective ventilation (Vt ≤ 4 mL/kg of ideal body weight, driving pressure ≤ 15 cmH_20, and respiratory rate ≤ 20/min). Prone positioning under V-V ECMO was strongly encouraged. Likewise, airway pressure release ventilation (APRV) or spontaneous-proportional pressure support to allowed early spontaneous breathing were recommended. A systemic anticoagulation was delivered with unfractioned heparin, to achieve an anti-Xa activity of 0.3-0.5 UI/mL. This target was lower in case of high risk of bleeding or hemorrhage. Coagulation and hemolysis parameters were monitored daily. The transfusion thresholds were 7-8 g/dL for hemoglobin (10 g/dL in case of persistent hypoxemia), and 50 G/L for platelets (or 100 G/L in case of bleeding).

Data collection and outcomes measures

Data were collected from our medical software IntelliSpace Critical Care and Anesthesia (ICCA), Philips Healthcare®, Böblingen, Germany.

Before ECMO cannulation, demographic characteristics, prognostic scores (PRESET, SAPSII and SOFA score [28–30]), comorbidities (obesity, diabetes, dyslipidemia, HTA, immunocompromised condition defined along the RESP score [20]), delays between the first symptoms - the ICU admission - the intubation and the ECMO initiation, ventilator parameters with driving pressure calculated according to Amato et al [31], mechanical power computed with surrogate formula [32], ARDS adjuvant treatments, COVID-19 therapies, and complications pre-ECMO were collected.

The outcomes were the hospital mortality, the 90 and 180-day mortality, the ECMO duration, the length of stay in ICU and hospital, the length of ECMO, mechanical ventilation, and catecholamines, the ECMO weaning, the rate of tracheotomy, and the adverse events under ECMO : central nervous system dysfunction (defined as the presence of acute stroke, cerebral embolism, seizure, or encephalopathy), hemorrhagic complications, thrombotic complications (defined by pulmonary embolism or deep vein thrombosis confirmed respectively by an injected thoracic computed tomography or an ultrasound echography), the necessity to change the ECMO circuit and its reason (clogged circuit, thrombocytopenia, hypofibrinogenemia, acquired Willebrand's disease, pump failure or membrane lung failure), massive hemolysis (defined as a plasma-free hemoglobin > 500 mg/L with clinical sign of hemolysis), the occurrence of cardiac arrest, pneumothorax, the necessity of renal replacement therapy and the occurrence of infections (antibiotic-treated blood stream infection and antibiotic-treated ventilation-acquired-pneumonia).

In the subgroup of patients older than 65 years, the survivors were called one year after the hospital discharge to assess their autonomy with the Lawton-Brody Instrumental Activities of Daily Living Scale (score range from 0 low function – dependent, to 8 high function – independent) [33] and the clinical frailty scale (score range from 1 very fit to 9 terminally ill) [34].

Objectives of the study

To describe the impact of age on outcome in patients receiving V-V ECMO for CARDS, the patients were classified in 3 age groups (18-49, 50-59 and ≥ 60 years old) as described in the RESP score [20]. The primary objective of this study was to compare the survival of hospital discharge of CARDS patients on V-V ECMO according to these three age groups.

Secondary objectives were to compare the survival of hospital discharge between patients < 50 and patients ≥ 50 years old, to describe the main characteristics before cannulation, the outcomes, the

prevalence of adverse events in the different age groups, and to compare survivors vs. non survivors in the subgroup of patients ≥ 65 years old.

Statistical analyses

Categorical and quantitative variables were reported as percentage (%) and medians (interquartile range) or means (standard deviation) as appropriate. Data normality was assessed by Shapiro-Wilk and Kolmogorov-Smirnov tests and by visual inspection using histograms of distribution. There was no imputation for missing data.

Hospital survival was described between the 18-49y, 50-59y and ≥ 60y groups and the <50y and ≥ 50y groups by the Kaplan–Meier approach. The date of death after hospital discharge was not available in all patients. For this reason, patients discharged alive from hospital were right-censored. Statistical difference between the survival curves was assessed by log-rank test.

For bivariate comparison between the three age groups, we used Fisher exact tests for categorical variables, and the Kruskal-Wallis test or One-Way ANOVA for continuous variables. Post-hoc pairwise multiple comparisons using the Scheffe procedure were used to determine which means differ between groups.

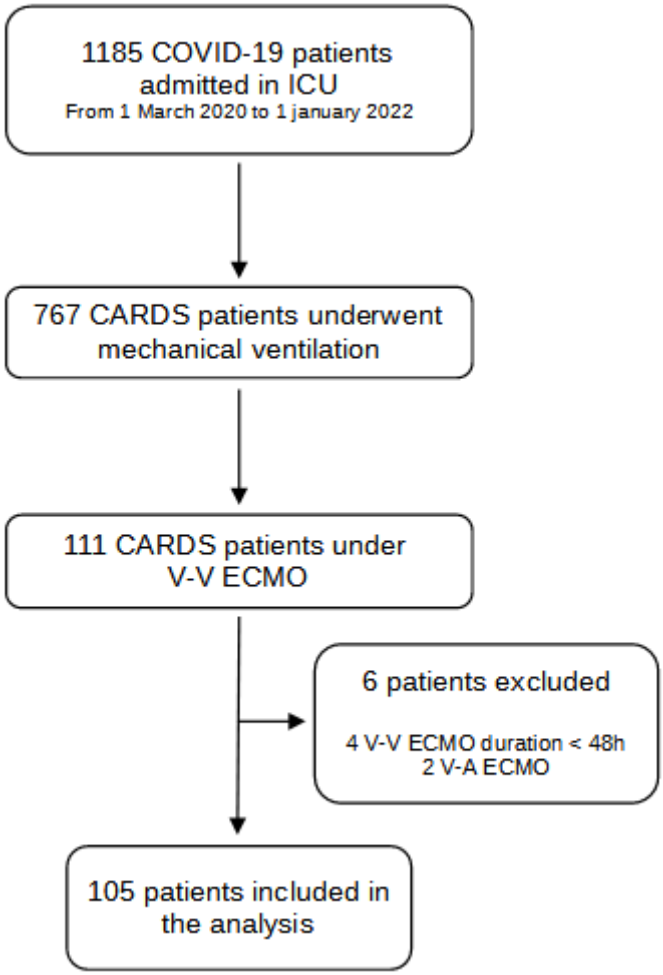
For bivariate comparison between the patients < 50 and ≥ 50 years old, we used $\chi 2$ or Fisher exact tests for categorical variables, and Mann-Whitney U or Unpaired t tests for continuous variables.

All of the analyses were computed at a two-sided α level of 5% with the software IBM SPSS Statistics 28.0.0.0®, Bois-Colombes, France.

Results

From 1 March 2020 to 1 January 2022, 767 patients with CARDS required invasive ventilation in our center, of which 111 were placed under V-V ECMO, as shown in *Figure 1*. Six patients were excluded from the analysis because of V-V ECMO duration under 48 hours (n=4) or V-A ECMO (n=2).

Figure 1. Flow chart



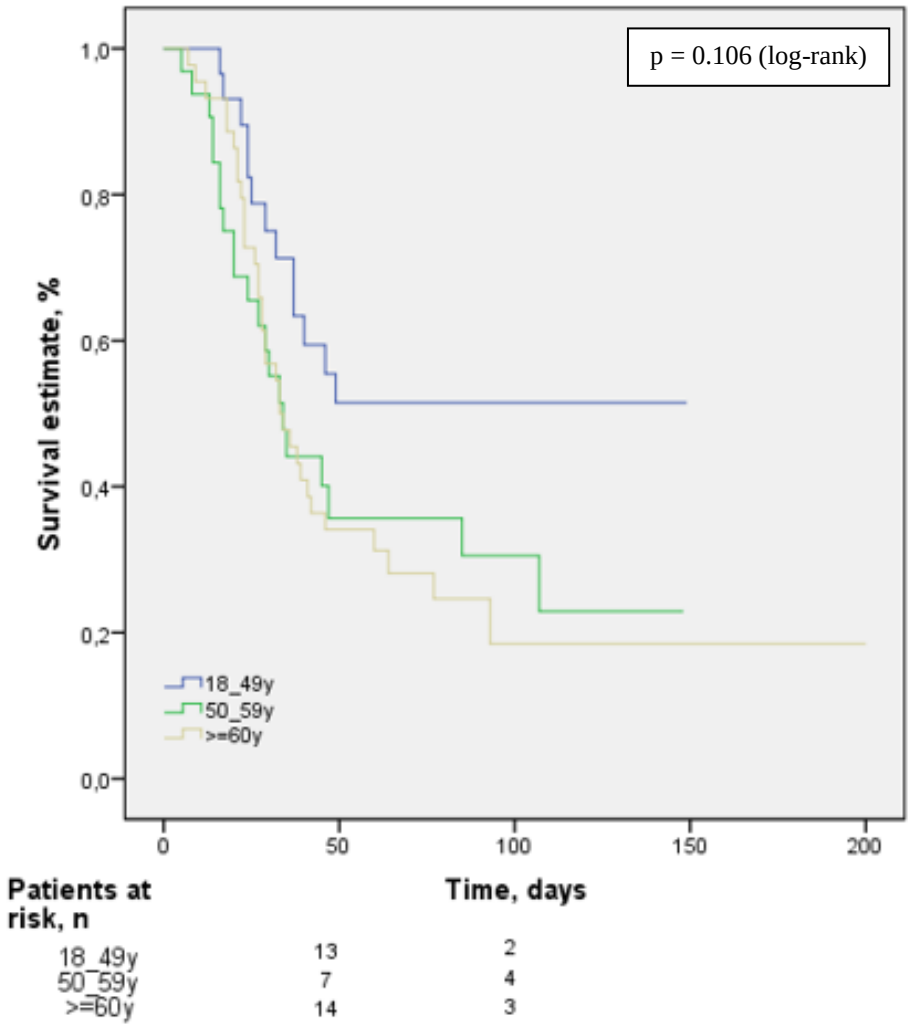
V-V ECMO: Veno-Venous Extracorporeal Membrane Oxygenation ; V-A ECMO: Veno-Arterial Extracorporeal Membrane Oxygenation.

The first indication for ECMO implantation was a PaO_2/FiO_2 < 80 mmHg for > 6 hours concerning 78/105 (74.3%) patients of the global cohort with no difference between the three age groups. Other indications were PaO_2/FiO_2 < 50 mmHg for > 3 hours (11.4%), persistent hypercapnic acidosis with

pH < 7.25 and $PaCO_2$ > 60 mmHg for > 6h (15.2%), and other reasons not included in EOLIA trial inclusion criteria for 10 patients (9.5%) (data not shown).

Thirty-nine patients (37.1%) survived to hospital discharge. *Figure 2* showed Kaplan-Meier hospital survival in the various age groups, and did not reveal statistical difference between each group (p=0.106 on log-rank test). Nevertheless, there was a trend to a higher survival in the 18-49y group (55.2%) than 50-59y group (34.4%) and ≥ 60y group (25%).

Figure 2. Kaplan-Meier survival analysis



The characteristics at ECMO initiation of each group are shown in *Table 1*. The 3 groups were notably comparable for temporality of ECMO initiation, ARDS adjuvant treatment, COVID-19 therapies and pre-ECMO complication. Although there was a trend to a higher SAPSII score in the ≥ 60y group, the others severity scores (SOFA, PRESET) were similar. Moreover, hypertension was significantly more frequent in this group (p=0.008). At last, respiratory mechanics (driving pressure and respiratory system compliance) were significantly more preserved in the 50-59y group.

Concerning biological parameters before ECMO, there was no significant difference between the three age groups except for a lower hemoglobin in the ≥ 60y group (9.1 [8.4 – 10.3]) g/dL compared to 18-49y and 50-59y groups (10 [8.5 – 12.3] g/dL and 9.95 [9 – 11.1] g/dL respectively, p=0.029). For more details, refer to *Table S1* (Supplemental Data).

The ECMO parameters at day 1 were similar between the three age groups (data not shown), with median FmO_2 at 90%, rotation per minute rate at 3500/min, ECMO blood flow at 5.2 L/min and sweep gas flow at 5 L/min in the overall population.

Table 1. Characteristics at ECMO initiation

Characteristics at ECMO initiation	All patients (N = 105)	18-49y (N = 29)	50-59y (N = 32)	≥60y (N = 44)	p-Value
Age	57 (49-63)	44 (36-46)	55 (52.5-57)	64 (61.5-67)	**0.0001**
Male – no (%)	85 (81)	23 (79.3)	27 (84.4)	35 (79.5)	0.89
SAPSII score	55 (46-64)	50 (43-51.5)	52.5 (50-61.5)	62 (51.5-67.5)	0.06
SOFA score	9 (8-12)	10 (8-12)	9 (8-11)	9 (8-11.5)	0.8
PRESET score	6 (4-7)	6 (4-6)	5 (4-6)	6 (5-7)	0.26
Comorbidities					
HTA – no (%)	46 (43.8)	8 (27.6)	11 (34.4)	27 (61.4)	**0.01**
Obesity (BMI>30) – no (%)	66 (62.9)	20 (69)	18 (56.2)	28 (63.6)	0.6
Diabetes – no (%)	33 (31.4)	8 (27.6)	8 (25)	17 (38.6)	0.45
Dyslipidemia – no (%)	29 (27.6)	6 (20.7)	7 (21.9)	16 (36.4)	0.25
Immunocompromised condition – no (%)	11 (10.5)	3 (10.3)	2 (6.2)	6 (13.6)	0.67
Temporality of ECMO initiation					
Time from first symptoms to ECMO – days	16 (13-22)	16 (13-20)	16 (12-21.5)	17.5 (13.5-25)	0.58
Time from ICU admission to ECMO – days	10 (6-15)	11 (7-13)	7.5 (5-13)	12.5 (7-15.5)	0.17
Time from intubation to ECMO – days	5 (2-9)	6 (1-10)	5 (2.5-7.5)	6 (3.5-10)	0.53
Respiratory Support					
Tidal volume ideal body weight ratio – mL/kg	6 (5.7-6.5)	6 (5.7-6.5)	5.95 (5.3-6.6)	6.1 (5.7-6.5)	0.96
Respiratory rate – breaths per minute	30 (28-32)	30 (28-32)	30 (26-32)	30 (28-32)	0.51
Ppeak – cm of water	40 (37-45)	42 (38-46)	40.5 (37-45)	39.5 (35.5-43.5)	0.35
Pplat – cm of water	30 (28-32)	31 (30-32)	30 (27-32)	30 (28-32)	0.1
PEEP – cm of water	12 (10-15)	12 (10-15)	13 (12-16)	12 (6-14)	0.07
Driving pressure – cm of water	18 (14-20)	19 (16-22)	15.5 (13-18)	18 (15-21.5)	**0.01**
Static compliance – mL/cm of water	22.9 (18.6-28.1)	21.9 (15.5-27.6)	25.1 (22.5-34.5)	21.1 (17.9-27)	**0.01**
Mechanical power – Joule/minute	35.3 (30.2-44.3)	36.6 (32.2-46.1)	38 (32.8-47.5)	33.9 (28.3-40.1)	0.26
Adjuvant treatment and COVID-19 therapies					
Prone Positionning – no (%)	103 (98.1)	28 (96.6)	31 (96.9)	44 (100)	0.34
Neuromuscular blockade – no (%)	104 (99)	29 (100)	31 (96.9)	44 (100)	0.58
Inhaled nitric oxide – no (%)	86 (81.9)	22 (75.9)	25 (78.1)	39 (88.6)	0.3
Glucocorticoids – no (%)	85 (81)	24 (82.8)	24 (75)	37 (84.1)	0.6
Antiviral – no (%)	14 (13.3)	3 (10.3)	6 (18.8)	5 (11.4)	0.62
Immunomodulators – no (%)	15 (14.3)	5 (17.2)	7 (21.9)	3 (6.8)	0.16
Complications pre-ECMO					
Renal replacement therapy – no (%)	10 (9.5)	1 (3.4)	2 (6.2)	7 (15.9)	0.19
Pulmonary embolism – no (%)	23 (21.9)	6 (20.7)	5 (15.6)	12 (27.3)	0.5
Pneumothorax – no (%)	14 (13.3)	4 (13.8)	2 (6.2)	8 (18.2)	0.31
Documented bacterial co-infection – no (%)	45 (42.9)	14 (48.3)	10 (31.2)	21 (47.7)	0.29

Data are expressed as median (IQR) or no (%).

SAPSII = Simplified Acute Physiology score II ; SOFA = Sequential Organe Function Assessment ; PRESET = PREdiction on Survival on ECMO Therapy ; ECMO = ExtraCorporeal Membrane Oxygenation ; ICU = Intensive Care Unit ; Ppeak = Peak pressure ; Pplat = Plateau pressure ; PEEP = Positive End-Expiratory Pressure.

Antiviral included Lopinavir-Ritonavir, Remdesivir and Hydroxychloroquine ; Immunomodulators included Tocilizumab and Baricitinib.

The outcomes and complications in each group are detailed in *Table 2*. The hospital, 90 and 180-day mortality were significantly lower in the 18-49y group compared to the older groups. The others outcomes and complications were not significantly different between the three age groups.

Table 2. Outcomes and complications under ECMO

Outcomes and Complications under ECMO	All patients (N = 105)	18-49y (N = 29)	50-59y (N = 32)	≥60y (N = 44)	p-Value
Outcomes					
Lenght of stay ICU – days	34 (23-53)	37 (25-60)	30.5 (17-47.5)	33 (23-46)	0.42
Lenght of stay Hospital – days	34 (23-60)	46 (25-63)	30.5 (18.5-47.5)	33.5 (23-60)	0.27
Lenght of catecholamines – days	12 (7-17)	12 (6-16)	10 (5.5-14.5)	13 (9-19)	0.11
Lenght of mechanical ventilation – days	26 (19-41)	32 (20-43)	25.5 (14.5-36)	25 (19.5-40.5)	0.54
ECMO weaning – no (%)	41 (39)	16 (55.2)	11 (34.4)	14 (31.8)	0.11
ECMO duration – days	13 (9-19)	14 (9-20)	13 (9.5-18.5)	13 (10-18)	0.97
Tracheotomy – no (%)	30 (28.6)	11 (37.9)	6 (18.8)	13 (29.5)	0.27
Hospital mortality – no (%)	66 (62.9)	13 (44.8)	21 (65.6)	32 (72.7)	**0.049**
90-day mortality – no (%)	66 (62.9)	13 (44.8)	21 (65.6)	32 (72.7)	**0.049**
180-day mortality – no (%)	67 (63.8)	13 (44.8)	21 (65.6)	33 (75)	**0.03**
Complications					
Ischemic stroke – no (%)	2 (1.9)	1 (3.4)	0 (0)	1 (2.3)	0.74
Haemorrhagic stroke – no (%)	11 (10.5)	2 (6.9)	3 (9.4)	6 (13.6)	0.72
Canulation site haemorrhage – no (%)	52 (49.5)	16 (55.2)	14 (43.8)	22 (50)	0.68
Other haemorrhage – no (%)	61 (58.1)	15 (51.7)	17 (53.1)	29 (65.9)	0.41
Thrombosis – no (%)	27 (25.7)	11 (37.9)	9 (28.1)	7 (15.9)	0.1
Circuit change – no (%)	41 (39)	11 (37.9)	14 (43.8)	16 (36.4)	0.82
Massive hemolysis – no (%)	16 (15.5)	4 (14.3)	3 (9.7)	9 (20.5)	0.48
Cardiac arrest – no (%)	5 (4.8)	1 (3.4)	1 (3.1)	3 (6.8)	0.86
Renal replacement therapy – no (%)	34 (32.4)	10 (34.5)	10 (31.2)	14 (31.8)	1
Pneumothorax – no (%)	18 (17.1)	7 (24.1)	5 (15.6)	6 (13.6)	0.54
Antibiotic-treated blood stream infection – no (%)	56 (53.3)	12 (41.4)	18 (56.2)	26 (59.1)	0.32
Antibiotic-treated ventilation-acquired-pneumonia – no (%)	73 (69.5)	21 (72.4)	19 (59.4)	33 (75)	0.35

Data are expressed as median (IQR) or no (%).

ICU = Intensive Care Unit ; ECMO = ExtraCorporeal Membrane Oxygenation.

Other site hemorrhage included respiratory tract, urinary tract, gastrointestinal tract, nose, pharynx and ear.

Based on this finding, patients were categorized as age < 50 and ≥ 50 years old for survival analysis. *Figure S1* (Supplemental Data) shows Kaplan-Meier hospital survival in these two groups. Patients < 50y had a significantly higher hospital survival (55.2%) compared to patients ≥ 50y (28.9%) (p=0.035 on log-rank test). The patient's characteristics at ECMO initiation were comparable between these two groups (*Table S2* - Supplemental Data), except for a significant higher prevalence of hypertension in patients ≥ 50y (50% vs. 27.6% in patients < 50y, p=0.038). No differences were found between < 50y and ≥ 50y groups concerning SAPS II score (50 [43-60] vs. 57.5 [50-66.5], p=0.111), SOFA score (10 [8-12] vs. 9 [8-11], p=0.711), PRESET score (6 [4-6] vs 6 [5-7], p=0,794), driving pressure (19 [16-22] vs. 17 [14-20] cmH_20, p=0.082) and respiratory system compliance (21.9 [15.5-27.6] vs. 22.9 [20-30] mL/cmH2O, p=0.202). The outcomes and complications comparison between < 50y and ≥ 50y groups are detailed in *Table S3* (Supplemental Data). Patients < 50y had a significant higher rate of ECMO weaning (55.2%) compared to patients ≥ 50y (32.9%, p=0.036), and a lower 180-day mortality (44.8% vs. 71.1%, p=0.012). Complications under ECMO were not significantly different between these two groups.

At last, the characteristics at ECMO initiation between survivors (n=5) and non survivors (n=15) in the subgroup of patients ≥ 65 years old (n=20) are shown in *Table 3*. To note, there was none immunocompromised patients in survivors. Moreover, survivors had a higher SAPS II score (68 vs. 57) and were less frequently treated by glucocorticoids (60% vs. 93.3%) than non survivors. No others differences were found between survivors and non survivors. Outcomes and complications under ECMO in this subgroup of patients ≥ 65y are detailed in *Table S4* (Supplemental Data). All survivors need tracheotomy, and the median length of mechanical ventilation was 53 (41-70) days. Furthermore, the median length of stay in ICU and hospital were respectively 67 (64-71) and 85 (77-117) days. One year after hospital discharge, the five survivors survived without loss of autonomy with a Lawton-Brody Instrumental Activities of Daily Living Scale at 8 [8-8]. Moreover, the median clinical frailty scale was at 3 [1-6].

Table 3. Characteristics at ECMO initiation in the subgroup of patients ≥ 65 years old

Characteristics at ECMO initiation	All patients (N = 20)	Survivors (N = 5)	Non survivors (N = 15)
Age - years	67 (66-68)	68 (65-69)	67 (66-67)
Male – no (%)	18 (90)	5 (100)	13 (86.7)
SAPSII score	60 (39.5-68.5)	68 (50-72)	57 (36-65.5)
SOFA score	10.5 (8-12.5)	11 (10-11)	9 (8-12.5)
Comorbidities			
HTA – no (%)	14 (70)	4 (80)	10 (66.7)
Obesity (BMI>30) – no (%)	11 (55)	3 (60)	8 (53.3)
Diabetes – no (%)	9 (45)	2 (40)	7 (46.7)
Dyslipidemia – no (%)	11 (55)	2 (40)	9 (60)
Immunocompromised condition – no (%)	4 (20)	0 (0)	4 (26.7)
Temporality of ECMO initiation			
Time from first symptoms to ECMO – days	17.5 (15.5-24.5)	18 (16-26)	17 (15.5-22)
Time from ICU admission to ECMO – days	13 (9.5-17.5)	14 (13-21)	13 (9.5-16)
Time from intubation to ECMO – days	7.5 (4-10)	9 (6-12)	7 (4-9.5)
Respiratory Support			
Tidal volume ideal body weight ratio – mL/kg	6.1 (5.7-6.5)	6.1 (5.7-6.3)	6 (5.7-6.7)
Respiratory rate – breaths per minute	30 (28-31)	30 (26-30)	30 (28-31)
Ppeak – cm of water	40.5 (37.5-44.5)	43 (42-44)	38 (37.5-43.5)
Pplat – cm of water	30 (28-32)	30 (28-32)	30 (28-32)
PEEP – cm of water	12 (6-14.5)	14 (10-14)	12 (6-14.5)
Driving Pressure – cm of water	18 (14.5-23)	18 (15-22)	18 (15-22.5)
Static Compliance – mL/cm of water	21.8 (16.9-27.7)	25.6 (20-26)	21.1 (16.9-27.7)
Mechanical Power – Joule/minute	35.1 (31.3-39.6)	35.3 (33.4-47.3)	34.9 (31.3-37.9)
Adjuvant treatment and COVID-19 therapies			
Prone Positionning – no (%)	20 (100)	5 (100)	15 (100)
Neuromuscular Blockade – no (%)	20 (100)	5 (100)	15 (100)
Inhaled nitric oxide – no (%)	16 (80)	4 (80)	12 (80)
Glucocorticoids – no (%)	17 (85)	3 (60)	14 (93.3)
Antiviral – no (%)	3 (15)	1 (20)	2 (13.3)
Immunomodulators – no (%)	1 (5)	0 (0)	1 (6.7)
Complications pre-ECMO			
Renal replacement therapy – no (%)	4 (20)	1 (20)	3 (20)
Pulmonary embolism – no (%)	4 (20)	1 (20)	3 (20)
Pneumothorax – no (%)	5 (25)	1 (20)	4 (26.7)
Documented baterial co-infection – no (%)	12 (60)	4 (80)	8 (53.3)

Data are expressed as median (IQR) or no (%).

ICU = Intensive Care Unit ; ECMO = ExtraCorporeal Membrane Oxygenation ; Ppeak = Peak pressure ; Pplat = Plateau pressure ; PEEP = Positive End-Expiratory Pressure ;

Antiviral included Lopinavir-Ritonavir, Remdesivir and Hydroxychloroquine ; Immunomodulators included Tocilizumab and Baricitinib.

No statistical analysis performed in regard of the small number of patients.

Discussion (Anglais)

We report here a single center retrospective study describing the impact of age on outcome in patients receiving V-V ECMO for CARDS. Hospital survival was not significantly different among the three age groups defined by the RESP score. Nevertheless, we observed a significant 26.3% lower hospital survival in patients ≥ 50y compared to patients < 50y without confounding factors, except a higher prevalence of hypertension in patients ≥ 50y. We also described a 25% hospital survival in the sub-group of patients ≥ 65 years old.

In our study of CARDS patients on V-V ECMO, the overall in-hospital mortality rate was 66/105 (62.9%). Data from the international ELSO Registry, as of August 14th 2022, showed that ECMO therapy was associated with a lower in-hospital mortality rate at 47% in 13,871 treated patients. One explanation is the older age (median 57 [49-63] years) in our cohort compared to the ELSO report (median 47 [37-56] years). Indeed, other studies reported a comparable high mortality such as a countrywide German database involving a total of 3,397 patients with a 68% in-hospital mortality (mean age = 57±11 years) [35]. Even so, data from the largest systematic review and meta-analysis (52 studies comprising 18,211 patients) on the same period (from 1 December 2019 to 26 January 2022) showed that ECMO therapy was associated with a lower mortality rate at 48.8% [19]. The pooled age of this study was also lower at 52.5 years (95% CI 50.7 to 54.3). The mortality rate has increased during the pandemic likely due to a combination of demographic (patient selection), disease (emerging viral variants), and intervention factors (treatment standards with non-invasive respiratory support, and corticosteroids, selecting the more severe patients for ECMO) [36]. However, the mortality rate varied a lot, in Ling et al. meta-analysis, among studies on the same period [19]. This heterogeneity during the different waves could be partly explain by the large difference in the median age of these studies.

To our knowledge, our study is the first to describe outcomes in CARDS patients under V-V ECMO when stratified by age. In this population, our data demonstrate that there was a low survival rate for

patients over the age of 50 years. Our results are consistent with a similar survival analysis stratified by age in non-COVID ARDS patients under V-V ECMO [37]. This study showed that in-hospital mortality increases incrementally with age, starting at 45 years old. These results bring out the physiologic changes with increasing age which decreased the ability to repair damaged lung cells. In the PRESERVE [19] and the RESP [18] score, which are the most commonly used prognosis scores to predict survival for patients receiving V-V ECMO, age is respectively the first and the second most harmful pre-ECMO variable. Nevertheless, these scores were generated from patient cohorts with non-COVID-19 related ARDS, and the RESP score performs poorly for patients with CARDS [38] . A recent analysis from more than 7,000 CARDS patients receiving V-V ECMO (International ELSO Registry) confirmed 1) that the RESP score performed poorly for patients with COVID-19 (best AUC 0.63 [95% CI, 0.59 to 0.67]; 2) that age was the single most important predictor of mortality. In this study, patients > 53 years old had a 0.66 probably of death [22]. These results highlight that age is the most robust prognosis factor for patients receiving V-V ECMO, notably in COVID-19 patients, and should be considered when deciding to initiate ECMO. However, a specific cutoff age above which V-V ECMO would be futile remains unknown.

At the beginning of the pandemic, the ELSO recommended that selection criteria become more stringent to use V-V ECMO for patients most likely to benefit and return to an acceptable quality of life. Thus, age ≥ 65 years was a relative contraindications to V-V ECMO initiation [23]. Indeed, the first ECMO randomized studies for adult respiratory failure used 65 years as a cutoff [39,40]. Conversely, the more recent EOLIA trial did not specified an upper limit of age [26]. A review of the ELSO registry between 1990 and 2013 identified 368 elderly patients (> 65 years) with a survival-to-hospital discharge rate at 41% [41]. The authors concluded that age should not be an absolute contraindication but should be considered on a case-by-case basis for ECMO use. In the recently published international registry-based cohort study of 7,345 patients with covid-19 associated acute respiratory failure [24], ECMO was associated with a reduction in hospital mortality by 7.1%

compared with conventional mechanical ventilation without ECMO. Although the use of ECMO was more effective in younger patients, its use was still effective in patients older than 65y [24]. However, data about COVID-19 patients > 65y under V-V ECMO remains scare in the literature. In fact, in large cohorts from ELSO registry, the upper quartile of the median age was always above 60y [22,42,43]. In the same way, in the largest meta-analysis by Ling et al. which included both small and large cohorts, the upper quartile of the median age was 54.3y [19]. In our cohort of CARDS patients under V-V ECMO, twenty patients were older than 65 years with a survival-to-hospital discharge at 25%. Although this percentage was lower than younger patients, it was not negligible because, in our cohort, these patients were discharged home with a good autonomy. To note, all survivors older than 65 years in our study were immunocompetent, required an extended ICU stay and a tracheotomy, needing a good physiological reserve before the ICU stay. Finally, V-V ECMO could be a valid therapeutic option in patients older than 65 years, if these patients are chosen carefully on a case-to-case basis.

Our study has several limitations. First, it was a retrospective single center cohort. This design exposed the study to unexpected confounders and may have resulted in underpowered analyses. Thus, the results may not be extended to all CARDS population. However, as all ECMO patients were referred to our tertiary center, patient management, based on the latest recommendations, during the period of the study was homogenous and allowed to make relevant comparison between the different age groups. Second, our effective was relatively small (n=105). Nevertheless, the description of 20 patients older than 65 years was quite original because data from the literature are rare in elderly COVID-19 patients receiving V-V ECMO. Third, our study included only patients cannulated for V-V ECMO. Thereby, we could not evaluate the number of patients recused for V-V ECMO and their outcomes. A survival comparison was not feasible.

Conclusion (Anglais)

Our study described the impact of age on outcome in patients receiving V-V ECMO for CARDS and revealed that the survival to hospital discharge was significantly lower in patients older than 50 years old. We also described a 25% survival to hospital discharge in the sub-group of elderly patients older than 65 years old with a good autonomy one year after discharge from hospital.

These results confirm that age is a major prognosis factor for COVID-19 patients receiving V-V ECMO, but should not be an absolute contraindication alone. VV-ECMO for CARDS in elderly patients should be discussed on a case-to-case basis. Further studies are needed to establish protocols including age in order to help physicians for the initialization of ECMO.

Discussion (Français)

Nous rapportons ici une étude monocentrique rétrospective décrivant l'impact de l'âge sur le devenir des patients sous ECMO V-V pour un SDRA dû au COVID. La survie hospitalière n'était pas statistiquement différente entre les trois groupes d'âge définis selon le RESP score. Néanmoins, il était observé une baisse significative de 26,3% de la survie hospitalière chez les patients ≥ 50 ans par rapport aux patients < 50 ans, sans facteurs confondants, excepté une plus forte prévalence d'hypertension chez les patients ≥ 50 ans. Il était également retrouvé une survie hospitalière à 25% dans le sous-groupe des patients ≥ 65 ans.

Dans notre étude de SDRA dû au COVID sous ECMO V-V, la mortalité hospitalière était à 66/105 (62,9%). Les données venant du registre international de l'ELSO, en date du 14 Août 2022, montrent que le traitement par ECMO était associé à une mortalité hospitalière plus basse, à 47% chez 13 871 patients. Une des explications est l'âge plus avancé (médiane 57 [49-63] ans) de notre cohorte par rapport au registre de l'ELSO (médiane 47 [37-56] ans). En effet, d'autres études ont rapporté un taux de mortalité élevé, comme une étude sur une base de données allemande impliquant 3 397 patients avec une mortalité intra-hospitalière à 68% (âge médian = 57 ± 11 ans) [35]. Les données de la plus grande revue systématique de la littérature et méta-analyse (52 études comprenant 18 211 patients) sur la même période que notre cohorte (du 1er Décembre 2019 au 26 Janvier 2022) montrent que le traitement par ECMO était associé avec une mortalité plus faible à 48,8% [19]. L'âge moyen de cette étude était aussi plus bas à 52,5 ans (intervalle de confiance à 95% de 50,7 à 54,3 ans). Le taux de mortalité a augmenté durant la pandémie, probablement dû à une combinaison de facteurs démographiques (sélection des patients), liés au SARS-COV-2 (émergence de nouveaux variants), et aux traitements (utilisation de la corticothérapie et support respiratoire non invasif, sélectionnant les patients les plus graves pour l'ECMO) [36]. En revanche, la mortalité rapportée variait énormément, dans la

méta-analyse de Ling et al, parmi les études de la même période de temps [19]. Cette hétérogénéité pouvait être expliquée en partie par les larges différences d'âge médian des études incluses.

A notre connaissance, notre étude est la première à décrire le devenir des patients en SDRA dû au COVID sous ECMO V-V selon une stratification par l'âge. Nos données démontrent que, dans cette population, la survie était plus faible chez les patients ≥ 50 ans. Nos résultats sont cohérents avec une analyse de survie similaire, avec une stratification par l'âge, sur une cohorte de patient en SDRA non-COVID sous ECMO V-V [37]. Cette étude montrait que la mortalité intra-hospitalière augmentait progressivement avec l'âge, à partir de 45 ans. Ces résultats illustrent les changements physiologiques, où un âge plus avancé est associé à une moindre capacité de réparation des cellules pulmonaires endommagées. Dans les scores PRESERVE [21] et RESP [20], qui sont ceux les plus communément utilisés pour prédire la survie chez les patients sous ECMO V-V, l'âge est respectivement le premier et deuxième facteur pré-ECMO le plus péjoratif. Néanmoins, ces scores ont été générés à partir de cohortes de patients avec des SDRA non-COVID, et il a été montré que le RESP score avait une performance médiocre chez les patients en SDRA dû au COVID [38]. Une méta-analyse récente de plus de 7 000 patients en SDRA dû au COVID sous ECMO V-V (registre international ELSO) confirmait que 1) le RESP score avait une performance médiocre chez ces patients (meilleure AUC à 0,63, intervalle de confiance à 95% [0,59 à 0,67]), 2) que l'âge était le facteur le plus prédictif de mortalité. Dans cette étude, les patients > 53 ans avait une probabilité à 0,66 de décès [22]. Ces résultats illustrent que l'âge est le meilleur facteur pronostique, et le plus robuste, pour les patients sous ECMO V-V, notamment chez les patients en SDRA dû au COVID, et qu'il doit être pris en compte pour décider l'initiation d'une ECMO. En revanche, un seuil d'âge précis à partir duquel le recours à l'ECMO V-V devient futile reste inconnu.

Au début de la pandémie, l'ELSO recommandait que les critères de sélections pour l'utilisation d'ECMO V-V soient plus stricts pour privilégier les patients les plus susceptibles de bénéficier du

traitement et de retrouver une qualité de vie acceptable au décours. Ainsi, un âge ≥ 65 ans était une contre-indication relative au recours à l'ECMO V-V [23]. En effet, les premières études randomisées sur le recours à l'ECMO dans la défaillance respiratoire utilisaient un âge de 65 ans comme seuil [39,40]. A l'inverse, l'essai EOLIA plus récent ne spécifiait pas de limite d'âge supérieure [26]. Un registre de l'ELSO réalisé entre 1990 et 2013 identifiait 368 patients âgés (≥ 65 ans) avec une survie hospitalière à 41% [41]. Les auteurs concluaient que l'âge ne devrait pas être une contre-indication absolue, mais devait être pris en compte au cas-par-cas pour le recours à l'ECMO. Dans une étude récente basée sur une cohorte internationale de 7 345 patients avec une défaillance respiratoire liée à la COVID-19 [24], l'utilisation d'ECMO V-V était associée avec une réduction de la mortalité hospitalière de 7,1% par rapport à une ventilation mécanique conventionnelle sans ECMO. Bien que le bénéfice de l'ECMO était plus important chez les plus jeunes patients, il persistait chez les patients ≥ 65 ans. Néanmoins, les données concernant les patients ≥ 65 ans en SDRA dû au COVID sous ECMO V-V restent pauvres dans la littérature. Toutes les cohortes importantes tirées du registre de l'ELSO ont un quartile supérieur d'âge médian en-dessous de 60 ans [22,42,43]. De la même manière, dans la méta-analyse de Ling et al, qui incluait à la fois des petites et des grandes cohortes, le quartile supérieur d'âge médian était de 54,3 ans [19]. Dans notre cohorte de SDRA dû au COVID sous ECMO V-V, vingt patients étaient âgés de 65 ans ou plus, avec une survie hospitalière à 25%. Bien que ce pourcentage soit plus bas que chez les patients plus jeunes, il reste non négligeable. En effet, les patients de plus de 65 ans ayant survécu ont tous retrouvé leur domicile avec une autonomie préservée. A noter que ces patients survivants étaient tous immunocompétents, et ont nécessité un séjour prolongé en réanimation ainsi que la réalisation d'une trachéotomie, requérant une bonne réserve physiologique préalable. Finalement, l'ECMO V-V pourrait être une option thérapeutique valide chez des patients âgés de 65 ans et plus sélectionnés soigneusement au cas-par-cas.

Notre étude a plusieurs limites. D'abord, il s'agit d'une étude monocentrique rétrospective. Ce design expose à des facteurs confondants inattendus, et à un manque de puissance dans les analyses. Les

résultats ne peuvent donc pas être généralisés à toutes les populations de SDRA dû au COVID. Néanmoins, comme tous les patients nécessitant une ECMO ont été référés dans notre centre, leur prise en charge, basée sur les dernières recommandations durant la période de l'étude, était homogène et permet de faire des comparaisons pertinentes entre les différents groupes d'âge. Deuxièmement, notre effectif était relativement petit (n=105). Néanmoins, la description de 20 patients âgés de 65 ans ou plus était originale car les données de la littérature sont rares chez les patients de cette tranche d'âge en SDRA dû au COVID et sous ECMO V-V. Troisièmement, notre étude a inclus seulement des patients canulés avec une ECMO V-V. Ainsi, le nombre de patients récusés à l'ECMO V-V et leur devenir n'est pas connu et ne permet pas une comparaison de survie.

Conclusion (Français)

Notre étude décrivait l'impact de l'âge sur le devenir des patients sous ECMO V-V pour un SDRA lié au COVID-19, et montrait que la survie hospitalière est significativement plus basse chez les patients âgés de 50 ans et plus. Nous retrouvons aussi une survie hospitalière à 25% dans le sous-groupe des patients âgés de 65 ans et plus, avec une bonne autonomie un an après la sortie de l'hôpital.
Ces résultats confirment que l'âge est un facteur pronostique majeur pour les patients COVID-19 sous ECMO V-V, mais qu'il ne devrait pas être une contre-indication à lui seul. Le recours à l'ECMO V-V chez les patients âgés avec un SDRA dû au COVID devrait être discuté au cas-par-cas. Des études ultérieures sont nécessaires pour établir un protocole incluant l'âge afin d'aider les cliniciens à décider de l'initiation de l'ECMO.

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Supplemental Data

Table S1. Biological Parameters at ECMO initiation

Biological parameters at ECMO initiation	All patients (N = 105)	18-49y (N = 29)	50-59y (N = 32)	≥60y (N = 44)	p-Value
pH	7.37 (7.26-7.42)	7.34 (7.29-7.42)	7.39 (7.29-7.43)	7.37 (7.27-7.42)	0.78
PaO_2/FiO_2 Ratio – mmHg	70 (62-80)	72 (57-75)	74.5 (68-87)	69 (59.5-79)	0.05
$PaCO_2$ – mmHg	54.5 (45.5-63.5)	59.5 (45-67)	54 (45-64)	53.5 (48-63)	0.93
HCO_3 – mmol/L	29.3 (25-34)	29.8 (24-35)	30.5 (28.7-36.5)	29.9 (25.3-36.3)	0.48
Lactate – mmol/L	1.6 (1.1-2.15)	1.4 (1.1-2.2)	1.5 (1.1-2)	1.6 (1.1-2.0)	0.76
Urea – g/L	0.6 (0.4-0.8)	0.5 (0.4-0.8)	0.6 (0.3-0.7)	0.7 (0.5-1)	0.27
Creatinine – mg/L	7 (6-16)	7 (6-14)	7.5 (6-13)	7.5 (6-20)	0.52
Bilirubin – mg/L	6(4-9)	6 (4-8)	5 (4-13)	5.5 (4-8)	0.46
ASAT – UI/L	45 (33-76.5)	52 (34-67)	57 (39-80)	46.5 (30-77.5)	0.43
Troponin – ng/L	30.5 (17-52)	24 (14-38)	28.5 (18-50)	29 (14.5-46)	0.78
White Blood Cells count – 10^9/L	12.1 (9.5-15.9)	15.15 (12-23.2)	10.6 (9.2-14.5)	12 (10.6-15.1)	0.06
Lymphocyte count – 10^9/L	0.7 (0.4-1)	0.9 (0.7-1.3)	0.7 (0.5-1.3)	0.7 (0.4-0.95)	0.09
Haemoglobin – g/dL	9.7 (8.4-11.2)	10 (8.5-12.3)	9.95 (9-11.1)	9.1 (8.4-10.3)	**0.03**
Platelets – 10^9/L	260.5 (191.5-350.5)	265 (186-335)	273.5 (208-369)	263 (218.5-339)	0.96
Prothrombin Time – %	79.5 (70-85.5)	81.5 (75-91)	75 (68-82)	80 (70.5-85)	0.96
D-Dimer – µg/mL	3.7 (2.2-4.1)	4 (2.5-5.3)	4.2 (3.3-9.2)	2.95 (1.85-4)	0.12
Fibrinogen – g/L	7.2 (5.8-8.2)	6.9 (5.7-8)	7.75 (6.4-9.1)	7.3 (5.9-8.2)	0.47
CRP – mg/L	177.5 (91-279.5)	171.5 (65-335)	176.5 (92-253)	208.5 (104.5-313.5)	0.27
PCT – ng/mL	0.7 (0.3-3.3)	0.45 (0.3-7.7)	0.5 (0.4-3.2)	0.85 (0.4-2.4)	0.94
Ferritine – ng/mL	1309 (800-1909)	1146 (809-1477)	1166 (941-1968)	1743 (653.5-3048)	0.09

Data are expressed as median (IQR). ECMO = ExtraCorporeal Membrane Oxygenation ; PaO_2/FiO_2 = Arterial partial pressure in oxygene to Inspired oxygen fraction ratio ; $PaCO_2$ = Arterial partial pressure in carbon dioxide ; ASAT = Aspartate aminotransferase ; CRP = C-reactive protein ; PCT = Procalcitonin.

Figure S1. Kaplan-Meier survival analysis in the < 50y vs. ⩾ 50y groups

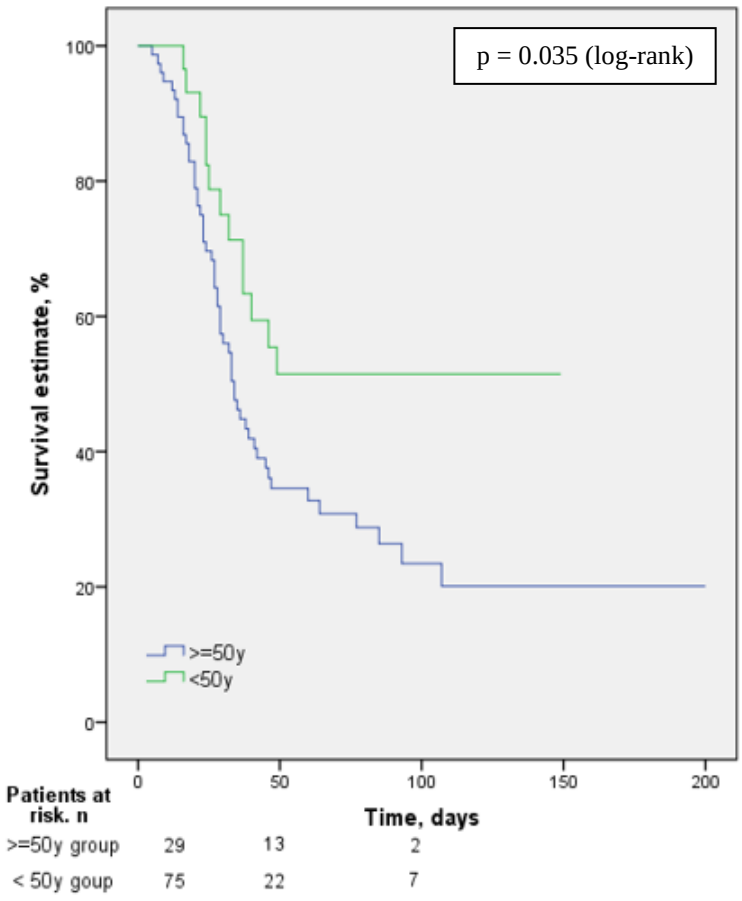

Table S2. Characteristics at ECMO initiation in the < 50y vs. ≥ 50y groups

Characteristics at ECMO initiation	All patients (N = 105)	< 50y (N = 29)	≥ 50y (N = 76)	p-value
Age	57 (49-63)	44 (36-46)	61 (55.5-65)	**0.0001**
Male – no (%)	85 (81)	23 (79.3)	62 (81.6)	1
SAPSII score	55 (46-64)	50 (43-60)	57.5(50-66.5)	0.11
SOFA score	9 (8-12)	10 (8-12)	9 (8-11)	0.71
PRESET score	6 (4-7)	6 (4-6)	6 (5-7)	0.79
Comorbidities				
HTA – no (%)	46 (43.8)	8 (27.6)	38 (50)	**0.04**
Obesity (BMI>30) – no (%)	66 (62.9)	20 (69)	46 (60.5)	0.42
Diabetes – no (%)	33 (31.4)	8 (27.6)	25 (32.9)	0.77
Dyslipidemia – no (%)	29 (27.6)	6 (20.7)	23 (30.3)	0.46
Immunocompromised condition – no (%)	11 (10.5)	3 (10.3)	8 (10.5)	1
Temporality of ECMO initiation				
Time from first symptoms to ECMO – days	16 (13-22)	16 (13-20)	16.5 (13-23)	0.49
Time from ICU admission to ECMO – days	10 (6-15)	11 (7-13)	9.5 (5-15)	0.86
Time from intubation to ECMO – days	5 (2-9)	6 (1-10)	5 (3-9)	0.75
Respiratory Support				
Tidal volume ideal body weight ratio – mL/kg	6 (5.7-6.5)	6 (5.7-6.5)	6 (5.5-6.5)	0.99
Respiratory rate – breaths per minute	30 (28-32)	30 (28-32)	30 (27-32)	0.4
Ppeak – cm of water	40 (37-45)	42 (38-46)	40 (36-44)	0.16
Pplat – cm of water	30 (28-32)	31 (30-32)	30 (28-32)	0.03
PEEP – cm of water	12 (10-15)	12 (10-15)	12 (10-15)	0.81
Driving Pressure – cm of water	18 (14-20)	19 (16-22)	17 (14-20)	0.08
Static Compliance – mL/cm of water	22.9 (18.6-28.1)	21.9 (15.5-27.6)	22.9 (20-30)	0.2
Mechanical Power – Joule/minute	35.3 (30.2-44.3)	36.6 (32.2-46.1)	35.1 (29.6-43.5)	0.34
Adjuvant treatment and COVID-19 therapies				
Prone Positionning – no (%)	103 (98.1)	28 (96.6)	75 (98.7)	0.48
Neuromuscular Blockade – no (%)	104 (99)	29 (100)	75 (98.7)	1
Inhaled nitric oxide – no (%)	86 (81.9)	22 (75.9)	64 (84.2)	0.48
Glucocorticoids – no (%)	85 (81)	24 (82.8)	61 (80.3)	0.99
Antiviral – no (%)	14 (13.3)	3 (10.3)	11 (14.5)	0.75
Immunomodulators – no (%)	15 (14.3)	5 (17.2)	10 (13.2)	0.76
Complications pre-ECMO				
Renal replacement therapy – no (%)	10 (9.5)	1 (3.4)	9 (11.8)	0.28
Pulmonary embolism – no (%)	23 (21.9)	6 (20.7)	17 (22.4)	1
Pneumothorax – no (%)	14 (13.3)	4 (13.8)	10 (13.2)	1
Documented baterial co-infection – no (%)	45 (42.9)	14 (48.3)	31 (40.8)	0.49

Data are expressed as median (IQR) or no (%).

SAPSII = Simplified Acute Physiology score II ; SOFA = Sequential Organe Function Assessment; PRESET = PREdiction on Survival on ECMO Therapy ; ECMO = ExtraCorporeal Membrane Oxygenation ; ICU = Intensive Care Unit ; Ppeak = Peak pressure; Pplat = Plateau pressure ; PEEP = Positive End-Expiratory Pressure.

Antiviral included Lopinavir-Ritonavir, Remdesivir and Hydroxychloroquine. Immunomodulators included Tocilizumab and Baricitinib.

Table S3. Outcomes and complications under ECMO in the < 50y vs. ≥ 50y groups

Outcomes and Complications under ECMO	All patients (N = 105)	< 50y (N = 29)	≥ 50y (N = 76)	p-Value
Outcomes				
Lenght of stay ICU – days	34 (23-53)	37 (25-60)	32.5 (21.5-46.5)	0.25
Lenght of stay Hospital – days	34 (23-60)	46 (25-63)	33 (22-59)	0.17
Lenght of catecholamines – days	12 (7-17)	12 (6-16)	12 (7-17)	0.89
Lenght of mechanical ventilation – days	26 (19-41)	32 (20-43)	25 (17-40.5)	0.29
ECMO weaning – no (%)	41 (39)	16 (55.2)	25 (32.9)	**0.04**
ECMO duration – days	13 (9-19)	14 (9-20)	13 (9.5-18)	0.95
Tracheotomy – no (%)	30 (28.6)	11 (37.9)	19 (25)	0.29
Hospital mortality – no (%)	66 (62.9)	13 (44.8)	53 (69.7)	**0.02**
90-day mortality – no (%)	66 (62.9)	13 (44.8)	53 (69.7)	**0.02**
180-day mortality – no (%)	67 (63.8)	13 (44.8)	54 (71.1)	**0.01**
Complications				
Ischemic stroke – no (%)	2 (1.9)	1 (3.4)	1 (1.3)	0.48
Haemorrhagic stroke – no (%)	11 (10.5)	2 (6.9)	9 (11.8)	0.72
Canulation site haemorrhage – no (%)	52 (49.5)	16 (55.2)	36 (47.4)	0.48
Other haemorrhage – no (%)	61 (58.1)	15 (51.7)	46 (60.5)	0.41
Thrombosis – no (%)	27 (25.7)	11 (37.9)	16 (21.1)	0.13
Circuit change – no (%)	41 (39)	11 (37.9)	30 (39.5)	1
Massive hemolysis – no (%)	16 (15.5)	4 (14.3)	12 (16)	1
Cardiac arrest – no (%)	5 (4.8)	1 (3.4)	4 (5.3)	1
Renal replacement therapy – no (%)	34 (32.4)	10 (34.5)	24 (31.6)	0.96
Pneumothorax – no (%)	18 (17.1)	7 (24.1)	11 (14.5)	0.26
Antibiotic-treated blood stream infection – no (%)	56 (53.3)	12 (41.4)	44 (57.9)	0.13
Antibiotic-treated ventilation-acquired-pneumonia – no (%)	73 (69.5)	21 (72.4)	52 (68.4)	0.87

Data are expressed as median (IQR) or no (%). ICU = Intensive Care Unit ; ECMO = ExtraCorporeal Membrane Oxygenation ; Other site hemorrhage included respiratory tract, urinary tract, gastrointestinal tract, nose, pharynx and ear.

Table S4. Outcomes and complications under ECMO in the ≥ 65y subgroup

Outcomes and Complications under ECMO	All patients (N = 20)	Survivors (N = 5)	Non survivors (N = 15)
Outcomes			
Lenght of stay ICU – days	31.5 (24.5-65.5)	67 (64-71)	28 (22.5-35)
Lenght of stay Hospital – days	31.5 (24.5-77)	85 (77-117)	28 (22.5-35)
Lenght of catecholamines – days	14.5 (10.5-19)	13 (12-14)	16 (10.5-19)
Lenght of mechanical ventilation – days	24.5 (20.5-42.5)	53 (41-70)	23 (19.5-26.5)
ECMO weaning – no (%)	6 (30)	5 (100)	1 (6.7)
ECMO duration – days	13.5 (11-18)	13 (12-14)	14 (11-18)
Tracheotomy – no (%)	7 (35)	5 (100)	2 (13.3)
Complications			
Ischemic stroke – no (%)	1 (5)	1 (20)	0 (0)
Haemorrhagic stroke – no (%)	2 (10)	1 (20)	1 (6.7)
Canulation site haemorrhage – no (%)	12 (60)	5 (100)	7 (46.7)
Other haemorrhage – no (%)	17 (85)	3 (60)	14 (93.3)
Thrombosis – no (%)	2 (10)	0 (0)	2 (13.3)
Circuit change – no (%)	8 (40)	2 (40)	6 (40)
Massive hemolysis – no (%)	4 (20)	0 (0)	4 (26.7)
Cardiac arrest – no (%)	2 (10)	0 (0)	2 (13.3)
Renal replacement therapy – no (%)	8 (40)	2 (40)	6 (40)
Pneumothorax – no (%)	2 (10)	1 (20)	1 (6.7)
Antibiotic-treated blood stream infection – no (%)	12 (60)	3 (60)	9 (60)
Antibiotic-treated ventilation-acquired-pneumonia – no (%)	15 (75)	3 (60)	12 (80)

.

Data are expressed as median (IQR) or no (%). ICU = Intensive Care Unit ; ECMO = ExtraCorporeal Membrane Oxygenation ; Other site hemorrhage included respiratory tract, urinary tract, gastrointestinal tract, nose, pharynx and ear.

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Titre de la thèse : Assistance respiratoire extra-corporelle veino-veineuse au cours du syndrome de détresse respiratoire aigu dû à la COVID-19 : Evaluation du devenir des patients selon une stratification par l'âge

Thèse - Médecine - Lille - 2022

Cadre de classement : Thèse d'exercice de médecine

DES + FST/option : DES Médecine Intensive Réanimation

Mots-clés: ECMO, COVID-19, Age, Mortality

Résumé :

Contexte :
La pandémie COVID-19 a augmenté de manière considérable le recours à l'ECMO V-V à travers le monde pour le traitement des SDRA réfractaires au traitement conventionnel. Bien que l'âge soit un facteur prédictif de mortalité bien établi, il n'existe pas à ce jour d'âge seuil contre-indiquant le recours à l'ECMO V-V. Par ailleurs, les données dans la littérature concernant les patients plus âgés sous ECMO sont limitées. Notre étude avait pour objectif de décrire l'impact de l'âge sur la survie des patients avec un SDRA COVID placés sous ECMO V-V.
Méthode :
Il s'agissait d'une étude rétrospective observationnelle, concernant tous les patients atteints d'un SDRA COVID placés sous ECMO V-V au CHU de Lille du 1er Mars 2020 au 1er Janvier 2022. Le recueil comportait les caractéristiques pré-ECMO des patients, les complications survenues sous ECMO et le devenir des patients avec notamment la mortalité hospitalière, à 90 et à 180 jours.
Résultats :
Au total, 105 patients étaient inclus dans l'analyse. La survie globale à 180 jours était de 36,2%. L'analyse de survie stratifiée selon les groupes d'âge définis par le RESP score retrouvait une tendance non significative à une survie plus élevée dans le groupe des 18-49 ans par rapport aux groupes 50-59 et ≥ 60 ans (55,2% vs. 34,4% et 25% respectivement, p=0,1). Une différence significative était, en revanche, retrouvée en comparant les patients < 50 ans à ceux ≥ 50 ans, (55,2% vs. 28,9% respectivement, p=0,035). Chez les patients de plus de 65 ans (n=20), la survie était de 25%. Les survivants ≥ 65 ans (n=5) conservaient une bonne autonomie un an après la sortie d'hospitalisation.
Conclusion :
Dans notre étude, un âge ≥ 50 ans était associé à un taux de survie hospitalière plus faible. Chez les patients ≥ 65 ans, la survie hospitalière était à 25%. Ces résultats confirment que l'âge est un facteur pronostique majeur, mais qu'il ne devrait pas être une contre-indication à lui seul.

Composition du Jury :
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