Diplomarbeit

Outcome of patients with ARDS (acute respiratory distress syndrome) and extracorporeal veno-venous membrane oxygenation – retrospective study

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Graz, am 08. Nov. 2019 *Dorit Wundara eh*

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Zusammenfassung

Einleitung: Das acute respiratory distress syndrome (ARDS) stellt ein schweres Krankheitsbild mit einer hohen Mortalität dar. Seit der Influenza-H1N1 Epidemie 2009 in Australien wird die Erfolgsrate einer extrakorporalen Membranoxygenierung(ECMO) bei ARDS Patient/Innen diskutiert. Aktuell wird dieses Therapieverfahren nur als "Rescue"-Therapie bei schwerem ARDS empfohlen, da in den bislang vorliegenden Studien kein signifikanter Überlebensvorteil gegenüber einer konventionellen Therapie gezeigt werden konnte. Der Sequential Organ Failure Assessment (SOFA) Score stellt einen bereits validierten Prädikator für das Outcome diverser Krankheitsbilder auf Intensivstationen (ICU) dar. In der vorliegenden Studie wurde die 30-Tagesmortalität von ARDS Patient/Innen welche mit einem ECMO Verfahren behandelt wurden in Abhängigkeit des SOFA-Scores am Tag des ECMO Einbaus untersucht.

Material und Methoden: In dieser retrospektiven Datenanalyse wurden alle ARDS Patient/Innen eingeschlossen, welche aufgrund der Schwere ihrer Erkrankung mit einem ECMO Verfahren an der internistischen Intensivstation der Medizinischen Universität Graz behandelt wurden. Es wurde der SOFA-Score am Tag des ECMO Einbaus erhoben. Mittels statistischer Methoden wurde untersucht, ob sich die 30-Tagesmortalität in Abhängigkeit des SOFA-Scores unterscheidet.

Ergebnisse: 34 Patient/Innen wurden in die Studie eingeschlossen (59% männlich, durchschnittliches Alter 55±13 Jahre). Davon sind gesamt 21 Patient/Innen (62%) im Rahmen ihrer Erkrankung verstorben. Die 30-Tagesmortalität betrug 59% (n=20). Der mittlere SOFA-Score betrug 13±3 Punkte. Der SOFA-Score unterschied sich zwischen der Gruppe der lebend Entlassenen und den Verstorbenen zwar signifikant (p=0,04), zeigte hinsichtlich der 30-Tagesmortalität zwischen Überlebenden und Verstorbenen allerdings keine relevanten Unterschiede (p=0,37).

Schlussfolgerung: Die in dieser Studie erhobene Mortalität liegt etwas oberhalbder Mortalitätsraten, welche in der Literatur beschrieben werden. Der SOFA-Score stellte keinen relevanten 30-Tagesmortalitätprädiktorvon ARDS Patient/Innen welche mit einem ECMO Verfahren behandelt wurden dar.

Abstract

Introduction: The acute respiratory distress syndrome (ARDS) is a serious, high-mortality disease. Since the 2009 influenza H1N1 epidemic in Australia and New Zealand the benefit of ECMO-therapy in patients with ARDS is discussed widely. At present, this therapy is only recommended as a rescue treatment for severe ARDS, as no significant survival benefit has been demonstrated over conventional therapy. The Sequential Organ Failure Assessment (SOFA) Score represents an already validated outcome predictor of various clinical conditions in intensive care units (ICU). In the present study, the 30-day mortality of ARDS patients treated with an ECMO procedure was evaluated by the SOFA-scores collected at the day of ECMO installation.

Material and Methods: This retrospective data analysis included all ARDS patients treated with an ECMO procedure at the ICUof the Department of Internal Medicineof the Medical University of Graz. The SOFA-score was recorded at the day of ECMO installation. Statistical methods were used to investigate whether the 30-day mortality differs depending on the SOFA-score.

Results: 34 patients were included in the study (59% male, mean age 55±13 years). Of these, a total of 21 patients (62%) died due to their ARDS. The 30-day mortality was 59% (n=20). The mean SOFA-score was 13±3 points. Although the SOFA-score differed significantly between the group of survivors and the deceased (p=0.04), there were no relevant differences in the 30-day mortality between survivors and non survivors (p=0.37).

Conclusion: The mortality in this study is slightly above the mortality rates described in the literature. The SOFA-score is not a relevant 30-day mortality predictor for ARDS patients in the present study.

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Glossary

AECC	American-European Consensus Conference
ALI	acute lung Injury
ALL	acute lymphoblastic leukaemia
AML	acute myeloid leukaemia
ANZ	Australia and New Zealand
ARDS	acute respiratory distress syndrome
av	arterio-venous
B-CLL	B-cell chronic lymphocytic leukaemia
BMI	body mass index
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
DAMP's	Danger associated molecular patterns
DO_2	systemic oxygen delivery
EBA	initial examination and observation unit
ECMO	extracorporeal membrane oxygenation
FCIM	faculty of intensive care medicine
FiO2	fraction of inspired oxygen
GCS	Glasgow Coma Scale
Hb	haemoglobin
HFNC	high flow nasal cannula
ICP	intracranial pressure
ICS	intensive care society
ICU	Intensive Care Unit
IBW	ideal body weight
KAGES	Styrian hospitals Limited Company
LKH	regional hospital
LVAD	left ventricular assistance device
MAS-CARE	Miami Atlantic Southeast Cardiopulmonary Rescue
MCI	myocardial infarction
MEDOCS	medical documentation system

MWU	Man-Whitney-U Test
NINS	renal insufficiency
NIV	non-invasive ventilation
NO	nitrogen monoxide
O_2	Oxygen
OD	overdose
PAD	peripheral artery disease
PAE	pulmonal artery embolism
PC	platelete concentrate
PECLA	pumpless extracorporeal membrane oxygenation
PEEP	Positive end-expiratory pressure
PEEPi	intrinsic Positive end-expiratory pressure
pH	potential hydrogenii
PHC	Permissive hypercapnia
PICCO	Pulse Contour Cardiac Output
PL	transpulmonary pressure
Ppeak	peak pressure
pPlat	plateau pressure
ΔP	driving pressure
Q_S/Q_T	intrapulmonary right to left shunt
RBC	packed red blood cells
RBC	red blood cells
RF	rated flow
RM	recruitment manoeuvre
RR	blood pressure
SaO2	oxygen saturation
SLE	Systemic Lupus Erythemadodes
SOFA	Sequential Organ Failure Assessment
SPSS	Statistical Package for the Social Sciences
St.p.	status post
TBC	tuberculosis
TNF	tumour necrosis factor
VALI	ventilator associated lung injury

VAV	veno-arterio-venous
VE-cadherin	Vascular endothelial cadherin
VEGF	Vascular endothelial growth factor
VILI	ventilator induced lung injury
VT	tidal volume
Vv	veno-venous
ΔP	pressure difference

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1 Introduction

The acute respiratory distress syndrome (ARDS) presents as a severe illness with various triggers. Hypoxia, pulmonary edema and inflammatory damage to the endothelium through cytokines and neutrophils are characteristic for ARDS. Since ARDS was first mentioned in 1967, by *Ashbaugh et al.(1),* mortality remained almost the same, despite various improvements in ARDS treatment.(2) Only 50 % of patients are able to return back to work after one year, whereas physical, physiological and cognitive impairments can last for 5 years or longer after the disease.(3) Therefore not only the mortality but also the long-time morbidity rate cannot be neglected and improvements in therapy and mortality are eligible.

The extracorporeal membrane oxygenation (ECMO) is a way to support the conventional treatment. In neonatology ECMO is established as treatment for various conditions. For example: meconium aspiration syndrome or diaphragmatic hernia. It almost vanished in adult medicine due to inadequate efficacy shown in RCTs in 1979 and 1994.(4,5) Since the Influenza H1N1– pandemic 2009/10 in Australia and New Zealand ECMO use increased in adult medicine. A study from *Australia and New Zealand ECMO Influenza Investigators* described a lower mortality despite prolonged use of life support, in patients treated with ECMO.(6) In the same year the CESAR Trial showed a significant improvement in survival without severe disability in ARDS patients treated with ECMO.(7)

In ARDS ECMO uses bypass technology to help lung-recovery by giving it time to revive. Furthermore, the ventilation can be less invasive, helping to reduce ventilator associated lung damage.(7)

So far ECMO is recommended as rescue therapy for selected patients with severe ARDS, because a significant benefit was not found in comparison to ARDS patients which were primarily treated with a conventional approach like lung protective ventilation, volume management and medicamentous treatment.(8-10)

Influencing factors for the survival of patients with ARDS, treated with ECMO, are mostly unknown. Therefore, retrospective Data was collected to determine 30-day mortality and to assess the SOFA-Score as a possible predictor of survival in ARDS patients, because it is already validated to predict survival in other critical illnesses.(11) The SOFA-Score may help to determine which patients would benefit from ECMO.

1.1 Acute respiratory distress syndrome

1.1.1 Definition

ARDS was first mentioned in 1967 by *Ashbaugh et al*.(1). He described it as a severe illness associated with a very high mortality. In 1994 the first uniform definition for ARDS was introduced by the American European Consensus Conference (AECC).(12) In 2012 the *ARDS Definition Task Force* introduced the Berlin-definition of ARDS. Their goal was to find a new, more accurate and better validated definition for ARDS, since the AECC definition was lacking explicit criteria. (Table 1) Therefore the former AECC definition was used as the base model. Epidemiological and physiological data from seven different datasets were collected and evaluated.(13)

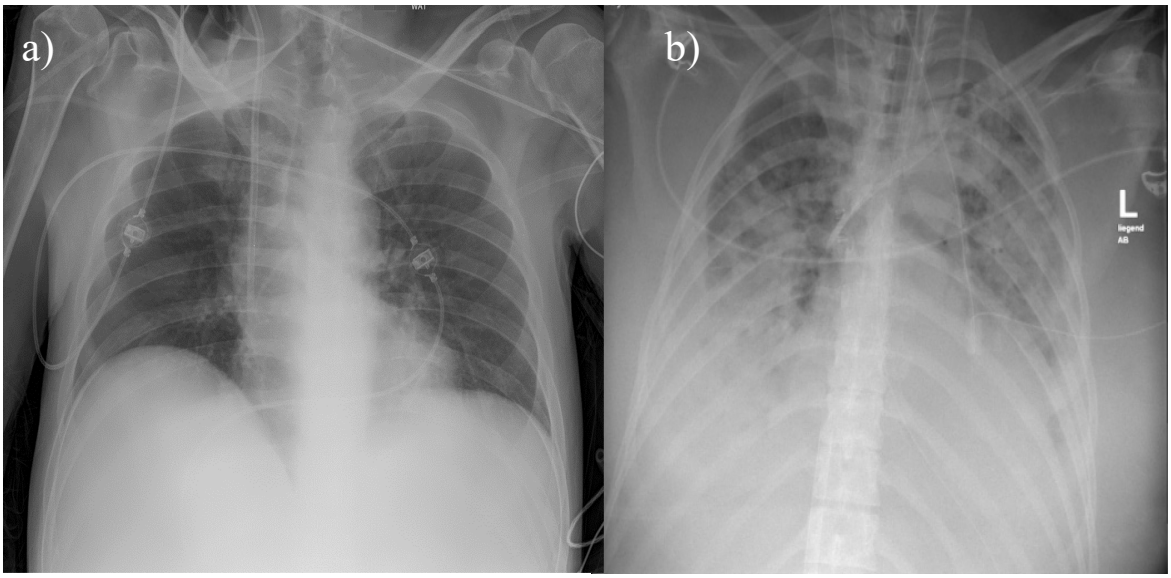

Figure 1; physiological chest radiograph vs. ARDS patient`s chest radiograph
(a)physiological chest radiograph, (b)chest radiograph of patient with ARDS, bilateral consolidations (4 CXR points Murray score)

The Murray lung injury (Table 2) score is used to estimate the severity of lung damage in ARDS patients. A score >2.5 indicates a severe lung injury. The score helps to decide if ECMO should be established in ARDS patients.(14,15)

	Berlin Definition	AECC Definition
Appearance of symptoms (timing)	within 1 week after known clinical insult or new or worsening respiratory symptoms	Acute onset
Imaging*	bilateral consolidations not fully explained by effusions, lobar/lung collapse or nodules	Bilateral infiltrates seen on frontal chest radiograph
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload (further investigation needed to exclude hydrostatic edema if no risk factor present)	
Oxygenation	PaO_2/FIO_2< 300 mmHg with PEEP or CPAP > 5cmH_2O	PaO_2/FiO_2< 200mmHg regardless of PEEP
Mild	PaO_2/FIO_2< 300 mmHg with PEEP or CPAP > 5cmH_2O	
Moderate	100mmHg < PaO_2/FIO_2 <200mmHg with PEEP> 5cmH_2O	
Severe	PaO_2/FIO_2 < 100mmHg with PEEP > 5cmH_2O	
Pulmonary artery wedge pressure		≤18mmHg or no clinical evidence of left atrial hypertension

Table 1; Berlin definition vs AECC definition for ARDS(12,13)

*chest radiograph or computed tomography scan, PaO2/Fio2=ratio between arterial partial pressure of oxygen and inspiratory fraction of oxygen, PEEP= positive end expiratory pressure, CPAP=continuous positive airway pressure

	0	1	2	3	4
PaO_2/FiO_2 mmHg	>300	225-299	175-224	100-174	≤100
CXR	One point for each infiltrated quadrant				
PEEP cmH_2O	≤5	6-8	9-11	12-14	>15
Compliance ml/cmH_2O	>80	60-79	40-59	20-39	<19

Table 2; Murray lung injury score(15)

Final score=collective score divided by the number of used components

PaO_2/FiO_2=ratio between arterial partial pressure of oxygen and inspiratory fraction of oxygen

CXR=Chest radiograph

PEEP= positive end expiratory pressure

1.1.2 Aetiology and Epidemiology

ARDS occurs with different disease patterns, through direct or indirect damage to the lung. (Table 3) More than 80% of cases are caused by a few diseases: mostly sepsis, bacterial pneumonia, trauma, mass transfusion, aspiration and drug intoxication. Rare causes of ARDS are traumatic brain injury, severe burns, toxic gas inhalation and almost drowning. Respiratory failure is present in about 10% of all intensive care unit (ICU) admissions, from which 20% can be defined as acute lung injury (ALI) or ARDS.(16)

In 2016 a prospective cohort study described an ICU incidence for ARDS of 0.48 cases/ICU bed over four weeks in Europe. In total, 10.4% of all admissions and 23.4% of mechanical ventilated patients were diagnosed with ARDS.(17)

direct damage	indirect damage
Pneumonia	Sepsis
Aspiration	Severe Trauma
Lung contusion	Mass Transfusion
Almost drowning	Intoxication
Toxic gas inhalation	Pancreatitis
	Cardiopulmonary Bypass

Table 3; possible causes of ARDS (16)

1.1.3 Pathophysiology

The main pathomechanism of ARDS is a mismatch in perfusion/ventilation proportion, which leads to hypoxaemia. Furthermore, immune system activation through direct or indirect damage leads to generation of O2 -radicals. Those radicals cause pulmonary edema and surfactant inactivation.(18)In the development of ARDS 3 stages(Figure 2) can be described. Each phase is determined by clinical and pathophysiological characteristics.(16)

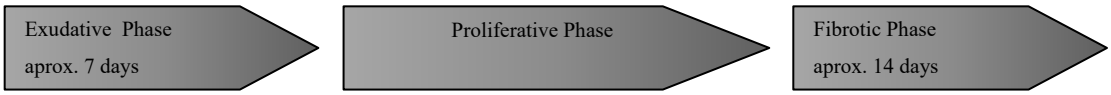

Figure 2; ARDS stages

1.1.3.1 Exudative Phase

The exudative phase is the first of the 3 stages and usually lasts 7 days.(16) Bonding of microbial products or danger associated molecular patterns (DAMP`s) to Toll-like receptors induce acute inflammation, which leads to the destruction of epithelial and endothelial structures of the lung.(19) Also platelet activity and coagulation are affected.(20) In this first stage levels of cytokines and lipid mediators are significantly increasing. Tumour necrosis factor (TNF), thrombin, vascular endothelial growth factor (VEGF) and leukocytes destabilise vascular endothelial cadherin-bonds, which are important to maintain the alveolar barrier and microcirculation. In the end this leads to a loss of the microvascular and the alveolar barrier. The consequence is a protein rich pulmonary edema.(16,21)

In addition to the pulmonary edema, hyaline membranes form from plasma protein-aggregation, surfactant proteins and detritus in the alveoli. These hyaline membranes trigger formation of atelectasis and reduce lung-compliance, which leads to intrapulmonary shunts. Furthermore, blood clots are formed due to microvascular damage. Therefore, the pulmonary blood flow is reduced, causing increased death space ventilation, pulmonary hypertension, hypoxaemia and hypercapnia. The patients show clinical symptoms like dyspnoea and tachypnoea until respiratory exhaustion, usually within 12-36 hours.(16)

1.1.3.2 Proliferative Phase

In the proliferative phase of ARDS first biological evidence for regression can be seen. Repair mechanisms like resorption of alveolar exudate with the transformation from a neutrophilic to an lymphocytic infiltration and proliferation of pneumocytes type II can be observed. Although clinical appearance of the patients improves, dyspnoea and hypoxaemia may persist. In this phase most patients can be successfully weaned from mechanical ventilation.(16)

1.1.3.3 Fibrotic Phase

Some patients can develop fibrosis of the lung, as the alveolar edema, present during ARDS, transforms into fibrotic tissue. Those fibrotic changes increase pneumothorax risk, dead space ventilation and decreases compliance. This transformation mainly takes place in the ductus alveolaris and the interstitium, thereby an emphysema develops. Furthermore, the vessels of pulmonary microcirculation are affected by fibrosis, which leads to pulmonary hypertension associated with increased right ventricular load and over time the function of the right ventricle is getting insufficient.(16,22)

1.1.4 Treatment

According to the faculty of intensive care medicine- and intensive care society (FICM-ICS)-guideline for the management of ARDS the treatment should focus on the main issues caused by ARDS. First, lung protective ventilation strategies with low tidal volumes are needed to maintain sufficient oxygenation and to prevent injuries to the lung. The establishment of lung protective ventilation is followed by conservative fluid management to reduce the pulmonary edema, and targeted anti-inflammatory/anti-infective treatment if needed. Patients with moderate to severe ARDS can benefit from prone positioning if executed for at least 12 hours per day with ventilation at a high positive end expiratory positive pressure (PEEP)-level.(8,9,23)

1.1.4.1 Ventilation:

To support the lung function and to maintain sufficient ventilation, mechanical ventilation is needed. One of the main problems in ARDS is insufficient oxygenation due to the formation of atelectasis. It is crucial to reopen the atelectasis and to keep them open. Therefore, a high PEEP (>8 cmH_2O) is needed. If possible, it is beneficial to allow spontaneous or augmented spontaneous breathing, It was shown that biphasic positive airway pressure ventilation (BIPAP) with spontaneous breathing lead to better oxygenation and a better ventilation/perfusion-proportion than ventilation strategies that don`t allow spontaneous breathing without hindrance (24). Furthermore, the function of the diaphragm is maintained. This contributes to the prophylaxis of atelectasis.

Mechanical ventilation can cause ventilator induced lung injuries (VILI), which have a huge impact on the outcome. It is important to keep the mechanical stress for the lung as low as possible and to reach almost physiological blood gas values. Regarding VILI, the most relevant ventilator settings are tidal volume (VT), respiratory rate (RR), PEEP, plateau pressure (pPlat) and driving pressure (ΔP). Considering these parameters, a lung protective ventilation strategy, “baby lung concept”, should be used with no more than 6ml/kg tidal-volume, an inspiratory pressure <30cmH_2O at ΔP<15cmH_2O. The baby lung concept contributes to a significant benefit in survival of ARDS patients.(8,23,25,26)

A high flow nasal cannula (HFNC) can be considered under permanent monitoring in early stages of ARDS. When using non-invasive ventilation (NIV) in early stages of ARDS, better oxygenation and less intubations can be observed. The use of NIV is associated with low ICU mortality.(27) Despite those positive observations, NIV should only be used in

specialised centres preferably with mild ARDS. Invasive ventilation is recommended for mild to severe ARDS, because a higher PEEP can be applied, which is important to treat the oxygenation disorder.(9)

Although different ventilation techniques have their pros and cons no recommendation is given on which type to use (pressure vs. volume controlled) in ARDS treatment. Ventilation parameters should be monitored closely to develop a personalized ventilation strategy for each patient.(9,26)

Permissive hypercapnia (PHC) is described to support lung protective ventilation strategies. It is possible to achieve lower pressure amplitudes in favour of higher arterial CO2-levels. Higher CO2-levels lead to vasoconstriction in the pulmonal vessels, resulting in a decreased shunt-perfusion and a redistribution to better ventilated areas and better oxygenation. At the same time the needed dose of vasopressors may increase due to peripheral vasodilation in a hypercapnic state. Moreover, anti-inflammatory effects are described for PHC. Since the CO2-levels are directly linked to the intracranial perfusion, PHC must not be used in patients with increased intracranial pressure (ICP). Other contraindications for PHC are insufficiency of the right or left ventricle, ischemic cardiomyopathy and cerebral seizures.(9,28)

1.1.4.2 Prone positioning:

Prone positioning has been found to be an effective recruitment strategy. It increases oxygenation in ARDS patients and has a benefit on survival in patients with severe hypoxaemia. Prone positioning does not increase hyper inflated tissue or plateau pressure and may reduce ventilator associated lung injury.(29-31)

Prone positioning means to turn the patient 180° from the dorsal position, resulting in the patient lying face down in aventral position. The goal of this change of position is to reduce the pleura-pressure-gradient, as well as to reduce the lung damage associated with mechanical ventilation. Therefore, the distribution of gas can be more homogeneous and the number of not ventilated areas decreases. Even if patients have a poor response to recruitment manoeuvres (chapter 1.1.4.1.4) in the supine position it is possible to recruit a significant amount of non-aerated tissue in prone position.(29) The positive effects of prone positioning can be seen within 24 hours.(32)

Although prone positioning is quite safe, complications can occur. Displacement, loss or obstruction of the orotracheal tube, pressure ulcer and the loss of venous and arterial lines

are the most common complications. To minimise the risk of complications prone positioning should be executed by trained personnel only.(29,31)

1.1.4.3 Pulmonal Vasodilators:

In some cases, permissive hypercapnia is used to maintain a lung protective ventilation with a small pressure amplitude. The hypercapnia leads to pulmonal vasoconstriction, which increases the right ventricular afterload. Pulmonal vasodilators (NO, Prostacycline, Iloprost) can reduce the afterload through selective reduction of the pulmonal-arterial pressure and lead to better oxygenation.(23) Nevertheless, this effect only lasts for 24-48 hours and no significant benefit for survival has been found.(33) The use of pulmonal vasodilators in adults is not recommended, since an increased risk for renal failure occurs.(8) It's suggested that pulmonal vasodilators can be used as bridging until extracorporeal membrane oxygenation (ECMO) is established or the onset of prone positioning effects.(9)

1.1.4.4 Recruitment manoeuvres

Recruitment manoeuvres (RMs) are based on the concept of "open the lung and keeping the lung open". According to the law of LaPlace collapsed alveoli or alveoli with low volume need more pressure to be opened than larger ones. Since high shear stress between open and atelectatic lung areas leads to lung damage, only ventilation modes with a small pressure amplitude should be used.(34) To keep the lung open, the critical opening pressure must be exceeded. This can be achieved with pressure-controlled ventilation, sustained inflation, intermittent sighs and extended sighs. These techniques use higher inspiratory pressure and/or PEEP over a specified time period, to recruit non-ventilated areas. The potential for recruitment is proportional to the areas that could be recruited. If the effect of RM lasts for a short time only, the applied PEEP should be reassessed since it could be too low. Since there is no evidence for the benefit of RMs for survival, the guidelines do not give a recommendation according the use of RMs.(9,23)A recent study by *Kung et al.* also didn`t find a benefit for survival when using RMs in patients with ARDS, although patients that survived >28 days in the RM group had significantly more ventilator and ICU free days than those in the control group.(35)

Criteria for the efficacy of RM`s:

- Increase of end expiratory lung volume
- Decrease of atelectatic consolidations in computer tomography
- Increase of regional ventilation in electric impedance tomography

Surrogate parameters:

- Increase in compliance
- Improvement in oxygenation ($PaO_2 \uparrow$)
- Improvement of alveolar ventilation ($PaCO_2 \downarrow$)

Table 4; criteria and surrogate parameters for the efficacy of recruitment manoeuvres(23)

1.1.5 Prognosis

In literature mortality rates for ARDS vary between 27-45% and succeed more than 60% for severe forms.(10,36,37) For example in the ALIEN study a ICU mortality of 42.7% and a in hospital mortality of 47.8% for ARDS without ECMO treatment was estimated.(38) The *EOLIA trial* described a 60-day mortality of 35% for patients treated with ECMO and 46% in patients with conventional treatment.(10)

In 2016 epidemiology patterns and the mortality of ARDS were analysed in 50 countries. Seemingly ARDS is under recognized and this can lead to a delay of treatment. The result was an overall ICU mortality of 35.3% and a hospital mortality of 40%.(17) A retrospective study from *Lee Y. L. et al.* described a hospital survival of 17.8%.(37)

Not only the high mortality but also the long-term problems can influence a patient's quality of life, years after treatment. Younger patients have a better rate of recovery. Nevertheless, most patients do not return to normal physical function up to 5 years after treatment. Those impairments can have an impact on mental health too. Half of the patients reported at least one episode of depression or anxiety within the 5 years. From the patients treated with ECMO, most returned to work within 2 years, but many needed modified work schedules or job- retraining.(39) In the *CESAR study* long term outcomes were similar in ECMO and non ECMO treated patients but the outcomes for social function and vitality had a lower health related quality of life measured with the short form 36 (SF-36) health survey. However, these outcomes can also be related to time spend in ICU and not only to ECMO treatment.(40,41)

1.2 Extracorporeal membrane oxygenation

If patients do not respond to the treatment, described in chapter 1.1.4, the use of extracorporeal membrane oxygenation (ECMO) is a possible rescue therapy during the acute phase of ARDS.(42)

ECMO is a form of extracorporeal life support that provides sufficient gas exchange and perfusion to support patients with respiratory or cardiac failure and to prevent VILI.(43)

The reason for respiratory or cardiac failure needs to be reversible to initiate ECMO. Inclusion criteria differ from centre to centre (chapter 1.2.4).(44,45)

Although there are different ECMO circuits the basic components are the same. Blood is drained from the venous system into a reservoir. A roller or impeller pump pushes the blood through a membrane oxygenator and a heater before it flows back into the patient´s system. If the reservoir collapses the pump flow is decreased to prevent exceeding the venous flow. The pumps are usually magnetically levitated, to achieve less heat generation or haemolysis. Systemic heparin administration is needed to prevent the formation of blood clots, since the blood interacts whit the ECMO components. This interaction leads to inflammatory and prothrombotic processes.(44-47) Although the successful use of ECMO without systemic anticoagulation was achieved before.(48)

The main goal when initiating veno-venous (vv)-ECMO for respiratory failure is to maintain or improve systemic oxygen delivery (DO_2), therefore ECMO should be at least equally capable of delivering oxygen and removing CO2 as the patient's system itself. Oxygen delivery is dependent on both, properties of the ECMO such as the possible blood flow or the membrane lung characteristics, as well as the patient's physiology, like haemoglobin (Hb) concentration or cardiac output. The blood flow determines the systemic perfusion and therefore is crucial to maintain O2 delivery to the organs. To achieve sufficient systemic perfusion adequate extracorporeal blood flow is needed. The recommended flow for adults on vv-ECMO is 50-100ml/kg/min. The flow is dependent on the pump performance, the tubing resistance and the vascular access. The bigger the vascular cannula the more flow is possible. If the desired flow cannot be reached despite optimal cannula placement or preload improvement, the placement of another cannula is recommended. In case of the patient developing a cardiac failure during vv-ECMO support it can be converted to veno-arterial (va)-ECMO. The gas exchange capability of the "membrane lung" is important for oxygenation. This capability is described as rated flow (RF): flow rate at which venous blood will be fully saturated at the outlet of the

"membrane-lung". To maintain adequate oxygen haemoglobin levels should not be too low, nor too high. Some centres recommend restrictive transfusion of packed RBC`s, due to the possible complications linked to transfusions. But the lower the haemoglobin concentration the higher is the needed flow. Reaching a higher flow is not possible for every patient and is associated with a higher risk for haemolysis. The management should be performed for each patient individually.(45,47)

ECMO is recommended as rescue therapy in selected patients with severe ARDS only.(8)

Depending on the indication for the installation of ECMO there are two different types: veno-venous(vv)-ECMO and veno-arterial(va)-ECMO that are used today. Furthermore, the arterio-venous(av)-ECMO exists as a device for extracorporeal CO_2 removal.

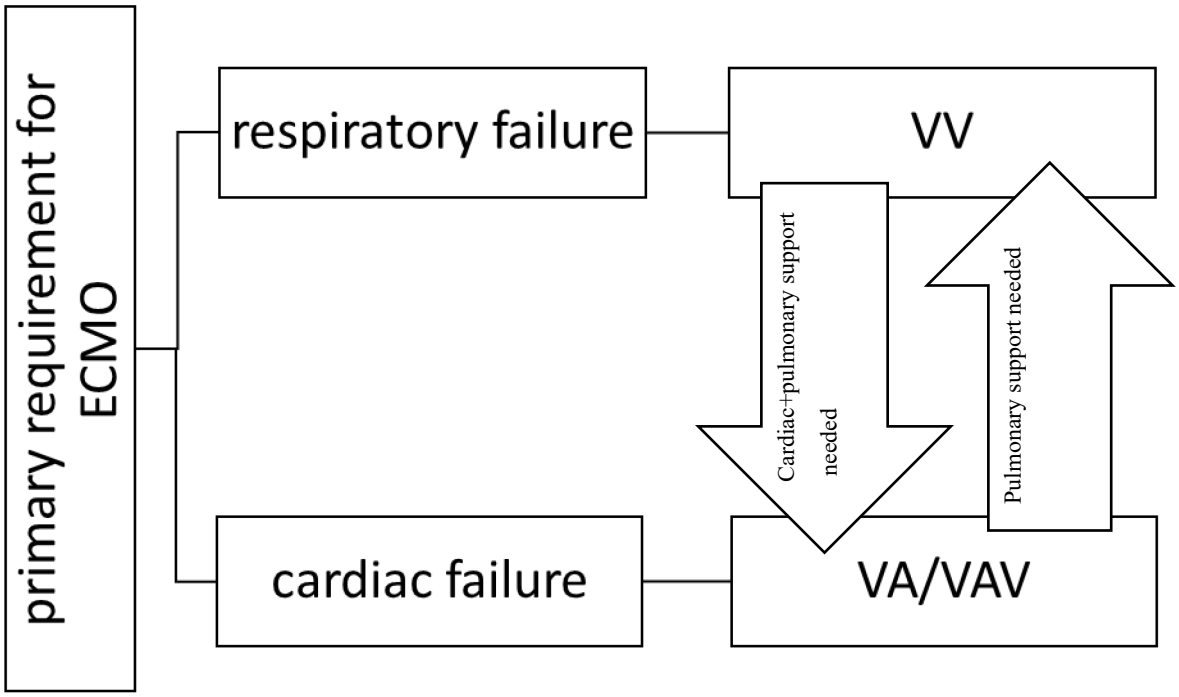

Figure 3; when to choose which ECMO(44)

1.2.1 Veno-arterial ECMO

The va-ECMO is used to support patients with cardiac failure with or without respiratory failure because it has positive cardiac effects. These effects are decreased preload, increased afterload, lower pulse pressure. It can provide cardiopulmonary support partially or fully.(44) Therefore, blood is drained from the right atrium with a central venous cannula, or directly from the right atrium in patients with an open chest. Unlike the vv-ECMO system the blood is actively pumped back into the arterial system, therefore the va-ECMO´s O_2-delivery capacity is higher than in a vv-ECMO. Indications are cardiogenic shock, graft failure post heart or heart lung transplantation, bridge to left ventricular assistant device (LVAD) implantation, intoxication, sepsis, pulmonary embolism, failure to wean after cardiopulmonary-bypass, cardiac or major vessel trauma, massive pulmonary haemorrhage, pulmonary trauma and acute anaphylaxis.(46,47,49,50)

1.2.2 Arterio-venous ECMO

The av-ECMO is a pumpless extracorporeal lung assist device (pECLA). It uses the pressure gradient between the arterial and the venous system of the patient to achieve blood flow through the oxygenator. Therefore, the av-ECMO is limited to patients with adequate ejection fraction and a mean arterial pressure >70mmHg only. For this reason, mostly the low flow vv-ECMO replaces the av-ECMO. Benefits are primarily described for COPD. It is possible to avoid intubation with the use of av-ECMO if non-invasive ventilation strategies fail. The system is effective for CO2 elimination in patients with permissive hypercapnia. The av-ECMO allows a decrease of CO_2-blood levels up to 50% within 2 hours after installation. However, this system does not oxygenate the blood efficiently.(51,52)

1.2.3 Veno-venous ECMO

The vv-ECMO does not support haemodynamics or circulation, but O2 delivery to the coronary and pulmonary circuit is increased. It is used to treat respiratory failure, whereby CO2is removed and oxygenation is improved in patients with adequate cardiac output. Parameters for the O2 sufficiency are SaO2, PaO2, cerebral venous saturation and the pre-membrane saturation trend. Indications for vv-ECMO are hypoxemic or hypercarbic respiratory failure due to ARDS, pneumonia, trauma, status asthmaticus, exacerbation of

chronic obstructive pulmonary disease, primary graft failure after lung transplantation, bridging till lung transplantation, bronchopleural fistulas or pulmonary air leaks.

There are different ways of cannulation. Preferential cannulation configuration is the jugular-femoral one followed by the femoro-femoral one. Usually the largest possible cannula is used. If clinically significant recirculation occurs during this procedure the location of the cannulas should be reassessed, since the level of recirculation is associated with the placement of the cannulas and seems to be highest in femoro-femoral cannulation.(44-46,53-56)

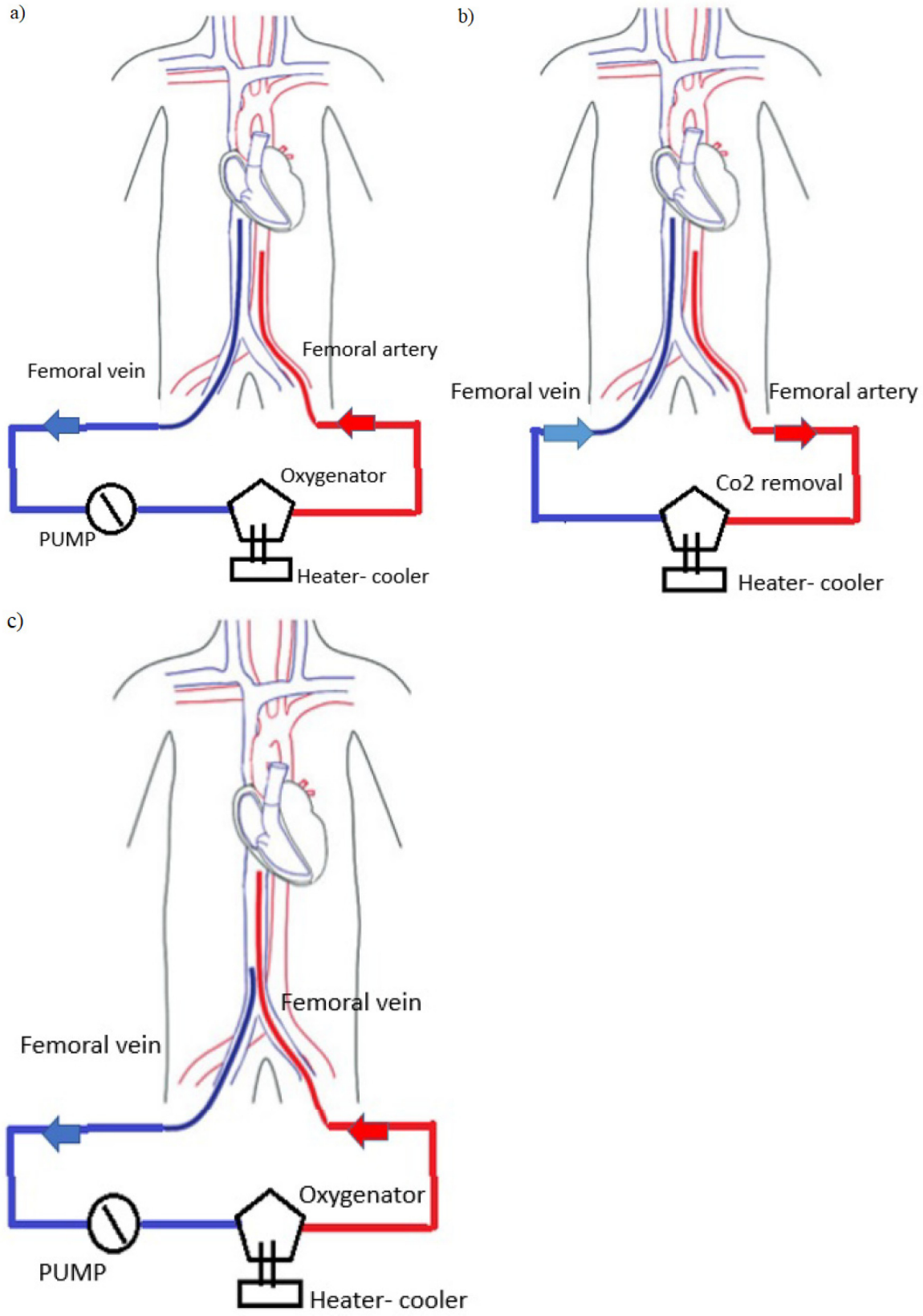

Figure 4; different ECMO curciuts and cannulation(57)
va-ECMO(a), av-ECMO(b), vv-ECMO(c)

For the treatment of ARDS mainly vv-ECMO systems are used. Therefore the following will refer to vv-ECMO only.

1.2.4 Entry criteria and indications

According to the ELSO-Guidelines the risk of mortality is 50% or more. It should be installed as soon as possible, because the best outcome for patients with ARDS is described early after onset.(47)

There are many different entry criteria circulating in the literature depending on ECMO centres. Entry criteria can be divided into slow and fast entry criteria, although not all centres differentiate between them. They usually are variations of the original fast and slow entry criteria (Table 5) used in the *US ECMO study* 1979.(58). Criteria that mostly are included are specific respirator settings and oxygenation assessed at a certain time. Some include assessment of lung compliance.(42)

slow entry	fast entry
maximal medical therapy for 48h	PaO2 < 50mmHg > 2h at FiO2 1.0 and PEEP ≥ 5 cm H_2O
PaO2 < 50mmHg > 12h at FiO2 0.6 and PEEP ≥ 5cm H_2O	
Qs/QT > 30% of cardiac output at FiO2 1.0 and PEEP ≥ 5cm H_2O	

Table 5; classic slow and fast entry criteria(58)

1.2.5 Contraindications

The installation of an vv-ECMO is not possible if severe pulmonary hypertension, unsupportable cardiac failure, cardiac arrest or severe immunosuppression are pre-existing.(49,59) Moreover, current intracranial haemorrhage, a recent brain injury (<72h) or a metastatic malignancy represent absolute contraindications for vv-ECMO. Considering the increased risk for complications and death in patients older than 65 years or ventilation with FiO2 >90% and pPlat>30cmH2O for more than 7 days these factors depict relative contraindications and must be considered individually with respect to risks and benefits. Since the increased use of surface heparinization in ECMO systems, increased risk of bleeding or other contraindications to anticoagulation are no longer considered absolute contraindications and should be considered in each patient individually. (42,44,59)

1.2.6 Complications

There are several known complications associated with ECMO, which can be mechanical or patient related. Although, compared to patient related complications mechanical problems are much less frequent. They can occur in every part of the circuit, beginning with oxygenator failure, malfunctioning of the pump or heat exchanger, disruption of the tubing system and cannula displacement.(42) From 1989 to 2016 10.6% of patients with respiratory failure experienced mechanical complications during vv-ECMO, although the number had decreased.(60) In the ELSO registry report 2012 mechanical complications occurred in 26.2%, whereas patient related complications occurred in 55.9% of cases.(61) Bleeding, neurological problems, such as stroke or seizures, additional organ failure, infection and metabolic disorders represent patient related adverse effects, with bleeding described as the most common complication.(42) In the recent *EIOLA trial* bleeding is described in almost half of the patients with ARDS and ECMO treatment. 46% of the patients experienced bleeding that led to transfusion and 2% needing more than 10 units of packed red cells. In addition, the ECMO group showed more cases of thrombocytopenia. Other than that, occurrence of complications did not significantly differ in the ECMO and non ECMO group.(10) As second most common complication nosocomial infections, primarily bloodstream infections and ventilator associated pneumonia are described.(41)

1.2.7 Weaning from vv-ECMO

Weaning from vv-ECMO is a complex process. This process includes consistent end organ recovery. Although duration of vv-ECMO correlates with the risk of adverse events and the outcome, weaning trials only should begin when signs of end organ improvement are seen, since the priority is organ recovery.(44,62) In some patients, experiencing serious adverse events, for example major bleeding, the priority shifts to quick disconnection from vv-ECMO. There are also cases where the duration of invasive ventilation must be as short as possible. Therefore, it is possible to wean patients from the respirator and extubate them while they are still on vv-ECMO support, for instance after lung transplantation.(63)

In 2018 a standardized weaning protocol for vv-ECMO was suggested by *Grant et al*., the *Miami Atlantic Southeast Cardiopulmonary Rescue (MAS-CARE) Network's vv-ECMO weaning protocol.* The protocol suggests that weaning from ECMO should begin after clinical recovery and following respirator settings should be reached: FiO_2< 50%, PEEP ≤ 10 mmHg, VT 6-8ml/kg ideal body weight (IBW), positive inspiratory pressure (PIP)< 30cmH2O, pPlat<25cmH2O, minute ventilation of 100ml/kg ideal body weight. The patient should tolerate these ventilator settings while maintaining SpO_2>90% and be normocapnic. In this protocol the first step of weaning is to reduce the ECMO-FiO_2 to 21%. If the patient tolerates this, maintaining SpO2 >90%, the blood flow is decreased to 3-4 L. As soon as it is possible to maintain these settings for at least 24 hours the gas flow can be reduced to 1 L. This process takes place stepwise and under serial blood gas evaluation, to monitor oxygenation and possible CO2 retention. After reaching these target settings the patient is considered successfully weaned and is a candidate for decannulation.(64)

Some centres recommend turning of heparin 30-60 minutes prior to decannulation. Others recommend assessment of coagulation status. If it is appropriate the cannulation site is supplied with sutures. The suture in combination with manual compression usually provides adequate haemostasis. To rule out possible thrombotic events after decannulation, venous doppler ultrasound of the cannulated vessels should be performed. (63,64)

When decannulating the jugular vein in spontaneously breathing patients an air embolism is possible. Therefore, a Valsalva manoeuvre should be performed during the removal of the cannula.(63)

1.3 Sequential Organ Failure Assessment (SOFA) Score

The SOFA-Score was developed to asses as well as to quantify organ failure in critical ill patients. Up to four points are assigned to each system: the respiratory -, the cardiovascular -, the hepatic -, the coagulation - and the neurological system (Table 6). High scores are associated with poor outcome. Initial SOFA-Score >11 predicts mortality of 95%, initial SOFA-Score ≤9 predicts mortality <33% .The SOFA-Score is intended to be used sequentially since the changes in the score can help with prognosis. A increasing score within the first 96 hours is associated with mortality >50%, regardless of the initial score.(11,65)

Variables	0	1	2	3	4
PaO_2	>400	≤400	≤300	≤200	≤100
Platelets 10^3/µl	>150	≤150	≤100	≤50	≤20
Bilirubin mg/dl	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12
Hypotension	No hypotension	MAP < 70 mmHg	Dopamine*<5 or dobutamine any dose	Dopamine*>5 or (nor)epinephrine* ≤0,1	Dopamine >* 15 or (nor)epinephrine*> 0,1
GCS	15	13-14	10-12	6-9	<6
Creatinine mg/dl or urine output ml/d	<1.2	1.2-1.9	2.0-3.4	3.4-4.9 or < 500	5.0 or < 200

Table 6;SOFA-Score(66) *doses are given in mcg/kg/min
GCS=Glasgow Coma Scale

2 Material and methods

2.1 Collection of Data:

After approval through local ethic committee of the medical university of Graz with the EK-number 28-176 ex 15/16 information was gathered via MEDOCS (communication and information network used by steirische Krankenanstaltengesellschaft (KAGES) and in the archives of the department of Internal Medicine of the Medical University Graz. All recorded patients treated with ECMO between 2009 and 2018 have been assessed and included in the study, whereat all patients had a reversible cause for ARDS and were 18 or older at time of ECMO implantation. Since the av- and the vv-ECMO are not comparable due to different working mechanisms, the av-ECMO patients were not further evaluated in this trial.

With the help of thesis advisors, a list with all relevant individual and procedure-related parameters was generated (Table 7).

Due to privacy protection these data have been made anonymous after collection.

The SOFA-Score (Table 6) was calculated with MDCalc (67) and afterwards reviewed.

2.2 Statistical analysis

Clinical characteristics of subjects were analysed using descriptive statistics. Therefore, different individual and procedure related parameters were collected (Table 7). Then the collective was divided into survivors and non-survivors. These two Groups were compared according to factors that may influence survival (pre-existing-conditions and comorbidities, age, body-mass-index (BMI), sex, SOFA-Score, c-reactive Protein (CRP), pCO2, pH, pO2/FiO2 and procedure related complications).For comparison of categorical values chi-square test and fisher-exact test were used if indicated. To evaluate distribution of continuous variables one sample Kolmogorov-Smirnov and Shapiro-Wilk test were performed. A Mann-Whitney-U Test was used when comparing two independent samples without normal distribution. In case of normal distribution t-test was used to evaluate differences between survivors and non-survivors. The Primary endpoint was the 30-day mortality and the secondary endpoint was the SOFA-Score as predictor for survival. Statistical significance was defined as a p-value of $< .05$. Statistical analyses were performed using IBM-SPSS Version 25.0 (SPSS Inc., Chicago, Illinois, USA) and Microsoft Excel for Office 365 (Microsoft Corporation, Redmond, USA).

individual related	procedure related
date of birth	indication for ECMO
age	type of ECMO
Sex	year of ECMO implantation
Height	days on ECMO
Weight	initial gas flow
BMI	initial blood flow
pre-existing conditions	size of cannulas
venous blood sample (implantation day)	complications
blood gas analysis (implantation day)	mechanical ventilation at admission
deceased (at ICU/ in hospital after ICU)	catecholamines
dismissed alive	advanced haemodynamic monitoring
survived < 30 days/> 30 days	
Transferring unit	
SOFA-Score on implantation day	

Table 7; overview of the collected parameters

2.3 vv-ECMO

In all patients treated with vv-ECMO the iLA-activve system (co. Novalung, Heilbronn, Germany) was used. The iLA-activve is an extracorporeal life support device that provides effective CO_2-elimination and oxygenation. It is a modular system. Depending on the cannulas and the oxygenator used the iLA-activve system can cover the high-flow, mid-flow and low-flow sector. The centrifugal pump is magnetically elevated and achieves flow rates up to 8L/min.(68,69)

3 Results

47 patients (29male/18female) have been evaluated, with the youngest being 21 and the oldest 81 years old. All patients were admissioned between 2009 and 2018. Survival and number of patients treated in each year are shown in Table 8.

		dismissed alive		
		no	yes	total
year of treatment	2009	0	1	1
	2010	1	1	2
	2011	0	1	1
	2012	3	1	4
	2013	4	4	8
	2014	2	4	6
	2015	7	2	9
	2016	2	6	8
	2017	5	2	7
total		24	22	46

Table 8; number of patients treated in each year

Twelve av-ECMO patients were excluded, due to different indications and differences in the technique. One patient was excluded because no information was found in the documentation system due to transfer from a foreign hospital (Figure 5). From the 34 remaining vv-ECMO patients all suffered from ARDS caused by pneumonia. Patient`s characteristics (n=34) are shown in Table 9.

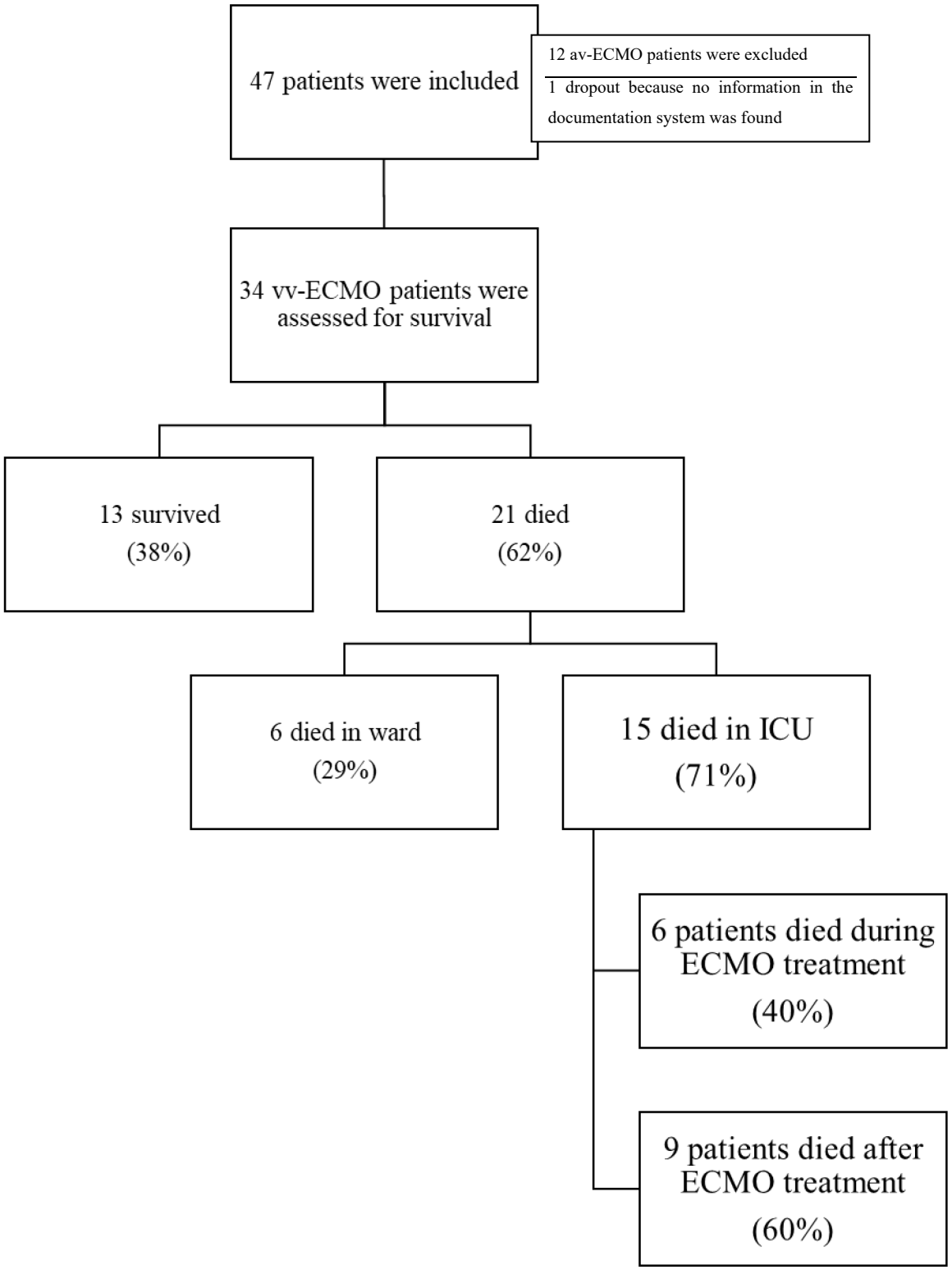

Figure 5; Flow of patients

	All(%) N=34	survivors(%) N=13	non survivors(%) n=21	p-value
male/female	20(59)/14(41)	9(69)/4(31)	11(52)/10(48)	0.48
age* in years	55±13	47±15	60±10	**0.01**
BMI*	27.4±5.2	29.2±6.6	26.4±4.3	0.23
COPD (no.)	3(9)	0	3(14)	0.28
current smoker (no.)	10(29)	5(38)	5(24)	0.43
diabetes mellitus type II (no.)	5(15)	2(15)	3(14)	>0.99
CKD (no.)	8(24)	3(23)	5(24)	>0.99
st.p. MCI (no.)	3(9)	1(8)	2(9)	>0.99
st.p. PAE (no.)	3(9)	0(0)	3(14)	0.28
art. hypertension (no.)	7(21)	2(15)	5(24)	>0.99
haematological patient (no.)	5(15)	1(8)	4(19)	0.63
SOFA*	13±3	12±2	14±3	**0.04**
pO_2/FIO_2*	87.6±40.9	71.8±23.7	96.2±46.1	0.14
pCO_2*	58.3±24.5	64.0±32.0	54.8±18.8	0.29
pO_2	83.9±23.7	67.5±20.5	77.7±25.1	0.43
pH*	7.35±0.14	7.31±0.19	7.37±0.1	0.45
platelet count (g/l)	170[13-720]	180[31-629]	167[13-720]	0.73
CRP*(mg/l)	241.2±137.5	271.4±123.9	225.4±144.8	0.40
needed dialysis (no.)	13(38)	3(23)	10(48)	0.28
needed tracheotomy (no.)	15(44)	6(46)	9(43)	>0.99
needed transfusions (no.)	28(82)	9(69)	19(90)	0.17
needed CPR (no.)	7(21)	2(15)	5(24)	0.68
bleeding(no.)	20(59)	7(54)	13(62)	>0.99
ischaemia (no.)	3(9)	1(8)	2(9)	>0.99
limb loss (no.)	1(3)	0(0)	1(5)	>0.99
inital gas flow*(l/minute)	3.7±1.7	3.3±2.2	3.8±1.4	0.28
inital blood flow*(l/minute)	3.7±0.8	3.8±0.7	3.7±0.8	0.77
days on vv-ECMO*	15±9	15±10	15±8	0.81
days in ICU*	25±17	27±17	23±17	0.44

Table 9; characteristics of all patients treated with vv ECMO for ARDS divided into survivors and non survivors at implantation day and during ECMO at implantation day
CPR=cardiopulmonary resuscitation; CKD= chronic kidney disease; PAE=pulmonary artery embolism; COPD= chronic obstructive pulmonal disease*mean±standard deviation or median [range]

Pre-existing conditions (PECs)[1]

The most common PECs are shown in Figure 6. Five patients (15%) had a pre-existing haematological malignancy (p=0.63). Three of these five patients (60%) suffered from acute myeloid leukaemia (AML). One underwent allogeneic stem cell transplantation before the onset of ARDS. From the remaining two patients one suffered from acute lymphoblastic leukaemia (ALL) and the other had b-cell chronic lymphocytic leukaemia.

Other PECs in descending frequency were coronary heart disease, adiposity, dermatomyositis, asthma bronchiale, chronic alcohol abuse and chronic recurrent pancreatitis, heart failure, hypothyroidism, rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis and a history of recent breast cancer.

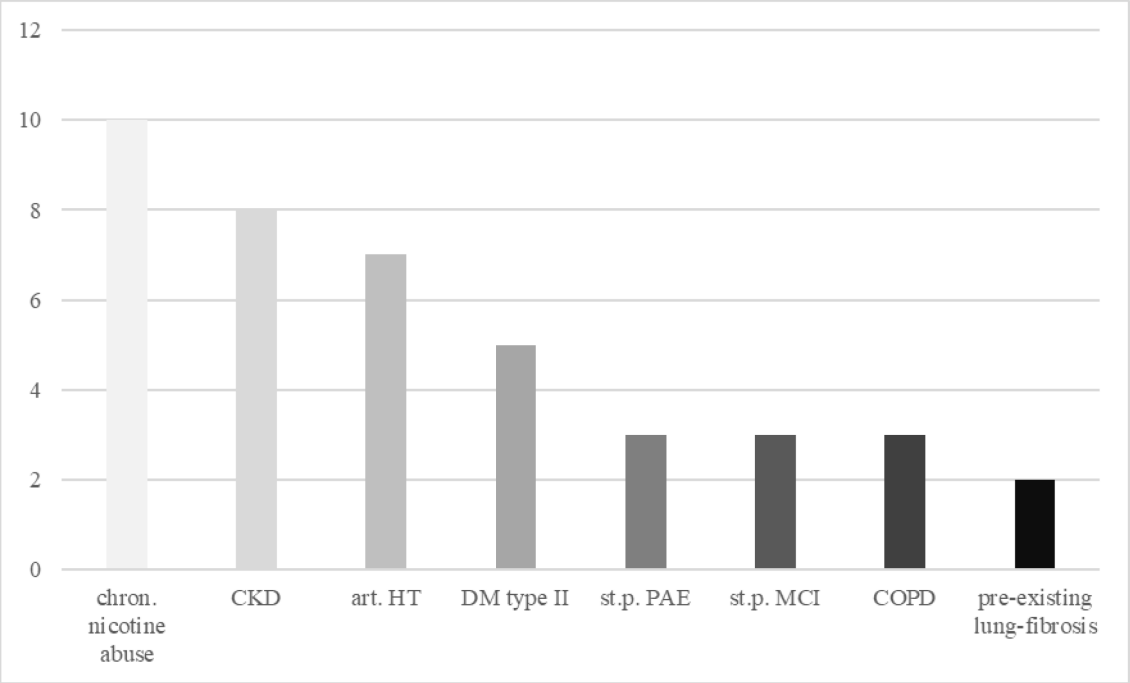

Figure 6; pre-existing conditions, CKD=chronic kidney disease, art. HT=arterial hypertension, DM=diabetes mellitus, st.p.=status post, PAE=pulmonary artery embolism, MCI= myocardial infarction

Adverse events

Bleeding, ischaemia or loss of extremities were assessed as vv-ECMO related adverse events. The most common adverse event was bleeding. Bleeding was defined as the necessity of ECMO related RBCs. It occurred in 20 (59%) patients, but there was no

[1] p-values are given for differences between survivors and non-survivors

difference in survivors and non-survivors (p>0.99). Most frequent puncture site bleeding followed by gastrointestinal bleedings occurred. The second adverse event was ischaemia. Three patients (9%) suffered from ischaemia of the limbs (p>0.99) and one patient (3%) lost a limb (p>0.99)(Figure 7). Seven patients (21%) needed cardiopulmonary resuscitation during their stay in ICU. In two of these seven patients (29%) CPR was successful and they were dismissed alive. Three patients (9%) developed heparin-induced thrombocytopenia type II (HIT II).

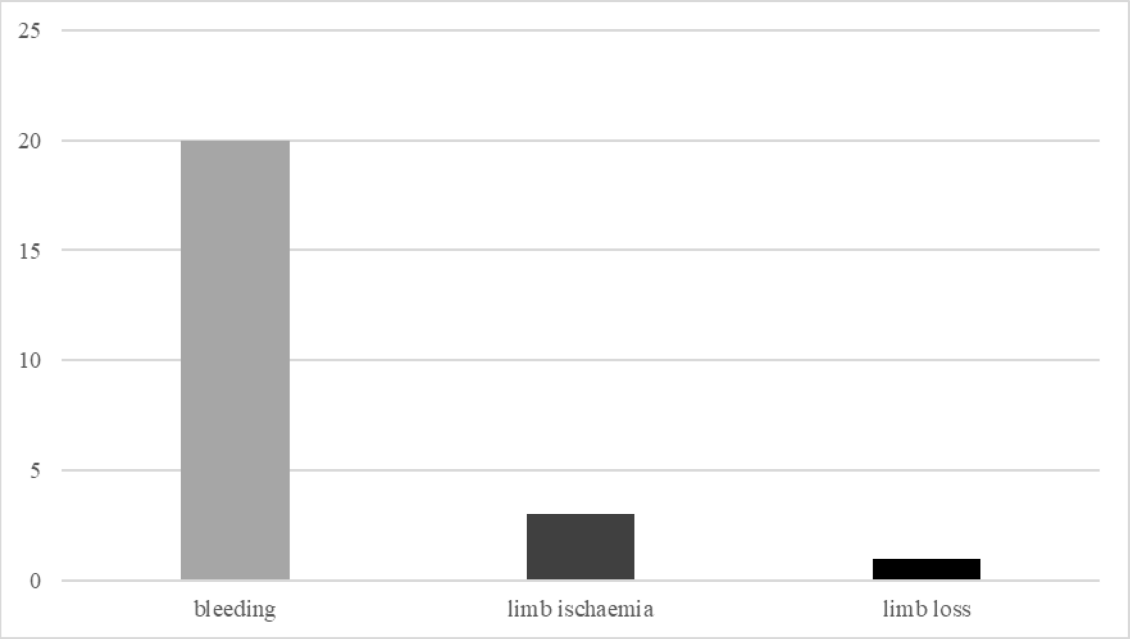

Figure 7; vv-ECMO related adverse events

Mortality and SOFA-Score

The overall mortality of the 34 patients was 62% (n=21). 15 patients (71%) died in ICU. From these 15 patients six (40%) died during ECMO treatment(Figure 6).The 30-day mortality was 59% as one patient died after this time period.

The SOFA-score was calculated for 31 patients, because the data for three of the 34 patients was incomplete. The mean SOFA-Score ad implantation day for all patients was 13±3. For patients who deceased within 30 days the mean SOFA-Score was 14±3 and for survivors of day 30 12±2 (p=0.37) (Figure 8). Without consideration of day 30 the mean SOFA-Score for the non survivors was 14±3 and 12±2 for the survivors (p=0.04) (Figure 9).

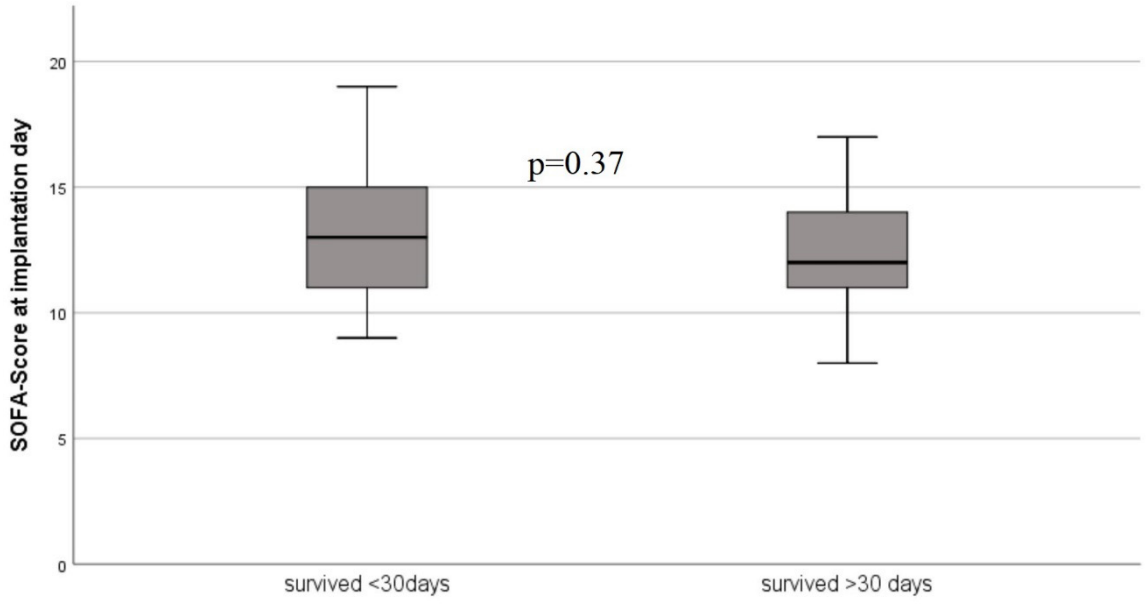

Figure 8; Boxplot SOFA-Score and patients that survived <30 days or >30 days

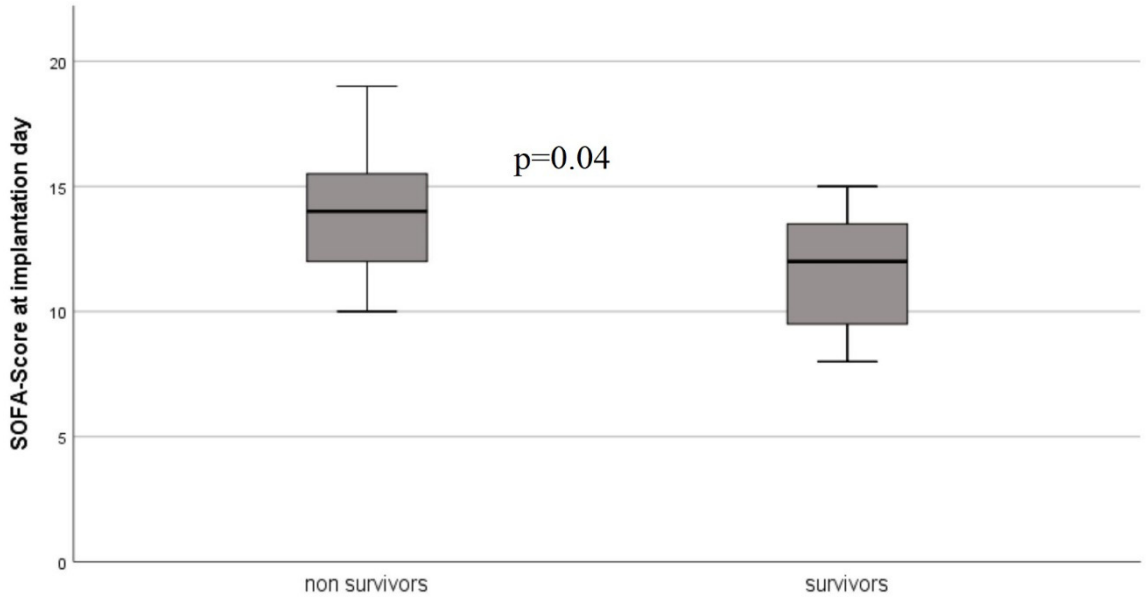

Figure 9; Boxplot SOFA-Score and survivors or non survivors

4 Discussion

Mortality

In this study we evaluated the mortality of patients with ARDS treated with vv-ECMO between 2009 and 2018 in the ICU of the department of Internal Medicine at the Medical University of Graz. We aimed to describe the mortality of this single-centre cohort retrospectively in association with the SOFA-Score.

Overall the mortality found in our study is comparable with the existing literature.(6,7,10,17,37,41,70,71)

In a German analysis from 2014, regarding the evolution of the epidemiology and mortality of ECMO treatment described an in-hospital-mortality for patients treated with vv-ECMO of 58.1%. A necessity for ECMO from 8-10 days correlated with a low mortality. Furthermore the mortality rate increased with age.(70)

A systematic review by *Máca et al.* screened 177 papers for ARDS mortality. They found mortality rates in a wide range from 13-80% for ARDS.(71) Unfortunately they included papers over a wide time period (1994-2015), as the treatment and definitions of ARDS changed over time. They also described mortality rates for different time periods separately. Thereby the 30-day-mortality from 2010-2015 described for retrospective studies was 26% and for prospective analyses it was 34%.(71) However, all stages of ARDS were included in this trial. Since we only included severe ARDS the mortality with 62% in our collective is higher. Furthermore, no information about the study population was given and no specific cause of ARDS was assessed.(71) *Stapleton et al.* for example states that ARDS in trauma patients is associated with a better outcome.(72) Factors that may influence the outcome are that we had no trauma related ARDS cases and the overall health of our study population was worse and the mean age was higher. These differences could lead to increased mortality in comparison to the study by *Máca et al*.

In 2017 *Bellani et al*. published the Lung Safe study. Incidence and outcome of ARDS were assessed in 50 countries. They reported a 28-day-mortality of 34.8% for all severities of ARDS, which is still lower than the mortality in our cohort, but ECMO was used in 3.2% of patients only.(17) The *Lung Safe study* and the systematic review by *Máca et al* did asses the mortality for ARDS in general.(17,73) They did not focus on a specific treatment as we focused on vv-ECMO. It is much more likely that vv-ECMO is used for more severe forms of ARDS, which are linked with a higher mortality. Considering that the patients were selected for ECMO treatment the probability for severe ARDS is very

high in our cohort. Therefore, mortality in our study is higher than in studies including different ARDS stages.

If compared to the recent *EIOLA* study, the *ANZ ECMO 2009 H1N1* trial or the *CESAR* trial, which focused on ARDS and ECMO, the mortality was higher in our cohort too, especially if we compare it to our 30-day mortality.(6,7,10)In the prospective *CESAR tria l*37% of patients treated with ECMO died within 6 months or before discharge from hospital.(7) Compared to our 30-day mortality the mortality in their study is lower. The mean age for patients allocated to the ECMO group was 40 years. The days spend in ICU were less for non survivors in the ECMO group (7) than in our study. The difference in mortality and length of ICU stay might be explained with the younger study population in the *CESAR trial*. Other than in our study the *CESAR trial* used a standardised treatment protocol and patients that received high pressure ventilation (>30cm H2O of PIP) or FiO2 >80% for more than seven days were excluded from the trial.(7) We did not assess the ventilator settings before ECMO. Therefore, inclusion of patients with high pressure ventilation and FiO2 >80% for more than seven days cannot be ruled out, which could explain the higher mortality in our study.

Moreover, the median SOFA-Score of 10.8±3.9 in the *EIOLA trial* for patients treated with ECMO was lower than in our study. The *EIOLA trial* described a 60-day mortality of 35% in the ECMO group.(10)An explanation for the higher mortality could be that a quarter of our patients showed immunocompromised conditions. A small study by *Stecher et al*. assessed the outcome especially in haematological patients with ECMO treatment. The hospital survival was 20% with acute leukaemia as the leading malignancy.(74) Some survival predicting scores for ECMO take immunocompromised conditions into account, since it is associated with a poor outcome. These scores are the PRESERVE-Score (75), RESP-Score (76), vv-ECMO-mortality score by *Cheng et al.* (77)and a score by *Enger et al* (78). In the *EIOLA trial* only 22% of patients in the ECMO group showed immunocompromised conditions.(10) *Wohlfarth et al*. conducted a small study examining the outcomes of patients with haematological malignancies and ECMO therapy. They described a ICU mortality of 50% (73), which is closer to our findings.

The main cause for ARDS in the *EIOLA trial* and the *ANZ ECMO H1N1 trial* was pneumonia as it was in our study.(10)The *ANZ ECMO H1N1 trial* described an in -ICU-mortality of 23%.(6) Although the cause for ARDS was similar in this study the median age (36 years) in the *ANZ ECMO trial* was much lower(6). Considering that old age is associated with higher mortality in patients with pneumonia(79), this could be an

explanation for the higher mortality in our study too. When looking at mortality rates from different regions, studies and hospitals there are many factors to take into consideration. Population based differences, like age, sex and comorbidities, or differences in the cause of ARDS, since trauma related ARDS is associated with better outcomes than ARDS related to infectious diseases (72). Another factor influencing the mortality is the type of study. Prospective studies are associated with a better outcome than retrospective ones (71). In prospective studies like the *EIOLA trial* physicians were aware that they are part of a study and therefore might have changed their behaviour and were more aware of the underlying pathology. The so-called Hawthorne effect can influence the outcome.(80)

Furthermore, the systematic review by *Máca et al.* showed a decreasing mortality with increasing numbers of centres included in studies.(71) Therefore we must consider that we conducted our trial in one single ICU and only treated patients with internal aliments. If we compare the mortality shown in our study to the ones of the *EIOLA*, the *CESAR* or the *ANZ ECMO trial*, which were conducted in multiple centres, we must consider the findings of *Máca et al.* (71), since the number of centres can influence the mortality rates when compared to other studies.

SOFA-Score and other predictors for survival

ECMO is a complex and costly treatment compared with the conventional management of ARDS (7). In the *ELSO registry report 2016* it was shown that although the use of vv-ECMO increased between 2009 and 2015 the hospital survival did not increase compared with the hospital mortality before 2009.(60) Clinically significant benefits for survival were only shown for severe ARDS up to now (10). It is important to select patients that benefit from ECMO. Therefore, it is crucial to find predictors for survival. We evaluated the SOFA-Score as possible predictor for survival in ARDS patients treated with ECMO. We could find a significant difference between the survivors and non survivors after discharge from hospital and the SOFA-Score. But no difference between the groups was found regarding the 30-day mortality and the SOFA-Score. The SOFA-Score is already validated in different disease patterns in ICU (11) and it is used in other validated vv-ECMO pre-scores, like the PRESERVE-Score (41). Therefore, the SOFA-Score can be seen as a valuable predictor for the hospital survival of ARDS patients treated with vv-ECMO. Moreover, *Czobor et al* found a correlation between age and SOFA-Score with survival in va-ECMO patients.(81) We were able to confirm these results for vv-ECMO patients.

An increase of the SOFA-Score within the first 48 hours after ICU admission is associated with a higher mortality than a decreased or unchanged SOFA-Score.(11) If the trends of the SOFA-Score in the first 48h after admission are taken into account it might help to find a more evident decision. In this study the SOFA-Score trends were not assessed, since we focused on pre-ECMO parameters. The evolution of the SOFA-score over time in ARDS patients should be examined in further studies.

The second factor that showed a correlation with survival was age. A significant correlation between age and hospital survival could be shown in this study. Age previously has been suggested as risk factor for patients treated with ECMO.(41,82,83)

Enger et al. conducted a prospective observational study, reviewing patients with ARDS and vv-ECMO in Germany. They were able to show a significant correlation between different factors assessed before ECMO installation. These factors were baseline blood levels of lactate and haemoglobin as well as minute ventilation, in addition to the age, the SOFA-Score and immunocompromised status as mentioned before.(78) Other factors that were shown to correlate with survival an implemented in different predictive models for the survival of patients with ARDS and vv-ECMO were: days of mechanical ventilation before ECMO (77,78), pre-ECMO hospital days (77,78,84), bilirubin (84), platelet count (77), creatinine or renal replacement therapy before ECMO (76,78,84), haematocrit (77,84), MAP, the use of vasoactive substances (84) and central-nervous-system (CNS) dysfunction (76). The *PRESERVE score by Schmidt et al.* also describes ventilation parameters at the time of initiating ECMO as predictors for survival, including PEEP, pPlat, driving pressure and lung-compliance (75). In our study we could not find a significant difference in survival regarding the other risk factors mentioned above. It is possible that our collective was too small to detect differences between survivors and non survivors regarding these parameters. Moreover, the scores were developed for specific groups. For example: the *ECMOnet score* was validated for Influenza A (H1N1) related ARDS, whereas the *PRESERVE score* was validated in patients with severe ARDS regardless of the underlying pathology.(41)

ARDS populations are very heterogenous and it is therefore very difficult to establish prediction models that are valid for all causes and severities of ARDS. Moreover, the use is still controversial and only recommended in selected patients with severe ARDS.(8) Therefore, it is important to find such predictors to help physicians decide if to establish ECMO or not.

Adverse events

ECMO related adverse events are often limiting factors of survival. We assessed three adverse events (bleeding, ischaemia and loss of limbs) for correlation with survival. Bleeding was present in more than half of our patients. We did not find significant difference in the incidence of bleeding complications between survivors and non survivors, although the occurrence of bleeding in our collective was much higher compared with a 21% chance of bleeding described in a metanalysis by *Munshi et al.*(85) or the 46% described in the *EIOLA trial*(10).Maybe our heterogenous definition of bleeding as the necessity of packed red blood cells during ECMO is an explanation for the higher rate of bleeding complications as well as the haematological patients, which already had impaired coagulation. Unfortunately, we did not assess the risk of bleeding related with haematological conditions. We did not asses if the bleeding was severe or light and could be stopped easily. Yet a difference in the between bleeding and survival was not found. However, bleeding is described as one of the most common complications related to ECMO (41) and as one of the most important factors limiting survival (86). For example, in the *ANZ ECMO H1N1 trial* bleeding, either intracranial haemorrhage or other haemorrhage was the main cause of death.(6) In the *EIOLA trial* almost half of the patients treated with ECMO experienced bleeding that lead to blood transfusions.(10) The mechanism behind bleeding complications during ECMO is dysfunction of the haemostatic system, mainly platelet dysfunction.(87) Different factors that influence the platelet function in therapy with implantable devices like ECMO, are described by *Casan et al.* Exposure to foreign surfaces, altered shear forces, due to the high velocity blood flow during ECMO can lead to platelet receptor shedding, proteolysis, increased platelet activation and secretion of inflammatory factors. These changes result in altered bleeding or thrombotic risk and may be exacerbated by various responses to antiplatelet or anticoagulant therapy during ECMO.(86) *Abrams et al* found a correlation between the development of thrombocytopenia and the platelet count at cannulation.(88)

In a small study with 25 patients *Czobor et al*. found a correlation between the cannula size and survival in patients treated with va-ECMO.(81) But larger cannulas allow higher flows and can reduce clotting.(45) Various responses to systemic anticoagulation and different baseline characteristics associated with a higher bleeding risk complicate the management of patients on ECMO. Individual management and close evaluation of anticoagulation help minimize the risk of bleeding.

Cannulation sites are also prone to infections. For example in the *ANZ ECMO H1N1 trial* 10% of infective complications were related to the cannulae.(6) In *EIOLA trail* 14% of patients showed signs of infection at cannulation site.(10) We did not detect signs of infections originating at cannulation sites. This difference in detected infections signs might be due to different definitions or reporting protocols for cannula-related infections or due to differences in the hygienic management and prophylactic administration of antibiotics.

4.1 Limitations:

This study has several limitations, which must be taken into consideration when discussing the results. First, with 34 patients only it was a very small collective that was examined. This limits the power of our statistical analysis. Therefore, the findings of this study need further assessment in larger studies.

Second, data was collected from one single ICU only. Since only data from one centre was assessed referral bias might be present. Next this study was conducted retrospectively. Therefore, there was no standardized treatment protocol, or randomization of the patients. Furthermore, some parameters we wanted to assess were not recorded in the documentation system and the number of patients treated varied strongly during the study time.

Partly bilirubin levels could not be collected, because no cholestasis parameters were tested. If this was the case bilirubin levels from the days before were evaluated. If those levels were within a normal range bilirubin was supposed to be <1,2mg/dl on implantation day.

Fourth, we lacked a control group. We assessed patients with ARDS and ECMO treatment only, therefore we do not know if our group of patients is comparable with other ARDS patients without ECMO treatment.

A follow up of the surviving patients and the further treatment in other hospitals, after discharge from the Medical University of Graz would have been interesting, but was not part of this study, since we focused on the 30-day-mortality and possible predictors for survival.

4.2 Conclusion

In conclusion the mortality found in our collective is slightly higher compared to other mortality rates described for ARDS and vv-ECMO. Although the SOFA-score differed significantly between the group of survivors and the deceased there were no relevant differences in the 30-day mortality between survivors and non survivors. Therefore, the SOFA-score was not a relevant 30-day mortality predictor for ARDS patients in the present study. Bleeding was the most common adverse event in our study and is also one of the most common adverse events during ECMO in the literature.

5 Literature

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