Supplementary materials ETALON II

Outcomes of Extracorporeal Membrane Oxygenation in COVID-19 Induced Acute Respiratory Distress Syndrome: an Inverse Probability Weighted Analysis

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Appendix I. Definitions

Baseline/demographics	
Active malignancy	Currently receiving active antimitotic treatment;
	or diagnosed within the past 6 months;
	or recurrent or metastatic;
	or inoperable.
Asthma	Inflammatory disease of the airways, characterized by reversible airflow obstruction and triggered bronchospasms. Asthma must have been recorded prior to this current hospital-admission and the patient must be using medication indicated for asthma.
Chronic kidney disease (1)	Increased serum creatinine value > 177 μmol/L (> 2.0 mg/dL).
	This renal insufficiency must have been recorded prior to this current hospital-admission as a chronic condition.
COPD (2)	Chronic (over 6 months) usage of bronchodilator drugs or steroids
	indicated for chronic pulmonary diseases. COPD must have been recorded prior to this current hospital-admission and the patient must be using medication indicated for COPD.
	E.g. chronic bronchitis, chronic bronchiolitis and emphysema.
COVID-19	PCR-proven Coronavirus disease 2019, caused by the novel coronavirus (2019-nCoV), also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
Diabetes mellitus (3)	Medication-dependent type of diabetes mellitus.
	Diagnosis must be recorded prior to this current hospital-admission.
Hypertension	Diagnosis must be recorded prior to this current hospital-admission.
Immunocompromised state (4)	Medical history of at least one of the following conditions:
	(1) use of immunosuppression for over 3 months (defined as viral immunosuppression, neoplastic disease, immunosuppressive drugs including steroids, chemotherapy, or congenital immunosuppression);
	(2) active hematologic malignancy (i.e., still requiring treatment);
	and (3) active neoplasm (i.e., a neoplasm that has not been resected, still requires treatment, or with metastasis).
Liver cirrhosis (5)	Pathological proven cirrhosis (through biopsy); **or** previous episodes of upper gastro-intestinal tract bleeding due to

portal hypertension; **or** previous episodes of liver failure, coma or hepatic encephalopathy.

Diagnosis must be recorded prior to this current hospital-admission.

Myocardial infarction	Diagnosis must be recorded prior to this current hospital-admission.
Pulmonary hypertension (6)	Presence of a mean pulmonary arterial pressure >20 mmHg Diagnosis must be recorded prior to this current hospital-admission

ECMO & COVID-19

Acute kidney injury (7)	Increase in serum creatinine by ≥ 26.5 µmol/L (≥ 0.3 mg/dL) within 48 hours; **or** increase in serum creatinine to ≥ 1.5 times baseline, which is known **or** presumed to have occurred within the prior 7 days.
$ECCO_2R$ (8)	Extracorporeal carbon dioxide removal ($ECCO_2R$) is the provision of carbon dioxide exchange through the use of an extracorporeal circuit consisting minimally of an optional blood pump artificial lung and vascular access cannulas using blood flows lower than required for oxygenation support.
FiO_2	Fraction of inspired oxygen, the molar or volumetric fraction of oxygen in the inhaled gas, provided by the mechanical ventilator.
Mechanical ventilation	Implementation of a ventilator during ICU-admission, deriving from a physical connection between the patient and the mechanical ventilator. The respiratory minute volume has to be measured by the ventilator. Mechanical ventilation does include continuous positive airway pressure (CPAP), but does **not** include high-flow nasal oxygen. Mechanical ventilation can be delivered via an endotracheal, tracheostomy or nasal tube.
P/F ratio	The ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2 expressed as a fraction, not a percentage).
Peak pressure (9)	Peak pressure is measured at the airway opening and is routinely displayed by mechanical ventilators. It represents the total pressure needed to push a volume of gas into the lung and is composed of pressures resulting from inspiratory flow resistance (resistive pressure), the elastic recoil of the lung and chest wall (elastic pressure), and the alveolar pressure present at the beginning of the breath.

Pulmonary embolism	Closure of a pulmonary artery or one of its branches, caused by a blood-borne clot or foreign material that plugs the vessel. It has to be shown and proven on imaging, e.g. CAT-scan.
Renal replacement therapy (10)	Management of renal function in case of e.g. acute or chronic kidney injury, provided via among others continuous renal replacement therapy (CRRT), hemodialysis, peritoneal dialysis, hemofiltration, hemodiafiltration, isolated ultrafiltration, plasmapheresis, hemoperfusion or plasmaperfusion.
Second run	Non-successful weaning, resulting in re-cannulation and re-initiation of ECMO after 6- 48 hours of de-cannulation. In case re-cannulation and re-initiation of ECMO occurs within 6 hours of removal of the cannulas, it is assumed as part of the first run.
VVA-ECMO (11)	A hybrid configuration of VV and VA extracorporeal support in which the extracorporeal circuit drains blood from the venous system and reinfuses into both the venous and systemic arterial systems. VVA ECMO provides both pulmonary (VV component) and cardiac (VA component) in patients with combined cardiopulmonary failure.

Complications & outcome	
Acute kidney injury	Increase in serum creatinine by ≥ 26.5 µmol/L (≥ 0.3 mg/dL) within 48 hours;

or increase in serum creatinine to ≥ 1.5 times baseline, which is known

or presumed to have occurred within the prior 7 days. |
| *Hemorrhagic event* (12) | Bleeding resulting into:

1) Surgical exploration or intervention by interventional radiologist; **or**

2) Required immediate transfusion of >3 units red blood cells per calendar day. |
| *Mortality location: anticipated death during ECMO* | ECMO withdrawal in anticipation of death |
| *New infection* | Culture (i.e. blood, respiratory tract) proven new infection during ECMO-run,

or suspicion of infection, with an indication for treatment. |
| *Pulmonary embolism* | Closure of a pulmonary artery or one of its branches, caused by a blood-borne clot or foreign material that plugs the vessel. It has to be shown and proven on imaging, e.g. CAT-scan. |
| *Renal replacement therapy* (10) | Management of renal function in case of e.g. acute or chronic kidney injury, provided via among others continuous renal replacement therapy (CRRT), hemodialysis, peritoneal dialysis, hemofiltration, |

	hemodiafiltration, isolated ultrafiltration, plasmapheresis, hemoperfusion or plasmaperfusion.
Successful weaning (13)	Survival for >48 hours after ECMO removal.
Thrombotic event (arterial)	Any symptomatic event in the patient (e.g. leg ischemia, stroke), proven by imaging and/or clinical presentation.
Thrombotic event (mechanical)	Thrombosis in cannula, pump or oxygenator.
Thrombotic event (venous)	Thrombosis in vein(s), for example deep venous thrombosis in upper or lower extremities, proven by imaging (e.g. ultrasound) or in case of newly initiated treatment due to high clinical suspicion.
Ventilator-associated pneumonia (14)	Ventilator-associated pneumonia (VAP) is defined as pneumonia that occurs > 48 hours or thereafter following endotracheal intubation, characterized by the presence of a new or progressive infiltrate, signs of systemic infection (fever, altered white blood cell count), changes in sputum characteristics, and detection of a causative agent.

Definitions: laboratory values

	pCO_2	kPa
	bicarbonate	mmol/L
	procalcitonin	ng/mL
	pO_2	kPa
	lactate	mmol/L
	CRP	mg/L

List of abbreviations

|	
ARDS	acute respiratory distress syndrome
AKI	acute kidney injury
BMI	body mass index
COVID-19	coronavirus disease 2019
ECMO	extracorporeal membrane oxygenation
$ECCO_2R$	extracorporeal carbon dioxide removal
ELSO	Extracorporeal Life Support Organization
EOLIA	ECMO to Rescue Lung Injury in Severe ARDS
ICU	intensive care unit
IPW	Inverse probability weighting
PCR	polymerase chain reaction test
RRT	renal replacement therapy
SOFA	sequential organ failure assessment
SMD	standardized mean difference
VA-ECMO	veno arterial extracorporeal membrane oxygenation
VILI	ventilator induced lung injury
VV-ECMO	veno venous extracorporeal membrane oxygenation

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Appendix II. Missing data per variable: alphabetical order

Missing data		
	No. missing	Percentage missing
Age	0	0.0
AKI	0	0.0
Asthma	0	0.0
BMI	10	3.2
CKD	1	0.3
Comorbidity count	0	0.0
COPD	0	0.0
COVID part of indication	0	0.0
CVD	1	0.3
Days till death	0	0.0
DM	0	0.0
Duration ICU - initiation ECMO	12	3.9
ECMO duration, days	13	4.2
Gender	0	0.0
Hemorrhagic complication	1	0.3
Hypertension	0	0.0
Infectious event	0	0.0
Institute	0	0.0
Lactate level pre-ECMO	59	19.1
Liver cirrhosis	1	0.3
Malignancy	1	0.3
MCI	0	0.0
Mechanical thrombotic event	1	0.3
P/F ratio	53	17.2
Pulmonary disease patient	1	0.3
Pulmonary hypertension	0	0.0
RRT	0	0.0
Second run	0	0.0
SOFA-score	77	24.9
Status at 60 days	0	0.0
Successful weaning	2	0.6
Total no. of complications	0	0.0
Venous thrombotic event	1	0.3
Year ICU admission	0	0.0

Abbreviations: AKI, acute kidney injury; COVID, coronavirus-disease 2019; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; MCI, myocardial infarction; RRT, renal replacement therapy; ICU, intensive care unit; CKD, chronic kidney disease; CVD, cardiovascular disease; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; SOFA, sequential organ failure assessment

Appendix III. Directed acyclic graph
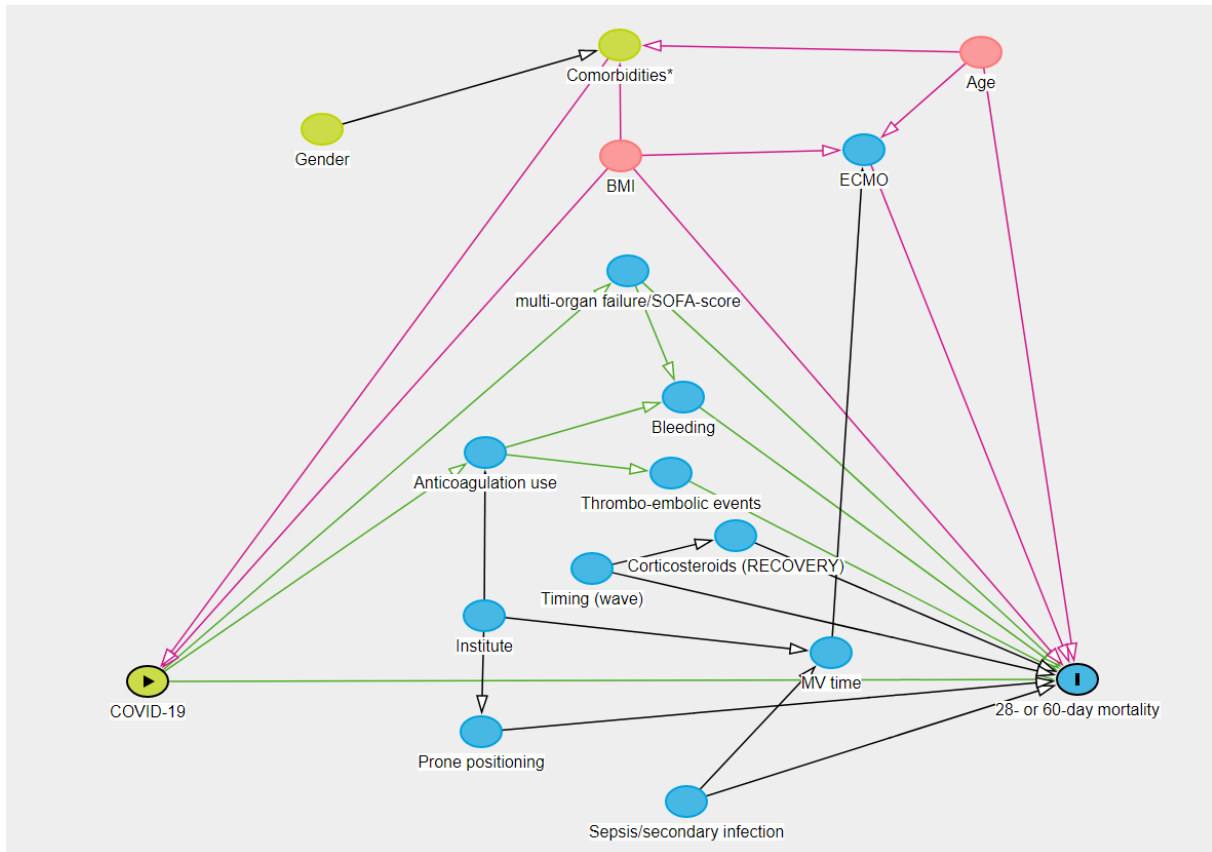
Directed acyclic graph (DAG) based on the influence of the presence of COVID-19 as cause for ARDS on survival. Green consists of (ancestor of) exposure, blue of (ancestor of) outcome and pink of ancestor of exposure and outcome, and thus as confounder. Minimal sufficient adjustment sets for estimating the total effect of COVID-19 on survival resulting from this DAG are:

- Age
- BMI
- Comorbidities: COPD, diabetes, hypertension, pulmonary hypertension, myocardial infarction, chronic kidney disease, other pulmonary diseases, liver cirrhosis

Additionally, the variable institute was incorporated in further IPW analysis.

Appendix IV. Inverse Probability Weighting

a. Inverse probability weighting

Confounding is an important pitfall in estimating a causal effect. There are different methods available to remove confounding. One of the conventional methods used is covariate adjustment using a regression model. However, such a regression model is prone to overfitting when too many covariates are included, resulting in reduced efficiency and accuracy of the model. Covariates can also be used to calculate the propensity score (PS), which is defined as the probability of a patients being exposed to the "dependent variable" (e.g. treatment, intervention, exposure to COVID-19), given this set of observed covariates. By summarizing all covariates in one single covariate, using the propensity score reduces the potential for overfitting. The PS is calculated by either using logistic regression or classification and regression tree analysis.

The PS can be used in different methods, such as stratification, propensity score matching (PSM) and inverse probability weighting (IPW). IPW can be used for estimating the average treatment effect (ATE): the effect of the treatment/exposure/intervention in the scenario that every patient in the population was offered treatment/exposure/intervention. In IPW, weights are assigned to patients based on the inverse of the PS. This results in a pseudo-population, in which patients with a high probability of the treatment/exposure/intervention are assigned a larger weight. This results in an independent distribution of covariates used to calculate the PS of the treatment/exposure/intervention assignment.

The weight is calculated by $\frac{1}{PS}$ if the patient is a member of the treatment/exposure/intervention group, and $\frac{1}{(1-PS)}$ if the patient is a member of the comparator group. In this resulting pseudo population, the balance of the covariates used to calculate the PS have to be compared, for example by calculating the standardized mean differences (SMD) prior and after weighting: a SMD of 0-0.1 is considered in balance. Finally, the analysis can be performed in the pseudo population to assess the primary outcome.

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b. Table

Covariate balance after IPW		
Standardized mean difference		
	Unweighted	*Weighted*
Covariate	COVID vs non-COVID	COVID vs non-COVID
Age	0.011	0.014
BMI	0.306	0.052
COPD	0.145	0.039
Diabetes	0.548	0.064
Hypertension	0.301	0.056
Pulmonary hypertension	0.014	0.020
Myocardial infarction	0.084	0.054
Institute	0.914	0.455
Gender	0.315	0.038
Chronic kidney disease	0.037	0.002
Other pulmonary disease	0.113	0.025
Liver cirrhosis	0.016	0.001
Squared continuous		
Age	0.009	0.014
BMI	0.289	0.052

BMI, body mass index; COPD, chronic obstructive pulmonary disease; IPW, inverse probability weighting

c. Figure
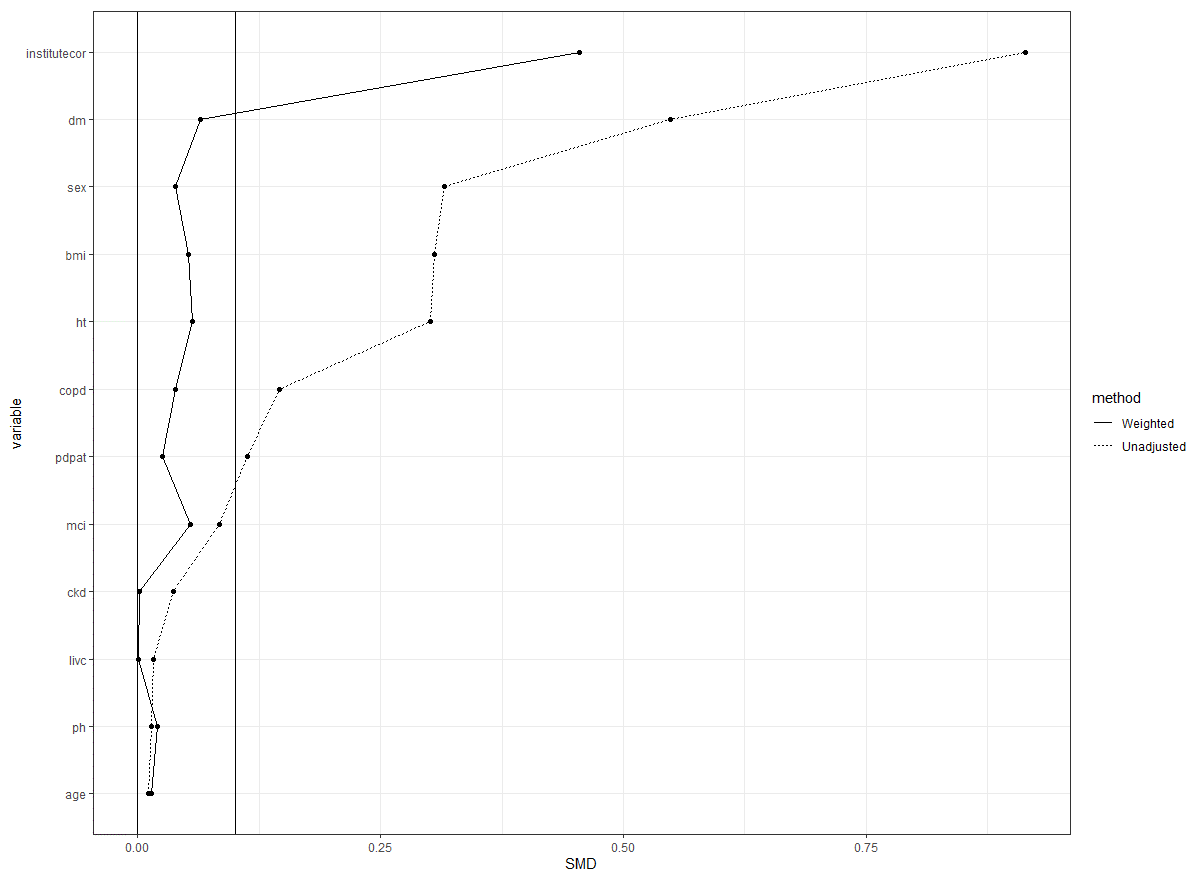
Appendix V. Sensitivity analysis

a. Table

Sensitivity analysis (logistic regression)			
	OR	95% CI	df
Intercept	8.17	(3.81-17.50)	233
Non-COVID ARDS	(ref)	(ref)	(ref)
COVID-ARDS	0.78	(0.15-4.08)	279
Age, years	0.96	(0.14-6.70)	280
BMI, kg/m^2	1.00	(0.14-6.93)	122
Female gender	(ref)	(ref)	(ref)
Male gender	1.33	(0.25-6.90)	277
No comorbidity	(ref)	(ref)	(ref)
COPD, yes	1.08	(0.30-3.89)	275
DM, yes	1.82	(0.38-8.85)	279
Hypertension, yes	1.81	(0.36-9.04)	279
Pulmonary hypertension, yes	1.15	(0.50-2.66)	280
Myocardial infarction, yes	1.38	(0.35-5.49)	280
CKD	0.31	(0.09-1.09)	279
Pulmonary disease	0.76	(0.17-3.34)	273
Liver cirrhosis	0.26	(0.12-0.55)	280
Sponsor hospital	(ref)	(ref)	(ref)
Center #2	0.59	(0.16-2.15)	280
Center #3	0.60	(0.20-1.78)	280
Center #4	0.67	(0.19-2.22)	280
Center #5	0.00	(0.00 - inf)	280
Center #6	3.41	(0.98-11.82)	280
Center #7	2.28	(0.70-7.42)	280
Center #8	2.40	(0.66-8.64)	280
Center #9	0.59	(0.19-1.91)	280
Center #10	0.00	(0.00 - inf)	280
Center #11	2.85	(0.97-8.41)	280
Center #12	2.64	(0.83-8.45)	280
Center #13	1.23	(0.37-4.12)	280
Center #14	2.49	(0.87-7.11)	280
Center #15	0.52	(0.14-1.87)	280

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CKD; chronic kidney disease; DM, diabetes mellitus; inf, infinite; ref, reference.

b. Figure

Multivariable logistic regression COVID ARDS & 60-day mortality
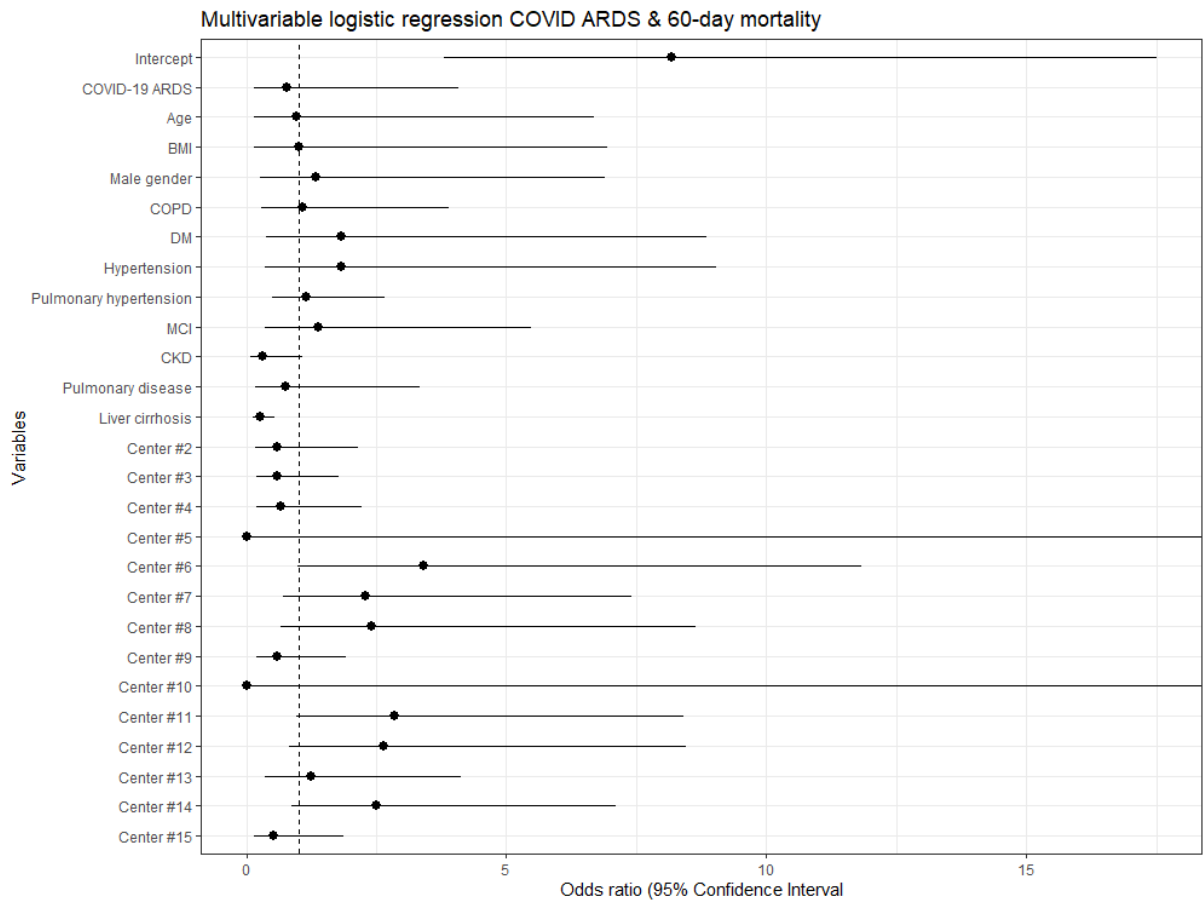
Abreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus-disease 2019; DM, diabetes mellitus; MCI, myocardiac infarction.

Appendix VI. Flowchart
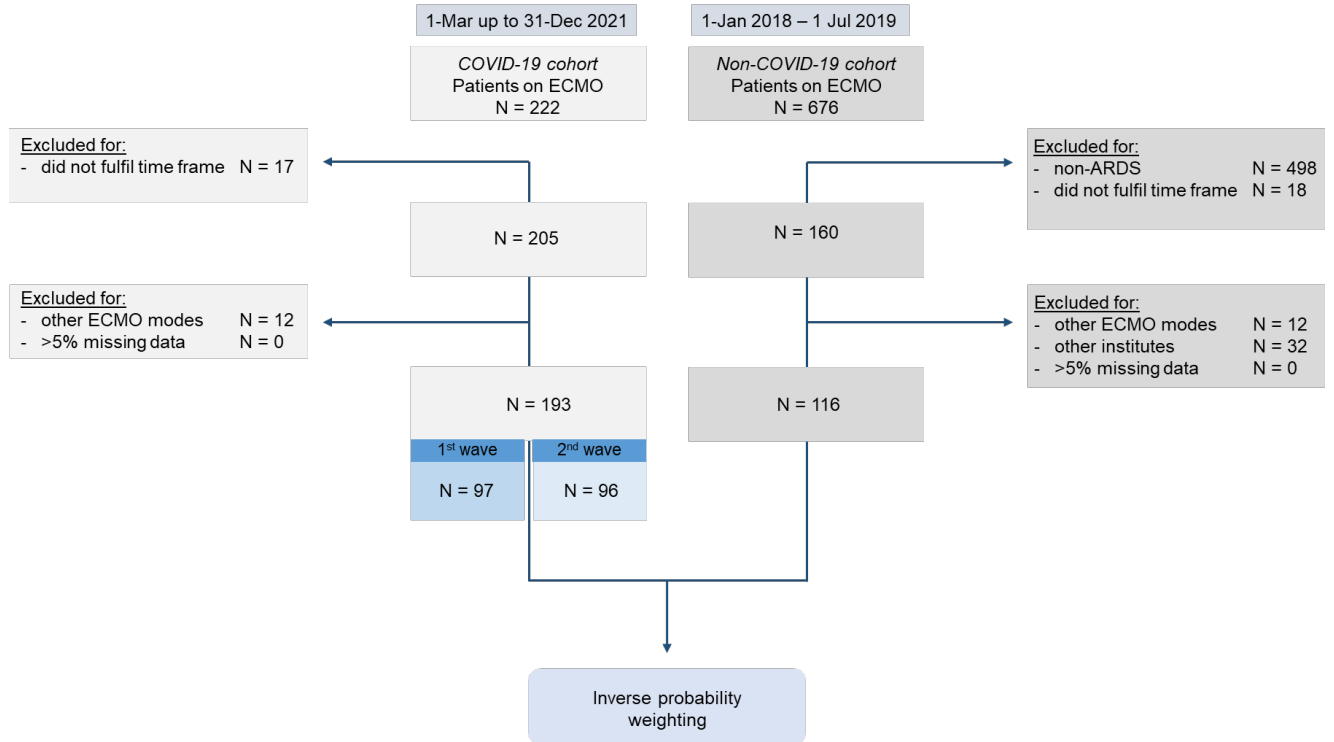
Appendix VII. COVID-19 related therapies during ECMO

COVID-19 related therapies							
	COVID-19 N = 193		First wave (n = 97)		Second wave (n = 96)		P-value
Additional therapies during ECMO							
Prone positioning	96	(50%)	45	(46%)	51	(53%)	0.43
Nitric oxide	46	(24%)	22	(23%)	24	(25%)	0.83
Beta blockade	14	(7%)	11	(11%)	3	(3%)	0.06
Upgrade ECMO: additional cannula	5	(3%)	2	(2%)	3	(3%)	0.99
Upgrade diameter cannula	4	(2%)	3	(3%)	1	(1%)	0.62
Upgrade membrane (larger/2nd membrane added)	2	(1%)	2	(2%)	0	(0%)	0.48
Neuromuscular blockers	130	(67%)	66	(68%)	64	(67%)	0.96
COVID-19 related medication		(0%)		(0%)		(0%)	
Interleukin antagonist (i.e. anti-IL6, anti-IL1)	3	(2%)	1	(1%)	2	(2%)	0.99
Complement inhibitors (i.e. C5(a)-inhibitors)	4	(2%)	3	(3%)	1	(1%)	0.62
Hydroxychloroquine	49	(25%)	49	(51%)	0	(0%)	**<0.001**
Lopinovir/ritonavir	13	(7%)	13	(13%)	0	(0%)	**0.001**
Remdesivir	16	(8%)	6	(6%)	10	(10%)	0.42
Imatinib	1	(1%)	1	(1%)	0	(0%)	1.00
Convalescent plasma	5	(3%)	1	(1%)	4	(4%)	0.36
Tociluzimab	13	(7%)	9	(9%)	4	(4%)	0.26
Intravenous globulins (IVIG)	2	(1%)	2	(2%)	0	(0%)	0.48
Corticosteroids	129	(67%)	45	(46%)	84	(88%)	**<0.001**
Cytokine absorber (e.g. CytoSorb)	25	(13%)	20	(21%)	5	(5%)	**<0.01**

Appendix VIII. COVID-19 vs. non-COVID-19

COVID-19 vs. non-COVID-19, unweighted and unimputed							
	Overall N = 309		Non-COVID N = 116		COVID N = 193		P-value
Demographics							
Age, years	54	[47 - 61]	55	[45 - 62]	53	[48 - 60]	0.62
BMI, kg/m^2	28.4	[25.2 - 32.1]	27.1	[24.3 - 32.2]	29.4	[27.3 - 32.2]	**0.001**
Male gender, no. (%)	224	(73)	74	(64)	150	(78)	**0.01**
Medical history							
mean comorbidity count	0.71	(±0.91)	0.53	(±0.72)	0.82	(±0.99)	**<0.01**
Hypertension	94	(30)	26	(22)	68	(35)	**0.03**
Myocardial infarction	20	(7)	9	(8)	11	(6)	0.64
Diabetes mellitus	57	(18)	8	(7)	49	(25)	**<0.001**
COPD	22	(7)	11	(10)	11	(6)	0.31
Pulmonary hypertension	5	(2)	2	(2)	3	(2)	1.00
Chronic kidney disease	15	(5)	5	(4)	10	(5)	0.96
Liver cirrhosis	5	(2)	2	(2)	3	(2)	1.00
Malignancy	18	(6)	14	(12)	4	(2)	**0.001**
Values prior to ECMO							
Lactate, mmol/L	1.6	[1.2 - 2.6]	1.65	[1.2 - 3.2]	1.6	[1.2 - 2.5]	0.31
SOFA	10	(± 3.2)	11	(± 3.5)	10	(± 3)	**0.001**
P/F ratio, mm Hg	69	[54 - 99]	70	[53 - 108]	69	[55 - 94]	0.78
ECMO characteristics							
Duration ICU admission - start ECMO, days	5	[1 - 11]	1	[0 - 4]	7	[5 - 14]	**<0.001**
ECMO duration, days	13	[8 - 22]	10	[6 - 21]	15	[9 - 24]	0.001
Second run	15	(5)	7	(6)	8	(4)	0.64
Complications							
Hemorrhagic event	160	(52)	53	(46)	107	(56)	0.11
Mechanical thrombotic event	49	(16)	23	(20)	26	(14)	0.19
Venous thrombotic event	30	(10)	10	(9)	20	(10)	0.75
AKI	168	(54)	64	(55)	104	(54)	0.91
Infectious event	163	(53)	49	(42)	114	(59)	**<0.01**
Renal replacement therapy	158	(51)	61	(53)	97	(50)	0.78
Outcomes							
Successful weaning	173	(56)	74	(64)	99	(52)	**0.04**
28-day mortality	106	(34)	39	(34)	67	(35)	0.25
60-day mortality	138	(45)	48	(41)	90	(47)	0.37

Variables stated as no. (%) for categorical variables, mean ± standard deviation for parametric and median [1st quartile - 3rd quartile] for non-parametric numeric data.

Abbreviations: AKI, acute kidney injury; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; ICU, intensive care unit; P/F ratio, $P_aO_2/FiO2$ ratio; SOFA, sequential organ failure assessment.

Appendix IX. Survival curves

Overall survival probability waves