Venovenous Extracorporeal Membrane Oxygenation in Patients with Acute Respiratory Failure from COVID-19: A Comparative Effectiveness Study

Martin Urner, doctoral fellow,[1,2,3] Adrian G Barnett, professor,[4] Gianluigi Li Bassi, associate professor,[5,6,7,8,9] Daniel Brodie, professor,[10,11] Heidi J Dalton, associate professor, [12,13] Niall D Ferguson, professor,[1,2,3,14,15,16] Silver Heinsar, doctoral fellow,[5,6,8,17] Carol L Hodgson, professor,[18,19] Giles Peek, professor,[20] Kiran Shekar, associate professor,[5,6,9] Jacky Y Suen, postdoctoral researcher,[5,6] John F Fraser, professor,[5,6,8] Eddy Fan(https://orcid.org/0000-0002-1210-9914), associate professor[1,2,3, 14,16]; on behalf of the COVID-19 Critical Care Consortium Investigators

1. Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada
2. Department of Medicine, University of Toronto, Toronto, ON, Canada
3. Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada
4. Australian Centre for Health Services Innovation and Centre for Healthcare Transformation, School of Public Health and Social Work, Queensland University of Technology, Brisbane, QLD, Australia
5. Critical Care Research Group, Adult Intensive Care Services, Prince Charles Hospital, Brisbane, QLD, Australia
6. Faculty of Medicine, University of Queensland, Brisbane, QLD, Australia
7. Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain
8. Intensive Care Unit, St Andrew's War Memorial Hospital and The Wesley Hospital, Uniting Care Hospitals, Brisbane, QLD, Australia
9. Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia
10. Department of Medicine, Columbia College of Physicians and Surgeons, New York, NY, USA
11. Center for Acute Respiratory Failure, New York-Presbyterian Hospital, New York, NY, USA
12. Pediatric Critical Care Medicine, Inova Fairfax Hospital, Falls Church, VA, USA
13. Heart and Vascular Institute, Inova Fairfax Hospital, Falls Church, VA, USA
14. Toronto General Hospital Research Institute, Toronto, ON, Canada
15. Department of Physiology, University of Toronto, Toronto, ON, Canada
16. Division of Respirology, Department of Medicine, University Health Network, Toronto, ON, Canada
17. Department of Intensive Care, North Estonia Medical Centre, Tallinn, Estonia
18. Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, VIC, Australia
19. Department of Intensive Care, Alfred Health, Melbourne, VIC, Australia
20. Congenital Heart Center, University of Florida, Gainesville, FL, USA

Supplementary Appendix

Corresponding Author
Eddy Fan, MD, PhD
Toronto General Hospital,
585 University Avenue, 9 MaRS-9013
Toronto, Ontario, Canada, M5G 2N2
Tel: (416) 340-5483
Email: eddy.fan@uhn.ca

Supplementary Appendix

This supplement has additional information on methods and results, organized as:

1. Summary of the analysis protocol and details on methods (Table S1, Figures S1)

Please, refer to the figures and tables within the next pages.

- **Table S1.** Summary of the protocol of a target trial estimating differences in outcomes of patients treated with extracorporeal membrane oxygenation (ECMO), if the ratio of arterial pressure of oxygen / fraction of inspiratory oxygen (PaO_2/FiO_2) was less than 80 mmHg, compared to treatment with conventional mechanical ventilation without the use of ECMO.
- **Figure S1.** Illustration of the three-step analytical procedure to obtain adherence-adjusted estimates.

Additional details on statistical analyses: calculation of inverse probability weights

Our models to compute the inverse probability weights included the following covariates in a flexible functional form: age, sex, Sequential Organ Failure Assessment (SOFA) and Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score, inability to walk, stage III kidney failure (defined as either urine output < 0.3 ml/kg body weight per hour for ≥ 24 hours, serum creatinine ≥ 4.0 mg/dl (353.6 μmol/l), or renal replacement therapy), presence of chronic neurological, cardiac, pulmonary, or liver disease, malignant neoplasms, treatment with vasoactive drugs, renal replacement therapy, neuromuscular blockade, prone position, inhaled nitric oxide, and ventilation parameters, such as airway plateau pressure, positive end-expiratory pressure (PEEP), fraction of inspired oxygen (FiO_2), ratio of partial pressure of arterial oxygen-to-fraction of inspired oxygen (PaO_2/FiO_2 ratio), arterial pH, duration of mechanical ventilation, and time. The inverse probability weight for each day was calculated as 1 divided by the cumulative probability of not being artificially censored. This means that patients with a high probability of not being censored (relatively unlikely to be put on ECMO) are down-weighted in the analysis, whilst those with a low probability of not being censored (relatively likely to be put on ECMO) are up-weighted.

Additional details on statistical analyses: missing data

We imputed missing measurements at baseline with the 'mice' package using fully conditionally specified models, including failure time and outcome[1]. For longitudinal missing values, we carried the last observation forward, similar to previous work[2]. Carrying forward the last available value reflects what the treatment team would do in clinical practice at the bedside. Details on missing data patterns and sensitivity analyses to detect potential influence of missing data or multiple imputation are provided in a separate section of the supplementary appendix.

Additional details on statistical analyses: secondary analyses

We analyzed if age and comorbidities associated with more severe COVID-19, such as diabetes mellitus, obesity, or arterial hypertension, were effect modifiers.[3 4] Based on previous work, we examined the following age groups: < 50 years, ≥ 50 and < 65 years, and ≥ 65 years.[5 6] To investigate whether the duration of mechanical ventilation preceding ECMO initiation (PaO_2/FiO_2 ratio < 80 mmHg[7]) modified the effectiveness of ECMO, we emulated different hypothetical scenarios where ECMO could only be initiated if the patient had received invasive mechanical ventilation for a specific number of days preceding cannulation.

Additional details on statistical analyses: sensitivity analyses

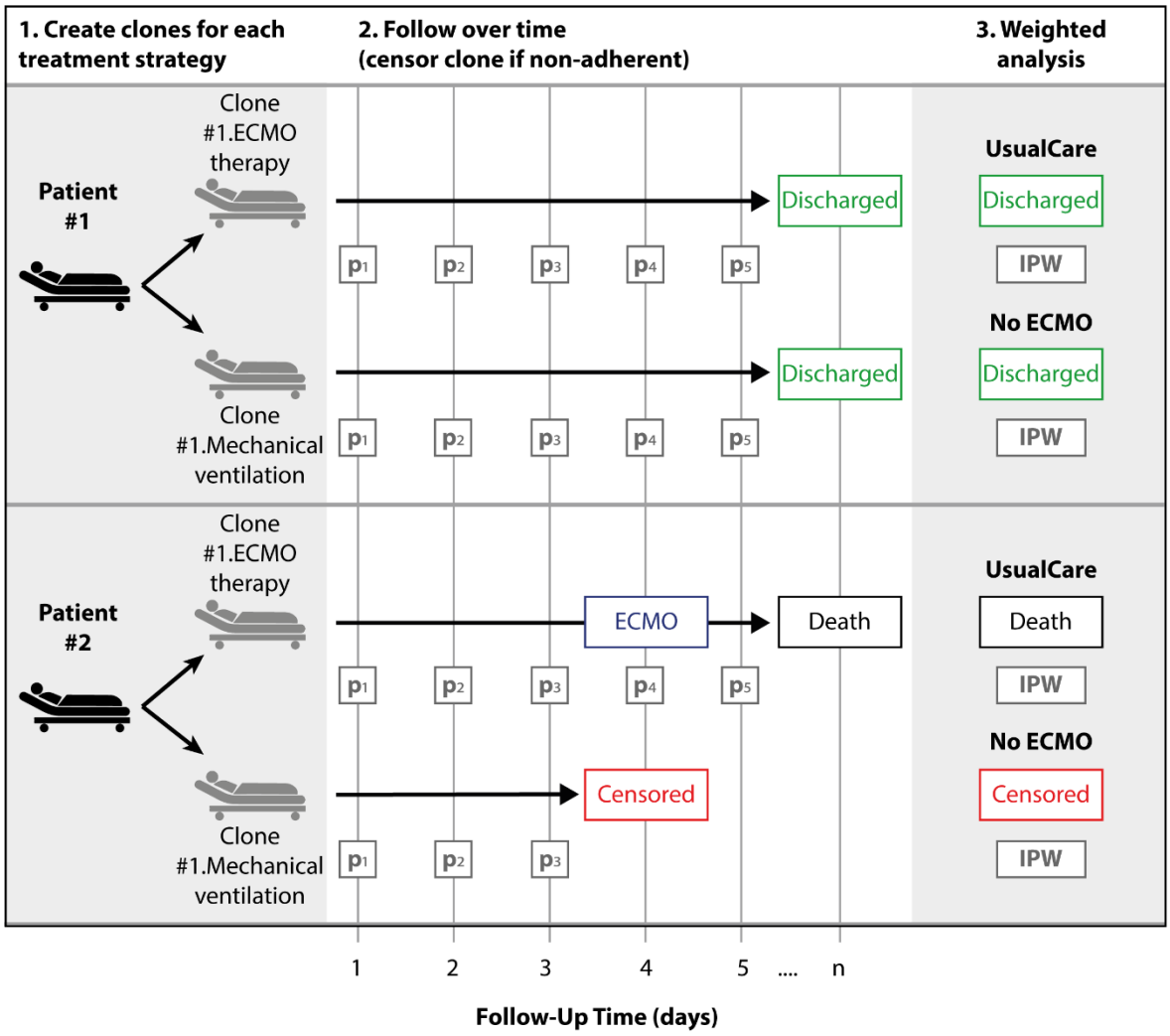
We performed a number of sensitivity analyses. First, we replicated the primary analysis with a control outcome instead of hospital mortality to detect the potential presence of uncontrolled confounding. A random variable drawn from a Bernoulli distribution with a 50:50 probability was used as control outcome variable, safely assuming the intervention does not have a causal effect on a random outcome variable. Also, we repeated the primary analyses using an alternative set of covariates for the construction of the inverse probability weights to detect a potential influence of model misspecification, missing data, or multiple imputation. Second, we repeated the primary analysis, excluding patients from the United States (which contributed the largest number of ECMO patients to the cohort), to investigate whether our estimates are robust for a potential country-specific heterogeneity in treatment. Also, we performed a sensitivity analysis in which we used inverse probability weighting to adjust for potential country-specific heterogeneity. Third, we estimated the effects for the primary analysis in patients with complete measurements and without variable imputation.

Table S1. Summary of the protocol of a target trial estimating differences in outcomes of patients treated with extracorporeal membrane oxygenation (ECMO), if the ratio of arterial pressure of oxygen / fraction of inspiratory oxygen (PaO_2/FiO_2) was less than 80mmHg, compared to treatment with conventional mechanical ventilation without the use of ECMO.

Component	Hypothetical randomized trial	Emulation
Eligibility	Patients of all ages with clinically suspected (determined by attending physician) or laboratory-confirmed SARS-CoV-2 infection (real-time PCR and/or next-generation sequencing) were eligible if they were admitted to an ICU between January 3, 2020, and January 26, 2021.	Same as hypothetical trial
Treatment strategies	1. Treatment with ECMO therapy if $PaO_2/FiO_2 < 80$mmHg 2. Treatment with conventional mechanical ventilation without the use of ECMO therapy	Same as hypothetical trial
Treatment assignment	Patients are randomly assigned to one of the strategies. Stratification was performed based on baseline severity of illness (i.e., PaO_2/FiO_2 ratio).	We assumed that patients were randomly assigned within levels of the following baseline variables: age, sex, APACHE III and SOFA score, as well as severity of respiratory failure.
Blinding	The treatment team was aware of the assigned treatment strategy.	Same as hypothetical trial
Follow-up	The follow-up started at the time of assignment to a ventilation strategy and ended at one of: • Death • Discharge home alive (competing event) • 60 days after enrollment (censoring event) whichever comes first	Same as hypothetical trial
Primary outcome	Hospital mortality	Same as hypothetical trial
Causal contrast	Per protocol effect	Observational analogue of the per protocol effect
Statistical analysis	In the per-protocol analysis, patients were censored when they deviated from their assigned strategy. The per-protocol effect was estimated after adjustment for baseline variables and for time-varying variables associated with adherence to the assigned treatment strategy.	Same as hypothetical trial, except that we created two clones per eligible patient and assigned one to each treatment strategy.[a]

[a] Adapted from M. Hernán and J. Robins on how to emulate a target trial using observational data.[8]

Figure S1. The figure illustrates a three-step analytical procedure to obtain adherence-adjusted estimates. Cloning, censoring, and weighting represents a robust analysis approach that eliminates immortal time bias in the estimates of absolute and relative risk.[9] First, we created clones of each patient and assigned these clones to the different treatment strategies: ECMO therapy, where patients were treated with extracorporeal membrane oxygenation (ECMO) if the PaO_2/FiO_2 was < 80 mmHg, and conventional mechanical ventilation without ECMO (illustrated below as 'mechanical ventilation'). Second, we censored clones that were non-adherent to their assigned treatment strategy during follow-up (e.g., initiation of extracorporeal membrane oxygenation in the group treated with conventional mechanical ventilation; see example for patient #2). For each day, we calculated the probability of not being censored (illustrated as grey "p" for each day of follow-up), based on factors that might have been considered by the treatment team to decide whether extracorporeal membrane oxygenation therapy should be initiated or not. Third, absolute risks, differences in absolute risks, and risk ratios (RR) were calculated with weighted marginal structural models. The weights were calculated from 1 divided by the cumulative probability of not being censored), illustrated as grey 'IPW' (inverse probability weight) in the illustration. A more comprehensive description of this analysis approach is available elsewhere.[9-11]



Additional details:

Randomly assigning patients to only one treatment strategy is statistically inefficient. Therefore, cloning was used to assign patients to multiple strategies.

Patients were artificially censored , if they deviated from their assigned treatment strategy. While the cloning procedure has prevented immortal time bias, artificial censoring introduced selection bias in the analysis.

Inverse probability weighting was used to address the selection bias due to artificial censoring.

2. Description of the cohort (Figure S2, Tables S2 to S7)

Please, refer to the figures and tables within the next pages.

- **Figure S2.** Study profile.
- **Table S2**. Comorbidities**.**
- **Table S3**. Specific therapies**.**
- **Table S4**. Complications**.**
- **Table S5**. Participating countries**.**
- **Table S6**. Ethnicity**.**
- **Table S7.** Characteristics of patients treated with Extracorporeal Membrane oxygenation (ECMO) before and after cannulation under observation of clinical practice.

Additional details:

In the following, we describe the study profile and give characteristics of the study cohort.

Audits of the COVID-19 Critical Care Consortium database:

The database quality audits of the COVID-19 Critical Care Consortium dataset are a continuing and intensive process encompassing: 1) data cleaning rules, 2) checks for outliers, 3) filtering rules setup during the initial development of the case report form, which was periodically monitored/adjusted, 3) data completeness checks. Finally, in the case any issue was detected during monitoring of data quality, or statistical analysis, these matters were followed up to address any data collection/process limitation in a timely manner. Importantly, the audit process often included follow-up with the site that entered the data for value verification and correction where possible.

Data protection:

Each collaborating site obtained approval from their Institutional Review Boards (IRBs) and executed a data sharing agreement (DSA), before recording any data into the REDCap case report form. Of note, in case IRB indicated that a DSA were not required, based on local regulations, we requested an official email and/or signed document to clearly state the reason for not requiring a DSA. Importantly, we used a REDCap case report form. REDCap is compliant with GDPR requirements and has mechanisms to process GDPR requests. The study fully

complied to valid requests under GDPR on demand, as part of the standard administration of the database. Finally, raw data of the COVID-19 Critical Care Consortium is only accessible to the Consortium data management core team in Brisbane, AU. The investigators wrote and tested the R code for the analysis a priori based on a simulated dataset (without real patient data) and subsequently submitted the code for execution to the Consortium data management core team in Brisbane, AU. The team provided to the Consortium core statistical team the aggregated R markdown output which was then used to write the manuscript. Individual patient data were at no time point accessible or transferred to the computers of the investigators.

Figure S2. Study profile. ECMO = Extracorporeal Membrane oxygenation.

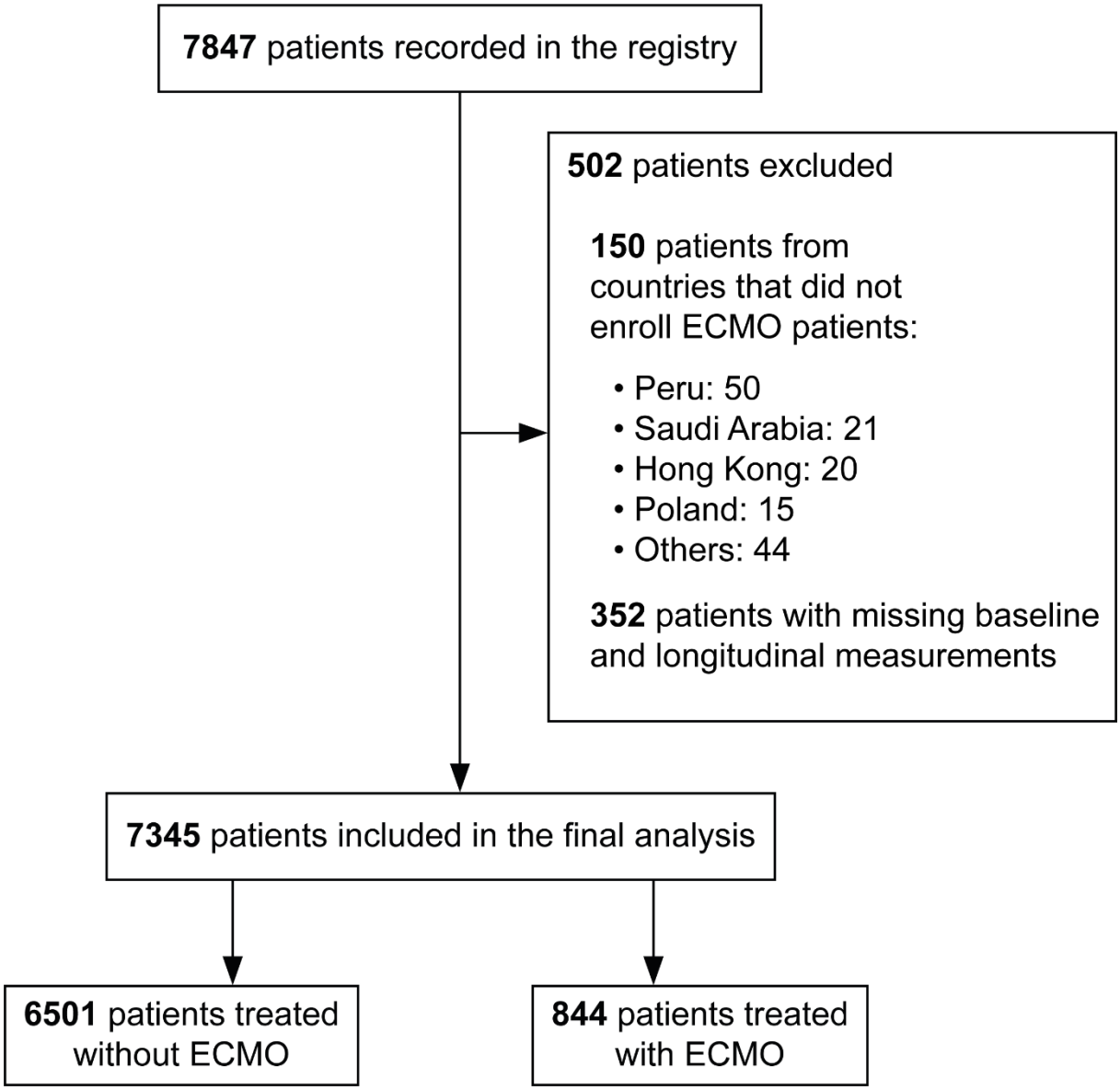


Table S2. Comorbidities, numbers and percentages by treatment under observed clinical practice.

	Overall	**Treatment without ECMO**	**Treatment with ECMO**
N	7,345	6,501	844
Chronic cardiac disease (%)	1,080 (15)	1,035 (16)	45 (5.3)
Arterial hypertension (%)	4,203 (57)	3,853 (59)	350 (41)
Obesity (%)	1,603 (22)	1,290 (20)	313 (37)
Chronic pulmonary disease (%)	602 (8.2)	561 (8.6)	41 (4.9)
Asthma (%)	386 (5.3)	308 (4.7)	78 (9.2)
Chronic kidney disease (%)	547 (7.4)	507 (7.8)	40 (4.7)
Genito-urinary comorbidities (%)	339 (4.6)	310 (4.8)	29 (3.4)
Gastro-pancreatic comorbidities (%)	313 (4.3)	266 (4.1)	47 (5.6)
Mild liver disease (%)	95 (1.3)	82 (1.3)	13 (1.5)
Severe liver disease (%)	234 (3.2)	211 (3.2)	23 (2.7)
Chronic neurological disorder (%)	279 (3.8)	256 (3.9)	23 (2.7)
Dementia (%)	145 (2.0)	145 (2.2)	0 (0)
Malignant neoplasm (%)	199 (2.7)	185 (2.8)	14 (1.7)
Rheumatologic disorder (%)	208 (2.8)	181 (2.8)	27 (3.2)
Endocrinological comorbidities (%)	1,353 (18)	1,217 (19)	136 (16)
Diabetes (%)	1,887 (26)	1,707 (26)	180 (21)
Diabetes type I (%)	53 (0.7)	46 (0.7)	7 (0.8)
Hematologic disease (%)	222 (3.0)	194 (3.0)	28 (3.3)
Asplenia (%)	15 (0.2)	11 (0.2)	4 (0.5)
Immunocompromised state (%)	48 (0.7)	40 (0.6)	8 (0.9)
HIV (%)	54 (0.7)	50 (0.8)	4 (0.5)
Tuberculosis (%)	42 (0.6)	38 (0.6)	4 (0.5)
Malnutrition (%)	100 (1.4)	90 (1.4)	10 (1.2)
Chronic alcohol abuse (%)	126 (1.7)	106 (1.6)	20 (2.4)
IV drug use (%)	23 (0.3)	21 (0.3)	2 (0.2)
Smoking (%)	2,521 (34)	2,136 (33)	385 (46)

Abbreviations: ECMO = Extracorporeal Membrane oxygenation. HIV = Human Immunodeficiency Virus. IV = Intravenous.

Table S3. Specific therapies, numbers and percentages by treatment under observed clinical practice.

	Overall	**Treatment without ECMO**	**Treatment with ECMO**
N	7,345	6,501	844
Number of patients receiving transfusions during follow-up			
Packed red blood cells (%)	97 (1.3)	29 (0.4)	68 (8.1)
Platelets (%)	12 (0.2)	7 (0.1)	5 (0.6)
Plasma (%)	25 (0.3)	12 (0.2)	13 (1.5)
Cryoprecipitates (%)	7 (<0.1)	6 (<0.1)	1 (0.1)
Anticoagulation therapy during follow-up			
Continuous infusion of unfractionated heparin, n (%)	966 (13)	471 (7.2)	495 (59)
Low molecular weight heparin, n (%)	2,646 (36)	2,447 (38)	199 (24)
Subcutaneous unfractionated heparin, n (%)	820 (11)	719 (11)	101 (12)
Argatroban, n (%)	57 (0.8)	18 (0.3)	39 (4.6)
Hirulog and bivalirudin, n (%)	46 (0.6)	8 (0.1)	38 (4.5)
Danaparoid Lepirudin, n (%)	6 (<0.1)	3 (<0.1)	3 (0.4)
Desirudin, n (%)	1 (<0.1)	0 (0)	1 (0.1)
Nafamostat Mesilate, n (%)	15 (0.2)	8 (0.1)	7 (0.8)
Other, n (%)	175 (2.4)	146 (2.2)	29 (3.4)
Treatment with corticosteroids during follow-up, no (%)	2,961 (40)	2,528 (39)	433 (51)
Number of patients receiving anti-infective drugs during follow-up			
Antibiotics (%)	4,429 (60)	3,804 (59)	625 (74)
Antifungal agents (%)	825 (11)	588 (9.0)	237 (28)
Antiviral agents (%)	2,136 (29)	1,792 (28)	344 (41)
Remdesivir (%)	736 (10)	598 (9.2)	138 (16)

Abbreviations: ECMO = Extracorporeal Membrane oxygenation.

The number of patients who received treatment with steroids is low, considering the results of the RECOVERY trial which have been published in February 2021. While the registry data does not allow us to identify the reason for the low rate of steroid treatment, multiple reasons might account for this finding, including the recruitment of patients before the results of the RECOVERY trial were available, as well as potential enrollment of patients who had already completed their treatment course with steroids.

Table S4. Complications, numbers and percentages by treatment under observed clinical practice.

Complication at any time point during follow-up	Overall	Treatment without ECMO	Treatment with ECMO
N	7,345	6,501	844
Acute renal failure (%)	1,489 (20)	1,171 (18)	318 (38)
Anemia (%)	1,423 (19)	1,064 (16)	359 (43)
Bacteremia (%)	764 (10)	530 (8.2)	234 (28)
Bacterial pneumonia (%)	1,182 (16)	894 (14)	288 (34)
Bronchiolitis (%)	37 (0.5)	31 (0.5)	6 (0.7)
Cardiac arrest (%)	694 (9.4)	580 (8.9)	114 (14)
Cardiac arrhythmia (%)	737 (10)	577 (8.9)	160 (19)
Cardiac ischemia (%)	196 (2.7)	164 (2.5)	32 (3.8)
Cardiomyopathy (%)	86 (1.2)	69 (1.1)	17 (2.0)
Endocarditis (%)	15 (0.2)	11 (0.2)	4 (0.5)
Heart failure (%)	287 (3.9)	259 (4.0)	28 (3.3)
Hyperglycemia (%)	1,447 (20)	1,193 (18)	254 (30)
Liver dysfunction (%)	628 (8.6)	487 (7.5)	141 (17)
Meningitis (%)	35 (0.5)	33 (0.5)	2 (0.2)
Myocardial infarction (%)	98 (1.3)	87 (1.3)	11 (1.3)
Myocarditis/pericarditis (%)	85 (1.2)	66 (1.0)	19 (2.3)
Pneumothorax (%)	290 (3.9)	158 (2.4)	132 (16)
Pleural effusion (%)	586 (8.0)	408 (6.3)	178 (21)
Pancreatitis (%)	32 (0.4)	21 (0.3)	11 (1.3)
Pulmonary embolism (%)	187 (2.5)	150 (2.3)	37 (4.4)
Rhabdomyolysis (%)	88 (1.2)	67 (1.0)	21 (2.5)
Seizure (%)	77 (1.0)	61 (0.9)	16 (1.9)
Stroke (%)	137 (1.9)	90 (1.4)	47 (5.6)
Coagulation disorder (%)	643 (8.8)	467 (7.2)	176 (21)
Complications related to haemorrhage / bleeding:			
Death from haemorrhagic shock	22 (1.1)	11 (0.7)	11 (2.9)
Gastrointestinal haemorrhage (%)	236 (3.2)	174 (2.7)	62 (7.3)
Stroke with subarachnoid haemorrhage, n (%)	26 (0.4)	10 (0.2)	16 (2.1)
Stroke with intraparenchymal haemorrhage, n (%)	42 (0.7)	18 (0.3)	24 (3.2)
Haemorrhage, other/not-specified, n (%)	445 (6.1)	290 (4.5)	155 (18)

Abbreviations: ECMO = Extracorporeal Membrane oxygenation.

Table S5. Participating countries, numbers and percentages by treatment under observed clinical practice.

	Overall	**Treatment without ECMO**	**Treatment with ECMO**
N	7,345	6,501	844
Italy	2,390 (33)	2,241 (34)	149 (18)
United States	1,305 (18)	1,006 (15)	299 (35)
Indonesia	838 (11)	827 (13)	11 (1.3)
Australia	398 (5.4)	379 (5.8)	19 (2.3)
Colombia	305 (4.2)	222 (3.4)	83 (9.8)
Spain	269 (3.7)	249 (3.8)	20 (2.4)
South Africa	205 (2.8)	202 (3.1)	3 (0.4)
Canada	202 (2.8)	183 (2.8)	19 (2.3)
Kuwait	192 (2.6)	136 (2.1)	56 (6.6)
Ireland	178 (2.4)	172 (2.6)	6 (0.7)
Qatar	155 (2.1)	153 (2.4)	2 (0.2)
Chile	138 (1.9)	129 (2.0)	9 (1.1)
Estonia	131 (1.8)	122 (1.9)	9 (1.1)
Japan	125 (1.7)	105 (1.6)	20 (2.4)
Germany	103 (1.4)	69 (1.1)	34 (4.0)
Belgium	93 (1.3)	75 (1.2)	18 (2.1)
Argentina	86 (1.2)	84 (1.3)	2 (0.2)
Brazil	86 (1.2)	69 (1.1)	17 (2.0)
Austria	46 (0.6)	28 (0.4)	18 (2.1)
South Korea	44 (0.6)	31 (0.5)	13 (1.5)
Portugal	16 (0.2)	0 (0)	16 (1.9)
China	12 (0.2)	10 (0.2)	2 (0.2)
Thailand	9 (0.1)	8 (0.1)	1 (0.1)
Netherlands	7 (<0.1)	1 (<0.1)	6 (0.7)
India	4 (<0.1)	0 (0)	4 (0.5)
Mexico	4 (<0.1)	0 (0)	4 (0.5)
Singapore	1 (<0.1)	0 (0)	1 (0.1)
Taiwan	1 (<0.1)	0 (0)	1 (0.1)
Uruguay	1 (<0.1)	0 (0)	1 (0.1)
Vietnam	1 (<0.1)	0 (0)	1 (0.1)

Abbreviations: ECMO = Extracorporeal Membrane oxygenation.

Table S6. Ethnicity, numbers and percentages by treatment under observed clinical practice.

	Overall	**Treatment without ECMO**	**Treatment with ECMO**
N	7,345	6,501	844
Aboriginal	40 (0.8)	31 (0.7)	9 (1.1)
Arab	286 (5.5)	232 (5.2)	54 (6.8)
Black	485 (9.3)	407 (9.2)	78 (9.8)
East Asian	255 (4.9)	207 (4.7)	48 (6.0)
Latin American	753 (14)	568 (13)	185 (23)
South Asian	714 (14)	681 (15)	33 (4.1)
West Asian	30 (0.6)	23 (0.5)	7 (0.9)
White	1,732 (33)	1,450 (33)	282 (35)
Other	524 (10)	461 (10)	63 (7.9)
Not available	411 (7.9)	374 (8.4)	37 (4.6)

Abbreviations: ECMO = Extracorporeal Membrane oxygenation.

Table S7. Characteristics of patients treated with Extracorporeal Membrane oxygenation (ECMO) before and after cannulation under observation of clinical practice.

	Measurements on the day before cannulation	**Measurements on the day of cannulation**	**Measurements on the day after cannulation**
Tidal volume, mL/kg PBW	6.2 (5.5 – 7.0)	6.0 (5.2 – 6.8)	5.7 (4.1 – 6.6)
Missing, no. (%)	542 (64.2)	470 (55.7)	549 (65)
Respiratory rate, min^{-1}	24 (18 – 30)	22 (14 – 30)	16 (10 – 25)
Missing, no. (%)	247 (29.3)	90 (10.7)	403 (47.7)
Airway plateau pressure, cmH_2O	24 (22 – 27)	24 (22 – 27)	24 (22 – 27)
Missing, no. (%)	640 (75.8)	590 (69.9)	627 (74.3)
PEEP, cmH_2O	11 (10 – 14)	11 (10 – 14)	11 (10 – 14)
Missing, no. (%)	462 (54.7)	352 (41.7)	504 (59.7)
FiO_2, %	75 (60 – 100)	80 (60 – 100)	69 (50 – 97)
Missing, no. (%)	356 (42.2)	237 (28.1)	454 (53.8)
PaO_2, mmHg	70 (59 – 88)	70 (58 – 88)	71 (60 – 88)
Missing, no. (%)	259 (30.7)	84 (10)	395 (46.8)
SaO_2, %	92 (88 – 95)	92 (87 – 96)	93 (88 – 96)
Missing, no. (%)	308 (36.5)	170 (20.1)	483 (57.2)
PaO_2/FiO_2 ratio, mmHg	117 (78 – 175)	–	–
Missing, no. (%)	384 (45.5)	–	–
Arterial pH	7.37 (7.30 – 7.44)	7.36 (7.28 – 7.44)	7.39 (7.32 – 7.45)
Missing, no. (%)	264 (31.3)	93 (11)	399 (47.3)
$PaCO_2$, mmHg	47 (38 – 57)	48 (39 – 59)	47 (40 – 56)
Missing, no. (%)	263 (31.2)	94 (11.1)	401 (47.5)
Serum bicarbonate, mmol/L	27 (23 – 31)	28 (23 – 32)	28 (24 – 32)
Missing, no. (%)	351 (41.6)	190 (22.5)	481 (57)
Lactate, mmol/L	1.6 (1.2 – 2.2)	1.7 (1.2 – 2.4)	1.6 (1.2 – 2.2)
Missing, no. (%)	421 (49.9)	290 (34.4)	507 (60.1)
ECMO flow, LPM	–	4.2 (3.6 – 4.7)	4.2 (3.5 – 4.7)
Missing, no. (%)	–	391 (46.3)	537 (63.6)
Gas flow, LPM	–	4.0 (3.0 – 5.0)	4.5 (3.5 – 6.0)
Missing, no. (%)	–	402 (47.6)	539 (63.9)

The table shows crude, summarized data (medians with interquartile ranges) calculated from daily measurements of time-varying variables for a total of 844 patient who received Extracorporeal Membrane oxygenation (ECMO) therapy at any time point during follow-up. When interpreting the table, it must be considered that the median and confidence intervals are influenced by censoring and different measurement times relative to the baseline. Daily measurements do not necessarily reflect the worst or best value of the day. Also, the daily measurements might or might not align with the time point of ECMO cannulation.

Table S8. Unadjusted, cumulative probability of events at 60 days with 95% confidence intervals (CI).

	Overall
n	7,345
Estimated outcome at 60 days	
Probability of death in hospital, % (95% CI)	35 (34 to 37)
Probability of death in hospital for ECMO patients, % (95% CI)	50 (46 to 54)
Probability of remaining in hospital, % (95% CI)	6 (5 to 7)
Probability of remaining in hospital for ECMO patients, % (95% CI)	16 (13 to 20)
Probability of discharge alive, % (95% CI)	59 (57 to 60)
Probability of being discharged alive for ECMO patients, % (95% CI)	34 (30 to 38)

The table shows unadjusted, cumulative probability of events at 60 days with 95% confidence intervals (CI), estimated using an Aalen-Johansen estimator. The probability for ECMO patients represents the cumulative probability of the event conditional on the receipt of ECMO therapy at any time point during follow-up.

3. Additional results (Tables S9 to S14)

List of figures and tables in the next pages:

- **Table S9**. Estimated risk of death or hospital discharge at 60 days in patients with COVID-19.
- **Table S10.** Influence of age on outcomes of patients with COVID-19.
- **Table S11.** Influence of various comorbidities on outcomes of patients with COVID-19.
- **Table S12.** Influence of the number of comorbidities on outcomes of patients with COVID-19.
- **Table S13.** Influence of the duration of mechanical ventilation preceding the initiation of ECMO therapy on treatment effectiveness.
- **Table S14.** Effects on outcomes if the decision of initiating extracorporeal membrane oxygenation (ECMO) had been based on different thresholds for the time-dependent ratio of arterial partial pressure of oxygen (PaO_2) / fraction of inspiratory oxygen (FiO_2).
- **Table S15.** Effects on outcomes if the decision of initiating extracorporeal membrane oxygenation (ECMO) had been based on different thresholds for time-dependent driving pressure (ΔP).

Additional details:

In the following, we provide additional details of the results of our primary and secondary analyses. We also report the results of control experiments that were used to detect potential model misspecification or uncontrolled confounding.

Table S9. Estimated risk of death or hospital discharge at 60 days in patients with COVID-19.

	Conventional mechanical ventilation	ECMO therapy if PaO_2/FiO_2 < 80mmHg	As-treated analysis (treatment as received)
Absolute risk % (95% CI)			
Mortality	33.2 (31.8 to 34.6)	26.0 (24.5 to 27.5)	34.8 (33.4 to 36.1)
Hospital discharge alive	60.6 (59.0 to 62.2)	67.5 (65.7 to 69.3)	58.3 (56.8 to 59.7)
Risk difference % (95% CI)			
Mortality	..	-7.1 (-8.2 to -6.1)	1.6 (1.0 to 2.2)
Hospital discharge alive	..	6.9 (5.9 to 8.0)	-2.4 (-2.9 to -1.8)
Risk ratio (95% CI)			
Mortality	..	0.78 (0.75 to 0.82)	1.05 (1.03 to 1.07)
Hospital discharge alive	..	1.11 (1.10 to 1.13)	0.96 (0.95 to 0.97)

Interventions were compared to a treatment strategy with conventional mechanical ventilation without the use of extracorporeal membrane oxygenation therapy (ECMO). In the as-treated analysis, outcomes were compared between treatment as received (which could have included treatment with ECMO) and treatment with conventional mechanical ventilation without the use of ECMO. PaO_2/FiO_2 = ratio of arterial pressure of oxygen / fraction of inspiratory oxygen. Sample size=7,345; Number of bootstrap samples=500.

Table S10. Influence of age on outcomes of patients with COVID-19.

	Estimated mortality		Estimated probability of discharge alive	
	Conventional mechanical ventilation	**ECMO therapy if PaO_2/FiO_2 ratio < 80mmHg**	**Conventional mechanical ventilation**	**ECMO therapy if PaO_2/FiO_2 ratio < 80mmHg**
Absolute risk % (95% CI)				
< 50 years	24.0 (21.2 to 26.8)	17.0 (14.0 to 20.1)	69.6 (66.5 to 72.6)	76.3 (72.7 to 79.8)
50 to 64 years	30.2 (28.0 to 32.5)	23.3 (20.8 to 25.8)	63.6 (61.1 to 66.1)	70.1 (67.2 to 73.0)
≥ 65 years	43.3 (40.7 to 45.8)	36.5 (33.6 to 39.5)	51.0 (48.3 to 53.7)	57.7 (54.5 to 60.8)
Risk difference % (95% CI)				
< 50 years	··	-7.0 (-9.5 to -4.5)	··	6.7 (4.3 to 9.1)
50 to 64 years	··	-6.9 (-9.0 to -4.9)	··	6.5 (4.5 to 8.4)
≥ 65 years	··	-6.7 (-8.4 to -5.0)	··	6.6 (5.0 to 8.3)
Risk ratio (95% CI)				
< 50 years	··	0.71 (0.62 to 0.81)	··	1.10 (1.06 to 1.13)
50 to 64 years	··	0.77 (0.71 to 0.84)	··	1.10 (1.07 to 1.13)
≥ 65 years	··	0.84 (0.81 to 0.88)	··	1.13 (1.10 to 1.16)

Interventions were compared to a treatment strategy with conventional mechanical ventilation without the use of extracorporeal membrane oxygenation therapy (ECMO). PaO_2/FiO_2 = ratio of arterial pressure of oxygen / fraction of inspiratory oxygen. Sample sizes: n=1,903 (age < 50 years), n=2,823 (age 50 to 64 years), and n=2619 (age ≥ 65 years); Number of bootstrap samples=500.

Table S11. Influence of various comorbidities on outcomes of patients with COVID-19.

	Estimated mortality		Estimated probability of discharge alive	
	Conventional mechanical ventilation	**ECMO therapy if PaO_2/FiO_2 ratio < 80mmHg**	**Conventional mechanical ventilation**	**ECMO therapy if PaO_2/FiO_2 ratio < 80mmHg**
Absolute risk % (95% CI)				
No comorbidities	24.3 (20.7 to 27.8)	19.5 (16.0 to 23.0)	69.1 (64.9 to 73.4)	73.9 (69.4 to 78.5)
Arterial hypertension	30.7 (28.8 to 32.6)	23.2 (21.1 to 25.2)	63.6 (61.5 to 65.7)	71.1 (68.7 to 73.5)
Diabetes	43.8 (40.9 to 46.6)	34.6 (31.2 to 38.0)	51.4 (48.5 to 54.4)	60.1 (56.5 to 63.8)
Obesity	39.4 (36.5 to 42.3)	28.4 (24.7 to 32.0)	54.5 (51.4 to 57.7)	64.4 (60.4 to 68.4)
Risk difference % (95% CI)				
No comorbidities	··	-4.8 (-7.5 to -2.1)	··	4.8 (2.1 to 7.5)
Arterial hypertension	··	-7.5 (-9.0 to -6.1)	··	7.5 (6.1 to 8.9)
Diabetes	··	-9.1 (-11.3 to -6.9)	··	8.7 (6.5 to 10.9)
Obesity		-11.1 (-14.2 to -8.0)		9.8 (6.9 to 12.8)
Risk ratio (95% CI)				
No comorbidities	··	0.80 (0.70 to 0.91)	··	1.07 (1.03 to 1.11)
Arterial hypertension	··	0.75 (0.71 to 0.80)	··	1.12 (1.10 to 1.14)
Diabetes		0.79 (0.74 to 0.84)		1.17 (1.13 to 1.21)
Obesity	··	0.72 (0.65 to 0.80)	··	1.18 (1.13 to 1.24)

Interventions were compared to a treatment strategy with conventional mechanical ventilation without the use of extracorporeal membrane oxygenation therapy (ECMO). PaO_2/FiO_2 = ratio of arterial pressure of oxygen / fraction of inspiratory oxygen. Sample sizes: n=998 (No comorbidities), n=4,203 (arterial hypertension), n=1,887 (Diabetes), and n=1,603 (obesity); Number of bootstrap samples=500.

Table S12. Influence of the number of comorbidities on outcomes of patients with COVID-19.

	Estimated mortality		Estimated probability of discharge alive	
	Conventional mechanical ventilation	**ECMO therapy if PaO_2/FiO_2 ratio < 80mmHg**	**Conventional mechanical ventilation**	**ECMO therapy if PaO_2/FiO_2 ratio < 80mmHg**
Absolute risk % (95% CI)				
≤ 3 comorbidities	27.8 (26.2 to 29.5)	21.8 (20.1 to 23.5)	65.7 (64.0 to 67.5)	71.8 (69.8 to 73.8)
> 3 comorbidities	48.2 (45.3 to 51.0)	39.7 (36.3 to 43.1)	46.3 (43.4 to 49.2)	53.7 (50.1 to 57.3)
Risk difference % (95% CI)				
≤ 3 comorbidities	··	-6.0 (-7.4 to -4.7)	··	6.0 (4.7 to 7.4)
> 3 comorbidities	··	-8.5 (-10.8 to -6.2)	··	7.4 (5.2 to 9.7)
Risk ratio (95% CI)				
≤ 3 comorbidities	··	0.78 (0.74 to 0.83)	··	1.09 (1.07 to 1.11)
> 3 comorbidities	··	0.82 (0.78 to 0.87)	··	1.16 (1.11 to 1.21)

Interventions were compared to a treatment strategy with conventional mechanical ventilation without the use of extracorporeal membrane oxygenation therapy (ECMO). PaO_2/FiO_2 = ratio of arterial pressure of oxygen / fraction of inspiratory oxygen. Sample sizes: n=5,709 (≤ 3 comorbidities) and n=1,636 (> 3 comorbidities); Number of bootstrap samples=500

Table S13. Influence of the duration of mechanical ventilation preceding the initiation of ECMO therapy on treatment effectiveness.

Days of mechanical ventilation preceding ECMO therapy	Risk ratio (95% CI)		Risk difference (95% CI)	
	Death	Hospital discharge	Death	Hospital discharge
≤1	0.91 (0.88 to 0.94)	1.04 (1.02 to 1.02)	-3.0 (-4.0 to -2.0)	2.2 (1.2 to 1.2)
2	0.90 (0.88 to 0.92)	1.05 (1.04 to 1.04)	-3.3 (-4.0 to -2.7)	3.1 (2.5 to 2.5)
3	0.92 (0.91 to 0.94)	1.04 (1.03 to 1.03)	-2.5 (-3.1 to -1.9)	2.3 (1.7 to 1.7)
4	0.93 (0.91 to 0.94)	1.04 (1.03 to 1.03)	-2.5 (-3.0 to -1.9)	2.3 (1.8 to 1.8)
5	0.95 (0.94 to 0.96)	1.03 (1.02 to 1.02)	-1.7 (-2.2 to -1.2)	1.6 (1.2 to 1.2)
6	0.96 (0.95 to 0.98)	1.02 (1.01 to 1.01)	-1.3 (-1.8 to -0.8)	1.2 (0.7 to 0.7)
7	0.97 (0.95 to 0.98)	1.02 (1.01 to 1.01)	-1.2 (-1.6 to -0.7)	1.1 (0.7 to 0.7)
8	0.97 (0.96 to 0.98)	1.02 (1.01 to 1.01)	-1 (-1.4 to -0.7)	1 (0.6 to 0.6)
9	0.98 (0.97 to 0.99)	1.01 (1.01 to 1.01)	-0.8 (-1.1 to -0.4)	0.7 (0.4 to 0.4)
10	0.98 (0.97 to 0.99)	1.01 (1.01 to 1.01)	-0.8 (-1.1 to -0.4)	0.7 (0.4 to 0.4)
11	0.98 (0.97 to 0.99)	1.01 (1.01 to 1.01)	-0.8 (-1.0 to -0.5)	0.8 (0.5 to 0.5)
≥12	0.97 (0.96 to 0.98)	1.02 (1.01 to 1.01)	-0.9 (-1.3 to -0.6)	0.9 (0.6 to 0.6)

A treatment strategy, where extracorporeal membrane oxygenation therapy (ECMO) therapy had to be initiated if the ratio of arterial pressure of oxygen / fraction of inspiratory oxygen (PaO_2/FiO_2) was < 80mmHg, was compared to treatment with conventional mechanical ventilation without the use of ECMO. In the different scenarios, ECMO therapy could only be initiated if the preceding duration of mechanical ventilation was within the indicated range / corresponded to the indicated number of days. Sample size: n=7,345; Number of bootstrap samples=500.

Table S14. Effects on outcomes if the decision of initiating extracorporeal membrane oxygenation (ECMO) had been based on different thresholds for the time-dependent ratio of arterial partial pressure of oxygen (PaO_2) / fraction of inspiratory oxygen (FiO_2).

	Absolute risk % (95% CI)	**Risk difference % (95% CI)**	**Risk ratio (95% CI)**
Estimated mortality			
Conventional mechanical ventilation	33.2 (31.8 to 34.6)	..	..
ECMO must only be initiated if: $PaO_2/FiO_2 \geq 80$ and < 120 mmHg	29.0 (27.4 to 30.7)	-4.2 (-5.4 to -2.9)	0.87 (0.84 to 0.91)
ECMO must only be initiated if: $PaO_2/FiO_2 \geq 120$ and < 150 mmHg	34.8 (33.0 to 36.6)	1.6 (0.5 to 2.7)	1.05 (1.02 to 1.08)
ECMO therapy must be initiated in all patients	63.5 (57.1 to 69.9)	30.3 (23.9 to 36.8)	1.91 (1.72 to 2.13)
Estimated probability of hospital discharge alive			
Conventional mechanical ventilation	60.3 (58.6 to 61.9)	..	..
ECMO must only be initiated if: $PaO_2/FiO_2 \geq 80$ and < 120 mmHg	65.8 (63.9 to 67.6)	5.5 (4.3 to 6.7)	1.09 (1.07 to 1.11)
ECMO must only be initiated if: $PaO_2/FiO_2 \geq 120$ and < 150 mmHg	59.7 (57.7 to 61.7)	-0.5 (-1.6 to 0.6)	0.99 (0.97 to 1.01)
ECMO therapy must be initiated in all patients	18.3 (13.6 to 23.1)	-41.9 (-46.8 to -37.0)	0.30 (0.23 to 0.39)

Interventions were compared to a treatment strategy with conventional mechanical ventilation without the use of extracorporeal membrane oxygenation therapy (ECMO). Sample size=7,345. Number of bootstrap samples=500.

Table S15. Effects on outcomes if the decision of initiating extracorporeal membrane oxygenation (ECMO) had been based on different thresholds for time-dependent driving pressure (ΔP).

	Absolute risk % (95% CI)	Risk difference % (95% CI)	Risk ratio (95% CI)
Estimated mortality			
Conventional mechanical ventilation	33.1 (31.6 to 34.5)	..	..
ECMO must be initiated if: $\Delta P > 12$ cmH_2O	31.3 (29.1 to 33.5)	-1.7 (-3.6 to 0.1)	0.95 (0.89 to 1.00)
ECMO must be initiated if: $\Delta P > 15$ cmH_2O	29.5 (27.8 to 31.2)	-3.6 (-4.7 to -2.5)	0.89 (0.86 to 0.93)
ECMO must be initiated if: $\Delta P > 17$ cmH_2O	30.1 (28.6 to 31.5)	-3.0 (-3.7 to -2.2)	0.91 (0.89 to 0.93)
ECMO must be initiated if: $\Delta P > 20$ cmH_2O	32.9 (31.4 to 34.3)	-0.2 (-0.7 to 0.4)	0.99 (0.98 to 1.01)
Estimated probability of hospital discharge alive			
Conventional mechanical ventilation	60.3 (58.7 to 61.9)	..	..
ECMO must be initiated if: $\Delta P > 12$ cmH_2O	62.0 (59.6 to 64.4)	1.7 (-0.3 to 3.6)	1.03 (1.00 to 1.06)
ECMO must be initiated if: $\Delta P > 15$ cmH_2O	63.6 (61.7 to 65.5)	3.3 (2.1 to 4.4)	1.05 (1.04 to 1.07)
ECMO must be initiated if: $\Delta P > 17$ cmH_2O	62.7 (61.0 to 64.5)	2.4 (1.6 to 3.2)	1.04 (1.03 to 1.05)
ECMO must be initiated if: $\Delta P > 20$ cmH_2O	60.2 (58.5 to 61.8)	-0.2 (-0.7 to 0.4)	1.00 (0.99 to 1.01)

Interventions were compared to a treatment strategy with conventional mechanical ventilation without the use of extracorporeal membrane oxygenation therapy (ECMO). Sample size=7,345. Number of bootstrap samples=500.

4. Sensitivity analyses (Figures S3 to S5)

Please, refer to the figures and tables within the next pages.

- **Figure S3.** Influence of treatment on a random outcome variable with 50:50 probability.
- **Figure S4.** Sensitivity analysis using an alternative set of covariates for calculation of the inverse probability weights (IPW).
- **Figure S5.** Influence of potential confounding due to country-specific heterogeneity in treatment effectiveness.

Additional details:

In the following the results of sensitivity analyses are presented to detect potential model misspecifications or residual confounding.

Figure S3. Influence of treatment on a random outcome variable with 50:50 probability. A treatment strategy, where extracorporeal membrane oxygenation (ECMO) therapy had to be initiated if the ratio of arterial partial pressure of oxygen (PaO_2) / fraction of inspiratory oxygen (FiO_2) was < 80 mmHg, was compared to treatment with conventional mechanical ventilation without the use of ECMO. The curves show no effect which is as expected for this control outcome. The shaded areas represent 95% confidence intervals.

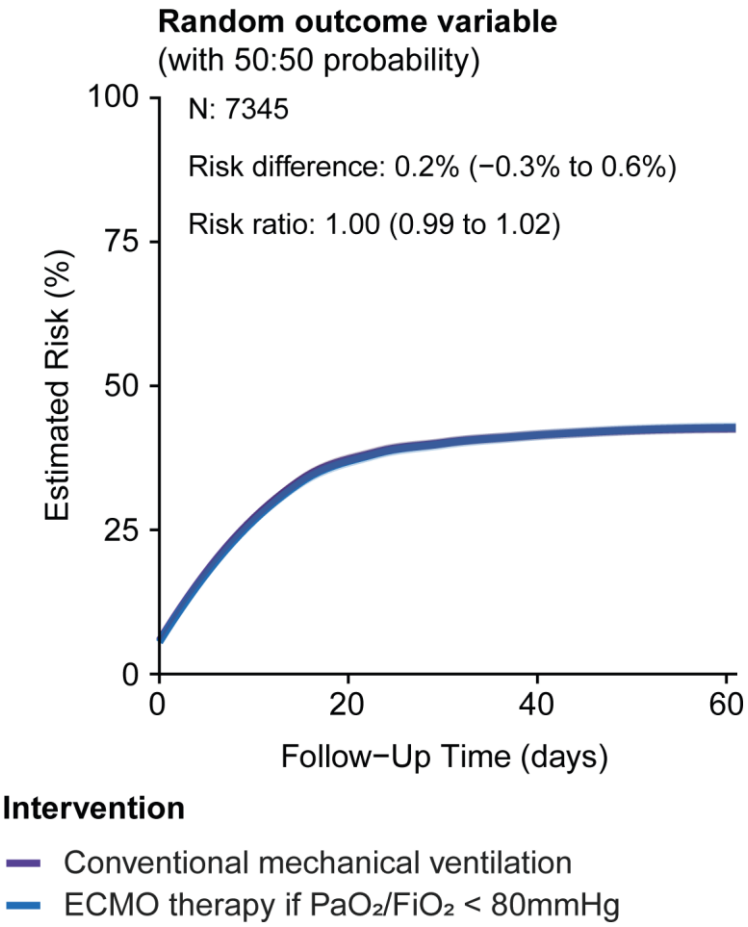


Figure S4. Sensitivity analysis using an alternative set of covariates for calculation of the inverse probability weights (IPW). A treatment strategy, where extracorporeal membrane oxygenation (ECMO) therapy had to be initiated if the ratio of arterial partial pressure of oxygen (PaO_2) / fraction of inspiratory oxygen (FiO_2) was < 80 mmHg, was compared to treatment with conventional mechanical ventilation without the use of ECMO. The following covariates were used for inverse probability weighting: age, presence of chronic neurological, cardiac, pulmonary, or liver disease, stage III kidney failure, malignant neoplasm, inability to walk, seizures, treatment with neuromuscular blockade, prone position, inhaled nitric oxide, treatment with vasoactive drugs, duration of mechanical ventilation. The shaded areas represent 95% confidence intervals.

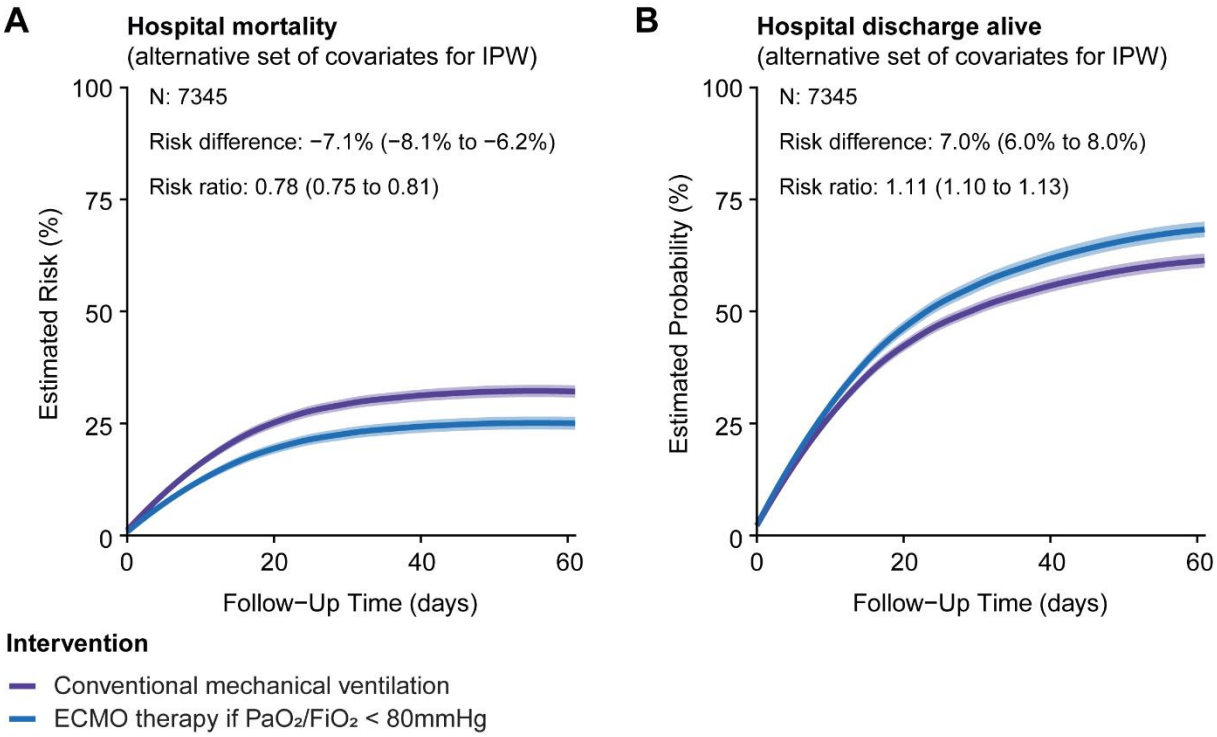
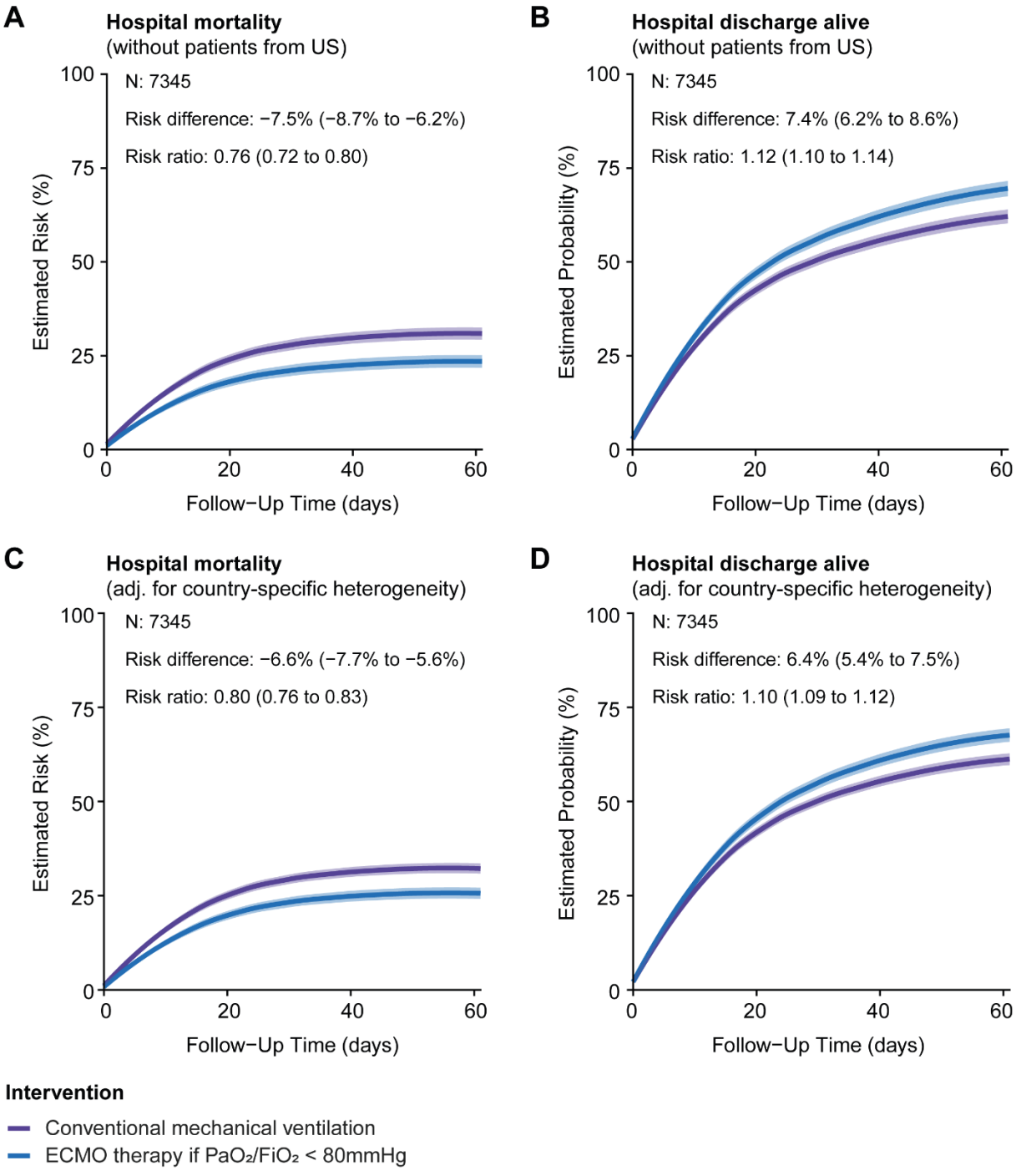


Figure S5. Influence of potential confounding due to country-specific heterogeneity in treatment effectiveness. A treatment strategy, where extracorporeal membrane oxygenation (ECMO) therapy had to be initiated if the ratio of arterial partial pressure of oxygen (PaO_2) / fraction of inspiratory oxygen (FiO_2) was < 80 mmHg, was compared to treatment with conventional mechanical ventilation without the use of ECMO. In a first analysis, we excluded patients from the United States of America (**panel A and B**). In a second analysis, inverse probability weighting to adjust for country-specific heterogeneity (**panel C and D**). The results were similar to the findings of the primary analysis. The shaded areas represent 95% confidence intervals.



5. Missing data (Figure S6 and S7, Table S15)

Please, refer to the figures and tables within the next pages.

- **Figure S6.** Histograms of imputed and observed variables.
- **Table S16**. Missing baseline covariate data of variables used for computation of the inverse probability weights.
- **Figure S7.** Estimated effects on hospital mortality in patients with COVID-19 related respiratory failure in patients with complete measurements at baseline and without variable imputation.

Additional details:

For the main analysis, we imputed missing measurements at baseline with the 'mice' package using fully conditionally specified models, including failure time and outcome. For longitudinal missing values, we carried the last observation forward, similar to previous work [2]. Carrying forward the last available value reflects what the treatment team would do in clinical practice at the bedside. We performed a complete case analysis with a reduced set of covariates for the calculation of the inverse probability weights to investigate the potential influence of missing variables.

Figure S6. Histograms of imputed and observed variables. APACHE II = Acute Physiology And Chronic Health Evaluation score II, PPlat = Plateau pressure. PEEP = positive end-expiratory pressure. Vt per PBW = Tidal volume per predicted body weight, $PaCO_2$ = arterial partial pressure of carbon dioxide, PaO_2 = arterial partial pressure of oxygen, SaO2 = arterial oxygen saturation. SOFA = severity of organ failure assessment score.

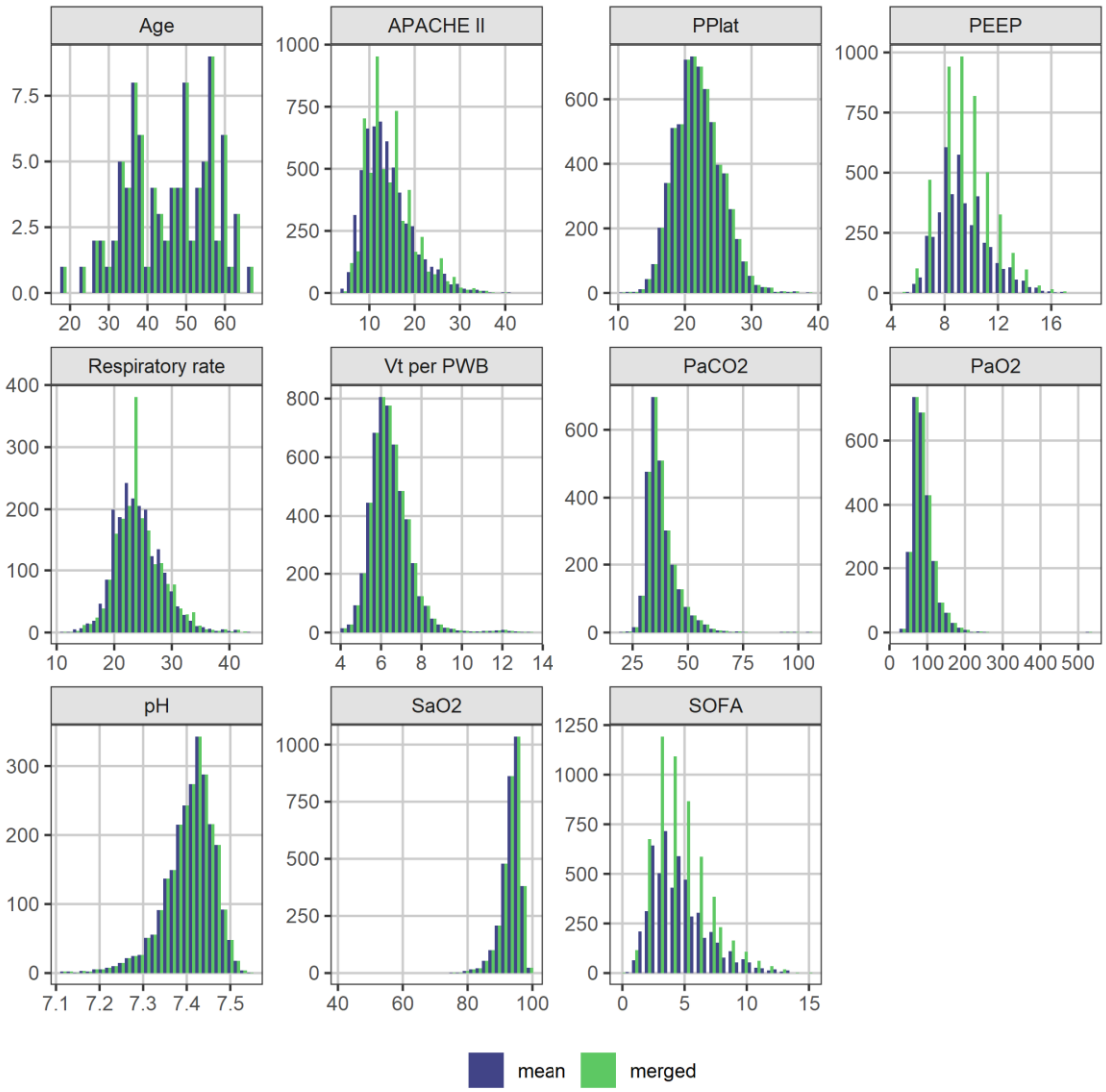
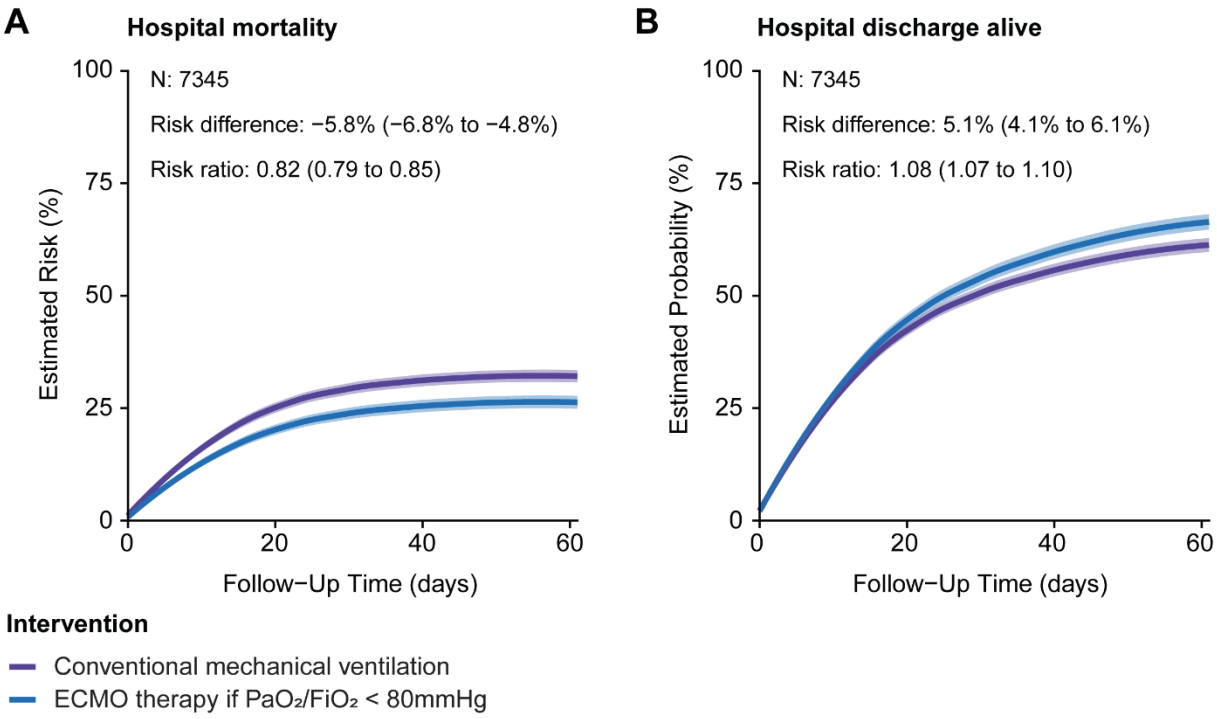


Table S16. Missing baseline covariate data of variables used for computation of the inverse probability weights.

Variable	No. of missing values (%)
Age, years	91 (1.2)
Sex	0 (0)
Severity of illness and pre-existing conditions	
APACHE II score	5,695 (77.5)
SOFA score	5,537 (75.4)
Inability to walk	0 (0)
Seizure disorder	0 (0)
Chronic cardiac disease	0 (0)
Chronic pulmonary disease	0 (0)
Severe liver failure	0 (0)
Pre-existing kidney failure requiring dialysis	0 (0)
Chronic neurological disease	0 (0)
Dementia	0 (0)
Malignant neoplasia	0 (0)
Stage III kidney failure (composite variable)	
Creatinine levels, μmol/L	2,048 (27.8)
Renal replacement therapy	2,794 (38.0)
Urine output, mL / kg / hr	5,424 (73.8)
Ventilation parameters	
Airway plateau pressure, cmH_2O	6,466 (88.0)
PEEP, cmH_2O	4,468 (60.8)
PaO_2 / FiO_2 ratio	3,556 (48.4)
FiO_2	3,106 (42.3)
Arterial pH	2,538 (34.6)
Specific treatments	
Vasoactive drugs	0 (0)
Neuromuscular blockade	0 (0)
Prone position	0 (0)
Inhaled nitric oxide	0 (0)

Abbreviations: APACHE II score = Acute Physiology And Chronic Health Evaluation II Score. SOFA score = Sequential Organ Failure Assessment score. FiO2 = fraction of inspired oxygen. PEEP = positive end-expiratory pressure. PaO_2 = arterial partial pressure of oxygen.

Figure S7. Complete case analysis without variable imputation. A treatment strategy, where extracorporeal membrane oxygenation (ECMO) therapy had to be initiated if the ratio of arterial partial pressure of oxygen (PaO_2) / fraction of inspiratory oxygen (FiO_2) was < 80 mmHg, was compared to treatment with conventional mechanical ventilation without the use of ECMO. The following covariates were used for inverse probability weighting: age, presence of chronic neurological, cardiac, pulmonary, or liver disease, stage III kidney failure, malignant neoplasm, inability to walk, seizures, treatment with neuromuscular blockade, prone position, inhaled nitric oxide, treatment with vasoactive drugs, duration of mechanical ventilation. The results were similar to the findings of the primary analysis. The shaded areas represent 95% confidence intervals.



6. Contributors and collaborators (Table S17 and S18)

Please, refer to the figures and tables within the next pages.

- **Table S17**. List of contributors.
- **Table S18.** List of collaborators.

Additional details:

We recognize the crucial importance of the ISARIC and SPRINT-SARI networks for the development and expansion of the COVID-19 Critical Care Consortium. We thank the generous support we received from ELSO and ECMONet. Finally, we acknowledge all members of the COVID-19 Critical Care Consortium and various collaborators (**Tables S17** and **S18**).

Table S17. List of contributors.

Prefix/First Name/Last Name	Site Name
Tala Al-Dabbous Dr Huda Alfoudri	Al Adan Hospital
Dr Subbarao Elapavaluru Ashley Berg Christina Horn	Allegheny General Hospital
Dr Stephan Schroll	Barmherzige Bruder Regansburg
Dr Jorge Velazco Wanda Fikes Ludmyla Ploskanych	Baylor Scott & White Health - Temple
Dr Dan Meyer Maysoon Shalabi-McGuire Trent Witt Ashley Ehlers	Baylor University Medical Centre, Dallas
Dr Lorenzo Grazioli	Bergamo Hospital
Dr E. Wilson Grandin Jose Nunez Tiago Reyes	Beth Israel Deaconess Medical Centre
Dr Mark Joseph Dr Brook Mitchell Martha Tenzer	Carilion Clinic
Dr Ryuzo Abe Yosuke Hayashi	Chiba University Graduate School of Medicine
Dr Hwa Jin Cho Dr In Seok Jeong	Chonnam National University Hospital
Dr Nicolas Brozzi Dr Jaime Hernandez-Montfort	Cleveland Clinic - Florida
Omar Mehkri Stuart Houltham	Cleveland Clinic - Ohio
Dr Jerónimo Graf Rodrigo Perez	Clinica Alemana De Santiago
Dr Roderigo Diaz Camila Delgado Joyce González Maria Soledad Sanchez	Clinica Las Condez
Dr Diego Fernando Bautista Rincón Melissa Bustamante Duque Dr Angela Maria Marulanda Yanten	Clinica Valle de Lilli
Dr Dan Brodie	Columbia University Medical Centre
Dr Desy Rusmawatiningtyas	Dr Sardjito Hospital (Paediatrics)
Gabrielle Ragazzo	Emory University Healthcare System
Dr Azhari Taufik Dr Margaretha Gunawan Dr Vera Irawany Muhammad Rayhan Dr Elizabeth Yasmin Wardoyo	Fatmawati Hospital
Dr Mauro Panigada Dr Silvia Coppola Dr Sebastiano Colombo Dr Giacomo Grasselli Dr Michela Leone Dr Alberto Zanella	Fondazione IRCCS Policlinico of Milan (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico)
Prof Massimo Antonelli Dr Simone Carelli	Fondazione Policlinico Universitario Agostino Gemelli IRCCS

Prefix/First Name/Last Name	Site Name
Domenico Grieco	
Motohiro Asaki	Fujieda Municipal General Hospital
Dr Kota Hoshino	Fukuoka University
Dr Leonardo Salazar Laura Duarte	Fundación Cardiovascular de Colombia
Dr Joseph McCaffrey Allison Bone	Geelong Hospital
Dr David Thomson Dr Christel Arnold-Day Jerome Cupido Zainap Fanie Dr Malcom Miller Dr Lisa Seymore Dawid van Straaten	Groote Schuur Hospital
Dr Ibrahim Hassan Dr Ali Ait Hssain Jeffrey Aliudin Al-Reem Alqahtani Khoulod Mohamed Ahmed Mohamed Darwin Tan Joy Villanueva Ahmed Zaqout	Hamad General Hospital - Weill Cornell Medical College in Qatar
Dr Ethan Kurtzman Arben Ademi Ana Dobrita Khadija El Aoudi Juliet Segura	Hartford HealthCare
Dr Gezy Giwangkancana	Hasan Sadikin Hospital (Adult)
Dr Shinichiro Ohshimo	Hiroshima University
Dr Koji Hoshino Saito Hitoshi Dr Yuka Uchinami	Hokkaido University Hospital
Dr Javier Osatnik	Hospital Alemán
Dr Anne Joosten	Hospital Civil Marie Curie
Dr Antoni Torres Ana Motos Dr Minlan Yang	Hospital Clinic, Barcelona
Carlos Luna	Hospital de Clínicas
Francisco Arancibia	Hospital del Tórax
Virginie Williams Alexandre Noel	Hospital du Sacre Coeur (Universite de Montreal)
Dr Nestor Luque	Hospital Emergencia Ate Vitarte
Dr Trieu Huynh Trung Sophie Yacoub	Hospital for Tropical Diseases
Marina Fantini	Hospital Mater Dei
Dr Ruth Noemi Jorge García Dr Enrique Chicote Alvarez	Hospital Nuestra Señora de Gracia
Dr Anna Greti Oscar Lomeli	Hospital Puerta de Hierro
Dr Adrian Ceccato	Hospital Universitari Sagrat Cor
Dr Angel Sanchez	Hospital Universitario Sant Joan d'Alacant
Dr Ana Loza Vazquez	Hospital Universitario Virgen de Valme
Dr Ferran Roche-Campo	Hospital Verge de la Cinta de Tortosa
Dr Divina Tuazon	Houston Methodist Hospital

Prefix/First Name/Last Name	Site Name
Dr Toni Duculan	
Hiroaki Shimizu	Kakogawa Acute Care Medical Center, Hyogo
Marcelo Amato Luciana Cassimiro Flavio Pola Francis Ribeiro Guilherme Fonseca	INCOR (Universidade de São Paulo)
Dr Heidi Dalton Dr Mehul Desai Dr Erik Osborn Hala Deeb	INOVA Fairfax Hospital
Dr Antonio Arcadipane Claudia Bianco Raffaele Cuffaro Gennaro Martucci Giovanna Occhipinti Matteo Rossetti Chiara Vitiello	ISMETT
Dr Sung-Min Cho Kate Calligy Dr Glenn Whitman	Johns Hopkins
Dr Hiroaki Shimizu Dr Naoki Moriyama	Kakogawa Acute Care Medical Center
Dr Jae-Burm Kim	Keimyung University Dong San Hospital
Dr Nobuya Kitamura Takashi Shimazui	Kimitsu Chuo Hospital
Dr Abdullah Al-Hudaib Dr Alyaa Elhazmi	King Faisal Specialist Hospital and Research Center
Dr Johannes Gebauer	Klinikum Passau
Dr Toshiki Yokoyama	Kouritu Tousei Hospital
Dr Abdulrahman Al-Fares Esam Alamad Fatma Alawadhi Kalthoum Alawadi Dr Sarah Buabbas	Kuwait ECLS program, Al-Amiri & Jaber Al-Ahmed Hospitals
Dr Hiro Tanaka	Kyoto Medical Centre
Dr Satoru Hashimoto Masaki Yamazaki	Kyoto Prefectural University of Medicine
Tak-Hyuck Oh	Kyung Pook National University Chilgok Hospital
Dr Mark Epler Dr Cathleen Forney Jared Feister Katherine Grobengieser Louise Kruse Joelle Williamson	Lancaster General Health
Dr Eric Gnall Dr Mara Caroline Sasha Golden Colleen Karaj Sherry McDermott Lynn Sher Dr Timothy Shapiro Lisa Thome Mark Vanderland Mary Welch	Lankenau Institute of Medical Research (Main Line Health)

Prefix/First Name/Last Name	Site Name
Prof Luca Brazzi	Le Molinette Hospital (Ospedale Molinette Torino)
Dr Tawnya Ogston	Legacy Emanuel Medical Center
Dr Dave Nagpal Karlee Fischer	London Health Sciences Centre
Dr Roberto Lorusso Maria de Piero	Maastricht University Medical Centre
Prof Mariano Esperatti	Mar del Plata Medical Foundation Private Community Hospital
Dr Diarmuid O'Briain	Maroondah Hospital
Dr Edmund G. Carton	Mater Misericordiae University Hospital
Ayan Sen Amanda Palacios Deborah Rainey	Mayo Clinic College of Medicine
Cassandra Seefeldt Dr Lucia Durham Dr Octavio Falcucci Amanda Emmrich Jennifer Guy Carling Johns Emily Neumann	Medical College of Wisconsin (Froedtert Hospital)
Dr Nina Buchtele Dr Michael Schwameis	Medical University of Vienna
Dr Stephanie-Susanne Stecher Delila Singh Dr Michaela Barnikel Lukas Arenz	Medizinische Klinik und Poliklinik II
Dr Akram Zaaqoq Lan Anh Galloway Caitlin Merley	MedStar Washington Hospital Centre
Dr Marc Csete Luisa Quesada Isabela Saba	Mount Sinai Medical Centre
Dr Daisuke Kasugai Hiroaki Hiraiwa Taku Tanaka	Nagoya University Hospital
Dr Eva Marwali	National Cardiovascular Center Harapan Kita (Paediatrics)
Yih-Sharng Chen	National Taiwan University Hospital
Prof John Laffey	National University of Ireland Galway
Marlice VanDyk Sarah MacDonald	Netcare Unitas ECMO Centre
Dr Ian Seppelt	Nepean Hospital
Dr Indrek Ratsep Lauri Enneveer Kristo Erikson Dr Getter Oigus Andra-Maris Post Piret Sillaots	North Estonia Medical Centre
Dr Effe Mihelis	Northwell Health
Mamoru Komats	Obihiro-Kosei General Hospital
Dr S. Veena Satyapriya Dr Amar Bhatt Marco Echeverria Juan Fiorda Alicia Gonzalez	Ohio State University Medical Centre

Prefix/First Name/Last Name	Site Name
Dr Nahush A. Mokadam Johnny McKeown Joshua Pasek Haixia Shi Alberto Uribe	
Dr Rita Moreno	Oklahoma Heart Institute
Bishoy Zakhary Hannah Johnson Nolan Pow	Oregon Health and Science University Hospital (OHSU)
Dr Marco Cavana Dr Alberto Cucino	Ospedale di Arco (Trento hospital)
Prof Giuseppe Foti Dr Marco Giani Dr Vincenzo Russotto	Ospedale San Gerardo
Prof Davide Chiumello Valentina Castagna	Ospedale San Paolo
Dr Andrea Dell'Amore	Padua University Hospital (Policlinico of Padova)
Dr Hoi-Ping Shum	Pamela Youde Nethersole Eastern Hospital
Dr Alain Vuysteke	Papworth Hospitals NHS Foundation Trust
Dr Asad Usman Andrew Acker Blake Mergler Nicolas Rizer Federico Sertic Benjamin Smood Alexandra Sperry Dr Madhu Subramanian	Penn Medicine (Hospital of the University of Pennsylvania)
Dr Navy Lolong Dr Ernita Akmal Dr Erlina Burhan Prof Menaldi Rasmin Bhat Naivedh	Persahabatan General Hospital
Dr Peter Barrett Julia Daugherty Dr David Dean	Piedmont Atlanta Hospital
Dr Antonio Loforte	Policlinico di S. Orsola, Università di Bologna
Dr Irfan Khan Olivia DeSantis Dr Mohammed Abraar Quraishi	Presbyterian Hospital Services, Albuquerque
Dr Gavin Salt	Prince of Wales
Dr Dominic So Darshana Kandamby	Princess Margaret Hospital
Dr Jose M. Mandei Hans Natanael	Prof Dr R. D. Kandou General Hospital - Paediatric
Eka YudhaLantang Anastasia Lantang	Prof Dr R. D. Kandou General Hospital - Adult
Anna Jung Dr Terese Hammond	Providence Saint John's Health Centre
George Ng Dr Wing Yiu Ng	Queen Elizabeth Hospital, Hong Kong
Dr Pauline Yeung	Queen Mary Hospital
Dr Shingo Adachi	Rinku general medical center (and Senshu trauma and critical care center)
Dr Pablo Blanco Ana Prieto	Rio Hortega University Hospital

Prefix/First Name/Last Name	Site Name
Jesús Sánchez	
Dr Meghan Nicholson	Rochester General Hospital
Dr Michael Farquharson	Royal Adelaide Hospital
Dr Warwick Butt Alyssa Serratore Carmel Delzoppo	Royal Children's Hospital
Dr Pierre Janin Elizabeth Yarad	Royal North Shore Hospital
Dr Richard Totaro Jennifer Coles	Royal Prince Alfred Hospital
Robert Balk Samuel Fox James Hays Esha Kapania Pavel Mishin Andy Vissing Garrett Yantosh	Rush University, Chicago
Dr Saptadi Yuliarito Dr Kohar Hari Santoso Dr Susanthy Djajalaksana	Saiful Anwar Malang Hospital (Brawijaya University) (Paediatrics)
Dr Arie Zainul Fatoni	Saiful Anwar Malang Hospital (Brawijaya University) (Adult)
Dr Masahiro Fukuda	Saiseikai Senri Hospital
Prof Keibun Liu	Saiseikai Utsunomiya Hospital
Prof Paolo Pelosi Denise Battaglini	San Martino Hospital
Dr Juan Fernando Masa Jiménez	San Pedro de Alcantara Hospital
Dr Sérgio Gaião Dr Roberto Roncon-Albuquerque	São João Hospital Centre, Porto
Jessica Buchner	Sentara Norfolk General Hospital
Dr Young-Jae Cho Dr Sang Min Lee	Seoul National University Hospital
Dr Su Hwan Lee	Severance Hospital
Dr Tatsuya Kawasaki	Shizuoka Children's Hospital
Dr Pranya Sakiyalak Prompak Nitayavardhana	Siriraj Hospital
Dr Tamara Seitz	Sozialmedizinisches Zentrum Süd - Kaiser-Franz-Josef-Spital
Rakesh Arora David Kent	St Boniface Hospital (University of Mannitoba)
Dr Swapnil Parwar Andrew Cheng Jennene Miller	St George Hospital
Daniel Marino Jillian E Deacon	St. Christopher's Hospital for Children
Dr Shigeki Fujitani Dr Naoki Shimizu	St Marianna Medical University hospital
Dr Jai Madhok Dr Clark Owyang	Stanford University Hospital
Dr Hergen Buscher Claire Reynolds	St Vincent's Hospital
Dr Olavi Maasikas Dr Aleksandr Beljantsev Vladislav Mihnovits	Tartu University Hospital
Dr Takako Akimoto	Teine Keijinkai Hospital

Prefix/First Name/Last Name	Site Name
Mariko Aizawa Dr Kanako Horibe Ryota Onodera	
Prof Carol Hodgson Meredith Young	The Alfred Hospital
Timothy Smith Cheryl Bartone	The Christ Hospital
Dr Timothy George	The Heart Hospital Baylor Plano, Plano
Dr Kiran Shekar Niki McGuinness Lacey Irvine	The Prince Charles Hospital
Brigid Flynn Abigail Houchin	The University of Kansas Medical Centre
Dr Keiki Shimizu Jun Hamaguchi	Tokyo Metropolitan Medical Center
Leslie Lussier Grace Kersker Dr John Adam Reich	Tufts Medical Centre (and Floating Hospital for Children)
Dr Gösta Lotz	Universitätsklinikum Frankfurt (University Hospital Frankfurt)(Uniklinik)
Dr Maximilian Malfertheiner Dr Esther Dreier Dr Lars Maier	Universitätsklinikum Regensburg (Klinik für Innere Medizin II)
Dr Neurinda Permata Kusumastuti	University Airlangga Hospital (Paediatric)
Dr Colin McCloskey Dr Al-Awwab Dabaliz Dr Tarek B Elshazly Josiah Smith	University Hospital Cleveland Medical Centre (UH Cleveland hospital)
Dr Konstanty S. Szuldrzynski Dr Piotr Bielański	University Hospital in Krakow
Dr Yusuff Hakeem	University Hospitals of Leicester NHS Trust (Glenfield Hospital)
Dr Keith Wille Rebecca Holt	University of Alabama at Birmingham Hospital (UAB)
Dr Ken Kuljit S. Parhar Dr Kirsten M. Fiest Cassidy Codan Anmol Shahid	University of Calgary (Peter Lougheed Centre, Foothills Medical Centre, South Health Campus and Rockyview General Hospital)
Dr Mohamed Fayed Dr Timothy Evans Rebekah Garcia Ashley Gutierrez Hiroaki Shimizu	University of California, San Francisco-Fresno Clinical Research Centre
Dr Tae Song Rebecca Rose	University of Chicago
Dr Suzanne Bennett Denise Richardson	University of Cincinnati Medical Centre
Dr Giles Peek Dalia Lopez-Colon	University of Florida
Dr Lovkesh Arora Kristina Rappapport Kristina Rudolph Zita Sibenaller Lori Stout Alicia Walter	University of Iowa

Prefix/First Name/Last Name	Site Name
Dr Daniel Herr Nazli Vedadi	University of Maryland - Baltimore
Dr Lace Sindt Cale Ewald Julie Hoffman Sean Rajnic Shaun Thompson	University of Nebraska Medical Centre
Dr Ryan Kennedy	University of Oklahoma Health Sciences Centre (OU)
Dr Matthew Griffee Dr Anna Ciullo Yuri Kida	University of Utah Hospital
Dr Ricard Ferrer Roca Cynthia Alegre Dr Sofia Contreras Dr JordI Riera	Vall d'Hebron University Hospital, Barcelona
Dr Christy Kay Irene Fischer Elizabeth Renner	Washington University in St. Louis/ Barnes Jewish Hospital
Dr Hayato Taniguci	Yokohama City University Medical Center
Gabriella Abbate Halah Hassan Dr Silver Heinsar Varun A Karnik Dr Katrina Ki Hollier F. O'Neill Dr Nchafatso Obonyo Dr Leticia Pretti Pimenta Janice D. Reid Dr Kei Sato Dr Kiran Shekar Aapeli Vuorinen Dr Karin S. Wildi Emily S. Wood Dr Stephanie Yerkovich	COVID-19 Critical Care Consortium

Table S18. List of collaborators.

Prefix/First Name/Last Name	Site Name
Dr Emma Hartley	Aberdeen Royal Infirmary (Foresterhill Health Campus)
Bastian Lubis	Adam Malik Hospital
Takanari Ikeyama	Aichi Childrens Health and Medical Center
Balu Bhaskar	American Hospital
Dr Jae-Seung Jung	Anam Korea University Hospital
Sandra Rossi Marta Fabio Guarracino	Azienda Ospedaliero Universitaria Parma
Prof Fabio Guarracino	Azienda Ospedaliero Universitaria Pisana
Stacey Gerle	Banner University Medical Centre
Emily Coxon	Baptist Health Louisville
Dr Bruno Claro	Barts Hospital
Dr. Gonzo Gonzalez-Stawinski	Baylor All Saints Medical Centre, Forth Worth
Daniel Loverde	Billings Clinic
Dr Vieri Parrini	Borgo San Lorenzo Hospital
Dr Diarmuid O'Briain Stephanie Hunter	Box Hill Hospital
Dr Angela McBride	Brighton and Sussex Medical School
Kathryn Negaard Dr Phillip Mason	Brooke Army Medical Centre
Dr Angela Ratsch	Bundaberg Hospital
Dr Mahesh Ramanan Julia Affleck	Caboolture Hospital
Ahmad Abdelaziz	Cairo University Hospital
Dr Sumeet Rai Josie Russell-Brown Mary Nourse	Canberra Hospital
Juan David Uribe	Cardio VID
Dr Adriano Peris	Careggi Hospital
Mark Sanders	Cedar Park Regional Medical Center
Dominic Emerson	Cedars-Sinai Medical Centre
Muhammad Kamal	Cengkareng Hospital
Prof Pedro Povoa	Centro Hospitalar de Lisboa
Dr Roland Francis	Charite-Univerrsitatsmedizi n Berlin
Ali Cherif	Charles Nicolle University Hospital
Dr Sunimol Joseph	Children's Health Ireland (CHI) at Crumlin
Dr Matteo Di Nardo	Children's Hospital Bambino Gesù
Micheal Heard	Children's Healthcare of Atlanta- Egleston Hospital
Kimberly Kyle	Children's Hospital
Ray A Blackwell	Christiana Care Health System's Centre for Heart and Vascular Health
Dr Michael Piagnerelli Dr Patrick Biston	CHU de Charleroi

Prefix/First Name/Last Name	Site Name
Hye Won Jeong	Chungbuk National University Hospital
Reanna Smith	Cincinnati Children's
Yogi Prawira	Cipto Mangunkusumo Hospital
Dr Giorgia Montrucchio Dr Gabriele Sales	Città della Salute e della Scienza Hospital – Turin, Italy
Nadeem Rahman Vivek Kakar	Cleveland Clinic, Abu Dhabi
Dr Michael Piagnerelli Dr Josefa Valenzuela Sarrazin	Clinica Las Condes
Dr Arturo Huerta Garcia	Clínica Sagrada Família
Dr Bart Meyns	Collaborative Centre Department Cardiac Surgery, UZ Leuven
Marsha Moreno	Dignity Health Medical Group- Dominican
Rajat Walia	Dignity Health St. Joseph's Hospital and Medical Center (SJHMC)
Dr Annette Schweda	Donaustauf hospital
Cenk Kirakli	Dr. Suat Seren Chest Diseases and Surgery Practice and Training Centre
Estefania Giraldo	Fundación Clinica Shaio (Shaio Clinic)
Dr Wojtek Karolak	Gdansk Medical University
Dr Martin Balik	General University Hospital
Elizabeth Pocock	George Washington University Hospital
Evan Gajkowski	Giesinger Medical Centre
Dr James Winearls Mandy Tallott	Gold Coast University Hospital
Kanamoto Masafumi	Gunma University Graduate School of Medicine
Dr Nicholas Barrett	Guy's and St Thomas NHS Foundation Trust Hospital
Yoshihiro Takeyama	Hakodate City Hospital
Sunghoon Park	Hallym University Sacred Heart Hospital
Faizan Amin	Hamilton General Hospital
Dr Erina Fina	Hasan Sadikin Hospital
Dr Serhii Sudakevych	Heart Institute Ministry of Health of Ukraine
Dr Angela Ratsch	Hervey Bay Hospital
Patrícia Schwarz Ana Carolina Mardini	Hospital de Clínicas de Porto Alegre
Ary Serpa Neto	Hospital Israelita Albert Einstein
Dr Andrea Villoldo	Hospital Privado de Comunidad
Alexandre Siciliano Colafranceschi	Hospital Pro Cardíaco
Dr Alejandro Ubeda Iglesias	Hospital Punta de Europa
Lívia Maria Garcia Melro Giovana Fioravante Romualdo	Hospital Samaritano Paulista
Diego Gaia	Hospital Santa Catarina
Helmgton Souza	Hospital Santa Marta
Dr Diego Bastos	Hospital Cura D'ars Fortaleza

Prefix/First Name/Last Name	Site Name
Filomena Galas	Hospital Sirio Libanes
Dr Rafael Máñez Mendiluce	Hospital Universitario de Bellvitge
Alejandra Sosa	Hospital Universitario Esperanza (Universidad Francisco Marroquin)
Dr Ignacio Martinez	Hospital Universitario Lucus Augusti
Hiroshi Kurosawa	Hyogo Prefectural Kobe Children's Hospital
Juan Salgado	Indiana University Health
Dr Beate Hugi-Mayr	Inselspital University Hospital
Eric Charbonneau	Institut Universitaire de Cardiologie et de Pneumologie de Quebec - Universite Laval
Vitor Salvatore Barzilai	Instituto de Cardiologia do Distrito Federal - ICDF
Veronica Monteiro	Instituto de Medicina Integral Prof. Fernando Figueira (IMIP)
Rodrigo Ribeiro de Souza	Instituto Goiano de Diagnostico Cardiovascular (IGDC)
Michael Harper	INTEGRIS Baptist Medical Center
Hiroyuki Suzuki	Japan Red Cross Maebashi Hospital
Celina Adams	John C Lincoln Medical Centre
Dr Jorge Brieva	John Hunter Hospital
George Nyale	Kenyatta National Hospital (KNH)
Jihan Fatani Dr Faisal Saleem Eltatar	King Abdullah Medical City Specialist Hospital
Dr. Husam Baeissa	King Abdullah Medical Complex
Ayman AL Masri	King Salman Hospital NWAF
Yee Hui Mok	KK Women's and Children's Hospital
Masahiro Yamane	KKR Medical Center
Hanna Jung	Kyung Pook National University Hospital
Dr Matthew Brain Sarah Mineall	Launceston General Hospital
Rhonda Bakken	M Health Fairview
Dr Tim Felton	Manchester University NHS Foundation Trust - Wythenshawe
Lorenzo Berra	Massachusetts General Hospital
Gordan Samoukoviv Dr Josie Campisi	McGill University Health Centre
Bobby Shah	Medanta Hospital
Arpan Chakraborty	Medica Super speciality Hospital
Monika Cardona	Medical University of South Carolina
Harsh Jain	Mercy Hospital of Buffalo
Dr Asami Ito	Mie University Hospital
Brahim Housni	Mohammed VI University hospital
Dafsah Arifa Juzar	National Cardiovascular Center Harapan Kita (Adult)
Sennen Low	National Centre for Infectious Diseases
Dr. Koji Iihara	National Cerebral and Cardiovascular Center
Joselito Chavez	National Kidney and Transplant Institute
Dr Kollengode Ramanathan	National University Hospital, Singapore

Prefix/First Name/Last Name	Site Name
Gustavo Zabert	National University of Comahue
Krubin Naidoo	Nelson Mandela Children's Hospital
Singo Ichiba	Nippon Medical School Hospital
Randy McGregor	Northwestern Medicine
Teka Siebenaler	Norton Children's Hospital
Hannah Flynn	Novant Health (NH) Presbyterian Medical Centre
Julia Garcia-Diaz Catherine Harmon	Ochsner Clinic Foundation
Kristi Lofton	Ochsner LSA Health Shreveport
Toshiyuki Aokage	Okayama University Hospital
Kazuaki Shigemitsu	Osaka City General Hospital
Dr Andrea Moscatelli	Ospedale Gaslini
Dr Giuseppe Fiorentino	Ospedali dei Colli
Dr Matthias Baumgaertel	Paracelsus Medical University Nuremberg
Serge Eddy Mba	Parirenyatwa General Hospital
Jana Assy	Pediatric and Neonatal Cardiac intensive care at the American University
Holly Roush	Penn State Heath S. Hershey Medical Centre
Kay A Sichting	Peyton Manning Children's Hospital
Dr Francesco Alessandri	Policlinico Umberto, Sapienza University of Rome
Debra Burns	Presbyterian Hospital, New York/ Weill Cornell Medical Centre
Ahmed Rabie	Prince Mohammed bin Abdulaziz Hospital
Carl P. Garabedian	Providence Sacred Heart Children's Hospital
Dr Jonathan Millar Dr Malcolm Sim	Queen Elizabeth II University Hospital
Dr Adrian Mattke	Queensland Children’s Hospital
Dr Danny McAuley	Queens University of Belfast
Jawad Tadili	Rabat university hospital
Dr Tim Frenzel	Radboud University Medical Centre
Aaron Blandino Ortiz	Ramón y Cajal University Hospital
Jackie Stone	Rapha Medical Centre
Dr Alexis Tabah Megan Ratcliffe Maree Duroux	Redcliffe Hospital
Dr Antony Attokaran	Rockhampton Hospital
Dr Brij Patel	Royal Brompton &Harefield NHS Foundation Trust
Derek Gunning	Royal Columbian Hospital
Dr Kenneth Baillie	Royal Infirmary Edinburgh
Dr Pia Watson	Sahlgrenska University Hospital
Kenji Tamai	Saiseikai Yokohamashi Tobu Hospital
Dr Gede Ketut Sajinadiyasa Dr Dyah Kanyawati	Sanglah General Hospital
Marcello Salgado	Santa Casa de Misericordia de Juiz de Fora

Prefix/First Name/Last Name	Site Name
Assad Sassine	Santa Casa de Misericórdia de Vitoria
Dr Bhirowo Yudo	Sardjito Hospital
Scott McCaul	Scripps Memorial Hospital La Jolla
Bongjin Lee	Seoul National University Children's Hospital
Yoshiaki Iwashita	Shimane University Hospital
Laveena munshi	Sinai Health Systems (Mount Sinai Hospital)
Dr Neurinda Permata Kusumastuti	Soetomo General Hospital (FK UNAIR)
Dr Nicole Van Belle	St. Antonius Hospital
Ignacio Martin-Loeches	St James's University Hospital
Dr Hergen Buscher	St Vincent's Hospital, Sydney
Surya Oto Wijaya	Sulianti Saroso Hospital
Dr Lenny Ivatt	Swansea Hospital
Chia Yew Woon	Tan Tock Seng Hospital
Hyun Mi Kang	The Catholic University of Seoul St Mary Hospital
Erskine James	The Medical Centre Navicent Health
Nawar Al-Rawas	Thomas Jefferson University Hospital
Tomoyuki Endo	Tohoku Medical and Pharmaceutical University
Dr Yudai Iwasaki	Tohoku University
Dr Eddy Fan Kathleen Exconde	Toronto General Hospital
Kenny Chan King-Chung	Tuen Mun Hospital
Dr Vadim Gudzenko	UCLA Medical Centre (Ronald Regan)
Dr Beate Hugi-Mayr	Universitätsspital Bern, Universitätsklinik für Herz- und Gefässchirurgie
Dr Fabio Taccone	Universite Libre de Bruxelles
Dr Fajar Perdhana	University Airlangga Hospital (Adult)
Yoan Lamarche	University de Montreal (Montreal Heart Institute)
Dr Joao Miguel Ribeiro	University Hospital CHLN
Dr Nikola Bradic	University Hospital Dubrava
Dr Klaartje Van den Bossche	University Hospital Leuven
Gurmeet Singh	University of Aberta (Mazankowski Heart Institute)
Dr Gerdy Debeuckelaere	University of Antwerp
Dr Henry T. Stelfox	University of Calgary and Alberta Health Services
Cassia Yi	University of California at San Diego
Jennifer Elia	University of California, Irvine
Shu Fang	University of Hong Kong
Thomas Tribble	University of Kentucky Medical Center
Shyam Shankar	University of Missouri
Dr Paolo Navalesi	University of Padova
Raj Padmanabhan	University of Pittsburgh Medical Centre
Bill Hallinan	University of Rochester Medical Centre (UR Medicine)
Luca Paoletti	University of South Carolina
Yolanda Leyva	University of Texas Medical Branch

Prefix/First Name/Last Name	Site Name
Tatuma Fykuda	University of the Ryukus
Jillian Koch	University of Wisconsin & American Family Children's Hospital
Amy Hackman	UT Southwestern
Lisa Janowaik	UTHealth (University of Texas)
Jennifer Osofsky	Vassar Brothers Medical Center (VBMC)
A/Prof Katia Donadello	Verona Integrated University Hospital
Josh Fine	WellSpan Health - York Hospital
Dr Benjamin Davidson	Westmead Hospital
Andres Oswaldo Razo Vazquez	Yale New Haven Hospital

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