THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Barbaro RP, MacLaren G, Boonstra PS, et al. Extracorporeal membrane oxygenation for COVID-19: evolving outcomes from the international Extracorporeal Life Support Organization Registry. *Lancet* 2021; published online Sept 29. http://dx.doi.org/10.1016/S0140-6736(21)01960-7.

Supplementary Appendix – Extracorporeal Membrane Oxygenation for COVID-19: Evolving outcomes from the international Extracorporeal Life Support Organization Registry

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Methods

Extracorporeal Life Support Organization Registry

The data elements, definitions, and entry instructions for the ELSO Registry Form and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Registry Addendum Form can be found at: https://www.elso.org/Registry/DataDefinitions,Forms,Instructions.aspx. Definitions for each variable can be found at the above link, but here we repeat the definition for "immunocompromised" as it is defined by ELSO. Immunocompromised is a potential SARS-CoV-2 comorbidity. SARS-CoV-2 comorbidities are those that existed prior to ECMO and were present during the same hospitalization as ECMO for COVID-19.

> "**Immunocompromised:** Patients who are immunocompromised are considered vulnerable and may include:
> a. Persons with primary or acquired immunodeficiency
> b. Persons on anti-rejection therapy following solid organ transplant or bone marrow transplant
> c. Persons on biologic therapeutic agents such as tumor necrosis factor inhibitors
> d. Persons with malignancy and ongoing or recent chemotherapy
> e. Persons receiving systemic immunosuppressive therapy, including corticosteroids equivalent to 20 mg/day of prednisone for ≥2 weeks[1]"

COVID-19 ECMO volume was defined as the hospital's number of COVID-19 ECMO cases during the study period (January 16 through May 1, 2020). We excluded from analysis suspected but unconfirmed COVID-19 cases and cases where no COVID-19 Addendum existed. We did not exclude cases without an addendum from our total count of COVID-19 ECMO volume.

ELSO has 5 organized chapters: (1) North America, (2) Latin America, (3) Europe, (4) Asia-Pacific and (5) South and West Asia and Africa. North America contains the United States and Canada. Latin America has member centres in Argentina, Brazil, the Cayman Islands, Chile, Colombia, Costa Rica, Mexico, Peru, and Uruguay. Europe has member centres from Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Netherlands, Norway, Poland, Portugal, Russia, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom. Asia-Pacific includes Australia, China, Indonesia, Japan, New Zealand, the Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam. Finally South and West Asia and Africa has member centres from Bahrain, Egypt, India, Kazakhstan, Kuwait, Nepal, Oman, Qatar, Saudi Arabia, South Africa, Sri Lanka, and the United Arab Emirates.

Cross-validated relative risks at early-adopting centres (Group A1 versus Group A2)

As stated in the main text, we divided patients into 3 groups based on the time and centre at which ECMO was initiated. First, Group A1: Patients with COVID-19 initiated on ECMO on or before May 1 at an "early-adopting centre." An early-adopting centre was one that reported using ECMO support for COVID-19 patients on or before May 1, a time frame identical to a previous study of the ELSO registry COVID-19 data.[2] Second, Group A2: Patients treated at an "early-adopting centre" that initiated ECMO support after May 1, 2020, through December 31, 2020, the second time period. Third, Group B: Patients treated in "late-adopting centres," defined as those that only provided ECMO for COVID-19 after May 1, and who were initiated on ECMO after May 1 through December 31, 2020.

An early-adopting centre was selected and all runs at the centre were temporarily held out. The Cox proportional hazards model was fit to the remaining patients in Group A1– that is, all ECMO cases except those in the held-out centre. No ECMO cases from Group A2 were ever used to *fit* the model for this cross-validation, because the objective was to "project" the relative risks from Group A1 onto Group A2. The hazard ratios (the exponentiated linear predictor from the Cox model) for all runs from the held-out centre – whether patients were in Group A1 or Group A2 – were predicted according to this fitted model. Because these patients were not used to estimate the model, their relative risk predictions will not be overfit. The process was repeated for every ECMO-supported patient at an early-adopting centre, so that ultimately every centre was held out exactly once.

Cross-validated relative risks at early-adopting versus late-adopting centres (**Group A2 versus Group B)**

The procedure was similar for predicting the cross-validated relative risks in the early-adopting (Group A2) versus late-adopting centres (Group B) cared for after May 1, 2020. A key difference, however, was that, after leaving out the runs from a single held-out centre, the model was fit to runs from *all* remaining centres – those in Group A2 and Group B. This is because a key goal for this comparison was to evaluate the association between a centre's COVID-19 ECMO volume on or before May 1, and its relative risk of mortality among COVID-19 ECMO runs starting after May 1, and patients in Group A2 and Group B contribute information toward estimating this association.

To estimate the hypothetical relative risk in the event that all centres had equal COVID-19 ECMO volume, we created an artificial copy of each centre's ECMO cases, replacing whatever the actual COVID-19 ECMO volume on or before May 1 was with a constant value. The specific choice of constant value is irrelevant since different choices of a constant value would just multiplicatively scale each relative risk up or down.

Methodology for permutation tests

A permutation test for a difference between two groups is a more flexible alternative to a t-test and is also more robust to underlying assumptions. It constructs the null distribution of a statistic, i.e. a median, mean, proportion, or chi-squared statistic, by randomly permuting group membership across the units of analysis and calculating the statistic according to this permuted dataset. The *observed* statistic is compared to many *permuted* statistics, which represent the null distribution of the statistic, and then the proportion of permuted statistics that are as extreme or more extreme than the observed statistic is taken to be the permutation-based p-value testing whether the statistic is different between groups. However, the permutation step must account for the study design.

Permutation test for difference in characteristics at early-adopting centres (Group A1 versus Group A2)

For this comparison, group membership is at the ECMO case level (i.e. ECMO initiation on or before May 1 versus after May 1), but the proportion of runs in each group is different for each centre. To maintain the within-centre distribution of patients receiving ECMO on or before May 1 versus those cared for after May 1, 500 permuted datasets were constructed by permuting the group status of ECMO cases within a centre. So, for example, if a centre had 10 patients in Group A1 and 2 in Group A2 in actuality, the permutation would switch the specific runs considered to be in each time period while maintaining the 10:2 ratio of patients in each time period in that centre.

Permutation test for difference in characteristics at early- and late-adopting centres (Group A2 and Group B)

For this comparison, group membership occurs at the centre-level (i.e. whether the centre had at least one COVID-19 ECMO run on or before May 1), and so a permuted dataset consisted of permuting group status across centres, not ECMO cases. So, for example, if Centre 1 had 10 ECMO cases, then all 10 patients in that centre would always be permuted to the same group, Group A2 or Group B. 500 permuted datasets were constructed in this way.

After permuting, the remaining steps to calculate the permutation-based p-value are the same: calculate the distribution of the 500 null test statistics and count the proportion that are as extreme or more extreme than the observed test statistic.

Proportional hazards assumptions for Cox models

We initially used a time-independent model and then used goodness-of-fit tests and graphical methods to assess the assumption of proportional hazards in the Cox models. We used these results to suggest appropriate changes to the model formulation so as to better satisfy the assumptions. Specifically, for each predictor in each imputed dataset in each Cox model, we calculated the resultant p-value from a score test for the inclusion of a time-dependent term as well as a global test across all predictors.[3, 4] We also plotted the scaled Schoenfeld residuals to inspect specific departures from proportionality. We report the findings below, separately for each of the Cox models constructed.

Model for Group A1 There was little-to-no evidence for non-proportionality in this model. Across the 10 imputed datasets, the p-values for the global tests ranged from 0.360 to 0.603.

Model For Group A2 There was significant evidence for non-proportionality in this model. Across the 10 imputed datasets, the p-values for the global tests were small: all 10 p-values were less than 0.0001. We therefore inspected the individual predictors. Figure S1 plots the Schoenfeld residuals and smoothed spline-based plots corresponding to the four smallest individual p-values: Pre-ECMO Cardiac Arrest (top left), Initial mode, VA/VVA vs. VV (top right), Co-infection (bottom left), and Pre-ECMO Chronic Respiratory Disease (bottom right). Proportionality is violated when these smooth curves deviate from a horizontal line. The most typical pattern for plots that seem to deviate from possible non-proportionality is that the coefficient estimate is larger in magnitude closer to the start of ECMO and then slowly attenuating. For example, the smoothed curve corresponding to pre-ECMO Cardiac Arrest (top left panel of Figure S1) is large initially, then gradually decreasing, suggesting that the greatest risk of mortality due to pre-existing cardiac arrest lies at the beginning of the ECMO run. Thus, a hazard ratio that is assumed to be constant would approximately average this curve and likely underestimate the initial mortality risk and overestimate

subsequent risk. Similarly, an initial mode of VA/VVA (top right panel of Figure S1) or a pre-existing comorbidity of chronic respiratory disease (bottom right) were associated with a higher mortality risk initially, whereas a pre-existing co-infection was associated with a lower mortality risk initially.

To address the non-proportionality that these analyses pointed to, we created three time strata: 0-2 days, 2-14 days, and >14+ days, and interacted these time strata with the four above-mentioned variables that most significantly violated non-proportionality. So, for example, instead of a single hazard corresponding to pre-ECMO cardiac arrest, we estimated three separate hazard ratios: one that is assumed to apply to patients within their first 2 days on ECMO, another that applies to patients between 2-14 days on ECMO, and a third that applies to patients after 14 days on ECMO. These three strata were motivated by the graphical results presented in Figure S1 as well as clinical considerations, since all of these variables are acute.

Figure S2 gives the revised plots of the smoothed Schoenfeld residuals after interacting with the three time strata. As expected, the overall fit for these variables was substantially improved. All model-based inferences reported in the main manuscript are based upon this time-stratified model.

Cox proportional hazards model fit to all patients (Group A1, A2 and B)

An alternative approach to directly quantify the relative risk of COVID-19 patients receiving ECMO support early in the pandemic versus later in the pandemic, is described here. A single omnibus model was fit to all patients across all groups (Group A1, A2, and B). It included all of the same predictors as in the Group A1/A2 models, four of which were interacted with time exactly as described above, *plus* two binary indicators for membership in Group A1 and membership in Group B. The hazard ratio corresponding to the Group A1 variable is interpreted as the relative risk of death among those receiving ECMO support early in the pandemic (A1) relative to later in the pandemic at an early-adopting center (A2). The hazard ratio is adjusted for all other patient- and center-level characteristics. The hazard ratio corresponding to the Group B variable is interpreted as the relative risk of death among those receiving ECMO at a late-adopting center versus at an early-adopting center, adjusting for all other patient- and center-level characteristics.

Interestingly, there was evidence of non-proportionality for the Group A1 variable. Figure S3 suggests that the time-varying log-hazard ratio is near 0 at the start of the ECMO run, then decreasing later on. There was no similar evidence of non-proportionality for the Group B variable.

Methodology for missing data

As was the case in our previous analysis,[1] there were missing data in the variables used as covariates in the Cox proportional hazards model. We followed an identical approach for efficiently using all available data while accounting for the missingness. Specifically, we employed multiple imputation with chained equations in the R package mice. The reader is referred to the Supplementary Appendix from our previous manuscript for the specific details, which we followed exactly.[1]

Results

Distribution of cross-validated risk of mortality for early-adopting centres (Group A1 vs Group A2)

The median cross-validated relative risk of mortality in patients cared for earlier in the pandemic was only 0.93 times that of the median cross-validated relative mortality risk among patients treated later in the pandemic, and there was substantial overlap in these distributions (see Figure S3).

Extreme assumption that all patients discharged to another hospital died

Considering only patients managed at early-adopting centres, we compared Group A1 and A2. If we assume all patients that were discharged to another hospital died, then under this extreme assumption the cumulative incidence of in-hospital mortality 90 days after ECMO initiation would have 7.8% lower for patients in Group A1 compared to Group A2 (p value <0.001).

Cross-validated relative risks at early-adopting centres (Group A1 vs Group A2) predicted risk of mortality

Patients in Group A2 had a lower relative risk of mortality after adjusting for pre-ECMO patient characteristics; the distribution of cross-validated relative risks across all patients was different (p <0.001; Figure S6).

Cox proportional hazards model fit to all patients results

The fitted omnibus model estimated the hazard ratio corresponding to Group A1 to be 0.824 (95% CI 0.704, 0.963), which suggests that relative risk of mortality at early-adopting centres is about 18% less in runs occurring on or prior to May 1. The estimated hazard ratio corresponding to Group B is 1.42 (95% CI 1.17, 1.73), suggesting that the relative risk of mortality at late-adopting centres is about 42% greater than runs in the same time period but at early-adopting centres. These findings are consistent with the results from the unadjusted cumulative incidences in Figure 1.

We did not attempt to further adjust this omnibus model to address this possible violation to the assumption of proportionality, for two reasons. First, this variable -- whether a run occurred on or prior to May 1 -- has no obvious underlying biological or clinical meaning but is rather a convenient dichotomy of early versus late. Second, this

violation does not nullify the main conclusion from this model, which is that the empiric increase in risk of death among patients treated later in the pandemic remains even after adjusting for other risk factors. Rather, Figure S8 suggests that the majority of this risk differential occurs in those runs in which the patient is still alive and supported with ECMO 3-4 weeks after ECMO initiation (i.e. the smoothed curve tends to drop close to the 510 hour mark).

Table S2: Counts and percentages of missing values

Variable name	Type	Number (Percent) missing	Used only in imputation modeling	Imputation model
Time to death/discharge	positive continuous, censored	0 (0%)		-
Patient age, years	positive continuous	0 (0%)		-
ECMO volume in 2019	positive continuous	0 (0%)		-
COVID-19 ECMO volume on or before May 1, 2020	positive continuous	0 (0%)		-
Initial mode	binary	0 (0%)		-
Acute kidney injury	binary	0 (0%)		-
Cancer	binary	0 (0%)		-
Immunocompromised	binary	0 (0%)		-
Chronic heart disease	binary	0 (0%)		-
Diabetes	binary	0 (0%)		-
Chronic respiratory disease	binary	0 (0%)		-
Asthma	binary	0 (0%)		-
ELSO Chapter	categorical	0 (0%)		
Patient sex	binary	2 (0·04%)		Two-level PMM
Co-infection	binary	3 (0·06%)		Two-level PMM
Pre-ECMO cardiac arrest	binary	55 (1%)		Two-level PMM
Patient transport status	categorical	261 (1%)	X	Polytomous regression
BMI	positive continuous	331 (7%)		Two-level PMM
Pre-ECMO intubation time	positive continuous	642 (13%)		Two-level PMM
PaO_2	positive continuous	777 (16%)	(ingredient for passive imputation of PaO_2:FiO_2)	Two-level PMM
$PaCO_2$	positive continuous	797 (17%)		Two-level PMM
PEEP	positive continuous	879 (18%)	X	Two-level PMM
FiO_2	positive continuous	884 (19%)	(ingredient for passive imputation of PaO_2:FiO_2)	Two-level PMM
PaO_2:FiO_2	positive continuous	965 (20%)		Passive imputation
PIP	positive continuous	1627 (34%)	X	Two-level PMM

BMI= body mass index. COVID-19=coronavirus disease 2019. ECMO=extracorporeal membrane oxygenation. FiO_2=the fraction of inspired oxygen. $PaCO_2$=partial pressure of arterial carbon dioxide. PaO_2=partial pressure of arterial oxygen. PaO_2:FiO_2=ratio of the PaO_2 to the FiO_2. PEEP=positive end-expiratory pressure. PIP=peak inspiratory pressure. PMM= predictive mean matching.

* The mode of mechanical ventilation, $PaCO_2$, PaO_2:FiO_2, PEEP, and PIP are the measures nearest to ECMO initiation within the prior 6 hours.

Table S2: Comparison of patient-level characteristics among those without a completed COVID-19 Addendum

	Without an Addendum			With an addendum
	Early-adopting centres on or before May 1	**Early-adopting centres after May 1**	**Late-adopting centres**	**All cases reported in manuscript**
Total Number of Cases	62	150	74	4812
Age	57 [49-64]	55 [45-62]	46 [41-57]	50 [42-58]
Male	42 (71%)	106 (71%)	56 (76%)	3523 (73%)
Support Type				
Respiratory	94 (58%)	146 (97%)	67 (91%)	4603 (96%)
Cardiac	2% (1)	2 (1%)	5 (7%)	166 (3%)
ECPR	5% (3)	2 (1%)	2 (3%)	43 (1%)

COVID-19=coronavirus disease 2019. ECPR=extracorporeal cardiopulmonary resuscitation. IQR=interquartile range.

***Table S3*:** Centre-level characteristics among centres utilizing ECMO support for COVID-19

	Early-adopting centres	**Late-adopting centres**	**p-value***
Centres by ELSO Chapter	236	113	<0.001
North American	145 (61%)	70 (62%)	
European	60 (25%)	10 (9%)	
South and West Asia and Africa and Asia-Pacific	21 (9%)	12 (11%)	
Latin American	10 (4%)	21 (19%)	
2019 adult hospital ECMO case volume	22 [2-60]	9 [0-24]	<0.001
2020 COVID-19 hospital ECMO case volume	13 [5-25]	4 [2-7]	<0.001

Data are median [IQR] or n (%). COVID-19=coronavirus disease 2019. ECMO=extracorporeal membrane oxygenation. ELSO=Extracorporeal Life Support Organization.
* *p*-values derived from ECMO-centre-based permutation tests of the null hypothesis that there is no difference in the medians (for quantitative) or proportions (for binary) between the left two columns.

***Table S4*:** Patient-level distribution of ECMO Support for COVID-19 across ELSO Regions

	Group A1	**Group A2**	**Group B**
Total Number of Cases	1182	2824	806
Cases by ELSO Chapter			
North American	660 (56%)	1976 (70%)	441 (55%)
European	444 (38%)	572 (20%)	44 (5%)
South and West Asia and Africa and Asia-Pacific	61 (5%)	178 (6%)	143 (18%)
Latin American	17 (1%)	98 (3%)	178 (22%)

Data are n (%). COVID-19=coronavirus disease 2019. ECMO=extracorporeal membrane oxygenation. ELSO=Extracorporeal Life Support Organization. Group A1 patients are those initiated on ECMO on or before May 1, 2020, at "early-adopting centres". Group A2 patients are those initiated on ECMO after May 1 at "early-adopting centres," those also reporting ECMO on or before May 1, 2020. Group B ECMO-supported patients are those at "late-adopting centres," which only provided ECMO for COVID-19 after May 1, 2020.

Table S5: Patient status at 90 days after ECMO across three cohorts with COVID-19

	Group A1	**Group A2**	**Group B**
Patient status at 90 days after ECMO initiation	1125	2515	686
Discharged alive to home or acute rehabilitation	352 (30%)	535 (19%)	185 (23%)
Discharged alive to long-term acute care or unspecified location	118 (10%)	312 (11%)	68 (8%)
Discharged to another hospital	204 (17%)	281 (10%)	46 (6%)
Remain in the hospital (discharged from ICU)	15 (1%)	52 (2%)	4 (0·6%)
Remain in the ICU	45 (5%)	130 (5%)	17 (2%)
In-hospital death	433 (37%)	1440 (51%)	464 (58%)
Unknown status	15 (1%)	74 (3%)	22 (3%)

Data are n (%). COVID-19=coronavirus disease 2019. ECMO=extracorporeal membrane oxygenation. ELSO=Extracorporeal Life Support Organization. ICU=intensive care unit. Group A1 patients are those initiated on ECMO on or before May 1, 2020, at "early-adopting centres". Group A2 patients are those initiated on ECMO after May 1 at "early-adopting centres," those also reporting ECMO on or before May 1, 2020. Group B ECMO-supported patients are those at "late-adopting centres," which only provided ECMO for COVID-19 after May 1, 2020.

Table S6: Prevalence of complications in ECMO-supported patients with COVID-19

	Group A1	Group A2	Group B	p-value* for A1 vs A2	p-value* for A2 vs B
Total cases reporting complications	1157	2767	782	-	-
Any complication except renal replacement therapy	641 (55·4%)	1849 (66·8%)	446 (57·0%)	<0·001	0·01
Any mechanical complication	317 (27·4%)	973 (35·2%)	172 (22·0%)	<0·001	<0·001
Seizure	6 (0·5%)	18 (0·7%)	7 (0·9%)	0·61	0·44
Central nervous system infarct	7 (0·6%)	52 (1·9%)	8 (1·0%)	0·01	0·08
Central nervous system hemorrhage	65 (5·6%)	196 (7·1%)	41 (5·2%)	0·07	0·11
Brain Death	15 (1·3%)	40 (1·4%)	12 (1·5%)	0·75	0·84
Creatinine 1·5-3, mg/dL	96 (8·3%)	302 (10·9%)	55 (7·0%)	0·14	0·06
Creatinine >3, mg/dL	52 (4·5%)	141 (5·1%)	24 (3·1%)	0·47	0·03
Arrhythmia	77 (6·7%)	289 (10·4%)	77(9·8%)	0·18	0·82
Cardiopulmonary resuscitation complicating ECMO†	32 (2·8%)	175(6·3%)	38(4·9%)	<0·001	0·21
Tamponade (blood)	7 (0·6%)	17 (0·6%)	5(0·6%)	1	0·91
Tamponade (not blood)	5 (0·4%)	6 (0·2%)	2(0·3%)	0·31	0·76
Pneumothorax	100 (8·6%)	358 (12·9%)	75(9·6%)	<0·001	0·06
Pulmonary hemorrhage	50 (4·3%)	99 (3·6%)	22 (2·8%)	0·18	0·42
Hemolysis	53 (4·6%)	218 (7·9%)	30 (3·8%)	0·47	0·19
Hyperbilirubinemia	32 (2·8%)	133 (4·8%)	45 (5·8%)	0·12	0·47
Gastrointestinal hemorrhage	56 (4·8%)	225 (8·1%)	66 (8·4%)	0·002	0·84
Cannula site bleeding	73 (6·3%)	194 (7·0%)	53 (6·8%)	0·53	0·87
Surgical site bleeding	46 (4·0%)	142 (5·1%)	45 (5·8%)	0·21	0·54
Fasciotomy	2 (0·2%)	13 (0·5%)	0 (0·0%)	0·24	0·02
Amputation	0 (0·0%)	4 (0·1%)	0 (0·0%)	0·49	0·48
Membrane lung failure	107 (9·2%)	370 (13·4%)	66 (8·4%)	0·002	0·06
Pump failure	10 (0·9%)	28 (1·0%)	12 (1·5%)	0·77	0·18
Circuit change	161 (13·9%)	467 (16·9%)	71 (9·1%)	0·01	0·02
Cannula problem	69 (6·0%)	245 (8·9%)	42 (5·4%)	0·03	0·12
Circuit clot	46 (4·0%)	114 (4·1%)	14 (1·8%)	0·78	0·03

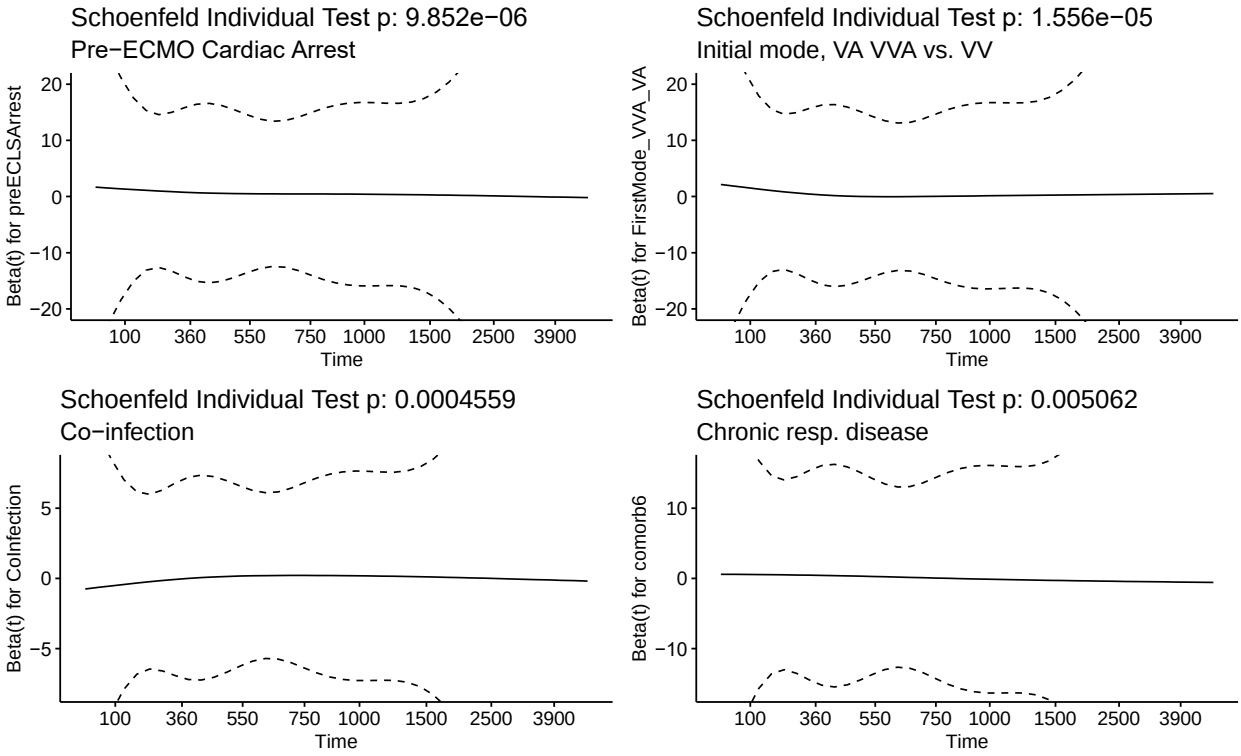
COVID-19=coronavirus disease 2019. ECMO=extracorporeal membrane oxygenation.
Group A1 patients are those initiated on ECMO on or before May 1, 2020, at "early-adopting centres". Group A2 patients are those initiated on ECMO after May 1 at "early-adopting centres," those also reporting ECMO on or before May 1, 2020. Group B ECMO-supported patients are those at "late-adopting centres," which only provided ECMO for COVID-19 after May 1, 2020.
* *p*-values derived from ECMO-centre-based permutation tests of the null hypothesis that there is no difference in the medians (for quantitative) or proportions (for binary) between the left two columns.
†This refers to a cardiac arrest that complicates an ECMO run and the subsequent initiation of cardiopulmonary resuscitation (CPR). It does not refer to a pre-ECMO cardiac arrest or ECMO initiated during cardiopulmonary resuscitation (ECPR). If a patient requires CPR after initiation of ECMO, this qualifies as CPR that complicates ECMO.

Table S7: Complication rates per 1000 hours of ECMO support in patients with COVID-19

	Group A1	Group A2	Group B	p-value* for A1 vs A2	p-value* for A2 vs B
Total cases reporting complications	1157	2767	782	-	-
Any complication except renal replacement therapy	2·57	2·84	2·55	0·95	0·33
Any mechanical complication	0·99	1·03	0·67	0·78	0·01
Seizure	0·01	0·01	0·02	0·83	0·30
Central nervous system infarct	0·01	0·03	0·02	0·13	0·19
Central nervous system hemorrhage	0·12	0·12	0·12	0·98	0·85
Brain Dead	0·03	0·02	0·03	0·59	0·36
Creatinine 1·5-3, mg/dL	0·18	0·19	0·14	0·92	0·30
Creatinine >3, mg/dL	0·1	0·08	0·06	0·32	0·18
Arrhythmia	0·16	0·2	0·3	0·87	0·2
Cardiopulmonary resuscitation complicating ECMO†	0·06	0·12	0·11	0·02	0·73
Tamponade (blood)	0·01	0·01	0·01	0·50	0·51
Tamponade (not blood)	0·01	0	0·01	0·18	0·61
Pneumothorax	0·21	0·26	0·23	0·15	0·38
Pulmonary hemorrhage	0·1	0·06	0·06	0·01	0·96
Hemolysis	0·1	0·2	0·13	0·40	0·48
Hyperbilirubinemia	0·06	0·08	0·12	0·76	0·18
Gastrointestinal hemorrhage	0·11	0·15	0·19	0·19	0·22
Cannula site bleeding	0·14	0·13	0·18	0·66	0·14
Surgical site bleeding	0·09	0·1	0·12	0·74	0·39
Fasciotomy	0	0·01	0	0·23	0·01
Amputation	0	0	0	0·48	0·31
Membrane lung failure	0·27	0·3	0·23	0·66	0·23
Pump failure	0·02	0·02	0·03	0·81	0·12
Circuit change	0·44	0·44	0·25	0·86	0·03
Cannula problem	0·14	0·17	0·12	0·65	0·25
Circuit clot	0·11	0·09	0·04	0·26	0·07

COVID-19=coronavirus disease 2019. ECMO=extracorporeal membrane oxygenation.
Group A1 patients are those initiated on ECMO on or before May 1, 2020, at "early-adopting centres". Group A2 patients are those initiated on ECMO after May 1 at "early-adopting centres," those also reporting ECMO on or before May 1, 2020. Group B ECMO-supported patients are those at "late-adopting centres," which only provided ECMO for COVID-19 after May 1, 2020.
* *p*-values derived from ECMO-centre-based permutation tests of the null hypothesis that there is no difference in the medians (for quantitative) or proportions (for binary) between the left two columns.
† This refers to a cardiac arrest that complicates an ECMO run and the subsequent initiation of cardiopulmonary resuscitation (CPR). It does not refer to a pre-ECMO cardiac arrest or ECMO initiated during cardiopulmonary resuscitation (ECPR). If a patient requires CPR after initiation of ECMO, this qualifies as CPR that complicates ECMO.

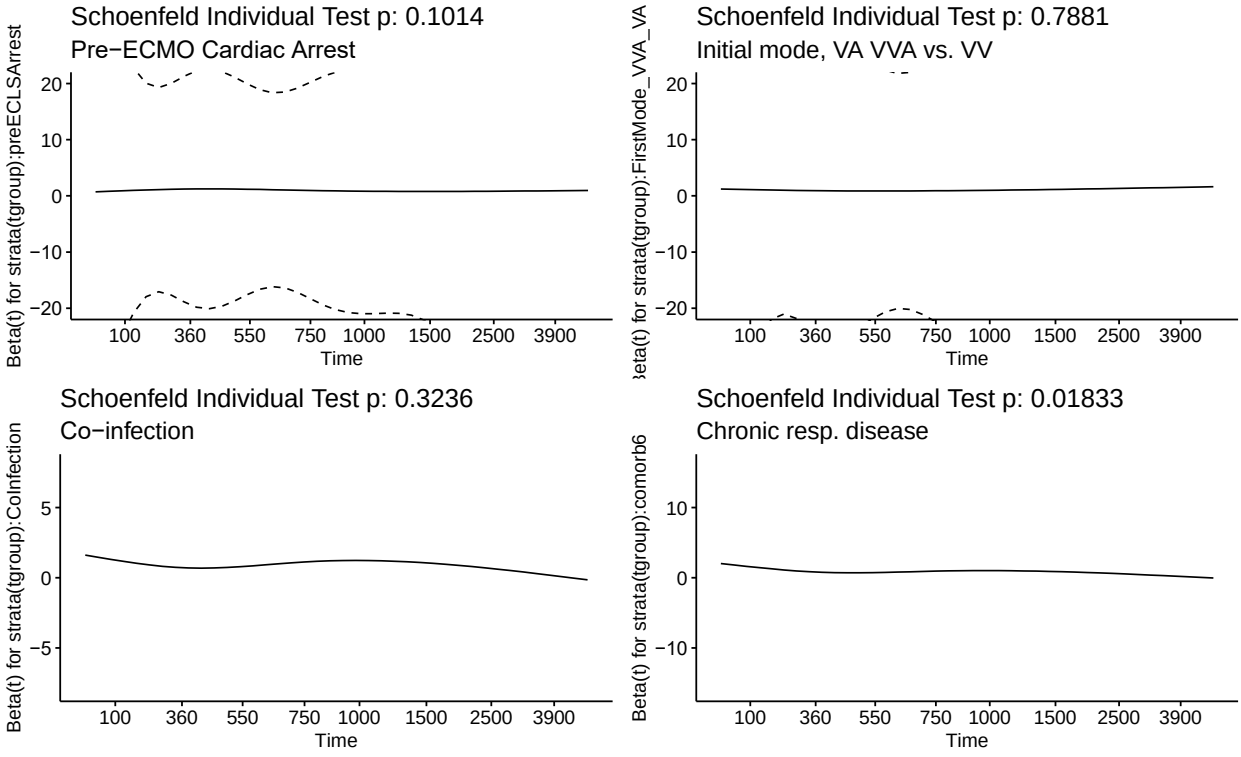
Figure S1: Plots of Schoenfeld residuals for the four most significant p-values from a test of non-proportionality from the Group A2 model fit to a single imputed dataset prior to adjustment



ECMO=extracorporeal membrane oxygenation. Resp=respiratory. VA=venoarterial. VV=venovenous. VVA=veno-venoarterial.

The solid black lines are spline-based estimates based upon the points, and the dashed lines correspond to two standard errors. The x-axis measures hours from start of extracorporeal membrane oxygenation.The highly significant p-values suggest that proportionality is violated in these variables.

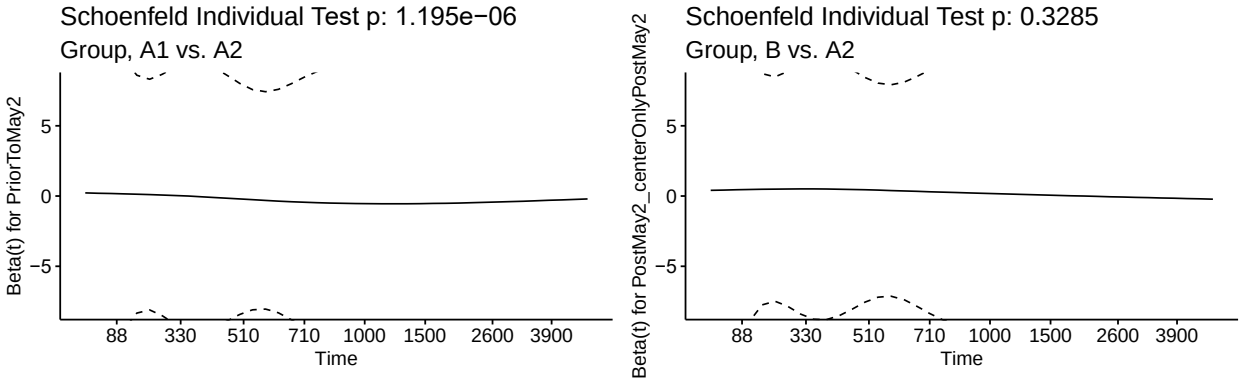
Figure S2: Plots of Schoenfeld residuals for the four most significant p-values from a test of non-proportionality from the Group A2 model fit to a single imputed dataset after adjusting the model to address non-proportionality



ECMO=extracorporeal membrane oxygenation. Resp=respiratory. VA=venoarterial. VV=venovenous. VVA=veno-venoarterial.

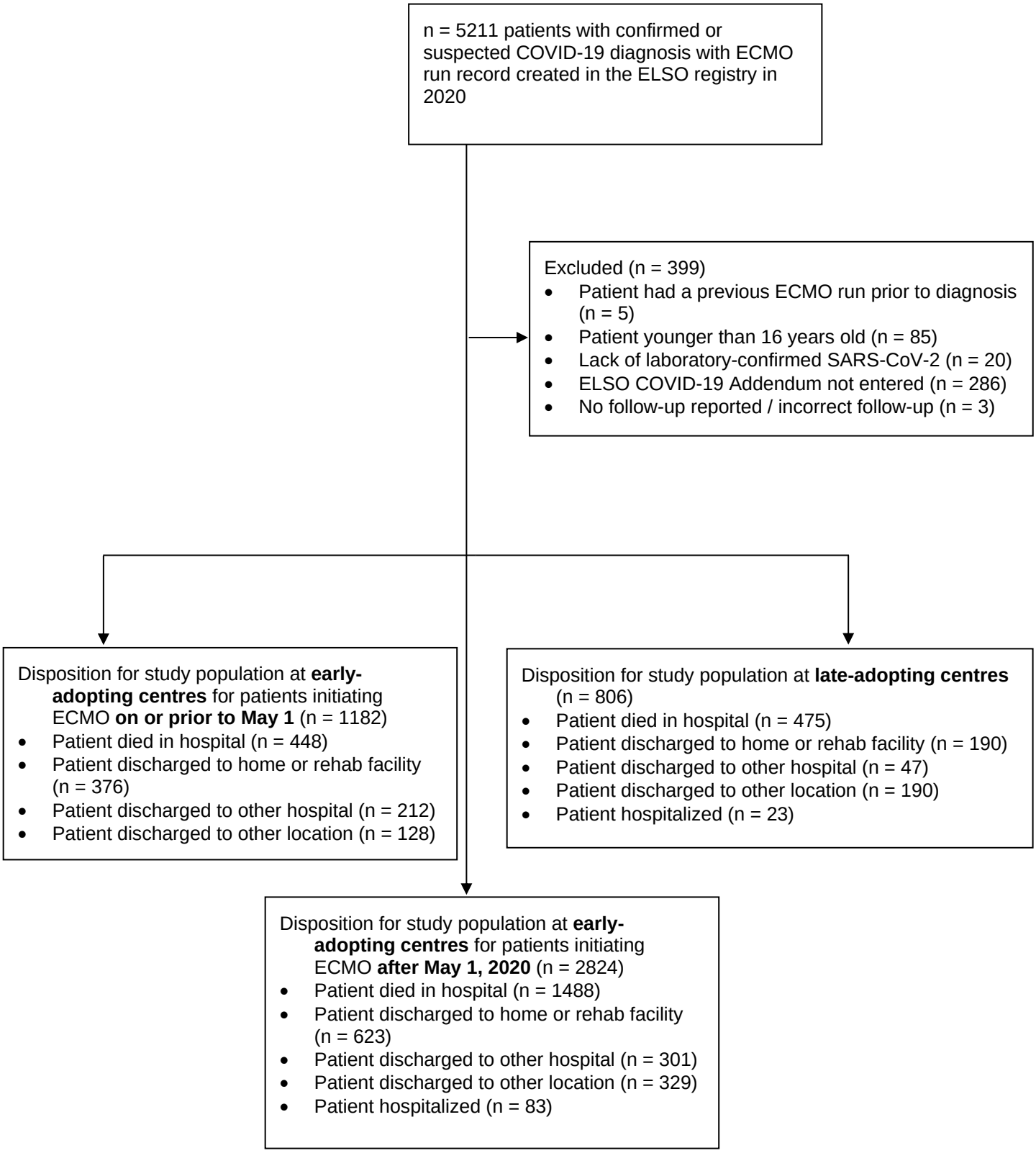
The solid black lines are spline-based estimates based upon the points, and the dashed lines correspond to two standard errors. The x-axis measures hours from start of extracorporeal membrane oxygenation.

Figure S3: Plots of Schoenfeld residuals from the omnibus model for the log-hazard ratios for Group A1 vs. A2 and Group B vs. A2



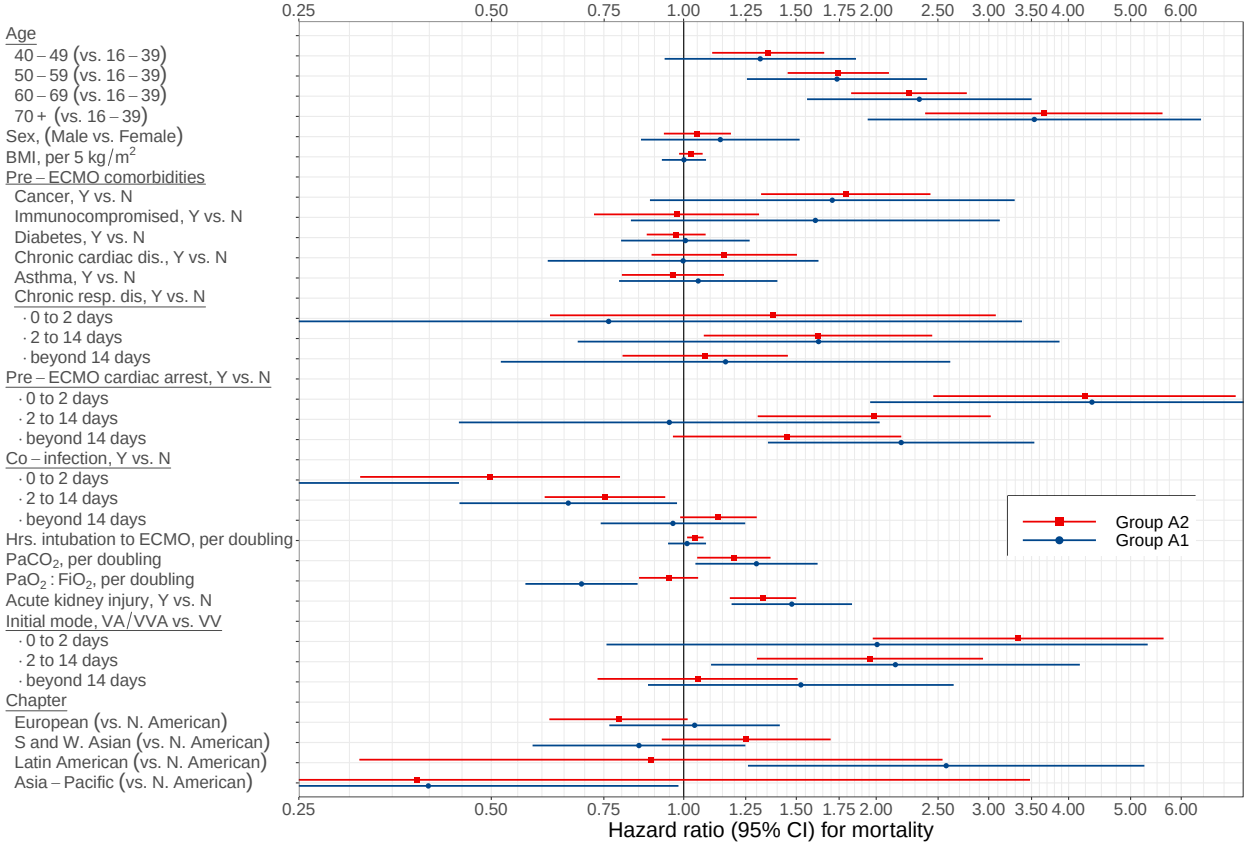
The solid black line is a spline-based estimate based upon the points, and the dashed lines correspond to two standard errors. The x-axis measures hours from start of extracorporeal membrane oxygenation.

***Figure S4*:** Cohort flow diagram for extracorporeal membrane oxygenation-supported patients with COVID-19



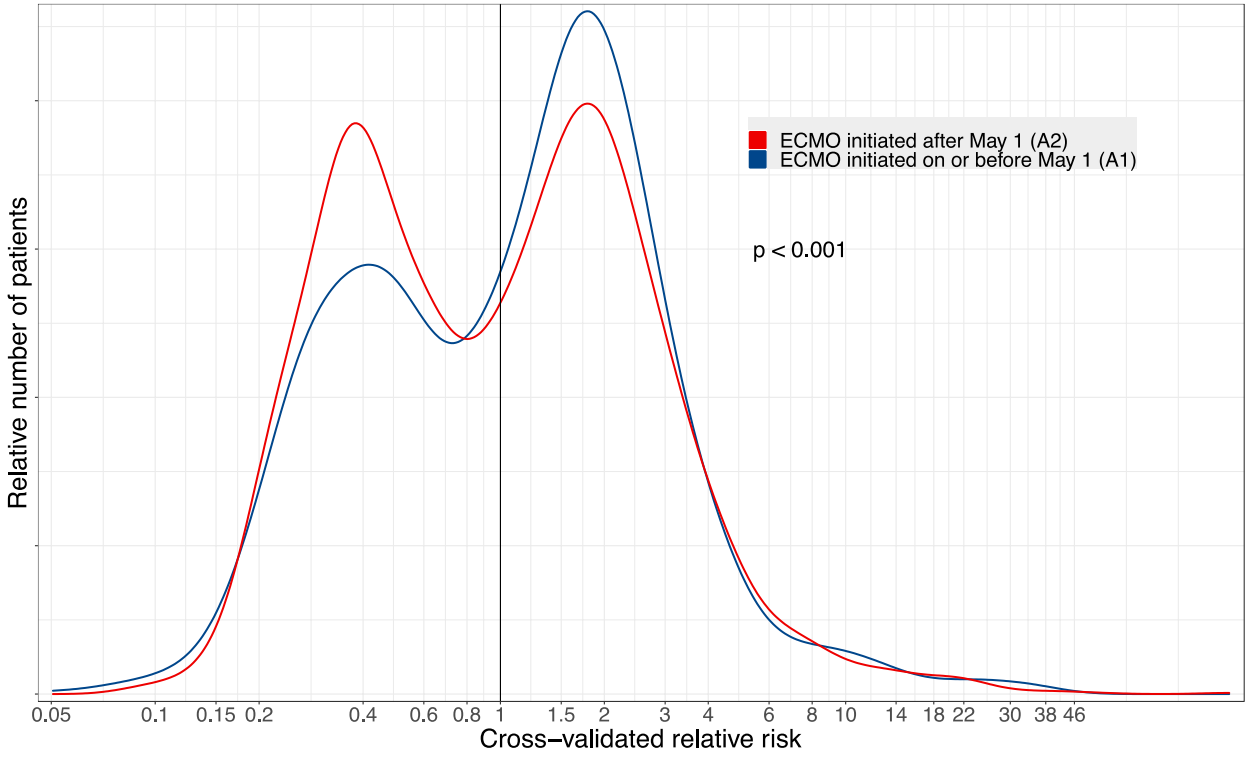
COVID-19=coronavirus disease 2019. ECMO=extracorporeal membrane oxygenation. ELSO=Extracorporeal Life Support Organization. ICU=intensive care unit. **Rehab=rehabilitation.** SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Figure S5: Cox model for factors associated with in-hospital mortality in ECMO among early-adopting centres



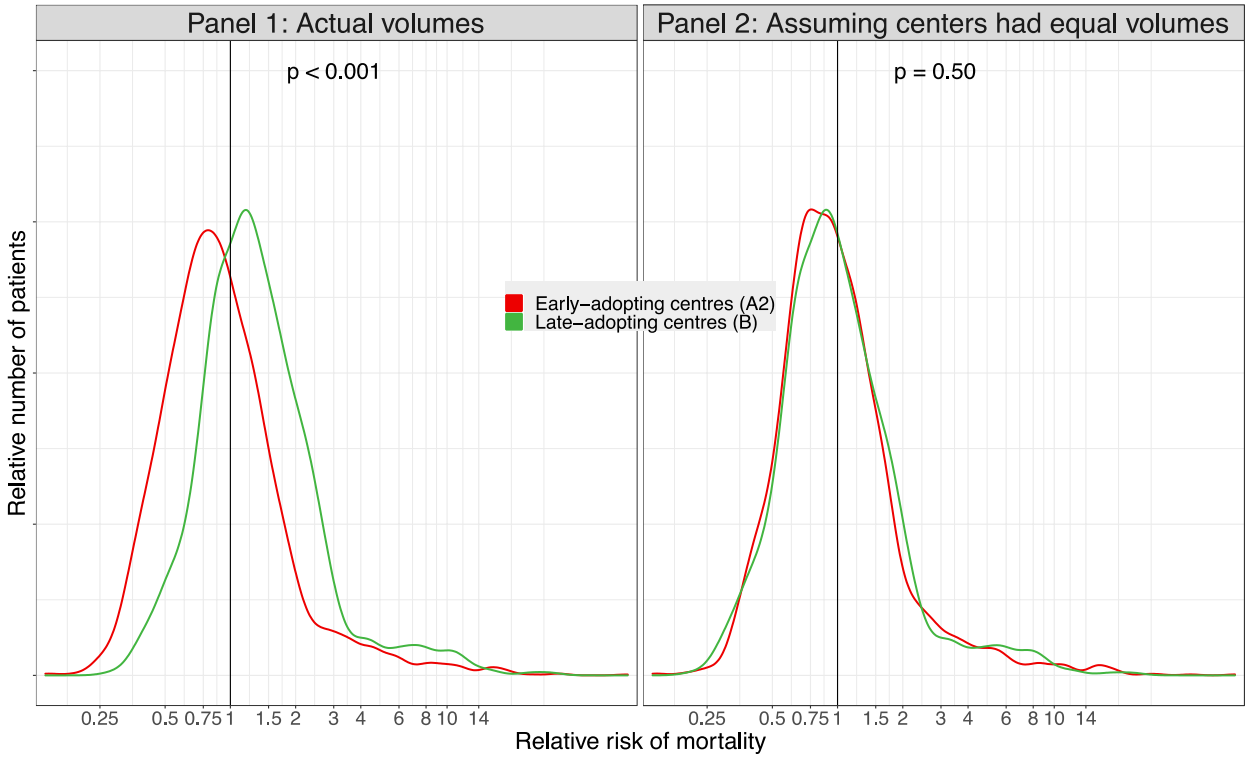
BMI=body mass index. ECMO=extracorporeal membrane oxygenation. Hrs=hours. N. American=North American. $PaCO_2$=partial pressure of arterial carbon dioxide. PaO_2:FiO_2=ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen.VA= venoarterial. VV=venovenous. VVA=veno-venoarterial.
Group A1 patients are those initiated on ECMO on or before May 1, 2020, at "early-adopting centres." Group A2 patients are those initiated on ECMO after May 1 at "early-adopting centres," those also reporting ECMO on or before May 1, 2020.

Figure S6: Cross-validated relative risk of mortality at early-adopting centres among those cared for on or before May 1, 2020, versus after May 1, 2020



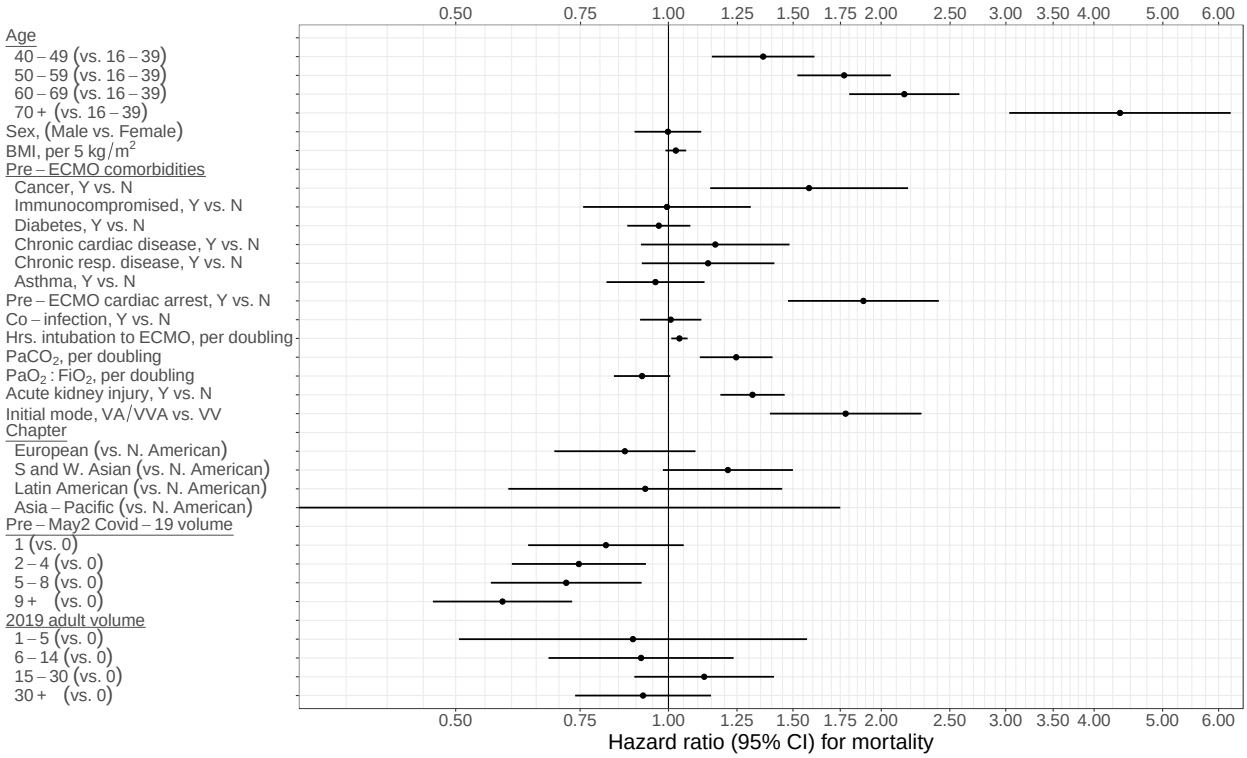
ECMO=extracorporeal membrane oxygenation.
The x-axis is the relative risk of mortality. The y-axis represents the number of patients. Patients with a relative-risk of mortality of 1 have an average risk of mortality, while those with a relative-risk of mortality greater than one have less than average risk of mortality.

Figure S7: Cross-validated relative risk of mortality at early versus late-adopting centres among those cared for after May 1, 2020



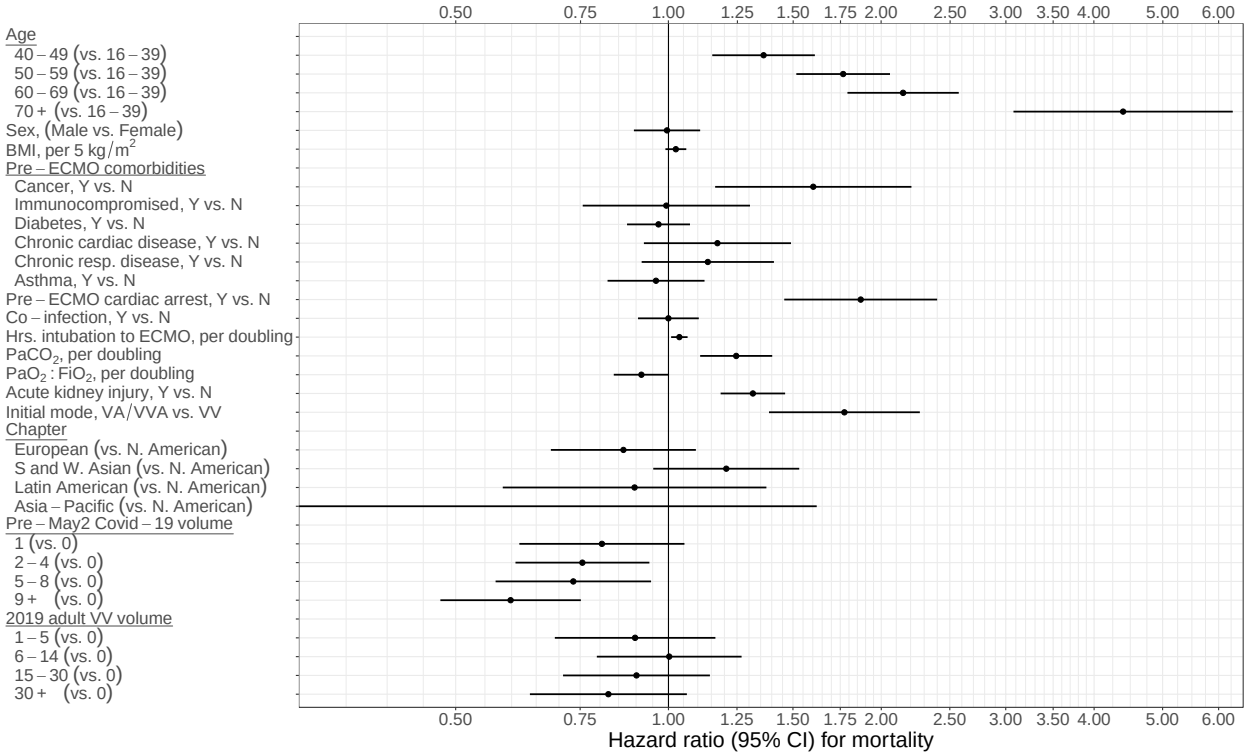
ECMO=extracorporeal membrane oxygenation.
The x-axis is the relative risk of mortality. The y-axis represents the number of patients. Patients with a relative-risk of mortality of 1 have an average risk of mortality, while those with a relative-risk of mortality greater than one have less than average risk of mortality. Panel 1 shows early-adopting centres' relative-risk of mortality in red and late-adopting centres' relative risk of mortality in blue after adjusting for centre volume of ECMO cases with coronavirus disease 2019 on or before May 1st. Late-adopting centres had no such experience. Panel 2 assumes early-adopting and late-adopting centres had the same volume. With this assumption the relative risk of mortality is mostly overlapping between centres and there is no difference in the relative risk of mortality (p=0.50).

Figure S8: Cox model for factors associated with in-hospital mortality in ECMO after May 1



BMI=body mass index. ECMO=extracorporeal membrane oxygenation. Hrs=hours. N. American=North American. $PaCO_2$=partial pressure of arterial carbon dioxide. PaO_2:FiO_2=ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen.Resp=respiratory. VA= venoarterial. VV=venovenous. VVA=veno-venoarterial.

Figure S9: Cox model for factors associated with in-hospital mortality in ECMO including venovenous ECMO volume



BMI=body mass index. ECMO=extracorporeal membrane oxygenation. Hrs=hours. N. American=North American. $PaCO_2$=partial pressure of arterial carbon dioxide. PaO_2:FiO_2=ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen.Resp=respiratory. VA= venoarterial. VV=venovenous. VVA=veno-venoarterial.

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