ONLINE DATA SUPPLEMENT

Association between Early Invasive Mechanical ventilation and Day-60 Mortality in acute hypoxemic respiratory failure related to COVID-19 pneumonia.

ESM1 Details on the methodology and statistical analysis

STRATEGIES FOR VENTILATION

Individualized decisions on respiratory support were made by the physicians in charge. The FiO_2 or PEEP level if appropriate (or both) were adjusted to maintain a SpO_2 of 92% or more. Ultimately, in patients under NI-OS, intubation was left at physicians' discretion.
Lung-protective mechanical ventilation strategy was recommended in mechanically ventilated patients: low tidal volume 6 mL/kg of predicted body weight, limited plateau pressure ≤30 cmH_2O, and prone ventilation for 16 hours sessions when and as long as PaO_2/FiO_2 ratio was ≤150 mm Hg.
Inspired oxygen fraction (FiO_2) was calculated as 0.21 + (oxygen flow) [$L.min^{-1}$] *0.03 in patients receiving oxygen delivered through a nonrebreather face mask.

DESCRIPTION OF THE NON-INVASIVE OXYGEN SUPPORT

IPPV was delivered to the patient through a face mask connected to an ICU ventilator, with pressure support applied in a noninvasive-ventilation mode. The pressure-support level was adjusted with the aim of obtaining an expired tidal volume of 6 to 8 ml per kilogram of predicted body weight, with an initial positive end-expiratory pressure (PEEP) between 2 and 10 cm of water. The minimally required duration of noninvasive ventilation was 8 hours per day for at least 2 calendar days. Noninvasive ventilation was applied during sessions of at least 1 hour. NIPPV sessions alternated with oxygen delivered through a nonrebreather face mask.

HFNC was delivered through a heated humidifier (Airvo-2, Fisher and Paykel Healthcare) and applied continuously through large-bore binasal prongs, with a gas flow rate of 30 liters per minute and adjusted based on the clinical response.

A Boussignac device (Vygon) connected to an oro-nasal mask composed of a transparent mask and a soft inflatable cushion, with a heat and moisture exchanger ("Filter Boussignac CPAP") was used for CPAP session. CPAP was started at 15L/min oxygen (which correspond to an average pressure of 8 cmH_2O. The level was decreased to 10L/min or increased to 20L/min as needed based on the clinical response and tolerance. For at least the first 6 to 12 hours, CPAP will be given continuously and then discontinuously (for at least 6 hours/day) based on patient tolerance. CPAP sessions alternated with oxygen delivered through a nonrebreather face mask.

INTRODUCTION TO THE CAUSAL INFERENCE IN OBSERVATIONAL DATA

An association between an exposure to a treatment and outcome may be suggestive of, but is not equivalent to causality. Only few studies can estimate causalty. Randomized controlled trials do, because all the potential confounding factors are controlled as opposed to observational studies. Unfortunately, they can't be achieved most of the time, contrary to observational studies which are much easier to implement. Consequently, several statistical strategies were proposed in order to balance the compared groups and afford a causal estimation of the effect into the observational studies. Propensity score was one of the first of them. The concept of propensity score focuses on baseline estimates to control for selection bias, which is interesting for our study which only assess the consequence of a treatment given at ICU admission and didn't depend on time dependent covariates.

THE WEIGHTS

Inverse probability of treatment weight (IPTW) estimator is now well known to ensure the balance between exposure groups in observational data. It goes through the creation of a "pseudo-population" in which each patient is his own control, allowing the estimation of an unbiased effect of the exposure on the outcome, close to the randomization (1, 2)

A potential drawback of the IPTW method is the possibility of extreme propensity scores that can result in very large weights that can bias the treatment effect estimates. This bias from extreme weights was adjusted using a stabilization technique which multiplied the treatment and comparison weights by a constant (i.e., "mean weight"). Therefore, all analyses were performed with stabilized weights.

Furthermore, to ensure the respect of the positivity assumption, weights were truncated at the 1-99th percentile. A weight mean of 1 and absence of outliers were retained as indicators for the positivity assumption respect [1].

Once the weights were derived, we fitted weighted Cox proportional-hazard model to estimate the hazard of early IMV on death within the first 60 days of ICU stay.

PROPENSITY SCORE MODEL DEVELOPMENT

We included in the weight model the following baseline covariates, recorded on admission and not affected by study groups: time between symptom onset and ICU admission, time between hospital and ICU admission, age, gender, body mass index, comorbidities including presence of chronic liver failure, cardio-vascular, respiratory and kidney chronic diseases, immunosuppression, clinical and laboratory features on admission, T°>39°C, renal SOFA item(> 2), GCS<15, PaO2/FiO2 ratio, respiratory rate, lactatemia, lymphocyte and neutrophil counts, ferritin, D-Dimers plasma level, C-reactive protein serum level, and treatments received on admission including Lopinavir Ritonavir, Hydroxychloroquine, Tocilizumab, Anakinra and corticosteroids received on admission. In the model, continuous variables were kept linearly unless in the absence of log linearity. All variables included in the weight model reflected knowledge available at baseline.

SAPS II score was not introduced because of collinearity with age, organ failures and several laboratory features. Most of the continuous variables were kept linearly into the model, except the non-log linear once.

Then to avoid selection bias, in our propensity score we only considered baseline covariates and did not used covariates that might be directly related to the ventilatory support such as PaCO2.

Finally, propensity scores ranged from 0.01 to 0.92 and from 0.02 to 0.97 in the no Early IMV and in the Early IMV groups respectively, with 93.8% in the region of common support [0.02 – 0.92]. All the covariates in the planned propensity score were kept in the final model. After applying IPTW, all covariates in the planned propensity score had weighted standardized differences below 10%, which is in favor of an equilibration of the covariates between subgroups and ensure the exchangeability at baseline for these confounders.

ESM2: Supplementary tables and figures

Table E 1: Characteristics of the population by ICUs of the Outcomerea© network.

	ICU n°1	ICU n°2	ICU n°3	ICU n°4	ICU n°5	ICU n°6	ICU n°7	ICU n°8	ICU n°9	ICU n°10
Number of patients	13	13	10	3	86	13	12	1	40	54
Age	62 [52 ; 68]	57 [52 ; 67]	64.6 [53 ; 71]	61 [42 ; 74]	59 [51 ; 69]	61 [55 ; 66]	57.6 [51.6 ; 62.6]	34 [34 ; 34]	67.6 [56.6 ; 73]	61 [54 ; 69]
Body-mass index, kg/cm²	29.4 [25.8 ; 32.4]	25.6 [24.6 ; 28.4]	28.4 [25.2 ; 31.2]	30.8 [23.6 ; 36.4]	28.8 [26 ; 33.2]	29.2 [23.8 ; 31.6]	28.4 [26.2 ; 31.8]	26.4 [26.4 ; 26.4]	27.8 [25.6 ; 31]	27.4 [25 ; 30.8]
At least one comorbidity	9 (69.2)	9 (69.2)	9 (90)	2 (66.6)	56 (65.2)	6 (46.2)	5 (41.6)	0	30 (75)	34 (63)
Time from first symptoms to ICU admission, days	8 [7 ; 12]	7 [4 ; 9]	9 [7 ; 11]	6 [6 ; 16]	10 [8 ; 12]	10 [9 ; 12]	10 [8.6 ; 11]	4 [4 ; 4]	11 [8 ; 13]	10 [8 ; 13]
SAPS II score	37 [29 ; 44]	33 [24 ; 37]	39.6 [27 ; 48]	29 [23 ; 46]	31 [24 ; 44]	31 [25 ; 35]	27 [15.6 ; 39.6]	0 [0 ; 0]	34 [29 ; 43]	36.6 [31 ; 47]
Severity of COVID-AHRF**										
Mild: PaO_2/FiO_2 200-300	2 (15.4)	7 (53.8)	1 (10)	1 (33.4)	14 (16.2)	2 (15.4)	4 (33.4)		5 (12.6)	3 (5.6)
Moderate: PaO_2/FiO_2 100-200	8 (61.6)	4 (30.8)	7 (70)	1 (33.4)	43 (50)	9 (69.2)	5 (41.6)	1 (100)	23 (57.6)	26 (48.2)
Severe: PaO_2/FiO_2 < 100	3 (23)	2 (15.4)	2 (20)	1 (33.4)	29 (33.8)	2 (15.4)	3 (25)		12 (30)	25 (46.2)
Early Invasive Mechanical Ventilation	11 (84.6)	7 (53.8)	2 (20)	2 (66.6)	32 (37.2)	9 (69.2)	5 (41.6)	0	15 (37.6)	34 (63)
Outcome										
ICU Ventilatory-free days	5 [1 ; 7]	2 [0 ; 4]	5 [2 ; 13]	8 [1 ; 28]	3 [1 ; 6]	2 [1 ; 6]	5 [2.6 ; 8]	5 [5 ; 5]	5.6 [2.6 ; 9]	2 [0 ; 4]
ICU Oxygen respiratory support free days	1 [1 ; 3]	0 [0 ; 0]	1 [0 ; 3]	1 [0 ; 26]	0 [0 ; 1]	0 [0 ; 1]	4.6 [2.6 ; 8]	0 [0 ; 0]	0 [0 ; 1]	0.6 [0 ; 2]
ICU LOS	17 [10 ; 21]	6 [4 ; 8]	14.6 [10 ; 20]	11 [11 ; 32]	9 [6 ; 19]	16 [9 ; 38]	11.6 [7.6 ; 17.6]	5 [5 ; 5]	10 [8 ; 15.6]	14.6 [10 ; 19]
Mortality at day 60	1 (7.6)	6 (46.2)	3 (30)	1 (33.4)	33 (38.4)	5 (38.4)	2 (16.6)	0	9 (22.6)	18 (33.4)

Table E 2: Comparison between included and excluded patients

Characteristics (N(%) Median [IQR])(missing)	Excluded (n=255)	Included (n=255)	p-value*
Age	60 [53 ; 70]	61 [52 ; 69]	0.92
Gender (Male)	130 (80.2)	181 (76.1)	0.32
Body-mass index, kg/cm²*	28.4 [25.5 ; 31.6]	28.4 [25.4 ; 31.9]	0.85
Comorbidities			
At least one comorbidity	88 (54.3)	153 (64.3)	0.05
Liver	4 (2.5)	4 (1.7)	0.58
Cardio-vascular	48 (29.6)	59 (24.8)	0.28
Respiratory	15 (9.3)	31 (13)	0.25
Kidney	14 (8.6)	21 (8.8)	0.95
Immunosuppression§	15 (9.3)	25 (10.5)	0.68
Charlson score (miss=5)	1 [0 ; 3]	1 [0 ; 3]	0.65
Time from first symptoms to ICU admission, days	10 [7 ; 12]	10 [7 ; 12]	0.99
Time from hospital to ICU admission, days	2 [1 ; 4]	2 [1 ; 4]	0.90
Invasive mechanical ventilation	90 (55.6)	109 (45.8)	.
NIPPV	3 (1.9)	9 (3.8)	.
CPAP	15 (9.3)	18 (7.6)	.
HFNC	36 (22.2)	86 (36.1)	.
Oxygen by mask	18 (11.1)	16 (6.7)	0.02
Severity of COVID-AHRF**			
PaO_2/FiO_2 > 300 (mmHg)	56 (36.1)	0 (0)	<0.01
Mild PaO_2/FiO_2 200-300 (mmHg)	18 (11.6)	39 (15.9)	.
Moderate PaO_2/FiO_2 100-200 (mmHg)	47 (30.3)	127 (51.8)	.
Severe PaO_2/FiO_2 < 100 (mmHg)	34 (21.9)	79 (32.2)	.
Outcomes			
ICU LOS (miss=22)	8 [4 ; 17]	11 [7 ; 19]	<0.01
ICU mortality (miss=22)	52 (37.1)	70 (29.4)	0.12

*Wilcoxon test for quantitative variables and Fisher exact test for categorical variables

**Worst PaO2/FiO2 during the 1st 2 days

§immunosuppression comprised patients with long term or high dosage corticosteroid therapy, anticancer chemotherapy, AIDS, non-AIDS immunosuppression. Patients with aplasia, bone or organ transplant recipients were excluded. A patient can have several causes of immunosuppression.

AHRF: Acute hypoxemic respiratory failure; ICU: intensive care unit; IMV: invasive mechanical ventilation; IQR: interquartile range; LOS: Length of stay

Table E 3: Baseline characteristics and comparison of COVID-19 AHRF patients with and without early invasive mechanical ventilation

Characteristics (N(%) Median [IQR]) (missing data)	**All (n=245)**	**No Early IMV (n=128)**	**Early IMV (n=117)**	**P-value***
Age	61 [52 ; 69]	61 [52 ; 70]	61 [52 ; 69]	0.58
Gender (Male)	187 (76.4)	93 (72.7)	94 (80.3)	0.16
Body-mass index, kg/cm² * (miss=10)	28.4 [25.4 ; 32]	27.8 [25.2 ; 31.1]	29.1 [25.7 ; 33.1]	0.13
Body-mass index ≥ 30	89 (36.4)	42 (32.8)	47 (40.2)	0.23
Comorbidities				
At least one comorbidity	157 (64)	88 (68.8)	69 (59)	0.11
Liver	4 (1.6)	3 (2.3)	1 (0.9)	0.36
Cardiovascular	61 (24.8)	28 (21.9)	33 (28.2)	0.25
Respiratory	33 (13.4)	21 (16.4)	12 (10.3)	0.16
Kidney	21 (8.6)	11 (8.6)	10 (8.5)	0.99
Immunosuppression§	24 (9.8)	16 (12.5)	8 (6.8)	0.14
Charlson score (miss=3)	1 [0 ; 3]	1 [0 ; 3]	1 [0 ; 3]	0.47
Time from first symptoms to ICU admission, days	10 [7 ; 12]	10 [8 ; 13]	9 [7 ; 12]	0.09
Time from hospital to ICU admission, days	2 [1 ; 4]	3 [1 ; 5]	2 [1 ; 3]	0.10
Clinical Characteristics and severity on admission				
Body temperature > 39°C	79 (32.2)	34 (26.6)	45 (38.5)	0.05
Organ failures				
SAPS II score	34 [26 ; 44]	30 [23 ; 37]	39 [31 ; 51]	<0.01
GCS < 15	36 (14.6)	10 (7.8)	15 (12.8)	0.20
SOFA Kidney item (>2)	25 (10.2)	10 (7.8)	15 (12.8)	0.20
Respiratory characteristics				
Respiratory (rate per minute) (miss=13)	29 [25 ; 34]	30 [27 ; 35]	28 [24 ; 33]	<0.01
Blood gas value on admission				
PaO_2 (mmHg)	72 [62 ; 95]	72.5 [62 ; 89.5]	72 [63 ; 105]	0.26
PaO_2/FiO_2 (mmHg)	121 [90 ; 174]	128.4 [98.3 ; 195.7]	110 [80 ; 155]	<0.01
pH (miss=3)	7.4 [7.4 ; 7.6]	7.5 [7.4 ; 7.5]	7.4 [7.4 ; 7.5]	<0.01
$PaCO_2$ (mmHg) (miss=3)	36 [32 ; 41]	34.5 [31 ; 38]	38 [34 ; 44]	<0.01
Lactate (mmol/l) (miss=7)	1.2 [1 ; 1.6]	1.2 [0.9 ; 1.6]	1.2 [1 ; 1.6]	0.80
Severity of COVID-AHRF**				
Mild: PaO_2/FiO_2 200-300	39 (16)	30 (23.4)	9 (7.7)	<0.01
Moderate: PaO_2/FiO_2 100-200	127 (51.8)	66 (51.6)	61 (52.1)	.
Severe: PaO_2/FiO_2 < 100	79 (32.2)	32 (25)	47 (40.2)	.
Highest ventilatory support on admission				
IMV	117 (47.8)			
Ventilation parameters				

Tidal volume (mL)	423.4 [380 ; 450]		423.4 [380 ; 450]	
Tidal volume (ml/kg)	6 [5.87 ; 6.34]		6 [5.87 ; 6.34]	
PEEP (cm H20)	12 [10 ; 14]		12 [10 ; 14]	
Plateau pressure (cm H_20)	26 [23 ; 29]		26 [23 ; 29]	
Compliance (ml/cm H_20)	36.67 [27.62 ; 53.33]		36.67 [27.62 ; 53.33]	
Prone position	42 (35.9)		42 (35.9)	<0.01
Nitric oxide	7 (6)		7 (6)	<0.01
Paralytic agents	98 (83.8)		98 (83.8)	<0.01
Non-invasive oxygen support				
NIPPV	9 (3.6)	9 (7)		
CPAP	18 (7.4)	18 (14.1)		
HFNC	85 (34.6)	85 (66.4)		
Oxygen by mask	16 (6.6)	16 (12.5)		
Main laboratory values				
Lymphocytes (cells/µl)	800 [500 ; 1100]	800 [555 ; 1120]	800 [500 ; 1000]	0.57
Neutrophils (cells/µl)	6720 [4600 ; 9400]	6710 [4515 ; 9300]	6800 [4700 ; 9600]	0.64
C-Reactive Protein (mg/dL)	161 [83.8 ; 224]	149.8 [67.7 ; 203]	176 [114 ; 251]	<0.01
Ferritin (µg/l)	1109 [548 ; 1884.8]	1252.5 [672.2 ; 1952.6]	856 [425 ; 1750]	0.04
D-dimers (µg/l)	1660 [788 ; 5110]	1377.5 [765.5 ; 4385.1]	1953 [805 ; 6065.6]	0.11
Treatments on admission				
Lopinavir-Ritonavir	95 (38.8)	57 (44.5)	38 (32.5)	0.05
Hydroxychloroquine	21 (8.6)	13 (10.2)	8 (6.8)	0.35
Tocilizumab	22 (9)	13 (10.2)	9 (7.7)	0.50
Anakinra	22 (9)	13 (10.2)	9 (7.7)	0.50
Corticosteroids	68 (28)	37 (28.9)	31 (27.2)	0.77
Outcomes				
Bloodstream infections	39 (16)	10 (7.8)	29 (24.8)	<0.01
HAP-VAP	71 (29)	22 (17.2)	49 (41.9)	<0.01
Late intubation	45 (35.4)	45 (35.4)		
Time between admission and intubation	2 [1 ; 5]	5 [3 ; 8]	1 [1 ; 1]	<0.01
ICU Ventilatory-free days	3 [1 ; 7]	5 [4 ; 8]	1 [0 ; 3]	<0.01
ICU Oxygen respiratory support free days	0 [0 ; 1]	0 [0 ; 1]	0 [0 ; 1]	0.45
ICU LOS	11 [7 ; 19]	8 [5 ; 16]	15 [10 ; 21]	<0.01
ICU death	73 (29.8)	25 (19.5)	48 (41)	<0.01
Mortality at day 60	78 (31.8)	28 (21.9)	50 (42.7)	<0.01

*Wilcoxon test for quantitative variables and Fisher exact test for categorical variables

**Worst PaO2/FiO2 during the 1st 2 days

§Immunosuppression concerned patients **with s** with long term or high dosage corticosteroid therapy, anticancer chemotherapy, AIDS, non-AIDS immunosuppression. Patients with aplasia, bone or organ transplant recipients were excluded. A patient can have several causes of immunosuppression.

AHRF: acute hypoxemic respiratory failure; IMV: invasive mechanical ventilation; HFNC: high flow oxygen nasal cannula, CPAP: continuous positive airway pressure, ICU: intensive care unit; LOS: length of stay; SAPS: simplified acute physiology score; SOFA: sequential organ failure assessment

Table E 4:Multivariable logistic model: factors included in the weighting model: factors associated with an early mechanical ventilation

Variables	OR	CI 95% OR			P-val
4th period admission	0.45	[0.15	;	1.33]	0.15
3rd period admission	2.42	[0.83	;	7.06]	0.11
2nd period admission	1.26	[0.51	;	3.14]	0.62
1st period admission	1				
Time from symptoms to ICU admission >10 days	0.55	[0.26	;	1.17]	0.12
Time from hospital to ICU admission > 4 days	0.8	[0.35	;	1.81]	0.59
Age	1.01	[0.97	;	1.04]	0.76
Gender (male)	1.94	[0.82	;	4.59]	0.13
Body mass Index	1.1	[1.02	;	1.19]	0.02
Chronic liver failure	0.02	[<0.01	;	0.33]	0.01
Chronic cardiac failure	3.16	[1.29	;	7.71]	0.01
Chronic respiratory failure	0.26	[0.09	;	0.78]	0.02
Chronic renal failure	1.32	[0.32	;	5.49]	0.7
Immunosuppression§	0.2	[0.05	;	0.87]	0.03
Angiotensin converting enzym (ACE) inhibitor before ICU admission	0.38	[0.14	;	1.05]	0.06
Immunomodulator treatements before ICU admission	1.84	[0.51	;	6.69]	0.35
Temperature >39°C	1.58	[0.72	;	3.47]	0.25
Lactatemia on admission mmol/L	1.34	[0.64	;	2.83]	0.44
SOFA score : Kidney item (> 2)	3.33	[0.95	;	11.71]	0.06
Neurological failure (GCS < 15)	1.8	[0.64	;	5.1]	0.27
PaO2/FiO2 < 150 on admission	1.69	[0.83	;	3.44]	0.15
Respiratory rate > 30/min	6.63	2.98		14.73	<0.01
Lymphocytes < 800 10^9 /l	0.95	[0.46	;	1.95]	0.89
Neutrophils < 8000 109 /l	0.91	[0.44	;	1.88]	0.79
Ferritin µg/l	1	[1	;	1]	0.62
C Reactive protein mg/l	1	[1	;	1.01]	0.02
D-dimers µg/l	1	[1	;	1]	0.82
Corticosteroids on admission	3.72	[1.29	;	10.75]	0.02
Lopinavir Ritonavir on admission	0.44	[0.21	;	0.91]	0.03
Hydroxychloroquine on admission	0.5	[0.14	;	1.74]	0.27
Tocilizumab on admission	0.26	[0.07	;	0.94]	0.04
Anakinra on admission	0.3	[0.06	;	1.39]	0.12

c-index=0.84; Hosmer Lemeshow=0.051

§immunosuppression concerned patients with s with long term or high dosage corticosteroid therapy, anticancer chemotherapy, AIDS, non-AIDS immunosuppression. Patients with aplasia, bone or organ transplant recipients were excluded. A patient can have several causes of immunosuppression.

GCS: Glasgow Coma score; CI: confidence interval; ICU: Intensive care unit; OR: Odds ratio; SOFA: sequential organ failure assessment

The multivariable logistic regression model assessing the occurrence of day-60 death with the same covariates as the weighted model had a c-index at 0.814 and a Hosmer-Lemeshow test at 0.87.

Table E 5: Effect of Early Invasive Mechanical ventilation on day-60 mortality under progressive truncation of inverse probability weights.

Truncation	Estimated weight		Early Invasive mechanical ventilation effect		
Percentiles	Mean(SD)	Minimum/maxium	HR	CI 95%	P-value
0,1	0.881/0.584	0.494/4.325	1.54	[0.94 ; 2.52]	0.080
1,99	0.878/0.564	0.496/3.864	1.74	[1.07 ; 2.83]	0.030
5 ,95	0.827/0.375	0.508/1.738	1.77	[1.08 ; 2.92]	0.020
10,9	0.812/0.338	0.516/1.544	1.85	[1.11 ; 3.09]	0.020
25,75	0.737/0.193	0.545/1.011	1.84	[1.07 ; 3.16]	0.030
50,5	0.661/0	0.661/0.661	1.83	[1.03 ; 3.26]	0.040

CI : confidence interval ; HR : hazard ratio ; SD: standard error

Table E 6: Confirmatory analysis using a case control analysis with matching on SOFA without the respiratory item, PaO2/FiO2 and age on admission and assessing the association between Early Mechanical Ventilation mortality at day 60.

	Controls	Cases
Number of patients	73	73
Age	63 [57 ; 72]	66 [57 ; 71]
Body Mass Index	27.8 [25.2 ; 31.6]	28.4 [24.8 ; 31.2]
At least one comorbidity	43 (59)	62 (85)
Time from symtoms to ICU admission	10 [8 ; 12]	9 [7 ; 11]
SAPS II, median (IQR)	34 [29 ; 41]	42 [31 ; 51]
SOFA without respiratory item	1 [0 ; 3]	2 [1 ; 4]
Severity of COVID-AHRF		
Mild: PaO2/FiO2 200-300	11 (15)	9 (12.4)
Moderate: PaO2/FiO2 100-200	39 (53.4)	33 (45.2)
Severe: PaO2/FiO2 < 100	23 (31.6)	31 (42.4)
Early invasive mechanical ventilation	32 (43.8)	45 (61.6)
ICU Ventilatory-free days	5 [2 ; 9]	1 [0 ; 3]
ICU Oxygen respiratory support free days	1 [0 ; 2]	0 [0 ; 0]
ICU LOS	12 [7 ; 20]	14 [8 ; 21]
Mortality at day 60	0	73 (100)

Case control analysis: Early Mechanical Ventilation and association with day 60 mortality:

Odd ratio =2.63, 95% CI 1.16 – 5.93, pval =0.02

Table E 7 : Confirmatory analysis using a multivariable Cox model for the risk of mortality at day 60

Variables	HR	HR CI 95%	P-value
Early Invasive mechanical ventilation	1.79	[1.08 ; 2.98]	0.02
Time from first symptoms to ICU admission >10 days	0.77	[0.45 ; 1.31]	0.33
Age > 70 y.o.	4.11	[1.73 ; 9.77]	<0.01
60 - 70 y.o.	2.69	[1.13 ; 6.38]	0.03
50 - 60 y.o.	1.18	[0.47 ; 2.94]	0.73
50 y.o.	1		<0.01
Chronic cardiac failure	1.83	[1.06 ; 3.16]	0.03
Chronic respiratory failure	2.07	[1.15 ; 3.7]	0.01
Chronic renal failure	1.61	[0.83 ; 3.12]	0.16
Immunosuppression§	2.43	[1.18 ; 4.99]	0.02
Temperature> 39°C	1.53	[0.91 ; 2.55]	0.11

§immunosuppression concerned patients with long term or high dosage corticosteroid therapy, anticancer chemotherapy, AIDS, non-AIDS immunosuppression. Patients with aplasia, bone or organ transplant recipients were excluded. A patient can have several causes of immunosuppression.

ICU: intensive care unit; y.o.: years old

Table E 8: Comparison of patients with Early-IMV, with late-IMV and without IMV during ICU stay

	Early IMV (n=117)	**Late IMV (n=45)**	**No IMV (n=83)**	**P-value***
Age	61 [52 ; 69]	63 [53 ; 70]	59 [51 ; 69]	0.55
Gender (Male)	94 (80.34)	30 (66.67)	63 (75.9)	0.19
Body-mass index, kg/cm² * (miss=10)	29.1 [25.7 ; 33.1]	28.2 [25.7 ; 31.1]	27.7 [24.8 ; 31.1]	0.27
Comorbidities				
At least one comorbidity	69 (58.97)	31 (68.89)	57 (68.67)	0.28
Liver	1 (0.85)	1 (2.22)	2 (2.41)	0.65
Cardio-vascular	33 (28.21)	8 (17.78)	20 (24.1)	0.38
Respiratory	12 (10.26)	8 (17.78)	13 (15.66)	0.35
Kidney	10 (8.55)	6 (13.33)	5 (6.02)	0.37
Immunosuppression§	8 (6.84)	7 (15.56)	9 (10.84)	0.23
Charlson score (miss=3)	1 [0 ; 3]	1 [0 ; 3]	1 [0 ; 3]	0.77
Time from first symptoms to ICU admission, days	9 [7 ; 12]	9 [7 ; 12]	11 [8 ; 14]	0.09
Time from hospital to ICU admission, days	2 [1 ; 3]	2 [1 ; 4]	3 [1 ; 5]	0.24
Clinical Characteristics and severity on admission				
Temperature > 39°C	45 (38.46)	18 (40)	16 (19.28)	0.01
Neurologic failure (GCS < 15)	15 (12.82)	4 (8.89)	6 (7.23)	0.42
SAPS II score	39 [31 ; 51]	34 [27 ; 39]	27 [22 ; 34]	<0.01
Respiratory characteristics				
Respiratory rate (miss=1)	28 [24 ; 33]	32 [29 ; 40]	30 [26 ; 34]	<0.01
PaO_2/FiO_2 (mmHg)	110 [80 ; 155]	123.33 [90 ; 194.46]	131.67 [105 ; 197.78]	0.01
Blood gases value on admission				
pH (miss=3)	7.44 [7.37 ; 7.5]	7.44 [7.4 ; 7.5]	7.49 [7.43 ; 7.5]	<0.01
PaO_2(mmHg)	72 [63 ; 105]	72 [63 ; 110]	73 [62 ; 89]	0.40
$PaCO_2$ (mmHg) (miss=3)	38 [34 ; 44]	33 [30 ; 38]	35 [32 ; 37]	<0.01
Lactate (mmol/l) (miss=7)	1.2 [1 ; 1.6]	1.2 [1 ; 1.6]	1.2 [0.9 ; 1.6]	0.88
Severity of COVID-AHRF**				
mild : PaO_2/FiO_2 200-300 (mmHg)	9 (7.69)	10 (22.22)	20 (24.39)	0.01
moderate PaO_2/FiO_2 100-200 (mmHg)	61 (52.14)	21 (46.67)	45 (53.66)	.
severe PaO_2/FiO_2 < 100 (mmHg)	47 (40.17)	14 (31.11)	18 (21.95)	.
Highest ventilatory support on admission				
IMV	117 (100)			<0.01
NIPPV		3 (6.67)	6 (7.23)	
CPAP		6 (13.33)	12 (14.46)	.
HFNC		30 (66.67)	55 (66.27)	.
Others		6 (13.33)	10 (12.05)	.
IMV during ICU stay	117 (100)	45 (100)	0	<0.01

Time from admission to IMV (days)	1 [1 ; 2]	3 [3 ; 4]	6 [4 ; 9]	<0.01
Ventilation parameters at intubation				
Tidal volume (mL)	423.4 [380 ; 450]	400 [369.1 ; 430]		0.05
Tidal volume (ml/kg)	6 [5.87 ; 6.34]	6 [5.72 ; 6.37]		0.90
PEEP (cmH_2O)	12 [10 ; 14]	12 [10 ; 14]		0.22
Plateau pressure (cmH_2O)	26 [23 ; 29]	25 [22 ; 27]		0.66
Compliance (ml/ cmH_2O)	36.67 [27.62 ; 53.33]	31.7 [26.73 ; 37.7]		0.03
Use of prone position during ICU stay	82 (70.09)	29 (64.44)	2 (2.41)	<0.01
Use of inhaled nitric oxide during ICU stay	33 (28.21)	15 (33.33)	0	<0.01
Use of paralytic agents during ICU stay	106 (90.6)	44 (97.78)	0	<0.01
Main laboratory values				
Neutrophils (cells/µl)	6800 [4700 ; 9600]	6300 [3950 ; 9220]	6900 [4790 ; 9300]	0.69
Lymphocytes (cells/µl)	800 [500 ; 1000]	700 [500 ; 1000]	800 [610 ; 1170]	0.30
C-Reactive Protein (mg/l)	176 [114 ; 251]	148.8 [68.3 ; 208]	151 [65 ; 191]	0.01
Ferritin (µg/l)	856 [425 ; 1750]	986 [442.14 ; 1937]	1326.28 [748.95 ; 1978]	0.05
D-dimers (µg/l)	1953 [805 ; 6065.6]	1293 [790 ; 3500]	1555.79 [743 ; 4770]	0.27
Treatment on admission				
Antiviral therapy	38 (32.48)	20 (44.44)	37 (44.58)	0.15
Tocilizumab	8 (6.84)	8 (17.78)	5 (6.02)	0.05
Anakinra	9 (7.69)	5 (11.11)	8 (9.64)	0.77
Hydroxychloroquine	9 (7.69)	6 (13.33)	7 (8.43)	0.52
Corticosteroids	31 (27.19)	10 (22.22)	27 (32.53)	0.44
Outcomes				
Bacteremia	29 (24.79)	9 (20)	1 (1.2)	<0.01
HAP-VAP	49 (41.88)	15 (33.33)	7 (8.43)	<0.01
VFD	1 [0 ; 3]	4 [2 ; 6]	7 [5 ; 9]	<0.01
OSFD	0 [0 ; 1]	0 [0 ; 1]	0 [0 ; 2]	0.65
ICU LOS	15 [10 ; 21]	16 [11 ; 22]	7 [5 ; 9]	<0.01
ICU Mortality	48 (41.03)	18 (40)	7 (8.43)	<0.01
Mortality at day 60	50 (42.74)	19 (42.22)	9 (10.84)	<0.01

*Kruskal-Wallis test for quantitative variables and Fisher exact test for categorical variables

**Worst PaO2/FiO2 during the 1st 2 days

§immunosuppression concerned patients with s with long term or high dosage corticosteroid therapy, anticancer chemotherapy, AIDS, non-AIDS immunodepression. Patients with aplasia, bone or organ transplant recipients were excluded. A patient can have several causes of immunosuppression.

IMV: invasive mechanical ventilation; HFNC: High flow oxygen nasal cannula , CPAP: Continuous Positive Airway Pressure, GCS: Glasgow coma scale; ICU: intensive care unit; SAPS: Simplified acute physiology score ; SOFA: sequential organ failure assessment; VFD: Ventilatory free days; OSFD: Oxygen support free days; LOS: length of stay

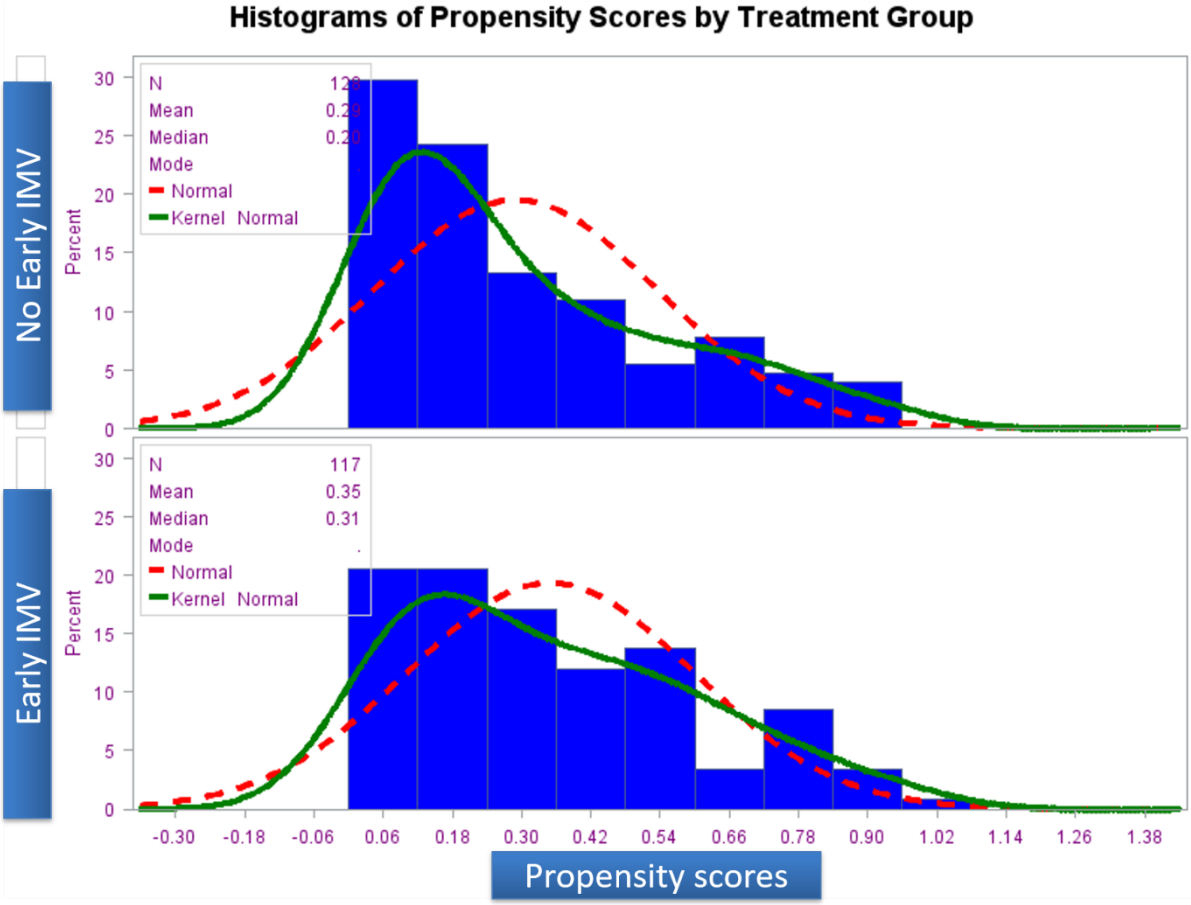

Figure E 1: Histograms of Propensity Scores according to groups: Early Invasive Mechanical Ventilation or no Early Invasive mechanical ventilation

*Early IMV defined as being under mechanical ventilation during the 1st two days after ICU admission

In the Early IMV groups and non-Early IMV, propensity scores ranged from 0.04 to 0.88 and from 0.09 to 0.84, respectively, with 97% in the region of common support [0.09 – 0.84].

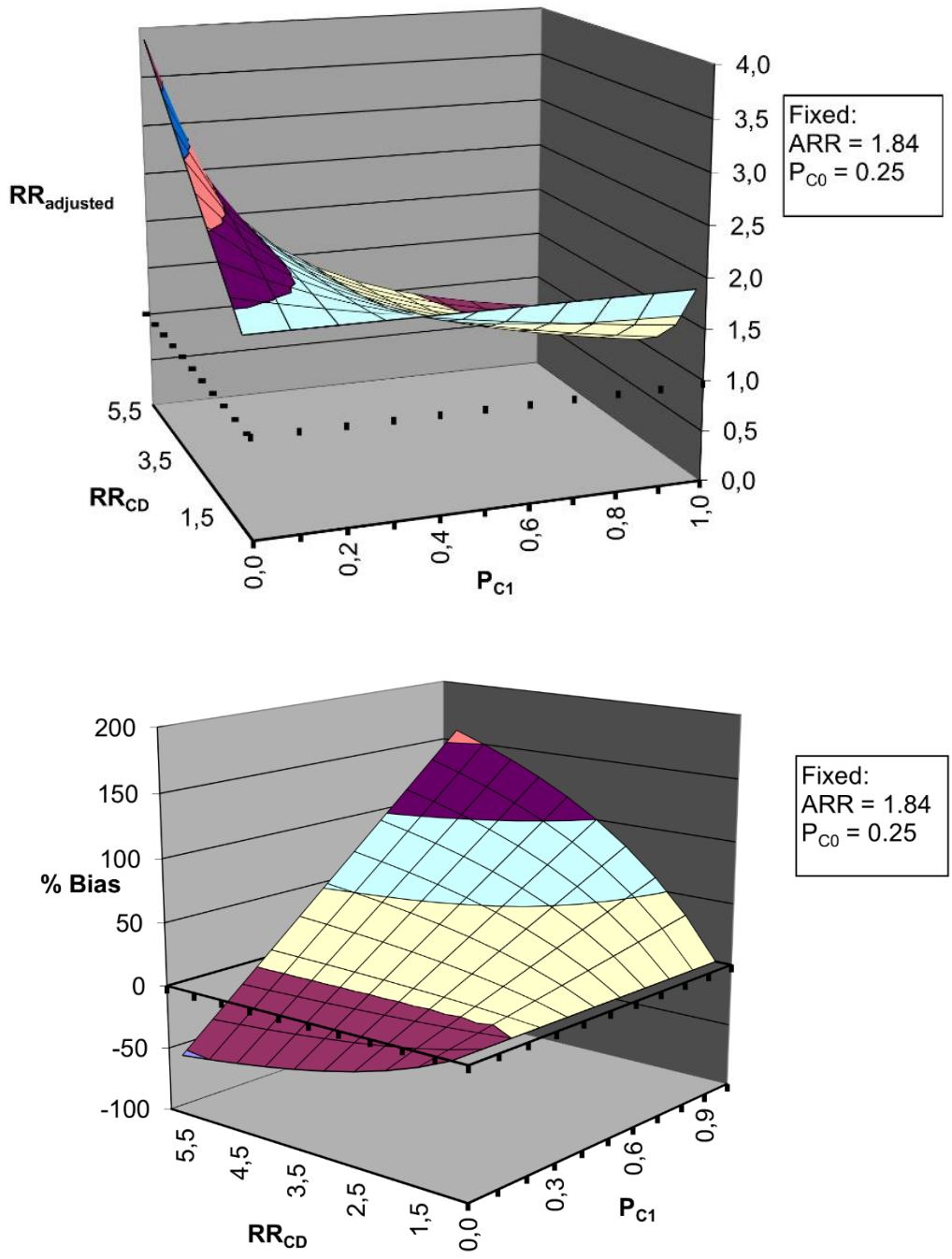

Figure E 2: Sensitivity analysis assessing the impact of the unknown confounders in the final estimation.

As a sensitivity analysis in order to estimate the impact of the unknown confounders in the final estimation, we performed the analysis based on on Schneeweiss et al (Schneeweiss, Pharmacoepidemiology and Drug Safety, 2006). We assumed that the prevalence of the confounder in the unexposed patients was 0.25 and then estimate the true HR depending on various level of prevalence of confounder in exposed patients and various associations between confounders and the outcome. The results are reported into the figure E3. As a result, in our figure, it appeared that only an unknown confounding factor with a high difference of prevalence between treatment groups and/or a strong association with the outcome could modify the results. We believed that we took into account most of those covariates into the propensity model and therefore minimized the risk to get biased results.

The definitions used are the following:

HR : « True » or fully adjusted exposure hazard ratio

AHR: Apparent (or observed) exposure hazard ratio

HRCD : Association between confounder and disease outcome

PC: prevalence of confounder

PC1: prevalence of confounder in the exposed

PC0: prevalence of confounder in the unexposed

$$\%bias = \frac{(AHR - HR)}{(HR - 1)} * 100$$

$$\text{HR} = \frac{AHR}{\left[\frac{P_{C1}(HR_{CD} - 1) + 1}{P_{C0}(HR_{CD} - 1) + 1}\right]}$$

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