

## **SUPPLEMENTARY ONLINE CONTENT**

**Effects of intubation timing in patients with COVID-19 throughout the four waves of the pandemic: a matched analysis**

**Supplementary Table S1**

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<b>Site and Region</b>
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### Supplementary Table S2

Periods that define the first, second, third and fourth waves in Spain.

<b>Wave</b>	<b>Begin Date of Wave</b>	<b>End Date of Wave</b>
Wave 1	02/29/2020	06/30/2020
Wave 2	06/30/2020	12/10/2020
Wave 3	12/10/2020	03/20/2021
Wave 4	03/20/2021	06/20/2021

**Supplementary Table S3** Characteristics and outcomes of critically ill patients with COVID-19 according to intubation timing (48-hour timepoint analysis).

Variables	Before PS matching (N = 2725)			After PS matching (N = 458)		
	Early intubation (n = 2164)	Delayed intubation (n = 561)	<i>p</i> value	Early intubation (n = 229)	Delayed intubation (n = 229)	<i>p</i> value
Age, years, median, (IQR)	65 (57; 72)	64 (55;70)	<b>0.007</b>	63 (56; 71)	64 (56; 71)	0.85
Sex, female, n (%)	630 (29.11)	154 (27.45)	0.46	65 (28.3)	66 (28.8)	1
BMI, Kg/m <sup>2</sup> , median, (IQR)	28.7 (25.9; 32.2)	28.7 (25.9; 31.9)	0.70	29.3 (26.6; 33.6)	29.2 (26.2; 32)	0.16
Hypertension, n (%)	1135 (52.4)	299 (53.2)	0.74	129 (56.3)	121 (52.8)	0.51
Diabetes mellitus, n (%)	537 (24.8)	144 (25.6)	0.70	60 (26.2)	60 (26.2)	1
Chronic cardiac failure, n (%)	272 (12.5)	70 (12.4)	1	33 (14.4)	31 (13.5)	0.89
COPD, n (%)	205 (9.4)	57 (10.1)	0.63	27 (11.7)	27 (11.7)	1
Immunodepression, n (%)	373 (17.2)	150 (26.7)	<b>&lt;0.001</b>	44 (19.2)	40 (17.4)	0.71
Received corticosteroids, n (%)	1824(85.1)	511 (92)	<b>&lt;0.001</b>	213 (93)	211 (92.1)	0.85
<b>Clinical characteristics at hospital admission</b>						
PaO <sub>2</sub> /FiO <sub>2</sub> , median, (IQR)	221.4 (136.2; 282.8)	207.1 (111.2; 274.7)	<b>0.04</b>	202.3 (122; 271.4)	195.2 (114; 271.4)	0.97
Respiratory rate, respiration per minute, median, (IQR)	24 (20; 30)	25 (20; 30)	0.12	25 (20; 31)	26 (20; 32)	0.29
PaCO <sub>2</sub> , mmHg, median, (IQR)	34 (30; 38)	34 (30.1; 37.4)	0.93	34 (30; 37.3)	33 (30; 37.1)	0.40
pH, median, (IQR)	7.45 (7.41; 7.47)	7.45 (7.41; 7.47)	0.36	7.45 (7.42; 7.48)	7.45 (7.42; 7.48)	0.90
HFNC, n (%)*	795 (36.7)	287 (51.1)	<b>&lt;0.001</b>	94 (41)	102 (44.5)	0.50

NIV n (%)**	727 (34.2)	236 (42.3)	<b>&lt;0.001</b>	76 (33.6)	113 (49.5)	<b>0.001</b>
CRP, mg/dL, median, (IQR)	12.7 (6.9; 20.6)	12 (6.6; 21.5)	0.76	13.3 (7.8; 22.1)	14.7 (8.3; 21.2)	0.72
Lymphocyte count, 10 <sup>9</sup> cells/L, median, (IQR)	0.8 (0.58; 1.1)	0.8 (0.59; 1.08)	0.61	0.79 (0.58; 1.04)	0.8 (0.6; 1.03)	0.69
Platelets, 10 <sup>9</sup> cells/L, median, (IQR)*	180 (144; 234)	184 (139; 238)	0.89	181 (143; 231)	190 (148; 246)	0.14
D-dimer, mg/L, median, (IQR)	0.66 (0.39; 1.13)	0.65 (0.37; 1.16)	0.63	0.66 (0.38; 1.1)	0.66 (0.4; 1.35)	0.40
Creatinine, mg/dL, median, (IQR)	0.97 (0.8; 1.2)	0.96 (0.7; 1.2)	0.99	0.96 (0.8; 1.27)	0.92 (0.7; 1.17)	0.13
Lactate, mg/dL, median, (IQR)	13.5 (9.9; 17.1)	12.6 (9.1; 17.1)	0.37	13.51 (9.9; 16.2)	11.71 (9; 15)	0.09
<b>Disease chronology</b>						
Time since symptom onset to ICU admission, days, median, (IQR)	9 (7; 12)	8 (6; 11)	<b>&lt;0.001</b>	8 (6; 11)	8 (7; 11)	0.63
Patients spending >2 days in hospital before ICU admission, n (%)	1165 (53.86)	196 (34.94)	<b>&lt;0.001</b>	67 (29.2)	64 (27.957)	0.83
Time since symptom onset to IMV, days, median, (IQR)	10 (7; 12)	12 (10; 16)	<b>&lt;0.001</b>	9 (7; 11)	12 (10; 16)	<b>&lt;0.001</b>
Time since hospital admission to IMV, days, median, (IQR)	3 (2; 5)	5 (3; 9)	<b>&lt;0.001</b>	2 (1; 3)	5 (3; 8)	<b>&lt;0.001</b>
Time since ICU admission to IMV, days, median, (IQR)	0 (0; 0)	3 (2; 5)	<b>&lt;0.001</b>	0 (0; 0)	3 (2; 5)	<b>&lt;0.001</b>
<b>Waves</b>						
1 <sup>st</sup> wave, n (%)	1382 (63.8)	196 (34.9)	<b>&lt;0.001</b>	117 (51)	93 (40.6)	<b>0.03</b>
2 <sup>nd</sup> wave, n (%)	524 (24.2)	228 (40.6)	<b>&lt;0.001</b>	63 (27.5)	102 (44.5)	<b>&lt;0.001</b>
3 <sup>rd</sup> wave, n (%)	198 (9.1)	98 (17.4)	<b>&lt;0.001</b>	43 (18.7)	32 (13.9)	0.20
4 <sup>th</sup> wave, n (%)	30 (1.3)	14 (2.5)	0.08	6 (2.6)	2 (0.87)	0.28
<b>Outcomes</b>						
IMV days, median, (IQR)†	13 (8; 29)	17 (8; 29)	0.21	13 (8; 24)	18 (9; 31.5)	<b>0.01</b>
ICU days, median, (IQR)†	18 (12; 36)	28 (18; 43)	<b>&lt;0.001</b>	17 (11; 32)	27 (16; 44)	<b>&lt;0.001</b>

Prone position, n (%)	1638 (76.04)	451 (80.68)	<b>0.02</b>	167 (72.9)	192 (84.2)	<b>0.004</b>
Neuromuscular blockade, n (%)	1839 (85.06)	463 (82.97)	0.23	189 (82.5)	198 (86.4)	0.30
ECMO, n (%)	35 (1.6)	23 (4.11)	<b>0.01</b>	6 (2.6)	11 (4.8)	0.32
ICU mortality, n (%)	740 (34.2)	218 (38.8)	<b>0.04</b>	62 (27.07)	94 (41.05.1)	<b>0.002</b>
Hospital mortality, n (%)	792 (36.6)	233 (41.5)	<b>0.03</b>	62 (27.07)	99 (43.23)	<b>&lt;0.001</b>
90-day mortality, n (%)	784 (39.8)	233 (45)	<b>0.03</b>	62 (30.2)	97 (44.5)	<b>0.003</b>

Early intubation is considered as  $\leq 48$  hours and delayed intubation, as  $> 48$  hours from ICU admission.

Definition of abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRP: C reactive protein; ECMO: extracorporeal membrane oxygenation; HFNC: high-flow nasal cannula; ICU: intensive care unit; IMV: invasive mechanical ventilation; IQR: interquartile range; NIV: non-invasive ventilation; PaCO<sub>2</sub>: partial pressure of CO<sub>2</sub> in the arterial blood; and PS: propensity score. Percentages calculated with non-missing data only.

Variables used to perform PS matching included age, sex, respiratory rate at hospital admission, PaO<sub>2</sub>/FIO<sub>2</sub> at hospital admission (categorised as  $>300$  mmHg;  $200$  mmHg  $< PaO_2/FIO_2 \leq 300$  mmHg;  $100$  mmHg  $< PaO_2/FiO_2 \leq 200$  mmHg;  $PaO_2/FIO_2 \leq 100$  mmHg), days between hospital and ICU admission (categorised as  $\leq$  or  $> 2$  days), chronic immunosuppression, corticosteroid treatment and COVID-19 wave. After excluding patients with missing values, we had a population of n=1117. Table 43 in supplemental material shows standardised mean differences in baseline covariates from the matched population. \*HFNC with or without NIV; \*\* NIV with or without HFNC. \* and \*\* received at least one session of NIV and/or HFNC since hospital admission before intubation. † Analysed only in survivors. Boldface entries indicate statistical significance.

### Supplementary Table S4

Distribution of baseline characteristics from the matched sample of patients with severe COVID-19 undergoing invasive mechanical ventilation.

Covariate	SMD early vs delayed general population	SMD early vs delayed HFNC	SMD early vs delayed NIV+/- HFNC
Age	0.04	0.16	0.04
Sex	0.09	0.03	0.13
BMI	0.13	0.02	<b>0.27</b>
Hypertension	0.026	0.16	0.09
Diabetes mellitus	0.04	0	0
Chronic cardiac failure	0.07	0.06	0.02
COPD	0.03	0.04	0.02
Immunodepression	0.07	0.02	0.07
Received corticosteroids	0.07	0.02	0.09
<b>Clinical characteristics at hospital admission</b>			
PaO <sub>2</sub> /F <sub>I</sub> O <sub>2</sub>	0.002	0.11	0.01
Respiratory rate	0.06	0.01	0.03
PaCO <sub>2</sub>	0.03	0.11	<b>0.2</b>
pH	0.07	0.07	0.19
HFNC	<b>0.64</b>	-	-
NIV	<b>0.25</b>	-	-
CRP	0.07	0.16	<b>0.21</b>
Lymphocyte count	0.02	0.02	<b>0.21</b>
Platelets	0.11	0.12	0.15
D-dimer	0.09	0.06	0.06
Creatinine	0.03	0.01	0.14
Lactate	0.04	0.12	0.04
<b>Disease chronology</b>			
Time since symptom onset to ICU admission	0.001	0.16	0.15
Patients spending >2 days in hospital before ICU admission	0.05	0.02	0.05
Time since symptom onset to IMV	0.1	<b>0.27</b>	0.02
Time since hospital admission to IMV	<b>0.21</b>	<b>0.48</b>	<b>0.40</b>
Time since ICU admission to IMV	<b>0.26</b>	<b>1.04</b>	<b>1.5</b>
<b>Waves</b>			
1st wave	0.03	0.15	0.12
2nd wave	0.13	0.16	<b>0.22</b>
3rd wave	0.11	0	0.10
4th wave	0.09	0.04	0.13

Early intubation is considered as  $\leq 24$  hours and delayed intubation, as  $> 24$  hours from ICU admission. Definition of abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRP: C reactive protein; ECMO: extracorporeal membrane oxygenation; HFNC: high-flow nasal cannula; ICU: intensive care unit; IMV: invasive mechanical ventilation; IQR: interquartile range; NIV: non-invasive ventilation; PaCO<sub>2</sub>: partial pressure of CO<sub>2</sub> in the arterial blood; PS: propensity score; SMD: standardised mean differences. Boldface entries indicate significant SMD.

## Supplementary Table S5

Distribution of baseline characteristics from the matched sample of patients with severe COVID-19 undergoing invasive mechanical ventilation (48-hour timepoint analysis).

Covariate	SMD early vs delayed general population	SMD early vs delayed HFNC	SMD early vs delayed NIV+/- HFNC
Age	0.06	0.20	0.11
Sex	0.08	0.05	0.05
BMI	0.16	0.03	<b>0.49</b>
Hypertension	0.07	0.03	0.01
Diabetes mellitus	0.000	0.000	0.07
Chronic cardiac failure	0.025	0.05	0.07
COPD	0.000	0.03	<b>0.21</b>
Immunodepression	0.04	0.000	0.000
Received corticosteroids	0.03	0.03	0.03
<b>Clinical characteristics at hospital admission</b>			
PaO <sub>2</sub> /F <sub>I</sub> O <sub>2</sub>	0.003	0.17	0.03
Respiratory rate	0.08	<b>0.22</b>	0.07
PaCO <sub>2</sub>	0.07	0.08	0.09
pH	0.02	0.04	0.12
HFNC	0.07	-	-
NIV	<b>0.33</b>	-	-
CRP	0.01	0.005	0.07
Lymphocyte count	0.12	0.15	0.08
Platelets	0.08	0.09	0.02
D-dimer	0.14	0.06	0.13
Creatinine	0.001	0.12	0.05
Lactate	0.15	0.06	<b>0.32</b>
<b>Disease chronology</b>			
Time since symptom onset to ICU admission	0.10	0.02	0.17
Patients spending >2 days in hospital before ICU admission	0.02	0.08	0.03
Time since symptom onset to IMV	0.19	<b>0.52</b>	0.03
Time since hospital admission to IMV	<b>0.29</b>	<b>0.76</b>	<b>1.04</b>
Time since ICU admission to IMV	<b>0.32</b>	<b>1.31</b>	<b>1.74</b>
<b>Waves</b>			
1st wave	0.2	<b>0.21</b>	0.17
2nd wave	<b>0.36</b>	0.20	<b>0.35</b>
3rd wave	0.11	0	0.18
4th wave	0.09	0.05	0.18

Early intubation is considered as  $\leq 48$  hours and delayed intubation, as  $> 48$  hours from ICU admission. Definition of abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; ECMO: extracorporeal membrane oxygenation; HFNC: high-flow nasal cannula; ICU: intensive care unit; IMV: invasive mechanical ventilation; IQR: interquartile range; NIV: non-invasive ventilation; PaCO<sub>2</sub>: partial pressure of

CO<sub>2</sub> in the arterial blood; PS: propensity score; SMD: standardised mean differences. Boldface entries indicate significant SMD.

## Supplementary Table S6

Changes throughout the pandemic as it relates to the use of non-invasive respiratory support therapies before invasive mechanical ventilation, time to intubation, and outcomes.

Variables	First wave N= 1578		Second wave N= 752		Third wave N= 296		Fourth wave N = 44	
	Early n =1148	Delayed n = 430	Early n =383	Delayed n =369	Early n = 139	Delayed n =157	Early n = 20	Delayed n = 24
Age, years, median, (IQR)	65 (57; 72) ¶	63 (54; 69)	65 (57; 73)	64 (56; 72)	68 (60; 72) ¶	64 (56; 70)	67 (58; 70)	64 (52; 71)
HFNC, n (%)*	492 (55.9) ¶	331 (88.7)	217 (71.6) ¶	341 (91.6)	97 (72.3) ¶	147 (94.2)	18 (90)	24 (100)
NIV, n (%)**	413 (14.7)	153 (36)	118 (32.5)	136 (35.5)	48 (34.5)	66 (42.5)	8 (40)	8 (33.3)
Time since symptom onset to IMV, days, median, (IQR)	10 (8; 13)	10 (8; 13)	9 (7; 12) ¶	11 (9; 15)	9 (7; 11) ¶	11 (8; 14)	11.5 (8; 13.5)	12 (9.75; 15)
Time since hospital admission to IMV, days, median, (IQR)	3 (2; 5)	3 (2; 5)	3 (2; 5) ¶	4 (3; 7)	3 (2; 4) ¶	4 (2; 7)	4 (2; 7.2)	3.5 (2.7.2)
Time since ICU admission to IMV, days, median, (IQR)	0 (0; 0) ¶	1 (1; 3)	0 (0; 0) ¶	2 (1; 4)	0 (0; 0) ¶	2 (1; 4)	0 (0; 0) ¶	2 (1; 4)
IMV days, median, (IQR)†	13 (8; 25)	14 (9; 26)	12.5 (7; 26)	14 (8; 32.3)	13 (7; 26)	14.5 (8; 37)	20 (11; 30.5)	11 (7.7; 17)
ICU days, median, (IQR)†	18 (11; 32.7) ¶	22 (13; 35.7)	17 (10; 33) ¶	25 (14; 45.7)	15.5 (9; 30) ¶	24 (12; 50)	29 (16; 36)	19 (16; 26.7)
Prone position, n (%)	907 (79.5)	321 (75.3)	225 (69.1) ¶	305 (79.6)	101 (72.6)	125 (79.6)	18 (90)	19 (79.1)
ECMO, n (%)	21 (1.8)	12 (2.7)	3 (0.8) ¶	16 (4.1)	1 (0.7)	2 (1.2)	1 (5)	1 (4.1)
Neuromuscular blockade, n (%)	995 (86.6)	360 (83.9)	298 (81.2)	312 (81.8)	120 (86.3)	136 (86.6)	14 (70)	20 (83.3)
ICU mortality, n (%)	436 (37.9)	143 (33.2)	113 (30.6) ¶	147 (38.3)	39 (28)	50 (31.8)	3 (15)	6 (25)
Hospital mortality, n (%)	462 (40.2) ¶	148 (34.4)	122 (33) ¶	157 (40.9)	47 (33.8)	59 (37.5)	3 (15)	6 (25)
90-day mortality, n (%)	457 (42.5) ¶	147 (35)	122 (37) ¶	155 (44.6)	46 (37.1)	59 (42.4)	4 (30.7)	6 (40)

Early intubation is considered as  $\leq 24$  hours and delayed intubation, as  $> 24$  hours from ICU

admission. Definition of abbreviations: ECMO: extracorporeal membrane oxygenation; HFNC: high-flow nasal cannula; ICU: intensive care unit; IMV: invasive mechanical ventilation; IQR: interquartile range; NIV: non-invasive ventilation. Percentages calculated with non-missing data only. Fifty-five patients from the general cohort were not included in this analysis as they did not belong to any of the four waves. \*High-flow nasal cannula with or without NIV; \*\* NIV with or without high-flow nasal cannula. \* and \*\* received at least one session of NIV and/or high-flow nasal cannula since hospital admission before intubation. † Analysed only in survivors. ¶  $p < 0.05$  vs. late intubation.

### Supplementary Table S7

Characteristics and outcomes of critically ill patients with COVID-19 receiving early or delayed intubation depending on prior use of high-flow nasal cannula or non-invasive ventilation (unmatched population).

Variables	High-flow nasal cannula N = 1082			Non-invasive mechanical ventilation with or without high-flow nasal cannula N = 963		
	Early intubation (n = 522)	Delayed intubation (n = 560)	<i>p value</i>	Early intubation (n = 588)	Delayed intubation (n = 375)	<i>p value</i>
Age, years, median, (IQR)	65 (56; 72)	63 (54; 70)	<b>0.01</b>	64 (56; 70)	64 (56; 72)	0.46
Sex, female, n (%)	163 (31.2)	152 (27.1)	0.14	155 (26.3)	105 (28)	0.60
BMI, Kg/m <sup>2</sup> , median, (IQR)	28.6 (25.9; 31.9)	28.7 (26.1; 32.4)	0.57	29.3 (25.9; 32.7)	29.5 (26.7; 32.6)	0.17
Hypertension, n (%)	248 (47.5)	280 (50)	0.42	298 (50.6)	209 (55.7)	0.12
Diabetes mellitus, n (%)	128 (24.5)	137 (24.4)	1	144 (24.4)	108 (28.8)	0.15
Chronic cardiac failure, n (%)	57 (10.9)	58 (10.3)	0.76	61 (10.3)	64 (17)	<b>0.003</b>
COPD, n (%)	48 (9.2)	55 (9.8)	0.75	46 (7.8)	34 (9)	0.55
Immunodepression, n (%)	91 (17.4)	119 (21.2)	0.12	108 (18.3)	98 (26.1)	<b>0.005</b>
Received corticosteroids, n (%)	447 (85.8)	498 (90.3)	<b>0.02</b>	519 (88.5)	340 (90.9)	0.28
<b>Clinical characteristics at hospital admission</b>						
PaO <sub>2</sub> /F <sub>I</sub> O <sub>2</sub> , median, (IQR)	242.8 (178.7; 298.8)	215.2 (118.3; 283.4)	<b>0.001</b>	222.5 (149.6; 280.9)	150 (89; 252.2)	<b>&lt;0.001</b>
Respiratory rate, respiration per	24 (20; 28)	24 (20; 30)	0.19	24 (20; 30)	27 (22; 32)	<b>0.005</b>

minute, median, (IQR)						
PaCO <sub>2</sub> , mmHg, median, (IQR)	34 (30.1; 38.5)	34 (30; 38)	0.84	33 (30; 38)	34.2 (30.3; 38)	0.12
pH, median, (IQR)	7.45 (7.41; 7.47)	7.45 (7.41; 7.47)	0.66	7.45 (7.41; 7.47)	7.44 (7.41; 7.48)	0.76
CRP, mg/dL, median, (IQR)	12.3 (7; 19.7)	11.9 (6.6; 20.6)	0.96	13.3 (6.9; 21.2)	13.5 (8.1; 22.2)	0.16
Lymphocyte count, 10 <sup>9</sup> cells/L, median, (IQR)	0.8 (0.6; 1.1)	0.8 (0.6; 1.1)	0.67	0.8 (0.58; 1.1)	0.73 (0.51; 1.02)	0.17
Platelets, 10 <sup>9</sup> cells/L, median, (IQR)	179 (138; 229)	182 (142; 238)	0.27	184 (148; 236)	193 (147; 245)	0.38
D-dimer, mg/L, median, (IQR)	0.62 (0.37; 1.09)	0.57 (0.34; 1.08)	0.42	0.66 (0.42; 1.08)	0.69 (0.39; 1.25)	0.78
Creatinine, mg/dL, median, (IQR)	0.98 (0.79; 1.17)	0.96 (0.79; 1.22)	0.70	0.97 (0.8; 1.2)	0.93 (0.76; 1.2)	0.25
Lactate, mg/dL, median, (IQR)	12.6 (9; 17.3)	13.3 (9.9; 17.9)	0.61	13.5 (9.9; 18)	13.4 (9.9; 16.5)	0.59
<b>Disease chronology</b>						
Time since symptom onset to ICU admission, days, median, (IQR)	9 (7; 11)	8 (6; 10)	<b>0.026</b>	10 (6; 12)	9 (7; 11)	0.33
Patients spending >2 days in hospital before ICU admission, n (%)	293 (56.1)	196 (35)	<b>&lt;0.001</b>	371 (63.1)	127 (33.8)	<b>&lt;0.001</b>
Time since symptom onset to IMV, days, median, (IQR)	9 (7; 12)	11 (8; 14)	<b>&lt;0.001</b>	10 (8; 14)	11 (9; 15)	<b>&lt;0.001</b>
Time since hospital admission to IMV, days, median, (IQR)	3 (2; 5)	4 (2; 6)	<b>&lt;0.001</b>	3 (2; 6)	4 (2; 7)	<b>&lt;0.001</b>
Time since ICU admission to IMV, days, median, (IQR)	0 (0; 0)	2 (1; 3)	<b>&lt;0.001</b>	0 (0; 0)	2 (1; 4)	<b>&lt;0.001</b>
<b>Waves</b>						
1 <sup>st</sup> wave, n (%)	307 (58.8)	211 (37.6)	<b>&lt;0.001</b>	413 (70.2)	153 (40.8)	<b>&lt;0.001</b>

2 <sup>nd</sup> wave, n (%)	134 (25.6)	226 (40.3)	<b>&lt;0.001</b>	118 (20)	136 (36.2)	<b>&lt;0.001</b>
3 <sup>rd</sup> wave, n (%)	57 (10.9)	85 (15.1)	<b>0.03</b>	48 (8.1)	66 (17.6)	<b>&lt;0.001</b>
4 <sup>th</sup> wave, n (%)	12 (2.3)	16 (2.8)	0.7	8 (1.3)	8 (2.1)	0.44
<b>Outcomes</b>						
IMV days, median, (IQR) †	13 (8; 25)	13 (8; 29)	0.92	12.5 (8; 24)	15.5 (9; 28.7)	<b>0.02</b>
ICU days, median, (IQR) †	18 (11; 33)	22 (13; 39)	<b>0.001</b>	17 (10; 29.2)	24 (14; 41)	<b>&lt;0.001</b>
Prone position, n (%)	382 (73.3)	429 (76.8)	0.18	496 (84.6)	301 (80.4)	0.09
ECMO, n (%)	9 (1.7)	12 (2.1)	0.66	13 (2.2)	18 (4.8)	<b>0.03</b>
Neuromuscular blockade, n (%)	432 (82.9)	480 (85.8)	0.2	509 (86.7)	304 (81.5)	<b>0.03</b>
ICU mortality, n (%)	143 (27.3)	176 (31.4)	0.16	187 (31.8)	145 (38.6)	<b>0.03</b>
Hospital mortality, n (%)	183 (32.6)	157 (30)	0.36	204 (34.6)	159 (42.4)	<b>0.01</b>
90-day mortality, n (%)	156 (33.1)	183 (36.4)	0.28	205 (36.9)	156 (44.9)	<b>0.01</b>

Early intubation is considered as  $\leq 24$  hours and delayed intubation, as  $> 24$  hours from ICU admission. Definition of abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; IMV: invasive mechanical ventilation; IQR: interquartile range; PaCO<sub>2</sub>: partial pressure of CO<sub>2</sub> in the arterial blood. Percentages calculated with non-missing data only. † Analysed only in survivors. Boldface entries indicate statistical significance.

### Supplementary Table S8

Characteristics and outcomes of critically ill patients with COVID-19 receiving early or delayed intubation depending on prior use of high-flow nasal cannula or non-invasive ventilation (48-hour timepoint analysis, unmatched population).

Variables	High-flow nasal cannula N = 1082			Non-invasive mechanical ventilation with or without high-flow nasal cannula N = 963		
	Early intubation (n = 795)	Delayed intubation (n = 287)	<i>p value</i>	Early intubation (n = 727)	Delayed intubation (n = 236)	<i>p value</i>
Age, years, median, (IQR)	64 (56; 71)	63 (53; 70)	0.07	64 (56; 70)	64 (56; 71)	0.43
Sex, female, n (%)	234 (29.4)	81 (28.2)	0.76	196 (26.9)	64 (27.1)	1
BMI, Kg/m <sup>2</sup> , median, (IQR)	28.7 (26; 32.2)	28.4 (25.7; 31.9)	0.40	29.4 (26.2; 33)	29.5 (26.2; 32)	0.28
Hypertension, n (%)	382 (48)	146 (50.8)	0.49	378 (51.9)	129 (54.6)	0.5
Diabetes mellitus, n (%)	192 (24.1)	73 (25.4)	0.68	189 (26)	63 (26.6)	0.86
Chronic cardiac failure, n (%)	89 (11.1)	26 (9)	0.37	85 (11.6)	40 (16.9)	<b>0.04</b>
COPD, n (%)	77 (9.6)	26 (9)	0.81	55 (7.5)	25 (10.5)	0.17
Immunodepression, n (%)	140 (17.6)	70 (24.3)	<b>0.01</b>	138 (18.9)	68 (28.8)	<b>0.002</b>
Received corticosteroids, n (%)	689 (87.2)	256 (90.7)	0.13	637 (87.8)	222 (94.4)	<b>0.003</b>
<b>Clinical characteristics at hospital admission</b>						
PaO <sub>2</sub> /F <sub>I</sub> O <sub>2</sub> , median, (IQR)	230 (152.5; 292.3)	225 (129.8; 285.9)	0.45	203.3 (119.5; 269.7)	163.1 (98.2; 261.1)	0.07
Respiratory rate, respiration per	24 (20; 30)	24 (20; 30)	0.82	25 (20; 32)	28 (22; 32)	0.11

minute, median, (IQR)						
PaCO <sub>2</sub> , mmHg, median, (IQR)	34 (30.2; 38.5)	33.4 (30; 36.6)	0.08	33 (30; 38)	34 (30.4; 37.7)	0.36
pH, median, (IQR)	7.45 (7.41; 7.47)	7.45 (7.41; 7.47)	0.43	7.45 (7.41; 7.47)	7.44 (7.41; 7.48)	0.54
CRP, mg/dL, median, (IQR)	12.3 (7; 20.2)	11.3 (6.1; 20.8)	0.40	13.5 (7.1; 21.4)	13.4 (8; 22)	0.56
Lymphocyte count, 10 <sup>9</sup> cells/L, median, (IQR)	0.8 (0.6; 1.1)	0.8 (0.6; 1.1)	0.68	0.78 (0.57; 1.09)	0.73 (0.52; 1.02)	0.4
Platelets, 10 <sup>9</sup> cells/L, median, (IQR)	180 (140; 233)	183 (140; 237)	0.91	185 (149; 237)	189 (142; 246)	0.84
D-dimer, mg/L, median, (IQR)	0.61 (0.36; 1.2)	0.56 (0.33; 1)	0.64	0.68 (0.41; 1.1)	0.69 (0.39; 1.24)	0.79
Creatinine, mg/dL, median, (IQR)	0.97 (0.79; 1.17)	0.98 (0.79; 1.28)	0.20	0.96 (0.8; 1.2)	0.93 (0.74; 1.1)	0.12
Lactate, mg/dL, median, (IQR)	12.6 (9.3; 17.1)	13.5 (9.9; 18)	0.29	13.5 (9.9; 18)	11.7 (9; 15.7)	<b>0.004</b>
<b>Disease chronology</b>						
Time since symptom onset to ICU admission, days, median, (IQR)	9 (7; 12)	8 (7; 11)	0.07	10 (7; 13)	8 (6; 11)	<b>&lt;0.001</b>
Patients spending >2 days in hospital before ICU admission, n (%)	387 (48.6)	102 (35.5)	<b>&lt;0.001</b>	414 (56.9)	84 (35.5)	<b>&lt;0.001</b>
Time since symptom onset to IMV, days, median, (IQR)	9 (7; 12)	12 (10; 15)	<b>&lt;0.001</b>	10 (8; 13)	12 (10; 17)	<b>&lt;0.001</b>
Time since hospital admission to IMV, days, median, (IQR)	3 (1; 5)	5 (3; 8)	<b>&lt;0.001</b>	3 (2; 5)	6 (3; 9)	<b>&lt;0.001</b>
Time since ICU admission to IMV, days, median, (IQR)	0 (0; 1)	3 (2; 4)	<b>&lt;0.001</b>	0 (0; 0)	3 (2; 5)	<b>&lt;0.001</b>
<b>Waves</b>						

1 <sup>st</sup> wave, n (%)	426 (53.5)	92 (32)	<b>&lt;0.001</b>	487 (66.9)	79 (33.4)	<b>&lt;0.001</b>
2 <sup>nd</sup> wave, n (%)	236 (29.6)	226 (40.3)	<b>&lt;0.001</b>	159 (21.8)	95 (40.2)	<b>&lt;0.001</b>
3 <sup>rd</sup> wave, n (%)	90 (11.3)	52 (18.1)	<b>0.04</b>	69 (9.4)	45 (19)	<b>&lt;0.001</b>
4 <sup>th</sup> wave, n (%)	20 (2.5)	8 (2.7)	0.82	10 (1.3)	6 (2.5)	0.24
<b>Outcomes</b>						
IMV days, median, (IQR) †	13 (8; 26)	13 (7; 29)	0.82	12.5 (8; 24)	15.5 (9; 28.7)	<b>0.02</b>
ICU days, median, (IQR) †	18 (12; 35)	24 (15; 41)	<b>0.001</b>	17 (10; 29.2)	24 (14; 41)	<b>&lt;0.001</b>
Prone position, n (%)	585 (73.7)	226 (79)	0.08	600 (82.8)	197 (83.4)	0.92
ECMO, n (%)	13 (1.6)	8 (2.7)	0.22	16 (2.2)	15 (6.3)	<b>0.004</b>
Neuromuscular blockade, n (%)	668 (84.1)	244 (85.3)	0.70	624 (85.9)	189 (80.7)	0.06
ICU mortality, n (%)	223 (28)	96 (33.4)	0.09	226 (31)	106 (44.9)	<b>&lt;0.001</b>
Hospital mortality, n (%)	240 (30.1)	100 (34.8)	0.15	248 (34.1)	115 (48.7)	<b>&lt;0.001</b>
90-day mortality, n (%)	239 (33.5)	100 (38.3)	0.17	247 (36.1)	114 (52)	<b>&lt;0.01</b>

Early intubation is considered as  $\leq 48$  hours and delayed intubation, as  $> 48$  hours from ICU admission. Definition of abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; IMV: invasive mechanical ventilation; IQR: interquartile range; PaCO<sub>2</sub>: partial pressure of CO<sub>2</sub> in the arterial blood. Percentages calculated with non-missing data only. † Analysed only in survivors. Boldface entries indicate statistical significance.

### Supplementary Table S9

Characteristics and outcomes of critically ill patients with COVID-19 receiving early or delayed intubation depending on prior use of high-flow nasal cannula or non-invasive ventilation (48-hour timepoint analysis, matched population).

Variables	High-flow nasal cannula N = 230			Non-invasive mechanical ventilation with or without high-flow nasal cannula N = 236		
	Early intubation (n = 115)	Delayed intubation (n = 115)	<i>p value</i>	Early intubation (n = 118)	Delayed intubation (n = 118)	<i>p value</i>
Age, years, median, (IQR)	60 (52; 68)	64 (54; 71)	0.08	63 (55; 70)	64 (58; 72)	0.37
Sex, female, n (%)	38 (33)	35 (30)	0.77	35 (29.6)	32 (27.1)	0.77
BMI, Kg/m <sup>2</sup> , median, (IQR)	29.3 (27.1; 33.5)	28 (25.7; 31.9)	<b>0.03</b>	31.1 (28.1; 35.7)	29.1 (26.1; 32)	<b>0.001</b>
Hypertension, n (%)	58 (50.4)	56 (48.7)	0.89	65 (55)	64 (54.2)	1
Diabetes mellitus, n (%)	29 (25.2)	29 (25.2)	1	37 (31.3)	33 (27.9)	0.66
Chronic cardiac failure, n (%)	13 (11.3)	15 (13)	0.84	14 (11.8)	14 (14.4)	0.70
COPD, n (%)	10 (8.7)	9 (7.8)	1	9 (7.6)	17 (14.4)	0.14
Immunodepression, n (%)	20 (17.3)	20 (17.3)	1	26 (22)	26 (22)	1
Received corticosteroids, n (%)	107 (93)	106 (92.1)	1	110 (93.2)	111 (94)	1
<b>Clinical characteristics at hospital admission</b>						
PaO <sub>2</sub> /F <sub>1</sub> O <sub>2</sub> , median, (IQR)	214.2 (149; 280.3)	193.3 (132; 275.2)	0.48	173.7 (95.8; 238.3)	164.2 (98.7; 261.4)	0.71
Respiratory rate, respiration per	24 (20; 29)	25 (20; 31)	0.11	27 (22; 35)	28 (22; 32)	0.61

minute, median, (IQR)						
PaCO <sub>2</sub> , mmHg, median, (IQR)	34 (31; 37)	33 (30; 37)	0.19	33 (30; 38)	33 (29; 38)	0.79
pH, median, (IQR)	7.45 (7.42; 7.47)	7.45 (7.43; 7.48)	0.89	7.45 (7.41; 7.48)	7.46 (7.42; 7.48)	0.45
CRP, mg/dL, median, (IQR)	12.7 (8.2; 21.4)	13 (7.3; 21.2)	0.71	14.1 (7.8; 20.8)	13.6 (8.3; 22.2)	0.36
Lymphocyte count, 10 <sup>9</sup> cells/L, median, (IQR)	0.8 (0.6; 1)	0.8 (0.6; 1)	0.60	0.8 (0.6; 1.08)	0.8 (0.6; 1.02)	0.92
Platelets, 10 <sup>9</sup> cells/L, median, (IQR)	191 (156; 243)	182 (146; 232)	0.49	187 (150; 231)	196 (149; 254)	0.33
D-dimer, mg/L, median, (IQR)	0.56 (0.41; 0.9)	0.54 (0.38; 0.97)	0.84	0.65 (0.4; 1)	0.69 (0.39; 1.39)	0.37
Creatinine, mg/dL, median, (IQR)	0.95 (0.78; 1.17)	0.94 (0.79; 1.23)	0.99	0.99 (0.8; 1.28)	0.91 (0.71; 1.11)	<b>0.05</b>
Lactate, mg/dL, median, (IQR)	12.6 (9.7; 16.2)	12.6 (9; 17.1)	0.95	13.4 (10.1; 16.2)	11.4 (9; 14.4)	<b>0.04</b>
<b>Disease chronology</b>						
Time since symptom onset to ICU admission, days, median, (IQR)	8 (6; 11)	8 (6; 10)	0.66	8 (6; 11)	8 (7; 12)	0.75
Patients spending >2 days in hospital before ICU admission, n (%)	31 (26.9)	27 (23.4)	0.64	39 (33)	37 (31.3)	0.88
Time since symptom onset to IMV, days, median, (IQR)	9 (6; 11)	11 (9; 14)	<b>&lt;0.001</b>	9 (7; 13)	12 (9; 16)	<b>&lt;0.001</b>
Time since hospital admission to IMV, days, median, (IQR)	2 (1; 3)	4 (3; 6)	<b>&lt;0.001</b>	2 (1; 3)	5.5 (3; 8)	<b>&lt;0.001</b>
Time since ICU admission to IMV, days, median, (IQR)	0 (0; 0)	3 (2; 4)	<b>&lt;0.001</b>	0 (0; 1)	3 (2; 5)	<b>&lt;0.001</b>
<b>Waves</b>						
1 <sup>st</sup> wave, n (%)	54 (46.9)	41 (35.6)	0.10	53 (44.9)	43 (36.4)	0.23
2 <sup>nd</sup> wave, n (%)	39 (33.9)	51 (44.3)	0.13	34 (28.8)	55 (46.6)	<b>0.007</b>
3 <sup>rd</sup> wave, n (%)	19 (16.5)	19 (16.5)	1	29 (24.5)	20 (16.9)	0.57
4 <sup>th</sup> wave, n (%)	3 (2.6)	4 (3.4)	1	2 (1.6)	0 (0)	0.49
<b>Outcomes</b>						
IMV days, median, (IQR) †	13 (9; 25)	15 (8; 32)	0.61	12 (8; 24)	19 (8; 30)	0.28

ICU days, median, (IQR) †	18 (12; 35)	27 (18; 46)	<b>0.003</b>	21 (12; 31)	29 (15; 45)	<b>0.02</b>
Prone position, n (%)	82 (71.3)	96 (83.4)	<b>0.04</b>	97 (82.9)	98 (83)	1
ECMO, n (%)	2 (1.7)	3 (2.6)	1	1 (0.8)	6 (5)	0.11
Neuromuscular blockade, n (%)	93 (80.8)	98 (85.2)	0.48	106 (90.6)	104 (88.1)	0.67
ICU mortality, n (%)	31 (21)	48 (32.6)	<b>0.003</b>	35 (29.6)	53 (44.9)	<b>0.02</b>
Hospital mortality, n (%)	22 (19.1)	43 (37.3)	<b>0.003</b>	36 (30.5)	55 (46.6)	<b>0.01</b>
90-day mortality, n (%)	31 (23.8)	51 (37.7)	<b>0.01</b>	37 (33.9)	54 (48.2)	<b>0.04</b>

Early intubation is considered as  $\leq 48$  hours and delayed intubation, as  $> 48$  hours from ICU admission. Definition of abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRP: C reactive protein; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; IMV: invasive mechanical ventilation; IQR: interquartile range; and PaCO<sub>2</sub>: partial pressure of CO<sub>2</sub> in the arterial blood. Percentages calculated with non-missing data only. Patients included in the subgroup analysis received at least one session of NIV and/or HFNC before intubation. Variables used to perform PS matching included age, sex, respiratory rate at hospital admission, PaO<sub>2</sub>/F<sub>I</sub>O<sub>2</sub> at hospital admission (categorised as  $>300$  mmHg;  $200 \text{ mmHg} < \text{PaO}_2/\text{F}_I\text{O}_2 \leq 300$  mmHg;  $100 \text{ mmHg} < \text{PaO}_2/\text{F}_I\text{O}_2 \leq 200$  mmHg;  $\text{PaO}_2/\text{F}_I\text{O}_2 \leq 100$  mmHg), days between hospital and ICU admission (categorised as  $\leq$  or  $> 2$  days), chronic immunosuppression, corticosteroid treatment and COVID-19 wave. After excluding patients with missing values, we had a population of 455 patients treated only with HFNC and 396 for patients with NIV +/- HFNC. Table 5 in the supplemental material shows standardised mean differences in baseline covariates from the matched population. † Analysed only in survivors. Boldface entries indicate statistical significance.

### Supplementary Table S10

Gas exchange, mechanical ventilation parameters and respiratory mechanics of critically ill patients with COVID-19 receiving either early or delayed intubation (matched population).

Variables	Early	Delayed	<i>p value</i>
	intubation	intubation	
	N = 307	N = 307	
PaO <sub>2</sub> /F <sub>I</sub> O <sub>2</sub> , median, (IQR)	109 (79; 156)	112 (79; 163)	0.78
Ventilatory ratio, median, (IQR)	1.61 (1.36; 1.98)	1.62 (1.36; 2.06)	0.59
Tidal volume /PBW, median, (IQR)	7.1 (6.32; 8.17)	6.86 (6.18; 7.56)	<b>0.01</b>
Respiratory rate, rpm, median, (IQR)	20 (18; 24)	21 (18; 24)	0.73
PEEP, cmH <sub>2</sub> O, median, (IQR)	12 (10; 14)	12 (10; 14)	0.80
Peak inspiratory pressure, cmH <sub>2</sub> O, median, (IQR)	31 (28; 36)	32 (29; 36)	0.27
Positive end-inspiratory pressure, cmH <sub>2</sub> O, median, (IQR)	24 (21; 28)	25 (23; 28)	<b>0.01</b>
Driving pressure, cmH <sub>2</sub> O, median, (IQR)	12 (9; 15)	13 (10; 15)	<b>0.03</b>

Early intubation is considered as  $\leq 24$  hours and delayed intubation, as  $> 24$  hours from ICU admission. Definition of abbreviations: IQR: interquartile range; PBW: predicted body weight; PEEP: positive end-expiratory pressure; RPM: respirations per minute. Percentages calculated with non-missing data only. Boldface entries indicate statistical significance.

### Supplementary Table S11

Gas exchange, mechanical ventilation parameters and respiratory mechanics of critically ill patients with COVID-19 receiving either early or delayed intubation (48-hour timepoint analysis, matched population).

Variables			
	Early	Delayed	
	intubation	intubation	<i>p value</i>
	N = 229	N = 229	
PaO <sub>2</sub> /F <sub>I</sub> O <sub>2</sub> , median, (IQR)	125 (83.3; 178.3)	101.8 (75.6; 148.7)	<b>0.007</b>
Ventilatory ratio, median, (IQR)	1.68 (1.39; 2.19)	1.59 (1.36; 1.92)	0.13
Tidal volume /PBW, median, (IQR)	7.02 (6.30; 7.79)	6.81 (6.18; 7.39)	<b>0.01</b>
Respiratory rate, rpm, median, (IQR)	20 (18; 24)	22 (20; 24)	0.13
PEEP, cmH <sub>2</sub> O, median, (IQR)	12 (10; 14)	12 (10; 14)	0.32
Peak inspiratory pressure, cmH <sub>2</sub> O, median, (IQR)	32 (29; 36)	32 (29; 37)	0.35
Positive end-inspiratory pressure, cmH <sub>2</sub> O, median, (IQR)	25 (22; 28)	26 (23; 28)	0.16
Driving pressure, cmH <sub>2</sub> O, median, (IQR)	12 (10; 15)	13 (10; 16)	0.14

Early intubation is considered as  $\leq 48$  hours and delayed intubation, as  $> 48$  hours from ICU admission. Definition of abbreviations: IQR: interquartile range; PBW: predicted body weight; PEEP: positive end-expiratory pressure; RPM: respirations per minute. Percentages calculated with non-missing data only. Boldface entries indicate statistical significance.