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Early View

Original research article

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

Jordi Riera, Enric Barbeta, Adrián Tormos, Ricard Mellado-Artigas, Adrián Ceccato, Anna Motos, Laia Fernández-Barat, Ricard Ferrer, Darío García-Gasulla, Oscar Peñuelas, José Ángel Lorente, Rosario Menéndez, Oriol Roca, Andrea Palomeque, Carlos Ferrando, Jordi Solé-Violán, Mariana Novo, María Victoria Boado, Luis Tamayo, Ángel Estella, Cristóbal Galban, Josep Trenado, Arturo Huerta, Ana Loza, Luciano Aguilera, José Luís García Garmendia, Carme Barberà, Víctor Gumucio, Lorenzo Socias, Nieves Franco, Luis Jorge Valdivia, Pablo Vidal, Víctor Sagredo, Ángela Leonor Ruiz-García, Ignacio Martínez Varela, Juan López, Juan Carlos Pozo, Maite Nieto, José M Gómez, Aaron Blandino, Manuel Valledor, Elena Bustamante-Munguira, Ángel Sánchez-Miralles, Yhivian Peñasco, José Barberán, Alejandro Ubeda, Rosario Amaya-Villar, María Cruz Martín, Ruth Jorge, Jesús Caballero, Judith Marin, José Manuel Añón, Fernando Suárez Sipmann, Guillermo Muñiz, Álvaro Castellanos-Ortega, Berta Adell-Serrano, Mercedes Catalán, Amalia Martínez de la Gándara, Pilar Ricart, Cristina Carbajales, Alejandro Rodríguez, Emili Díaz, Mari C de la Torre, Elena Gallego, Luisa Cantón-Bulnes, Nieves Carbonell, Jessica González, David de Gonzalo-Calvo, Ferran Barbé, Antoni Torres, on behalf of the CiberesUCICOVID Consortium

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

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Abstract:

Background: The primary aim of our study was to investigate the association between intubation timing and hospital mortality in critically ill patients with COVID-19-associated respiratory failure. We also analysed both the impact of such timing throughout the first four pandemic waves and the influence of prior non-invasive respiratory support on outcomes.

Methods: This is a secondary analysis of a multicentre, observational and prospective cohort study that included all consecutive patients undergoing invasive mechanical ventilation due to COVID-19 from across 58 Spanish intensive care units (ICU) participating in the CIBERESUCICOVID project. The study period was between 29 February 2020 and 31 August 2021. Early intubation was defined as that occurring within the first 24 hours of intensive care unit (ICU) admission. Propensity score (PS) matching was used to achieve balance across baseline variables between the early intubation cohort and those patients who were intubated after the first 24 hours of ICU admission. Differences in outcomes between early and delayed intubation were also assessed. We performed sensitivity analyses to consider a different timepoint (48 hours from ICU admission) for early and delayed intubation.

Results: Of the 2725 patients who received invasive mechanical ventilation, a total of 614 matched patients were included in the analysis (307 for each group). In the unmatched population, there were no differences in mortality between the early and delayed groups. After PS matching, patients with delayed intubation presented higher hospital mortality (27.3% vs. 37.1%, p =0.01), ICU mortality (25.7% vs. 36.1%, p = 0.007) and 90-day mortality (30.9% vs. 40.2%, p = 0.02) when compared to the early intubation group. Very similar findings were observed when we used a 48-hour timepoint for early or delayed intubation. The use of early intubation decreased after the first wave of the pandemic (72%, 49%, 46% and 45% in the first, second, third and fourth wave, respectively; first vs. second, third and fourth waves p < 0.001). In both the main and sensitivity analyses, hospital mortality was lower in patients receiving high-flow nasal cannula (n = 294) who were intubated earlier. The subgroup of patients undergoing NIV (n = 214) before intubation showed higher mortality when delayed intubation was set as that occurring after 48 hours from ICU admission, but not when after 24 hours.

Conclusions: In patients with COVID-19 requiring invasive mechanical ventilation, delayed intubation was associated with a higher risk of hospital mortality. The use of early intubation significantly decreased throughout the course of the pandemic. Benefits of such an approach occurred more notably in patients who had received high-flow nasal cannula.

Key words: COVID-19, intubation timing, early intubation, delayed intubation.

Take-home message: In patients who require intubation and invasive mechanical ventilation due to COVID-19-associated acute respiratory failure, delays in implementation may increase the risk of mortality.

Introduction

Debate has arisen as it relates to determining when to start invasive mechanical ventilation (MV) in critically ill patients with coronavirus infectious disease 2019 (COVID-19) presenting with respiratory failure [1-3]. Clinicians who advocate treating such patients with non-invasive respiratory support [i.e., high-flow nasal cannula (HFNC), non-invasive ventilation (NIV) and continuous positive airway pressure (CPAP)] argue that this strategy may avoid intubation and minimise the likelihood of well-known complications associated with invasive MV [2,3]. On the other hand, increasing time on non-invasive support with spontaneous ventilation has been shown to possibly put patients at risk of self-inflicted lung injury (PSILI) and increase their chances of death if invasive MV is finally needed [4,5] . In randomised clinical trials, NIV and CPAP have shown to reduce intubation requirements in patients with COVID-19-associated acute respiratory failure [6,7]. However, patients in whom such interventions failed presented a longer time elapsing since the start of non-invasive respiratory support to intubation [6]. It remains unknown whether this delay in invasive MV start worsens clinical outcomes. Whilst there have been investigations exploring intubation timing and clinical outcomes, results have been conflicting. Some studies in which intubation was delayed have reported an association with worse outcomes [5, 8], whereas others have found none [9].

The main objective of this study was to compare the risk of hospital mortality between patients intubated within the first 24 hours of ICU admission (early intubation) and those intubated after that time frame (delayed intubation). As a secondary objective, we analysed changes in these practices and their impact throughout the initial four pandemic waves in Spain. Furthermore, we investigated whether the prior use of NIV or HFNC had any influence on mortality between the early and delayed intubation groups. Finally, we performed a sensitivity analysis considering a different timepoint (intubation within or after 48 hours from ICU admission) for early and delayed intubation.

Materials and Methods

Study design

This is a secondary analysis of a multicentre, observational and prospective cohort study that included all consecutive patients undergoing invasive MV due to COVID-19 from across 58 Spanish intensive care units (ICU) participating in the CIBERESUCICOVID project (NCT04457505) (details of participating centres in Table 1, supplemental material). The study period was between 29 February 2020 and 31 August 2021. Two cohorts were established: early intubation and delayed intubation. The former was defined as those patients receiving the procedure within the first 24 hours of ICU admission, whilst the latter as those receiving the procedure after the first day of ICU admission. Clinical outcomes were compared between the early and delayed intubation groups. Moreover, we analysed the influence of the Spanish epidemic waves on the proportion of patients intubated within or after 24 hours of ICU admission, determining whether these different periods had any impact on outcomes. We also did a subgroup analysis based on the non-invasive respiratory support used prior to intubation and performed sensitivity analyses considering a 48-hour timepoint (intubation within or after 48 hours from ICU admission) to explore other understandings of early or delayed intubation. Table 2 (supplemental material) lists the periods that comprised each wave.

The study was approved by the Institution's Internal Review Board (Comité Ètic d'Investigació Clínica, registry number HCB/2020/0370). De-identified data were collected and stored in Research Electronic Data Capture (REDCap). Trained local researchers incorporated data from patients' medical records into a separate database. Prior to statistical analyses, three independent and experienced data collectors trained in critical care (PC, AM, CS) reviewed the data; in cases of query, site investigators were contacted. Missing analyses were performed, and site investigators were approached to obtain as much reliable and complete data as possible.

Study population and data collection

Inclusion criteria comprised the following characteristics: age ≥ 18 years; ICU admission and a confirmed diagnosis of SARS-CoV-2 by real-time reverse-transcription quantitative polymerase chain reaction (RT-qPCR) testing on nasopharyngeal swabs or lower respiratory tract aspirates. Exclusion criteria included the following: no requirement for orotracheal intubation; requirement for emergent intubation at hospital admission or outside of the ICU; no available data at either baseline or hospital discharge; and ICU admission due to other reasons (Figure 1).

After enrolment, prior epidemiologic data regarding demographics, comorbidities, clinical symptoms and disease chronology were recorded. Site researchers subsequently collected data acquired at hospital and ICU admission. Follow-up was extended to death or hospital discharge. Data registered included vital signs; non-invasive respiratory support devices (i.e., conventional oxygen, HFNC and NIV); the use of adjunctive therapies (i.e., prone position); laboratory findings and arterial blood gases. We, furthermore, collected data on pharmacologic treatments administered at and during hospital or ICU admission until either ICU or hospital discharge, or death. Worst event values were preferentially recorded.

Objectives and outcomes

The primary aim of this study was to evaluate hospital mortality in relation to intubation timing implemented (i.e., early or delayed intubation). For secondary objectives, we analysed differences in ICU and 90-day mortality; duration of both ICU admission and invasive MV; and the need for rescue therapies. We also evaluated changes in intubation timing and their respective effects throughout the pandemic. Finally, we assessed both primary and secondary outcomes, considering the type of non-invasive respiratory support used before intubation.

Statistical analysis

Number and percentage of patients were reported as categorical variables, whilst the median (first quartile−third quartile) as continuous variables. Percentages were calculated, excluding missing data. Categorical variables were compared using either the Chi-squared test or Fisher's exact test, whereas

continuous variables were compared using the nonparametric Mann–Whitney U test or the parametric T-test.

Propensity score (PS) matching [10,11] was used to achieve balance between the early and delayed intubation groups. To match the two cohorts in both the 24- and 48-hour timepoint analyses, we used a 1:1 nearest-neighbour matching, without replacement and within a caliper width of 0.005 for the general population and 0.05 for subgroup analyses. The propensity score was determined—irrespective of outcome—using a multivariable logistic regression to predict the influence of several predetermined variables on early/delayed intubation. Variables were chosen for inclusion in PS calculations according to methods set forth by Brookhart et al. [12]. Criteria to include variables in this model were based on those that could affect the likelihood of outcome occurrence and study treatments to be received. When determining independent variables to predict the likelihood of intubation within the first 24 hours of ICU admission or afterwards, we selected age, sex, chronic immunosuppression, respiratory rate at hospital admission, PaO_2/F_IO_2 at hospital admission (categorised as >300 mmHg; 200 mmHg < PaO_2/F_IO_2 ≤ 300 mmHg; 100 mmHg < PaO_2/F_IO_2 ≤ 200 mmHg; PaO_2/F_IO_2 ≤ 100 mmHg), time from hospital admission to ICU admission (≤ or > 2 days), treatment with corticosteroids for COVID-19, and COVID-19 wave. An adequate model fit with calibration of the PS was demonstrated by logistic modelling that included covariates (24-hour timepoint: goodness-of-fit, p =0.28 for general population; p = 0.16 for HFNC and p = 0.13 for NIV; 48-hour timepoint: goodness-of-fit, p = 0.07 for general population; p = 0.53 for HFNC and p = 0.08 for NIV). Proper adjustment was assessed with standardised mean differences (SMD) in the matched population, whilst covariate imbalance was defined with an SMD threshold > 0.2 [13].

First, to evaluate the effect of timing of intubation on in-hospital mortality, a logistic regression model was used in the matched population; odds ratio (OR) and 95% confidence interval (CI) were calculated. Then, to describe in-hospital mortality, we also employed a competing risk model [14], considering hospital discharge as a competing risk for mortality. Survival curves for patients with early and delayed intubation were obtained and compared using the cumulative incidence function and Gray's test, respectively [15]. Patients who were transferred to another hospital were censored in the survival analyses.

Finally, we performed exploratory subgroup analyses for the type of non-invasive respiratory support used before intubation and each epidemic wave in Spain.

The level of significance was set at 0.05 (two-tailed), and all statistical analyses were performed with Python 3.7 and R version 4.0.3.

Results

During the study period, 7301 patients required admission to participating ICUs. Of these, 2835 were not intubated; 1741 were excluded for other reasons (Figure 1). The study, therefore, included a total of 2725 subjects, of whom 1694 received early intubation and 1031 received delayed intubation.

Characteristics of the population

Median age was 64 (56-71) years, and most patients were male (71.2%). More than half of the cohort (57.9%) was recruited during the first wave of the pandemic. The most frequent comorbidity was hypertension (52.6%). Chronic immunosuppression was present in 523 (19.1%) patients, and most patients (86.5%) received corticosteroids at ICU admission for COVID-19. Despite this, patients exhibited a high inflammatory response and lymphopenia. At hospital admission, median PaO_2/F_IO_2 and respiratory rate were 219 (128; 281) mmHg and 24 (20; 30) breaths per minute, respectively. At this time point, 576 (21.6%) and 346 (12.8%) patients received support with HFNC and NIV, respectively. Table 1 describes the characteristics of the cohort according to intubation timing. In summary, those receiving early intubation were older and less chronically immunocompromised. They also presented a slightly lower body mass index. At hospital admission, PaO_2/F_IO_2 of patients intubated early was slightly higher and respiratory rate mildly lower. Time since symptom onset to intubation was shorter in the early intubation group.

Mortality according to intubation timing

Overall hospital mortality was 37.6%. The unmatched analysis found no differences in hospital mortality—37.8% for patients receiving early intubation and 37.2% for those receiving delayed intubation ($p = 0.77$). Patients with a similar probability of belonging to the early or delayed intubation group were selected based on the variables chosen for PS matching. After excluding patients with missing values in the variables used for the PS, we identified a cohort of 307 cases and 307 controls. Time since both symptom onset and hospital admission to intubation was two days more in the delayed intubation group. In the matched cohort, hospital mortality in patients receiving delayed intubation was significantly higher (37.1% vs. 27.3%, $p = 0.01$). Logistic regression analyses revealed that, in comparison with delayed intubation,

intubation within the first 24 hours of ICU admission was associated with a reduction in hospital mortality risk; the odds ratio was 0.63 (95% CI 0.45–0.89, p=0.01). Figure 2 shows survival curves obtained by the cumulative incidence function. Similarly, 90-day mortality was 30.9% 40.2% in the in the early and delayed intubation groups, respectively (p = 0.02). ICU mortality was also higher in patients intubated after 24 hours of ICU admission (25.7% in the early intubation group vs. 36.1% in the delayed intubation group, p = 0.007). In the sensitivity analyses, we considered intubation within the first 48 hours from ICU admission as early. We found that hospital mortality was higher in the delayed intubation group (43.27% vs. 27.07 % p = <0.001). Time since symptom onset and hospital admission to intubation were three days more in the delayed intubation group (Table 3, supplemental material).

Table 1. Characteristics and outcomes of critically ill patients with COVID-19 according to intubation timing.

Variables	**Before PS matching (N = 2725)**			**After PS matching (N = 614)**		
	Early intubation (n = 1694)	**Delayed intubation (n = 1031)**	***p value***	**Early intubation (n = 307)**	**Delayed intubation (n = 307)**	***p value***
Age, years, median, (IQR)	65 (57; 72)	63 (55;71)	**<0.001**	64 (56; 71)	64 (57; 71)	0.83
Sex, female, n (%)	499 (29.4)	285 (27.6)	0.31	100 (32.5)	87 (28.3)	0.29
BMI, Kg/m^2, median, (IQR)	28.4 (25.7; 31.8)	29.1 (26.2; 32.3)	**0.01**	29.4 (26.4; 33.5)	29.3 (26.1; 32.3)	0.19
Hypertension, n (%)	885 (52.2)	549 (53.2)	0.63	165 (53.7)	169 (54.2)	0.80
Diabetes mellitus, n (%)	416 (24.5)	265 (25.7)	0.52	78 (25.4)	84 (27.3)	0.64
Chronic cardiac failure, n (%)	209 (12.3)	133 (12.9)	0.67	37 (12)	45 (14.6)	0.40
COPD, n (%)	164 (9.4)	98 (9.5)	0.89	38 (12.3)	35 (11.4)	0.80
Immunodepression, n (%)	286 (16.8)	237 (22.9)	**<0.001**	53 (17.2)	45 (14.6)	0.44
Received corticosteroids, n	1425(84.9)	910 (89.2)	**0.002**	281 (91.5)	274 (89.2)	0.41

(%)						
Clinical characteristics at hospital admission						
PaO_2/F_IO_2 , median, (IQR)	230.1 (156.7; 290.4)	190.7 (98.6; 267.7)	<**0.001**	214.2 (142.8; 267.2)	216.6 (114; 275.7)	0.97
Respiratory rate, respiration per minute, median, (IQR)	24 (20; 29)	25 (20; 31)	<**0.001**	25 (20; 31.5)	25 (20; 30)	0.43
$PaCO_2$, mmHg, median, (IQR)	33.2 (30; 38)	34 (30.3; 38)	0.18	34 (30; 38)	33.6 (29.9; 37.7)	0.46
pH, median, (IQR)	7.45 (7.41; 7.47)	7.45 (7.41; 7.47)	0.37	7.45 (7.42; 7.48)	7.45 (7.42; 7.48)	0.63
HFNC, n (%)*	836 (61.7)	876 (91.1)	<**0.001**	178 (71.7)	263 (91.9)	<**0.001**
NIV n (%)**	588 (35.8)	375 (36.6)	0.53	90 (29.7)	127 (41.6)	**0.002**
CRP, mg/dL, median, (IQR)	12.5 (6.9; 20.3)	12.6 (6.9; 21.4)	0.31	13.5 (8; 20.7)	13.7 (7.9; 20.8)	0.66
Lymphocyte count, 10^9 cells/L, median, (IQR)	0.8 (0.58; 1.1)	0.8 (0.58; 1.09)	0.73	0.8 (0.6; 1.1)	0.8 (0.6; 1.06)	0.49
Platelets, 10^9 cells/L, median, (IQR)*	179 (143; 231)	186 (142; 239)	0.18	189 (154; 233)	178 (145; 233)	0.12
D-dimer, mg/L, median, (IQR)	0.67 (0.4; 1.11)	0.64 (0.37; 1.17)	0.29	0.63 (0.38; 1.1)	0.63 (0.37; 1.16)	0.83
Creatinine, mg/dL, median, (IQR)	0.98 (0.8; 1.2)	0.95 (0.7; 1.2)	0.61	0.96 (0.8; 1.21)	0.93 (0.7; 1.2)	0.62
Lactate, mg/dL, median, (IQR)	12.6 (9; 17.1	13.4 (9.9; 17.1)	0.31	12.61 (9; 16.2)	11.71 (9; 16)	0.88
Disease chronology						
Time since symptom onset to ICU admission, days, median, (IQR)	10 (7; 13)	8 (6; 11)	<**0.001**	9 (7; 11)	8 (7; 11)	0.38
Patients spending >2 days in hospital before ICU admission, n (%)	1002 (59.18)	359 (34.82)	<**0.001**	108 (35.18)	100 (32.57)	0.55
Time since symptom onset to IMV, days, median, (IQR)	10 (7; 13)	11 (8; 14)	<**0.001**	9 (7; 11)	11 (8; 14)	<**0.001**
Time since hospital admission to IMV,	3 (2; 5)	4 (2; 6)	<**0.001**	2 (1; 3)	4 (2; 6)	<**0.001**

days, median, (IQR)						
Time since ICU admission to IMV, days, median, (IQR)	0 (0; 0)	2 (1; 3)	**<0.001**	0 (0; 0)	2 (1; 3)	**<0.001**
Waves						
1st wave, n (%)	1148 (67.7)	430 (41.7)	**<0.001**	150 (48.8)	145 (47.2)	0.74
2nd wave, n (%)	369 (21.7)	383 (37.1)	**<0.001**	102 (33.2)	122 (39.7)	0.11
3rd wave, n (%)	139 (8.2)	157 (15.2)	**<0.001**	50 (16.2)	38 (12.3)	0.20
4th wave, n (%)	20 (1.18)	24 (2.3)	**0.02**	5 (1.6)	2 (0.6)	0.45
Outcomes						
IMV days, median, (IQR)†	13 (8; 25)	14 (8; 29)	0.22	13 (8; 24)	18 (9; 31.5)	**0.01**
ICU days, median, (IQR)†	17.5 (11; 33)	23 (14; 40)	**<0.001**	17 (11; 32)	27 (16; 44)	**<0.001**
Prone position, n (%)	1292 (76.6)	797 (77.6)	0.57	220 (71.6)	220 (78.4)	0.06
Neuromuscular blockade, n (%)	1442 (85.2)	860 (83.6)	0.27	247 (80.7)	262 (85.3)	0.13
ECMO, n (%)	27 (1.5)	31 (3)	**0.01**	6 (1.9)	6 (1.9)	1
ICU mortality, n (%)	598 (35.3)	360 (35)	0.86	79 (25.7)	111 (36.1)	**0.007**
Hospital mortality, n (%)	641 (37.8)	384 (37.2)	0.77	84 (27.3)	114 (37.1)	**0.01**
90-day mortality, n (%)	636 (41)	381 (40.5)	0.83	85 (30.9)	113 (40.2)	**0.02**

Early intubation was considered as ≤ 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; $PaCO_2$: partial pressure of CO_2 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_2/F_IO_2 at hospital admission (categorised as >300 mmHg; 200 mmHg < PaO_2/F_IO_2 ≤ 300 mmHg; 100 mmHg < PaO2/FiO2 ≤ 200 mmHg; PaO_2/F_IO_2 ≤ 100 mmHg), days between hospital and ICU admission (categorised as ≤ 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 4 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.

Changes in intubation timing throughout the pandemic

During the first wave of the pandemic, most patients receiving MV were intubated within the first 24 hours of ICU admission (n = 1148; 72%). The mortality rate in this early intubation cohort was higher than those receiving delayed intubation; however, these patients were older and the time since symptom onset to intubation was not shorter than that in patients with delayed intubation (Table 6, supplemental material). In the subsequent waves, the number of patients receiving early intubation progressively decreased (49% in the second wave, 46% in the third wave and 45% in the fourth wave, with a $p < 0.001$ vs. the first wave) (Figure 3). The mortality rate also changed: the second wave saw a significant decrease in death in patients who underwent early intubation. In the third and fourth waves, mortality was also lower in the early intubation cohort; however, this was not statistically significant. Findings about the impact of early intubation on mortality remained intact when we balanced cohorts and considered the wave during which patients received the intervention (Table 1).

Subgroup analysis of patients treated with NIV vs HFNC

Before intubation, whereas 963 (35.5%) underwent NIV with or without HFNC, 1712 (73.95%) patients received at least one session of HFNC with or without NIV and 1082 (39.5%) patients exclusively received HFNC (without NIV) (supplementary table 7). After PS matching, we obtained a population of 294 patients treated only with HFNC and 214 patients with NIV (Table 2). We identified a higher mortality risk in patients with HFNC and delayed intubation (21.7% vs. 34.6%, $p = 0.01$). However, we did not observe such a difference in those patients receiving NIV before intubation (32.7% vs. 39.2%, $p = 0.39$). In the sensitivity analyses, we found higher mortality in patients receiving both HFNC and NIV and with delayed intubation. In patients treated with HFNC, hospital mortality was 37.3% in those with delayed intubation and 19.1% in

those with early intubation (p = 0.003). For patients with NIV, it was 46.6% and 30.5% in the delayed and early intubation groups, respectively (p = 0.01) (Table 8 and 9, supplemental material).

Table 2 – Characteristics and outcomes of critically ill patients with COVID-19 receiving either early or delayed intubation depending on prior use of HFNC or NIV (matched population).

Variables	**High-flow nasal cannula N = 294**			**Non-invasive mechanical ventilation with or without high-flow nasal cannula N = 214**		
	Early intubation (n = 147)	**Delayed intubation (n = 147)**	***p value***	**Early intubation (n = 107)**	**Delayed intubation (n = 107)**	***p value***
Age, years, median, (IQR)	63 (56; 69)	66 (57; 71)	0.23	64 (56; 70)	64 (58; 71)	0.73
Sex, female, n (%)	46 (31.2)	44 (29.9)	0.89	29 (27.1)	23 (21.5)	0.42
BMI, Kg/m^2, median, (IQR)	28.5 (26; 31.6)	28.3 (25.9; 31.9)	0.71	30.9 (27.5; 34.1)	29.8 (26.5; 32)	0.06
Hypertension, n (%)	65 (44.2)	77 (52.3)	0.19	62 (57.9)	57 (53.2)	0.58
Diabetes mellitus, n (%)	34 (23.1)	34 (23.1)	1	29 (27.1)	29 (27.1)	1
Chronic cardiac failure, n (%)	15 (10.2)	18 (12.2)	0.71	13 (12.1)	14 (13)	1
COPD, n (%)	16 (10.8)	18 (12.2)	0.85	13 (12.1)	14 (13)	1
Immunodepression, n (%)	20 (13.6)	19 (12.9)	1	23 (21.5)	20 (18.6)	0.73
Received corticosteroids, n (%)	133 (90.4)	134 (91.1)	1	98 (91.5)	95 (88.7)	0.64
Clinical characteristics at hospital admission						
PaO_2/F_IO_2, median,	230 (172;	231.4		194.2	207.1	

(IQR)	290.4)	(146.5; 307.3)	0.80	(130.9; 263.5)	(114; 271.1)	0.81
Respiratory rate, respiration per minute, median, (IQR)	25 (20; 30)	25 (20; 30)	0.99	24 (20; 32)	25 (22; 30)	0.88
$PaCO_2$, mmHg, median, (IQR)	34 (30; 37)	34 (30.1; 38)	0.41	33 (30; 37)	32 (29; 37)	0.46
pH, median, (IQR)	7.45 (7.42; 7.48)	7.45 (7.43; 7.47)	0.75	7.45 (7.41; 7.48)	7.46 (7.43; 7.48)	0.35
CRP, mg/dL, median, (IQR)	13.9 (8.4; 21.2)	13 (7; 18.5)	0.11	14.1 (8.2; 21)	14.6 (10.3; 24.8)	0.11
Lymphocyte count, 10^9 cells/L, median, (IQR)	0.8 (0.6; 1)	0.8 (0.6; 1)	0.85	0.8 (0.6; 1.13)	0.7 (0.5; 1.01)	0.13
Platelets, 10^9 cells/L, median, (IQR)	188 (145; 238)	176 (139; 232)	0.34	179 (147; 220)	193 (152; 233)	0.82
D-dimer, mg/L, median, (IQR)	0.57 (0.38; 0.9)	0.54 (0.38; 0.99)	0.74	0.65 (0.42; 1)	0.71 (0.39; 1.29)	0.31
Creatinine, mg/dL, median, (IQR)	0.94 (0.8; 1.16)	0.92 (0.79; 1.17)	0.56	0.99 (0.81; 1.28)	0.95 (0.79; 1.3)	0.75
Lactate, mg/dL, median, (IQR)	12.7 (9; 16.8)	10.8 (8.9; 16.2)	0.31	12 (9.9; 14.4)	11.4 (9.2; 15.5)	0.79
Disease chronology						
Time since symptom onset to ICU admission, days, median, (IQR)	9 (7; 11)	8 (7; 11)	0.057	9 (7; 13)	9 (8; 12)	0.92
Patients spending >2 days in hospital before ICU admission, n (%)	52 (35.3)	50 (34)	0.90	54 (50.4)	51 (47.6)	0.78
Time since symptom onset to IMV, days, median, (IQR)	9 (7; 12)	11 (8; 13)	**0.001**	9 (7; 13)	12 (9; 15)	**<0.001**
Time since hospital admission to IMV, days, median, (IQR)	2 (1; 3)	4 (2; 6)	**<0.001**	3 (2; 5)	6 (3; 9)	**<0.001**
Time since ICU admission to IMV, days, median, (IQR)	0 (0; 0)	1 (1; 3)	**<0.001**	0 (0; 0)	2 (1; 4)	**<0.001**
Waves						
1^{st} wave, n (%)	70 (47.6)	59 (40.1)	0.68	57 (53.2)	51 (47.6)	0.49
2^{nd} wave, n (%)	55 (37.4)	67 (45.5)	0.19	30 (28)	41 (38.3)	0.14
3^{rd} wave, n (%)	18 (12.2)	18 (12.2)	1	19 (17.7)	15 (14)	0.57
4^{th} wave, n (%)	4 (2.7)	3 (2)	1	1 (0.9)	0 (0)	1
Outcomes						
IMV days, median,	13 (8; 24)	15 (9; 31)	0.24	16 (9; 27)	18 (9; 31)	0.42

(IQR) †						
ICU days, median, (IQR) †	17 (11; 34)	24 (14; 42)	**0.004**	22 (12; 31)	24 (15; 39)	0.08
Prone position, n (%)	97 (66.4)	117 (79.5)	**0.01**	92 (85.9)	87 (81.3)	0.46
ECMO, n (%)	3 (2)	2 (1.3)	1	5 (4.6)	3 (2.8)	0.72
Neuromuscular blockade, n (%)	113 (76.8)	123 (83.6)	0.18	95 (89.6)	94 (87.8)	0.82
ICU mortality, n (%)	31 (21)	48 (32.6)	**0.003**	34 (31.7)	41 (38.3)	0.39
Hospital mortality, n (%)	32 (21.7)	51 (34.6)	**0.01**	35 (32.7)	42 (39.2)	0.39
90-day mortality, n (%)	31 (23.8)	51 (37.7)	**0.01**	36 (34.2)	41 (40.2)	0.39

Early intubation was considered as ≤ 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; and $PaCO_2$: partial pressure of CO_2 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_2/F_IO_2 at hospital admission (categorised as >300 mmHg; 200 mmHg < PaO_2/F_IO_2 ≤ 300 mmHg; 100 mmHg < PaO_2/F_IO_2 ≤ 200 mmHg; PaO_2/F_IO_2 ≤ 100 mmHg), days between hospital and ICU admission (categorised as ≤ 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 3 in supplemental material shows standardised mean differences in baseline covariates from the matched population. † Analysed only in survivors. Boldface entries indicate statistical significance.

Discussion

In this large cohort study focusing on the effects of intubation timing in patients with COVID-19, we identified a higher risk of hospital mortality in those individuals with delayed intubation (> 24 hours of ICU admission) compared to those intubated within 24 hours of ICU admission. Likewise, we observed an increase in both ICU and 90-day mortality and ICU length of stay and MV duration in those patients intubated after the first 24 hours of ICU admission. Very similar findings were also confirmed when we considered early or delayed intubation with a different timepoint (intubation within 48 hours of ICU admission for early intubation).

The subgroup of patients treated with HFNC in whom intubation was delayed presented higher mortality irrespective of the timepoint used for early or delayed intubation. However, the group of patients treated with NIV prior to intubation (delayed) presented with higher mortality when the timepoint was considered as after 48 hours of ICU admission. Finally, we also found that patients more frequently received intubation and invasive MV within 24 hours of ICU admission in the first wave than in subsequent ones.

Whilst the association between delayed intubation and mortality has been well documented in acute respiratory failure [5,8, 16 - 18], it remains to be clarified in patients with COVID-19. In this population, the association between longer intubation timing and worse clinical outcomes has been controversial, given that several studies reported benefits from early intubation and others showed opposite results. A meta-analysis that comprised 12 observational studies comparing early and delayed intubation (also defined as occurring within or after the first 24 hours of ICU admission) did not report differences in mortality [9]. However, most of the studies included had relevant limitations, such as retrospective nature [19-28] and lack of covariate adjustment [20-27]; significant heterogeneity in study design and clinical characteristics [19-28]; and analyses circumscribed to the first waves of each region [19-28]. On the other hand, similar to our results, one study reported higher chances of survival in patients in whom intubation and invasive MV were started within the first 48 hours of non-invasive respiratory support [29]. Two important factors may explain the differences in outcomes noted in this study [29] and ours when compared to that mentioned earlier [9]. First and foremost, to minimise confounding bias, we selected a population with a similar baseline risk of intubation and mortality using PS matching. We considered covariates that were known to play a significant

role in both the intubation strategy and survival. Second, in PS matching, we accounted for time since hospitalisation to ICU admission. The resulting population, therefore, had a longer time (2 days) of spontaneous breathing from both symptom onset and hospital admission to intubation. Considering that PSILI is inevitably related to spontaneous breathing, this ensured that the delayed intubation group had longer exposure to such event. This message has yet to be suggested in literature and could prove useful in other types of acute respiratory failure.

Importantly, in patients intubated after 24 hours of ICU admission, we found worse respiratory mechanics compared to those intubated earlier (higher driving and positive end-inspiratory pressures with lower tidal volumes and similar positive-end expiratory pressures). This finding is consistent with prior literature [30] and may suggest further lung damage as a result of longer exposure to uncontrolled and spontaneous ventilation. When we considered a 48-hour timepoint for early or delayed intubation, we also observed worse oxygenation during the first day of MV in patients belonging to the latter group. Whilst this could partially explain differences observed in survival, the exact mechanisms that increase the risk of death due to a delayed start in invasive MV are not completely known.

We also examined the potential effect of the type of non-invasive respiratory support used before invasive MV. In the subgroup of patients treated exclusively with HFNC, we reported an increased risk of hospital mortality in those with delayed intubation, irrespective of the timepoint used. However, we did not observe the same association in patients treated with NIV before intubation when we considered early intubation as that occurring within 24 hours of ICU admission. The negative results in this subgroup should not be misinterpreted. The sensitivity analyses performed in the subgroup of patients with NIV, in whom we explored intubation ranges from a 48-hour-timepoint perspective, showed higher mortality in those with delayed treatment. The lack of differences in mortality between the early and delayed intubation groups in the 24-hour timepoint analysis could be explained by the already high mortality of patients treated with NIV. This would suggest that NIV failure could increase the risk of mortality even if intubation is not delayed. The association of NIV failure and higher mortality has been widely reported in acute respiratory failure and has a strong physiologic background [31-33]. The higher mortality found in patients treated with

HFNC would rather suggest that spontaneous ventilation, even without the presence of positive inspiratory pressure, may also be deleterious.

In our study, we evaluated trends in intubation timing throughout the different waves included, finding a significant decrease in early intubation rates. The probable rationale for this finding is the increased confidence of clinicians in treating COVID-19-associated acute respiratory failure non-invasively. In fact, a greater use of NIV and HFNC have been reported in the later periods of the pandemic [34]. In light of our results and others [6,7,29], caution is warranted when assessing the potential benefits (avoidance of intubation) and risks (delayed intubation) of applying such non-invasive therapies in COVID-19.

The strengths of our study include the large population included, the assessment across different periods (four waves), the granularity of data with 58 ICUs included, and the PS analyses performed.

Our study has limitations, though. First, it was not designed in the framework of a target-emulated trial. We excluded patients who were not intubated, and a high proportion of individuals did not need this intervention. Therefore, as some patients may benefit from a wait-and-see approach, we cannot draw firm conclusions on the best strategy for intubation. Second, the arbitrary cut-off point of 24 hours used to define early intubation may elicit critique. However, we defined this time point in accordance with prior literature [9] and clinical prudence. Sensitivity analyses showed robustness of the findings. Third, as result of our design, immortal time bias may have occurred; patients intubated after the 24 hours of ICU admission had to survive to be included. Fourth, since treatment was not randomly allocated, both residual and unmeasured confounding are possible, even after careful covariate adjustment. Fifth, we did not have solid information about the clinical situation immediately before intubation so we used data from hospital admission. Further, we do not have the total time spent on neither non-invasive respiratory support nor in NIV and HFNC settings. Sixth, generalisation of the results may be hindered due to the prevalence of immunisation and changes made in clinical management after the patient recruitment period.

In conclusion, in patients with COVID-19 requiring invasive MV, delayed intubation was associated with a higher risk of hospital mortality when compared to earlier intubation. Patients undergoing HFNC before intubation presented an increased risk of mortality when intubation was delayed irrespective of the timepoint used to consider early or delayed intubation. Patients with NIV presented a higher mortality risk when

delayed intubation was that occurring after 48 hours of ICU admission. Finally, more patients received intubation within 24 hours of ICU admission in the first pandemic wave.

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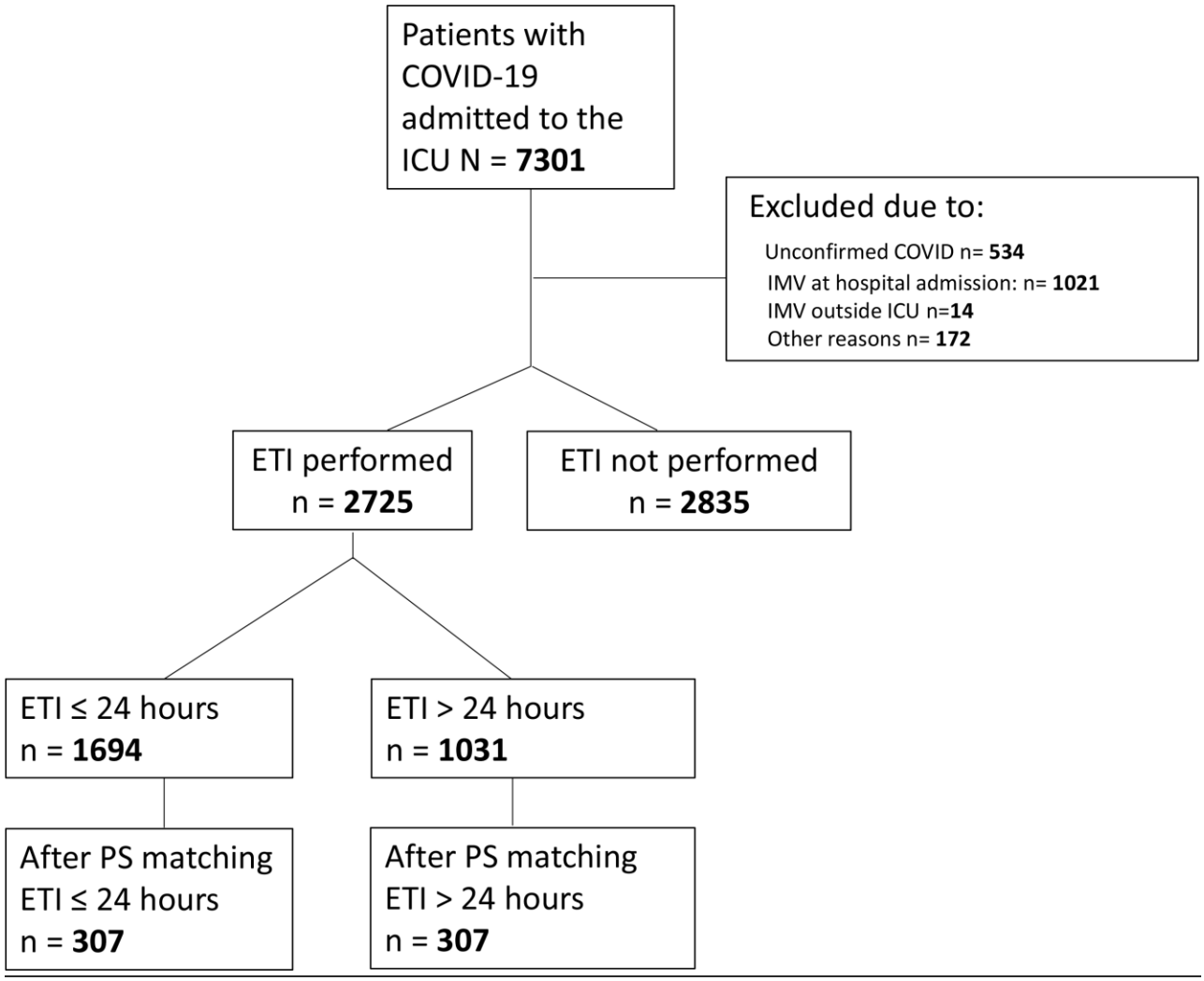
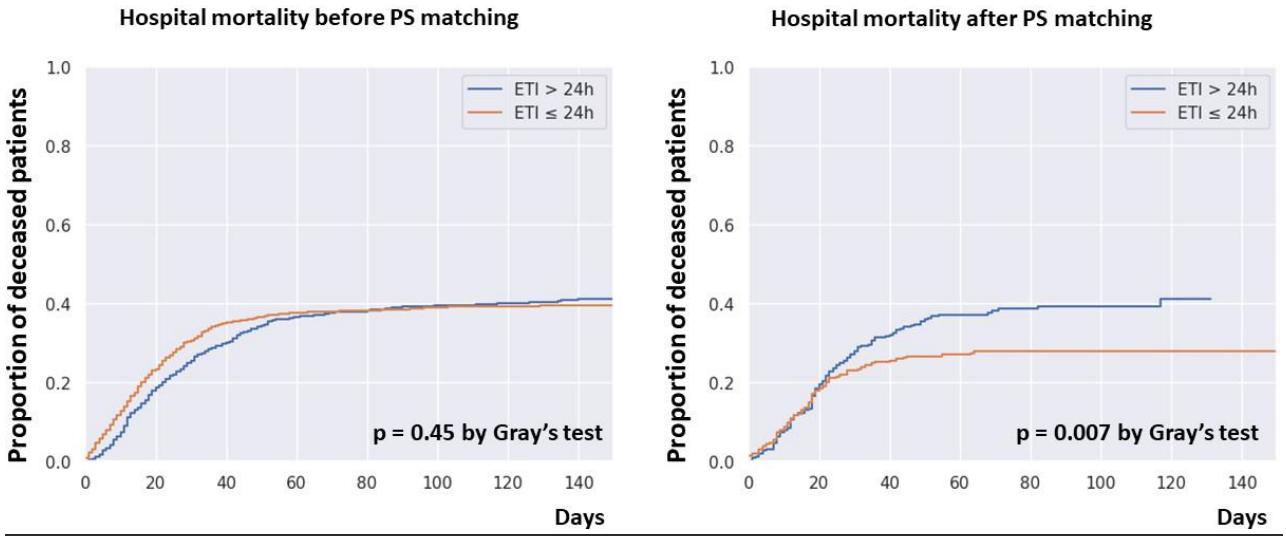
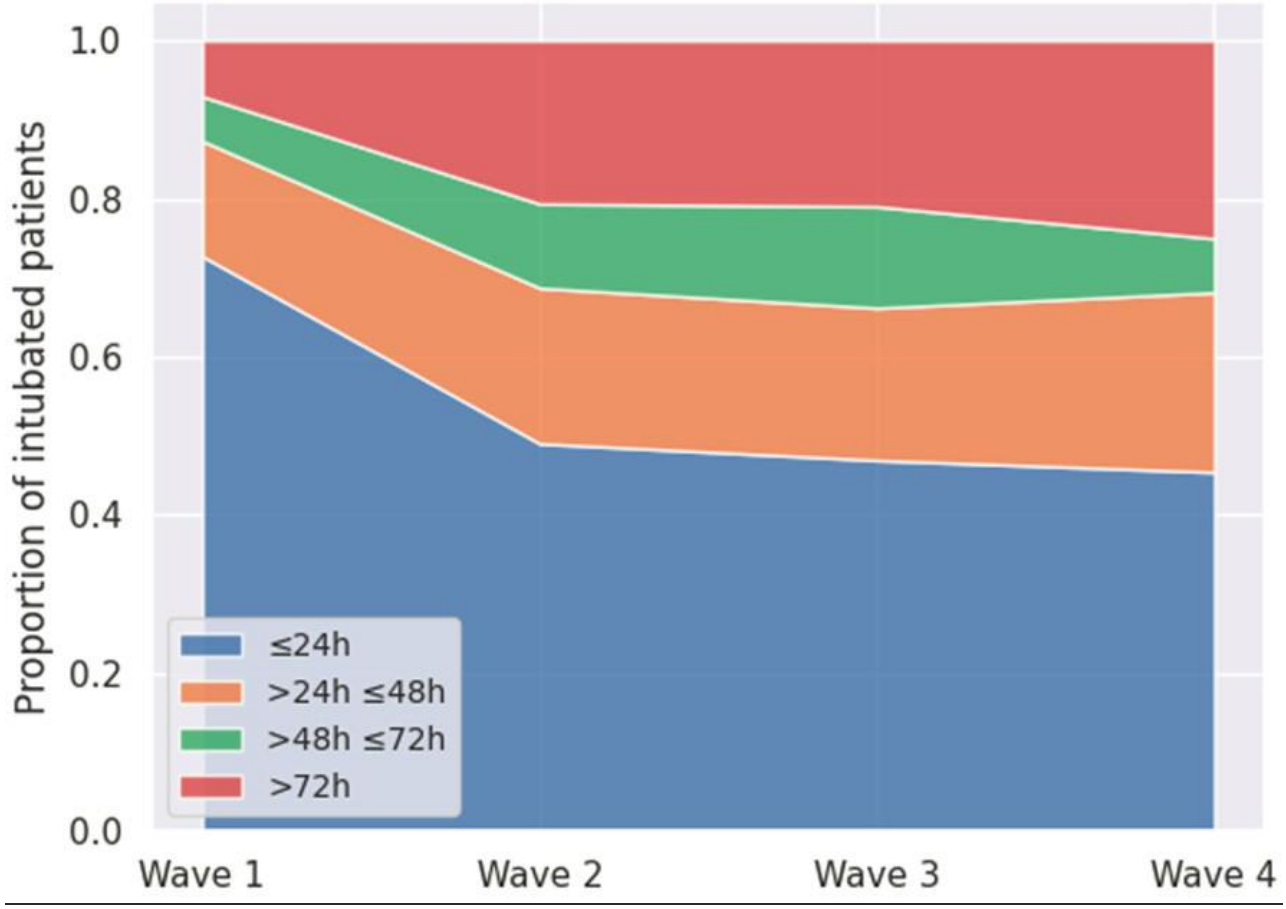
Figure 1. Study flowchart. Inclusion period was from 29 February 2020 to 31 August 2021. Propensity score matching was performed with the following variables: sex, age, respiratory rate at hospital admission, PaO_2/FiO_2 ratio at hospital admission (categorised as >300 mmHg; 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg; 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg; PaO_2/FiO_2 ≤ 100 mmHg), days between hospital and ICU admission (categorised as ≤ or > 2 days), immunodepression, corticosteroid treatment and COVID-19 wave. Definition of abbreviations: ETI: endotracheal intubation; ICU: intensive care unit; IMV: invasive mechanical ventilation; PS: propensity score.

Figure 2. Survival curves of both the overall cohort and adjusted population, as obtained by propensity score matching. In total, 81 of 614 (13.19%) patients were transferred to another hospital and censoured from the survival analysis. Definition of abbreviations: ETI: endotracheal intubation; ICU: intensive care unit.

Figure 3. Proportion of patients with COVID-19 intubated ≤24h; >24 and ≤48h; >48 and ≤72 or >72h since ICU admission in the first, second, third and fourth waves. Proportion of patients intubated ≤24h since ICU admission in the first, second, third and fourth waves. First vs. second, third and fourth waves, $p < 0.001$.


Patients with COVID-19 admitted to the ICU N = 7301
Excluded due to:
Unconfirmed COVID n= 534
IMV at hospital admission: n= 1021
IMV outside ICU n=14
Other reasons n= 172
ETI performed n = 2725
ETI not performed n = 2835
ETI ≤ 24 hours n = 1694
ETI > 24 hours n = 1031
After PS matching ETI ≤ 24 hours n = 307
After PS matching ETI > 24 hours n = 307


Hospital mortality before PS matching
Proportion of deceased patients
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
140
Days
ETI > 24h
ETI ≤ 24h
p = 0.45 by Gray's test
Hospital mortality after PS matching
Proportion of deceased patients
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
140
Days
ETI > 24h
ETI ≤ 24h
p = 0.007 by Gray's test


1.0
0.8
0.6
0.4
0.2
0.0
Proportion of intubated patients
≤24h
>24h ≤48h
>48h ≤72h
>72h
Wave 1
Wave 2
Wave 3
Wave 4

SUPPLEMENTARY ONLINE CONTENT

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

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Supplementary Table 1

Site and Region
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HOSPITAL UNIVERSITARI SON ESPASES / Palma de Mallorca
HOSPITAL UNIVERSITARI SAGRAT COR / Barcelona
HOSPITAL UNIVERSITARIO DE CRUCES / Barakaldo
HOSPITAL UNIVERSITARIO RIO HORTEGA / Valladolid
HOSPITAL UNIVERSITARIO DE JEREZ DE LA FRONTERA / Jerez de la Frontera
HOSPITAL CLINICO UNIVERSITARIO DE SANTIAGO / Santiago de Compostela
HOSPITAL UNIVERSITARI MÚTUA DE TERRASSA / Terrassa
CLÍNICA SAGRADA FAMÍLIA / Barcelona
HOSPITAL VIRGEN DE VALME / Sevilla
HOSPITAL DE BASURTO / Bilbao
HOSPITAL SAN JUAN DE DIOS DEL ALJARAFE / Bormujos
HOSPITAL SANTA MARIA / Lleida
HOSPITAL CLÍNIC DE BARCELONA / Barcelona
HOSPITAL UNIVERSITARI DE BELLVITGE / Hospitalet de Llobregat, L'
HOSPITAL SON LLATZER / Palma de Mallorca
HOSPITAL DE LEÓN / León
COMPLEXO HOSPITALARIO UNIVERSITARIO DE OURENSE / Ourense
HOSPITAL UNIVERSITARIO DE SALAMANCA / Salamanca
HOSPITAL UNIVERSITARIO PRÍNCIPE DE ASTURIAS / Alcalá de Henares
HOSPITAL UNIVERSITARIO LUCUS AUGUSTI / Lugo
COMPLEJO ASISTENCIAL UNIVERSITARIO DE PALENCIA / Palencia
HOSPITAL UNIVERSITARIO REINA SOFÍA / Córdoba
HOSPITAL GENERAL DE SEGOVIA / Segovia
HOSPITAL GENERAL UNIVERSITARIO GREGORIO MARAÑÓN / Madrid
HOSPITAL RAMÓN Y CAJAL / Madrid
HM UNIVERSITARIO PUERTA DEL SUR / Móstoles
HOSPITAL UNIVERSITARIO "SAN AGUSTÍN" / Avilés
HOSPITAL CLÍNICO UNIVERSITARIO DE VALLADOLID / Valladolid
HOSPITAL UNIVERSITARIO SAN JUAN DE ALICANTE / Sant Joan d'Alacant
HOSPITAL UNIVERSITARIO MARQUÉS DE VALDECILLA / Santander
HOSPITAL UNIVERSITARIO HM NUEVO BELEN / Madrid
HOSPITAL PUNTA DE EUROPA / Algeciras
HOSPITAL UNIVERSITARIO HM MONTEPRÍNCIPE / Boadilla del Monte
HOSPITAL UNIVERSITARIO VIRGEN DEL ROCÍO / Sevilla
HOSPITAL UNIVERSITARIO DE TORREJÓN / Torrejón de Ardoz
HOSPITAL NUESTRA SEÑORA DE GRACIA / Zaragoza
HOSPITAL UNIVERSITARI ARNAU DE VILANOVA DE LLEIDA. / Lleida
HOSPITAL UNIVERSITARIO MADRID SANCHINARRO / Madrid
HOSPITAL DEL MAR. / Barcelona
HOSPITAL UNIVERSITARIO DE GETAFE / Getafe
HOSPITAL UNIVERSITARIO LA PAZ / Madrid
HOSPITAL UNIVERSITARIO DE LA PRINCESA / Madrid
HOSPITAL UNIVERSITARIO HM TORRELODONES / Torrelodones
HOSPITAL UNIVERSITARIO CENTRAL DE ASTURIAS / Oviedo
HOSPITAL UNIVERSITARIO Y POLITÉCNICO LA FE / Valencia
HOSPITAL DE TORTOSA VERGE DE LA CINTA / Tortosa
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HOSPITAL UNIVERSITARIO ALVARO CUNQUEIRO / Vigo
HOSPITAL UNIVERSITARI JOAN XXIII DE TARRAGONA / Tarragona
HOSPITAL DE SABADELL / Sabadell
HOSPITAL DE MATARÓ / Mataró
HOSPITAL UNIVERSITARIO SAN PEDRO DE ALCÁNTARA / Cáceres
HOSPITAL VIRGEN MACARENA / Sevilla
HOSPITAL CLÍNICO UNIVERSITARIO DE VALENCIA / Valencia

Supplementary Table 2

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

Wave	Begin Date of Wave	End Date of Wave
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 3 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)**	***p value***	**Early intubation (n = 229)**	**Delayed intubation (n = 229)**	***p value***
Age, years, median, (IQR)	65 (57; 72)	64 (55;70)	**0.007**	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^2, 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)	**<0.001**	44 (19.2)	40 (17.4)	0.71
Received corticosteroids, n (%)	1824(85.1)	511 (92)	**<0.001**	213 (93)	211 (92.1)	0.85
Clinical characteristics at hospital admission						
PaO_2/F_IO_2, median, (IQR)	221.4 (136.2; 282.8)	207.1 (111.2; 274.7)	**0.04**	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
$PaCO_2$, 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)	**<0.001**	94 (41)	102 (44.5)	0.50

NIV n (%)**	727 (34.2)	236 (42.3)	<**0.001**	76 (33.6)	113 (49.5)	**0.001**
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, 10^9 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, 10^9 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
Disease chronology						
Time since symptom onset to ICU admission, days, median, (IQR)	9 (7; 12)	8 (6; 11)	<**0.001**	8 (6; 11)	8 (7; 11)	0.63
Patients spending >2 days in hospital before ICU admission, n (%)	1165 (53.86)	196 (34.94)	<**0.001**	67 (29.2)	64 (27.9.57)	0.83
Time since symptom onset to IMV, days, median, (IQR)	10 (7; 12)	12 (10; 16)	<**0.001**	9 (7; 11)	12 (10; 16)	<**0.001**
Time since hospital admission to IMV, days, median, (IQR)	3 (2; 5)	5 (3; 9)	<**0.001**	2 (1; 3)	5 (3; 8)	<**0.001**
Time since ICU admission to IMV, days, median, (IQR)	0 (0; 0)	3 (2; 5)	<**0.001**	0 (0; 0)	3 (2; 5)	<**0.001**
Waves						
1st wave, n (%)	1382 (63.8)	196 (34.9)	<**0.001**	117 (51)	93 (40.6)	**0.03**
2nd wave, n (%)	524 (24.2)	228 (40.6)	<**0.001**	63 (27.5)	102 (44.5)	<**0.001**
3rd wave, n (%)	198 (9.1)	98 (17.4)	<**0.001**	43 (18.7)	32 (13.9)	0.20
4th wave, n (%)	30 (1.3)	14 (2.5)	0.08	6 (2.6)	2 (0.87)	0.28
Outcomes						
IMV days, median, (IQR)†	13 (8; 29)	17 (8; 29)	0.21	13 (8; 24)	18 (9; 31.5)	**0.01**
ICU days, median, (IQR)†	18 (12; 36)	28 (18; 43)	<**0.001**	17 (11; 32)	27 (16; 44)	<**0.001**

Prone position, n (%)	1638 (76.04)	451 (80.68)	**0.02**	167 (72.9)	192 (84.2)	**0.004**
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)	**0.01**	6 (2.6)	11 (4.8)	0.32
ICU mortality, n (%)	740 (34.2)	218 (38.8)	**0.04**	62 (27.07)	94 (41.05.1)	**0.002**
Hospital mortality, n (%)	792 (36.6)	233 (41.5)	**0.03**	62 (27.07)	99 (43.23)	**<0.001**
90-day mortality, n (%)	784 (39.8)	233 (45)	**0.03**	62 (30.2)	97 (44.5)	**0.003**

Early intubation is considered as ≤ 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; PaCO2: partial pressure of CO2 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, PaO2/FIO2 at hospital admission (categorised as >300 mmHg; 200 mmHg < PaO2/FIO2 ≤ 300 mmHg; 100 mmHg < PaO2/FiO2 ≤ 200 mmHg; PaO2/FIO2 ≤ 100 mmHg), days between hospital and ICU admission (categorised as ≤ 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 4

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	**0.27**
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
Clinical characteristics at hospital admission			
PaO_2/F_IO_2	0.002	0.11	0.01
Respiratory rate	0.06	0.01	0.03
$PaCO_2$	0.03	0.11	**0.2**
pH	0.07	0.07	0.19
HFNC	**0.64**	-	-
NIV	**0.25**	-	-
CRP	0.07	0.16	**0.21**
Lymphocyte count	0.02	0.02	**0.21**
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
Disease chronology			
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	**0.27**	0.02
Time since hospital admission to IMV	**0.21**	**0.48**	**0.40**
Time since ICU admission to IMV	**0.26**	**1.04**	**1.5**
Waves			
1st wave	0.03	0.15	0.12
2nd wave	0.13	0.16	**0.22**
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; $PaCO_2$: partial pressure of CO_2 in the arterial blood; PS: propensity score; SMD: standardised mean differences. Boldface entries indicate significant SMD.

Supplementary Table 5

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	**0.49**
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	**0.21**
Immunodepression	0.04	0.000	0.000
Received corticosteroids	0.03	0.03	0.03
Clinical characteristics at hospital admission			
PaO_2/F_IO_2	0.003	0.17	0.03
Respiratory rate	0.08	**0.22**	0.07
$PaCO_2$	0.07	0.08	0.09
pH	0.02	0.04	0.12
HFNC	0.07	-	-
NIV	**0.33**	-	-
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	**0.32**
Disease chronology			
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	**0.52**	0.03
Time since hospital admission to IMV	**0.29**	**0.76**	**1.04**
Time since ICU admission to IMV	**0.32**	**1.31**	**1.74**
Waves			
1st wave	0.2	**0.21**	0.17
2nd wave	**0.36**	0.20	**0.35**
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; $PaCO_2$: partial pressure of

CO_2 in the arterial blood; PS: propensity score; SMD: standardised mean differences. Boldface entries indicate significant SMD.

Supplementary Table 6

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 7

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)**	***p value***	**Early intubation (n = 588)**	**Delayed intubation (n = 375)**	***p value***
Age, years, median, (IQR)	65 (56; 72)	63 (54; 70)	**0.01**	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^2, 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)	**0.003**
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)	**0.005**
Received corticosteroids, n (%)	447 (85.8)	498 (90.3)	**0.02**	519 (88.5)	340 (90.9)	0.28
Clinical characteristics at hospital admission						
PaO_2/F_IO_2, median, (IQR)	242.8 (178.7; 298.8)	215.2 (118.3; 283.4)	**0.001**	222.5 (149.6; 280.9)	150 (89; 252.2)	**<0.001**
Respiratory rate, respiration per	24 (20; 28)	24 (20; 30)	0.19	24 (20; 30)	27 (22; 32)	**0.005**

minute, median, (IQR)						
$PaCO_2$, 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, 10^9 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, 10^9 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
Disease chronology						
Time since symptom onset to ICU admission, days, median, (IQR)	9 (7; 11)	8 (6; 10)	**0.026**	10 (6; 12)	9 (7; 11)	0.33
Patients spending >2 days in hospital before ICU admission, n (%)	293 (56.1)	196 (35)	<**0.001**	371 (63.1)	127 (33.8)	<**0.001**
Time since symptom onset to IMV, days, median, (IQR)	9 (7; 12)	11 (8; 14)	<**0.001**	10 (8; 14)	11 (9; 15)	<**0.001**
Time since hospital admission to IMV, days, median, (IQR)	3 (2; 5)	4 (2; 6)	<**0.001**	3 (2; 6)	4 (2; 7)	<**0.001**
Time since ICU admission to IMV, days, median, (IQR)	0 (0; 0)	2 (1; 3)	<**0.001**	0 (0; 0)	2 (1; 4)	<**0.001**
Waves						
1^{st} wave, n (%)	307 (58.8)	211 (37.6)	<**0.001**	413 (70.2)	153 (40.8)	<**0.001**

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

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; $PaCO_2$: partial pressure of CO_2 in the arterial blood. Percentages calculated with non-missing data only. † Analysed only in survivors. Boldface entries indicate statistical significance.

Supplementary Table 8

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)**	***p value***	**Early intubation (n = 727)**	**Delayed intubation (n = 236)**	***p value***
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^2, 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)	**0.04**
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)	**0.01**	138 (18.9)	68 (28.8)	**0.002**
Received corticosteroids, n (%)	689 (87.2)	256 (90.7)	0.13	637 (87.8)	222 (94.4)	**0.003**
Clinical characteristics at hospital admission						
PaO_2/F_IO_2, 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 minute, median,	24 (20; 30)	24 (20; 30)	0.82	25 (20; 32)	28 (22; 32)	0.11

(IQR)						
$PaCO_2$, 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, 10^9 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, 10^9 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)	**0.004**
Disease chronology						
Time since symptom onset to ICU admission, days, median, (IQR)	9 (7; 12)	8 (7; 11)	0.07	10 (7; 13)	8 (6; 11)	**<0.001**
Patients spending >2 days in hospital before ICU admission, n (%)	387 (48.6)	102 (35.5)	**<0.001**	414 (56.9)	84 (35.5)	**<0.001**
Time since symptom onset to IMV, days, median, (IQR)	9 (7; 12)	12 (10; 15)	**<0.001**	10 (8; 13)	12 (10; 17)	**<0.001**
Time since hospital admission to IMV, days, median, (IQR)	3 (1; 5)	5 (3; 8)	**<0.001**	3 (2; 5)	6 (3; 9)	**<0.001**
Time since ICU admission to IMV, days, median, (IQR)	0 (0; 1)	3 (2; 4)	**<0.001**	0 (0; 0)	3 (2; 5)	**<0.001**
Waves						
1st wave, n (%)	426 (53.5)	92 (32)	**<0.001**	487 (66.9)	79 (33.4)	**<0.001**

2nd wave, n (%)	236 (29.6)	226 (40.3)	<**0.001**	159 (21.8)	95 (40.2)	<**0.001**
3rd wave, n (%)	90 (11.3)	52 (18.1)	**0.04**	69 (9.4)	45 (19)	<**0.001**
4th wave, n (%)	20 (2.5)	8 (2.7)	0.82	10 (1.3)	6 (2.5)	0.24
Outcomes						
IMV days, median, (IQR) †	13 (8; 26)	13 (7; 29)	0.82	12.5 (8; 24)	15.5 (9; 28.7)	**0.02**
ICU days, median, (IQR) †	18 (12; 35)	24 (15; 41)	**0.001**	17 (10; 29.2)	24 (14; 41)	<**0.001**
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)	**0.004**
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)	<**0.001**
Hospital mortality, n (%)	240 (30.1)	100 (34.8)	0.15	248 (34.1)	115 (48.7)	<**0.001**
90-day mortality, n (%)	239 (33.5)	100 (38.3)	0.17	247 (36.1)	114 (52)	<**0.01**

Early intubation is considered as ≤ 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; $PaCO_2$: partial pressure of CO_2 in the arterial blood. Percentages calculated with non-missing data only. † Analysed only in survivors. Boldface entries indicate statistical significance.

Supplementary Table 9

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)**	***p value***	**Early intubation (n = 118)**	**Delayed intubation (n = 118)**	***p value***
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^2, median, (IQR)	29.3 (27.1; 33.5)	28 (25.7; 31.9)	**0.03**	31.1 (28.1; 35.7)	29.1 (26.1; 32)	**0.001**
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
Clinical characteristics at hospital admission						
PaO_2/F_IO_2, 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 minute, median,	24 (20; 29)	25 (20; 31)	0.11	27 (22; 35)	28 (22; 32)	0.61

(IQR)						
$PaCO_2$, 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, 10^9 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, 10^9 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)	**0.05**
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)	**0.04**
Disease chronology						
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)	<**0.001**	9 (7; 13)	12 (9; 16)	<**0.001**
Time since hospital admission to IMV, days, median, (IQR)	2 (1; 3)	4 (3; 6)	<**0.001**	2 (1; 3)	5.5 (3; 8)	<**0.001**
Time since ICU admission to IMV, days, median, (IQR)	0 (0; 0)	3 (2; 4)	<**0.001**	0 (0; 1)	3 (2; 5)	<**0.001**
Waves						
1st wave, n (%)	54 (46.9)	41 (35.6)	0.10	53 (44.9)	43 (36.4)	0.23
2nd wave, n (%)	39 (33.9)	51 (44.3)	0.13	34 (28.8)	55 (46.6)	**0.007**
3rd wave, n (%)	19 (16.5)	19 (16.5)	1	29 (24.5)	20 (16.9)	0.57
4th wave, n (%)	3 (2.6)	4 (3.4)	1	2 (1.6)	0 (0)	0.49
Outcomes						
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)	**0.003**	21 (12; 31)	29 (15; 45)	**0.02**

Prone position, n (%)	82 (71.3)	96 (83.4)	**0.04**	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)	**0.003**	35 (29.6)	53 (44.9)	**0.02**
Hospital mortality, n (%)	22 (19.1)	43 (37.3)	**0.003**	36 (30.5)	55 (46.6)	**0.01**
90-day mortality, n (%)	31 (23.8)	51 (37.7)	**0.01**	37 (33.9)	54 (48.2)	**0.04**

Early intubation is considered as ≤ 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 $PaCO_2$: partial pressure of CO_2 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_2/F_IO_2 at hospital admission (categorised as >300 mmHg; 200 mmHg < PaO_2/F_IO_2 ≤ 300 mmHg; 100 mmHg < PaO_2/F_IO_2 ≤ 200 mmHg; PaO_2/F_IO_2 ≤ 100 mmHg), days between hospital and ICU admission (categorised as ≤ 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 10

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 intubation	**Delayed intubation**	
	N = 307	**N = 307**	***p value***
PaO_2/F_IO_2, 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)	**0.01**
Respiratory rate, rpm, median, (IQR)	20 (18; 24)	21 18; 24)	0.73
PEEP, cmH_2O, median, (IQR)	12 (10; 14)	12 (10; 14)	0.80
Peak inspiratory pressure, cmH_2O, median, (IQR)	31 (28; 36)	32 (29; 36)	0.27
Positive end-inspiratory pressure, cmH_2O, median, (IQR)	24 (21; 28)	25 (23; 28)	**0.01**
Driving pressure, cmH_2O, median, (IQR)	12 (9; 15)	13 (10; 15)	**0.03**

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 11

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 intubation	**Delayed intubation**	
	N = 229	**N = 229**	***p value***
PaO_2/F_IO_2, median, (IQR)	125 (83.3; 178.3)	101.8 (75.6; 148.7)	**0.007**
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)	**0.01**
Respiratory rate, rpm, median, (IQR)	20 (18; 24)	22 20; 24)	0.13
PEEP, cmH_2O, median, (IQR)	12 (10; 14)	12 (10; 14)	0.32
Peak inspiratory pressure, cmH_2O, median, (IQR)	32 (29; 36)	32 (29; 37)	0.35
Positive end-inspiratory pressure, cmH_2O, median, (IQR)	25 (22; 28)	26 (23; 28)	0.16
Driving pressure, cmH_2O, median, (IQR)	12 (10; 15)	13 (10; 16)	0.14

Early intubation is considered as ≤ 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.