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 coronavirus disease 2019 (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 noninvasive 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 (ICUs) 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 h of ICU admission. Propensity score matching was used to achieve a balance across baseline variables between the early intubation cohort and those patients who were intubated after the first 24 h of ICU admission. Differences in outcomes between early and delayed intubation were also assessed. We performed sensitivity analyses to consider a different time-point (48 h 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 propensity score matching, patients with delayed intubation presented higher hospital mortality (27.3% *versus* 37.1%; p=0.01), ICU mortality (25.7% *versus* 36.1%; p=0.007) and 90-day mortality (30.9% *versus* 40.2%; p=0.02) compared with the early intubation group. Very similar findings were observed when we used a 48-h time-point 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 waves, respectively; first *versus* 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 (HFNC) (n=294) who were intubated earlier. The subgroup of patients undergoing noninvasive ventilation (n=214) before intubation showed higher mortality when delayed intubation was set as that occurring after 48 h from ICU admission, but not when after 24 h.

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 HFNC.

Introduction

Debate has arisen relating to determining when to start invasive mechanical ventilation in critically ill patients with coronavirus disease 2019 (COVID-19) presenting with respiratory failure [1–3]. Clinicians who advocate treating such patients with noninvasive respiratory support (*i.e.* high-flow nasal cannula (HFNC), noninvasive 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 mechanical ventilation [2, 3]. On the other hand, increasing time on noninvasive support with spontaneous ventilation has been shown to possibly put patients at risk of self-inflicted lung injury and increase their chances of death if invasive mechanical ventilation is finally needed [4, 5]. In randomised clinical trials, NIV and CPAP have been 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 noninvasive respiratory support to intubation [6]. It remains unknown whether this delay in invasive mechanical ventilation start worsens clinical outcomes. While 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 no association [9].

The main objective of this study was to compare the risk of hospital mortality between patients intubated within the first 24 h of intensive care unit (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 time-point (intubation within or after 48 h 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 mechanical ventilation due to COVID-19 from across 58 Spanish ICUs participating in the CIBERESUCICOVID project (ClinicalTrials.gov: NCT04457505) (details of participating centres are provided in supplementary table S1). 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 h of ICU admission, while the latter was defined 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 pandemic waves on the proportion of patients intubated within or after 24 h of ICU admission, determining whether these different periods had any impact on outcomes. We also performed a subgroup analysis based on the noninvasive respiratory support used prior to intubation and performed sensitivity analyses considering a 48-h time-point (intubation within or after 48 h from ICU admission) to explore other understandings of early or delayed intubation. Supplementary table S2 lists the periods that comprised each wave.

The study was approved by the Hospital Clínic de Barcelona's Internal Review Board (Comité Ètic d'Investigació Clínica; registry number HCB/2020/0370) and informed consent was obtained from either patients or their relatives. De-identified data were collected and stored in a Research Electronic Data Capture (REDCap) database. 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 (A. Motos and two other collaborators) 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by real-time reverse transcriptase quantitative PCR testing on nasopharyngeal swabs or lower respiratory tract aspirates. Exclusion criteria included: 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 epidemiological 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, noninvasive respiratory support devices (i.e. conventional oxygen, HFNC and NIV), use of adjunctive therapies (i.e. prone position), laboratory findings and arterial blood gases. Furthermore, we collected data on pharmacological 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 mechanical ventilation, and the need for rescue therapies. We also evaluated changes in intubation timing and their respective effects throughout
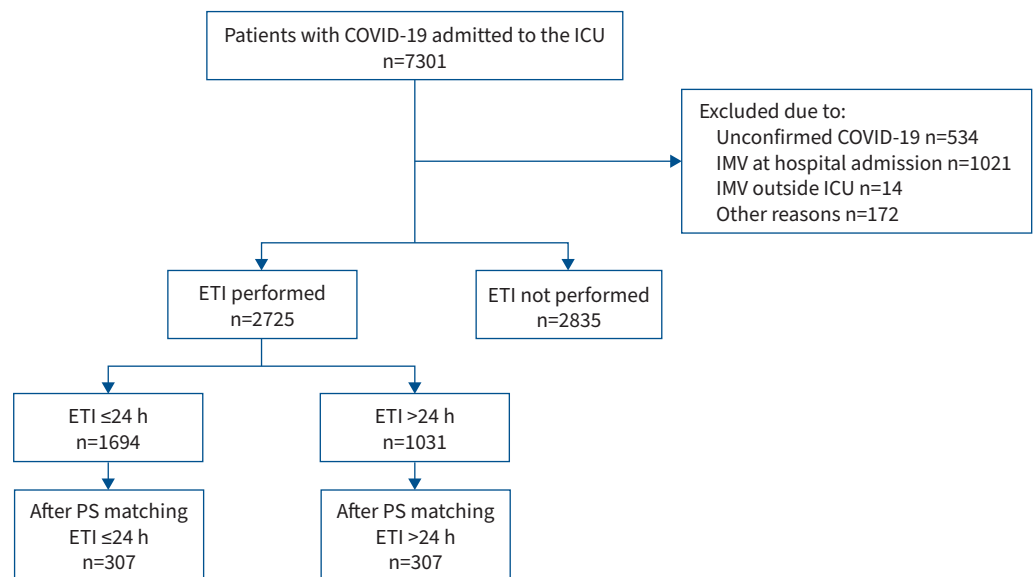
FIGURE 1 Study flowchart. Inclusion period was from 29 February 2020 to 31 August 2021. Propensity score (PS) matching was performed with the following variables: sex, age, respiratory rate at hospital admission, arterial oxygen tension/inspiratory oxygen fraction at hospital admission (categorised as >300, 200–⩽300, 100–⩽200 or ⩽100 mmHg), time from hospital admission to intensive care unit (ICU) admission (categorised as ⩽2 or >2 days), immunodepression, corticosteroid treatment and COVID-19 wave. ETI: endotracheal intubation; IMV: invasive mechanical ventilation.

the pandemic. Finally, we assessed both primary and secondary outcomes considering the type of noninvasive respiratory support used before intubation.

Statistical analysis

Number (percentage) of patients was reported for categorical variables, while median (interquartile range) was reported for 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 parametric t-test.

Propensity score matching was used to achieve a balance between the early and delayed intubation groups [10, 11]. To match the two cohorts in both the 24- and 48-h time-point 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 propensity score 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 h of ICU admission or afterwards, we selected age, sex, chronic immunosuppression, respiratory rate at hospital admission, arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) at hospital admission (categorised as >300, 200–⩽300, 100–⩽200 or ⩽100 mmHg), time from hospital admission to ICU admission (⩽2 or >2 days), treatment with corticosteroids for COVID-19 and COVID-19 wave. An adequate model fit with calibration of the propensity score was demonstrated by logistic modelling that included covariates (24-h time-point: goodness-of-fit, p=0.28 for general population, p=0.16 for HFNC and p=0.13 for NIV; 48-h time-point: 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 (SMDs) in the matched population, while 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 ratios and 95% confidence intervals were calculated. Then, to describe in-hospital mortality, we also employed a competing risks 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 noninvasive respiratory support used before intubation and each pandemic wave in Spain.

The level of significance was set at 0.05 (two-tailed). All statistical analyses were performed with Python version 3.7 (www.python.org) and R version 4.0.3 (www.r-project.org).

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 (IQR) 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 (IQR) P_{aO_2}/F_{IO_2} and respiratory rate were 219 (128–281) mmHg and 24 (20–30) breaths·min^{-1}, 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, P_{aO_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 propensity score matching. After excluding patients with missing values for the variables used for the propensity score, we identified a cohort of 307 cases and 307 controls. Time since both symptom onset and hospital admission to intubation was 2 days more in the delayed intubation group. In the matched cohort, hospital mortality in patients receiving delayed intubation was significantly higher (37.1% versus 27.3%; p=0.01). Logistic regression analyses revealed that, compared with delayed intubation, intubation within the first 24 h of ICU admission was associated with a reduction in hospital mortality risk (OR 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% and 40.2% in the early and delayed intubation groups, respectively (p=0.02). ICU mortality was also higher in patients intubated after 24 h of ICU admission (25.7% in the early intubation group versus 36.1% in the delayed intubation group; p=0.007). In the sensitivity analyses, we considered intubation within the first 48 h from ICU admission as early. We found that hospital mortality was higher in the delayed intubation group (43.27% versus 27.07%; p<0.001). Times since symptom onset and hospital admission to intubation were 3 days more in the delayed intubation group (supplementary table S3)

Changes in intubation timing throughout the pandemic

During the first wave of the pandemic, most patients receiving mechanical ventilation were intubated within the first 24 h of ICU admission (n=1148 (72%)). The mortality rate in this early intubation cohort was higher than in 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 (supplementary table S6). 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; p<0.001 versus 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).

TABLE 1 Characteristics and outcomes of critically ill patients with COVID-19 according to intubation timing from intensive care unit (ICU) admission: early (⩽24 h) and delayed (>24 h)

	Before propensity score matching (n=2725)			After propensity score 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	65 (57–72)	63 (55–71)	**<0.001**	64 (56–71)	64 (57–71)	0.83
Female	499 (29.4)	285 (27.6)	0.31	100 (32.5)	87 (28.3)	0.29
BMI, kg·m^{-2}	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	885 (52.2)	549 (53.2)	0.63	165 (53.7)	169 (54.2)	0.80
Diabetes mellitus	416 (24.5)	265 (25.7)	0.52	78 (25.4)	84 (27.3)	0.64
Chronic cardiac failure	209 (12.3)	133 (12.9)	0.67	37 (12)	45 (14.6)	0.40
COPD	164 (9.4)	98 (9.5)	0.89	38 (12.3)	35 (11.4)	0.80
Immunodepression	286 (16.8)	237 (22.9)	**<0.001**	53 (17.2)	45 (14.6)	0.44
Received corticosteroids	1425 (84.9)	910 (89.2)	**0.002**	281 (91.5)	274 (89.2)	0.41
Clinical characteristics at hospital admission						
P_{aO_2}/F_{IO_2}, mmHg	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, breaths·min^{-1}	24 (20–29)	25 (20–31)	**<0.001**	25 (20–31.5)	25 (20–30)	0.43
P_{aCO_2}, mmHg	33.2 (30–38)	34 (30.3–38)	0.18	34 (30–38)	33.6 (29.9–37.7)	0.46
pH	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[#,+]	836 (61.7)	876 (91.1)	**<0.001**	178 (71.7)	263 (91.9)	**<0.001**
NIV[¶,+]	588 (35.8)	375 (36.6)	0.53	90 (29.7)	127 (41.6)	**0.002**
CRP, mg·dL^{-1}	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
Lymphocytes, ×10^9 cells·L^{-1}	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^{-1}	179 (143–231)	186 (142–239)	0.18	189 (154–233)	178 (145–233)	0.12
D-dimer, mg·L^{-1}	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^{-1}	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^{-1}	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	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	1002 (59.18)	359 (34.82)	**<0.001**	108 (35.18)	100 (32.57)	0.55
Time since symptom onset to IMV, days	10 (7–13)	11 (8–14)	**<0.001**	9 (7–11)	11 (8–14)	**<0.001**
Time since hospital admission to IMV, days	3 (2–5)	4 (2–6)	**<0.001**	2 (1–3)	4 (2–6)	**<0.001**
Time since ICU admission to IMV, days	0 (0–0)	2 (1–3)	**<0.001**	0 (0–0)	2 (1–3)	**<0.001**
COVID-19 wave						
First wave	1148 (67.7)	430 (41.7)	**<0.001**	150 (48.8)	145 (47.2)	0.74
Second wave	369 (21.7)	383 (37.1)	**<0.001**	102 (33.2)	122 (39.7)	0.11
Third wave	139 (8.2)	157 (15.2)	**<0.001**	50 (16.2)	38 (12.3)	0.20
Fourth wave	20 (1.18)	24 (2.3)	**0.02**	5 (1.6)	2 (0.6)	0.45
Outcomes						
IMV duration, days[§]	13 (8–25)	14 (8–29)	0.22	13 (8–24)	18 (9–31.5)	**0.01**
ICU duration, days[§]	17.5 (11–33)	23 (14–40)	**<0.001**	17 (11–32)	27 (16–44)	**<0.001**
Prone position	1292 (76.6)	797 (77.6)	0.57	220 (71.6)	220 (78.4)	0.06
Neuromuscular blockade	1442 (85.2)	860 (83.6)	0.27	247 (80.7)	262 (85.3)	0.13
ECMO	27 (1.5)	31 (3)	**0.01**	6 (1.9)	6 (1.9)	1
ICU mortality	598 (35.3)	360 (35)	0.86	79 (25.7)	111 (36.1)	**0.007**
Hospital mortality	641 (37.8)	384 (37.2)	0.77	84 (27.3)	114 (37.1)	**0.01**
90-day mortality	636 (41)	381 (40.5)	0.83	85 (30.9)	113 (40.2)	**0.02**

Data are presented as median (interquartile range) or n (%), unless otherwise stated; percentages calculated with nonmissing data only. BMI: body mass index; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; P_{aCO_2}: arterial carbon dioxide tension; HFNC: high-flow nasal cannula; NIV: noninvasive ventilation; CRP: C-reactive protein; IMV: invasive mechanical ventilation; ECMO: extracorporeal membrane oxygenation. Variables used to perform propensity score matching included age, sex, respiratory rate at hospital admission, P_{aO_2}/F_{IO_2} at hospital admission (categorised as >300, 200–⩽300, 100–⩽200 or ⩽100 mmHg), time from hospital admission to ICU admission (categorised as ⩽2 or >2 days), chronic immunosuppression, corticosteroid treatment and COVID-19 wave. After excluding patients with missing values, we had a population of n=1117. Supplementary table S4 shows standardised mean differences in baseline covariates from the matched population. [#]: HFNC with or without NIV; [¶]: NIV with or without HFNC; [+]: received at least one session of NIV and/or HFNC since hospital admission before intubation; [§]: analysed only in survivors. Bold indicates statistical significance.
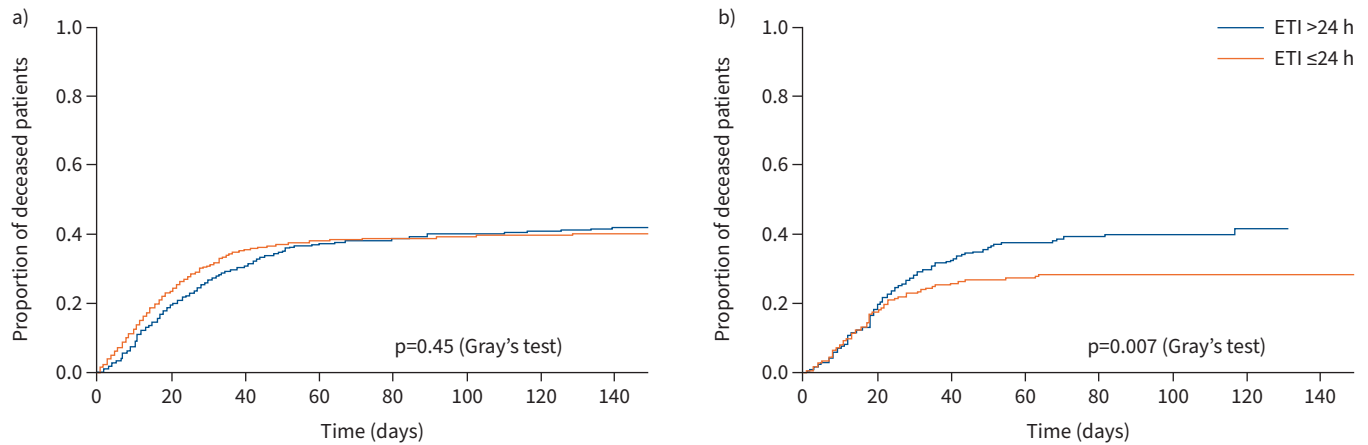
FIGURE 2 Survival curves for the a) overall cohort and b) adjusted population, as obtained by propensity score matching. In total, 81 out of 614 (13.19%) patients were transferred to another hospital and censored from the survival analysis. ETI: endotracheal intubation.

Subgroup analysis of patients treated with NIV versus 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 S7). After propensity score 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% versus 34.6%; p=0.01). However, we did not observe such a difference in those patients receiving NIV before intubation (32.7% versus 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) (supplementary tables S8 and S9).

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 h of ICU
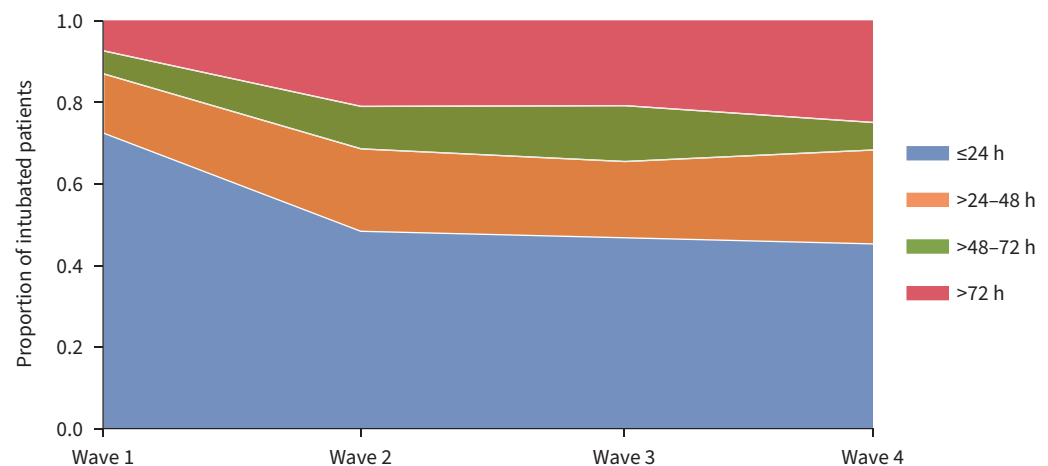
FIGURE 3 Proportion of patients with COVID-19 intubated ⩽24, >24–48, >48–72 or >72 h since intensive care unit (ICU) admission in the first, second, third and fourth waves in Spain. Proportion of patients intubated ⩽24 h since ICU admission in the first, second, third and fourth waves: first versus second, third and fourth waves p<0.001.

TABLE 2 Characteristics and outcomes of critically ill patients with COVID-19 receiving either early (⩽24 h) or delayed (>24 h) intubation from intensive care unit (ICU) depending on prior use of high-flow nasal cannula (HFNC) or noninvasive ventilation (NIV) (matched population)

	HFNC (n=294)			NIV with or without HFNC (n=214)		
	Early intubation (n=147)	Delayed intubation (n=147)	p-value	Early intubation (n=107)	Delayed intubation (n=107)	p-value
Age, years	63 (56–69)	66 (57–71)	0.23	64 (56–70)	64 (58–71)	0.73
Female	46 (31.2)	44 (29.9)	0.89	29 (27.1)	23 (21.5)	0.42
BMI, kg·m^{-2}	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	65 (44.2)	77 (52.3)	0.19	62 (57.9)	57 (53.2)	0.58
Diabetes mellitus	34 (23.1)	34 (23.1)	1	29 (27.1)	29 (27.1)	1
Chronic cardiac failure	15 (10.2)	18 (12.2)	0.71	13 (12.1)	14 (13)	1
COPD	16 (10.8)	18 (12.2)	0.85	13 (12.1)	14 (13)	1
Immunodepression	20 (13.6)	19 (12.9)	1	23 (21.5)	20 (18.6)	0.73
Received corticosteroids	133 (90.4)	134 (91.1)	1	98 (91.5)	95 (88.7)	0.64
Clinical characteristics at hospital admission						
P_{aO_2}/F_{IO_2}, mmHg	230 (172–290.4)	231.4 (146.5–307.3)	0.80	194.2 (130.9–263.5)	207.1 (114–271.1)	0.81
Respiratory rate, breaths·min^{-1}	25 (20–30)	25 (20–30)	0.99	24 (20–32)	25 (22–30)	0.88
P_{aCO_2}, mmHg	34 (30–37)	34 (30.1–38)	0.41	33 (30–37)	32 (29–37)	0.46
pH	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^{-1}	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
Lymphocytes, ×10^9 cells·L^{-1}	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^{-1}	188 (145–238)	176 (139–232)	0.34	179 (147–220)	193 (152–233)	0.82
D-dimer, mg·L^{-1}	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^{-1}	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^{-1}	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	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	52 (35.3)	50 (34)	0.90	54 (50.4)	51 (47.6)	0.78
Time since symptom onset to IMV, days	9 (7–12)	11 (8–13)	**0.001**	9 (7–13)	12 (9–15)	**<0.001**
Time since hospital admission to IMV, days	2 (1–3)	4 (2–6)	**<0.001**	3 (2–5)	6 (3–9)	**<0.001**
Time since ICU admission to IMV, days	0 (0–0)	1 (1–3)	**<0.001**	0 (0–0)	2 (1–4)	**<0.001**
COVID-19 wave						
First wave	70 (47.6)	59 (40.1)	0.68	57 (53.2)	51 (47.6)	0.49
Second wave	55 (37.4)	67 (45.5)	0.19	30 (28)	41 (38.3)	0.14
Third wave	18 (12.2)	18 (12.2)	1	19 (17.7)	15 (14)	0.57
Fourth wave	4 (2.7)	3 (2)	1	1 (0.9)	0 (0)	1
Outcomes						
IMV duration, days[#]	13 (8–24)	15 (9–31)	0.24	16 (9–27)	18 (9–31)	0.42
ICU duration, days[#]	17 (11–34)	24 (14–42)	**0.004**	22 (12–31)	24 (15–39)	0.08
Prone position	97 (66.4)	117 (79.5)	**0.01**	92 (85.9)	87 (81.3)	0.46
ECMO	3 (2)	2 (1.3)	1	5 (4.6)	3 (2.8)	0.72
Neuromuscular blockade	113 (76.8)	123 (83.6)	0.18	95 (89.6)	94 (87.8)	0.82
ICU mortality	31 (21)	48 (32.6)	**0.003**	34 (31.7)	41 (38.3)	0.39
Hospital mortality	32 (21.7)	51 (34.6)	**0.01**	35 (32.7)	42 (39.2)	0.39
90-day mortality	31 (23.8)	51 (37.7)	**0.01**	36 (34.2)	41 (40.2)	0.39

Data are presented as median (interquartile range) or n (%), unless otherwise stated; percentages calculated with nonmissing data only. BMI: body mass index; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; P_{aCO_2}: arterial carbon dioxide tension; CRP: C-reactive protein; IMV: invasive mechanical ventilation; ECMO: extracorporeal membrane oxygenation. Patients included in the subgroup analysis received at least one session of NIV and/or HFNC before intubation. Variables used to perform propensity score matching included age, sex, respiratory rate at hospital admission, P_{aO_2}/F_{IO_2} at hospital admission (categorised as >300, 200–⩽300, 100–⩽200 or ⩽100 mmHg), time from hospital admission to ICU admission (categorised as ⩽2 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 with or without HFNC. Supplementary table S5 shows standardised mean differences in baseline covariates from the matched population. [#]: analysed only in survivors. Bold indicates statistical significance.

admission) compared with those intubated within 24 h of ICU admission. Likewise, we observed an increase in both ICU and 90-day mortality, ICU length of stay, and mechanical ventilation duration in those patients intubated after the first 24 h of ICU admission. Very similar findings were also confirmed when we considered early or delayed intubation with a different time-point (intubation within 48 h of ICU admission for early intubation).

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

While 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 by PAPOUTSI et al. [9] that comprised 12 observational studies comparing early and delayed intubation (also defined as occurring within or after the first 24 h of ICU admission) did not report differences in mortality. 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 mechanical ventilation were started within the first 48 h of noninvasive respiratory support [29]. Two important factors may explain the differences in outcomes noted in this study [29] and ours when compared with PAPOUTSI et al. [9]. First and foremost, to minimise confounding bias, we selected a population with a similar baseline risk of intubation and mortality using propensity score matching. We considered covariates that were known to play a significant role in both the intubation strategy and survival. Second, in propensity score 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 patient self-inflicted lung injury is inevitably related to spontaneous breathing, this ensured that the delayed intubation group had longer exposure to such an event. This message has yet to be suggested in the literature and could prove useful in other types of acute respiratory failure.

Importantly, in patients intubated after 24 h of ICU admission, we found worse respiratory mechanics compared with 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-h time-point for early or delayed intubation, we also observed worse oxygenation during the first day of mechanical ventilation in patients belonging to the latter group. While this could partially explain differences observed in survival, the exact mechanisms that increase the risk of death due to a delayed start in invasive mechanical ventilation are not completely known.

We also examined the potential effect of the type of noninvasive respiratory support used before invasive mechanical ventilation. 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 time-point 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 h 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-h time-point 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-h time-point 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 physiological 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 noninvasively. In fact,

greater use of NIV and HFNC was 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 noninvasive 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 propensity score analyses performed. Our study also has limitations. 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 h 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 24 h 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. Furthermore, we do not have the total time spent on neither noninvasive 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 mechanical ventilation, delayed intubation was associated with a higher risk of hospital mortality when compared with earlier intubation. Patients undergoing HFNC before intubation presented an increased risk of mortality when intubation was delayed irrespective of the time-point used to consider early or delayed intubation. Patients with NIV presented a higher mortality risk when delayed intubation was that occurring after 48 h of ICU admission. Finally, more patients received intubation within 24 h of ICU admission in the first pandemic wave.

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