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Short communication

“Early” and “delayed” intubation of COVID-19 patients: Different definitions, different populations

Samuel Chosidow*, Damien Contou, Megan Fraissé, Olivier Pajot, Hervé Mentec, Radj Cally, Gaëtan Plantefève

Service de Réanimation Polyvalente, Centre Hospitalier Victor Dupouy, 69, rue du Lieutenant-Colonel Prud'hon, Argenteuil 95100, France

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Main text

The Coronavirus Disease 2019 (COVID-19) pandemic has raised the question of the timing of initiation of invasive mechanical ventilation (IMV). Some authors have advocated early intubation, arguing that it would lower the risk of unprepared urgent intubation and lessen patient self-inflicted lung injury as well as droplet aerosolization for healthcare workers [1]. Others have recommended using more conventional criteria for initiation of IMV [2]. Several studies have compared “early” to “delayed” intubation strategies in COVID-19 patients but could not evidence definite messages [3]. “Early” and “delayed” intubation have mainly been defined according to the duration between Intensive Care Unit (ICU) admission and intubation. In clinical practice however, the decision to initiate IMV usually relies on the patient's clinical features, including respiratory rate (RR) and oxyhemoglobin saturation (SpO_2) [4,5]. An “early” approach to IMV can therefore be construed as intubating patients showing less severe or partial signs of respiratory distress [6]. We aimed to assess the discrepancies in the categorization of patients using two definitions of “early” and “delayed” intubation: one classifying patients based on their clinical features prior to intubation (*clinical definition*), the other classifying patients using a conventional temporal criterion (*temporal definition*).

We conducted a retrospective monocenter study including consecutive intubated COVID-19 patients (positive severe acute respiratory syndrome coronavirus 2 Reverse Transcriptase-Polymerase Chain Reaction) admitted to our ICU between March 1st and December 31st, 2020. Baseline was defined as the first day the patients received at least 15 L/min of supplemental oxygen independent of the delivery system (non-rebreather mask with reservoir bag or high-flow nasal cannula (HFNC)). Data collected on the day of intubation were collected before intubation occurred. The decision to intubate was based on clinical acumen: no definite RR, SpO_2 or time thresholds were used by our team. Using the *clinical definition*, patients were categorized into two groups: those with a RR>35 breaths/min and a SpO_2<90% (with at least 15 L/min of supplemental oxygen or FiO2 ≥ 80% with HFNC, excepting transient desaturations) on the day of intubation were categorized in the “delayed” intubation group while patients not fulfilling both these criteria were classified in the “early” intubation group. With the *temporal definition*, patients were classified based on the median duration between baseline and intubation. This study was approved by the Institutional Review Board of the French Intensive Care Society (CE SRLF 2021−41). The discrepancies between the classifications were assessed. Furthermore, ICU mortality was compared between groups and the number of cardiac arrest on induction of anesthesia was retrieved. Continuous variables are reported as median [Interquartile range] and compared between groups using the Student *t*-test. Categorical variables are reported as numbers and percentages and compared using the χ^2 test.

One hundred and fourteen patients were included. Baseline characteristics, clinical features on the day of intubation and outcome are

Abbreviations: COVID-19, Coronavirus disease 2019; HFNC, High-flow nasal cannula; ICU, Intensive care unit; IMV, Invasive Mechanical Ventilation; RR, Respiratory Rate; SpO2, Oxyhemoglobin saturation

* Corresponding author.
E-mail address: samuel.chosidow@gmail.com (S. Chosidow).

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Table 1
Baseline characteristics, clinical features on the day of intubation and outcome of 114 intubated COVID-19 patients categorized in "early" and "delayed" intubation groups using the *clinical definition* and the *temporal definition*.

Baseline characteristics, clinical features on the day of intubation and outcome	Total $N = 114$	*Clinical definition*		*Temporal definition*	
		"Early" intubation $N = 54$	"Delayed" intubation $N = 60$	"Early" intubation $N = 59$	"Delayed" intubation $N = 55$
Baseline characteristics					
Age (years)	65 [57−70]	66 [57−70]	65 [58−70]	65 [57−70]	65 [58−70]
Male gender, N (%)	91 (80%)	43 (80%)	48 (80%)	46 (78%)	45 (82%)
Diabetes, N (%)	48 (42%)	19 (35%)	29 (48%)	29 (49%)	19 (35%)
Body Mass index (kg/m^2)	29 [26−33]	29 [26−34]	29 [27−33]	31 [28−35]	28 [26−32]
Immunosuppression[a], N (%)	15 (13%)	9 (17%)	6 (10%)	8 (14%)	7 (13%)
Charlson Comorbidity Index	3 [2−4]	3 [2−4]	3 [2−4]	3 [2−4]	3 [2−4]
SAPS II	32 [28−39]	32 [27−38]	33 [28−40]	36 [28−42]	30 [27−36]
Days from hospital admission to baseline	2 [0−3]	2 [0−4]	1 [0−3]	2 [0−4]	2 [0−4]
Days from symptoms onset to baseline	7 [6−10]	8 [6−10]	7 [5−10]	7 [6−10]	7 [6−10]
Dexamethasone therapy, N (%)	37 (33%)	9 (17%)	28 (47%)	9 (15%)	28 (51%)
Hospitalization during the first wave (March-June 2020)	77 (67%)	45 (83%)	32 (53%)	50 (85%)	27 (49%)
Clinical features on the day of intubation					
Hours from baseline to intubation	36 [12−86]	36 [13−68]	35 [11−107]	12 [3-25]	86 [60−144]
Standard oxygen therapy, N (%)	59 (52%)	33 (61%)	26 (43%)	46 (78%)	13 (24%)
Maximum oxygen flow (liters per minute via a non-rebreather mask with reservoir bag)	15 [15−30]	15 [15−30]	15 [15−30]	15 [15−30]	15 [15−30]
Non-invasive Ventilation, N (%)	32 (28%)	13 (24%)	19 (32%)	6 (10%)	26 (47%)
HFNC, N (%)	40 (35%)	13 (24%)	27 (45%)	10 (17%)	30 (55%)
Highest RR (/min)	41 [36−48]	36 [32−44]	45 [40−50]	42 [37−49]	40 [36−47]
Lowest SpO_2 (%)	88 [84−90]	91 [89−92]	85 [83−88]	88 [84−90]	88 [84−91]
Lowest mean arterial pressure (mmHg)	91 [78−100]	90 [70−99]	92 [80−102]	88 [72−102]	93 [81−99]
Highest heart rate (/min)	105 [94−123]	100 [91−113]	110 [99−125]	105 [92−124]	105 [96−123]
Highest temperature (°C)	38.5 [37.8−39.0]	38.3 [37.5−39.0]	38.6 [37.9−39]	38.6 [38.0−39.1]	38.3 [37.7−39.0]
Outcomes					
ICU mortality, N (%)	67 (59%)	28 (52%)	39 (65%)	32 (54%)	35 (64%)

Abbreviations: SAPS II, Simplified Acute Physiology Score; HFNC, High-Flow Nasal Cannula; ICU, Intensive Care Unit; RR, Respiratory Rate; SpO2, Oxyhemoglobin saturation.
[a] including active solid cancer or hematological malignancy, organ transplant, HIV or immunosuppressive drugs.

detailed in Table 1. Using the *clinical definition*, 54 patients were classified in the "early" intubation group and 60 in the "delayed" intubation group. On the day of intubation, RR (36 *vs*. 45 breaths/min, $p < 0.001$) and SpO_2 (91 *vs*. 85%, $p < 0.001$) significantly differed between groups. There was no difference between these groups regarding the delay between baseline and intubation (36 *vs*. 35 h, $p = 0.75$) (Table 1 and Supplementary Material Fig. 1). With the *temporal definition* that uses the median delay between baseline and intubation (median 36 h), 59 patients were classified in the "early" intubation group and 55 in the "delayed" intubation group. Fifty-seven patients (50%) were mismatched when comparing these classifications. Precisely, 48% of the "early" intubation group and 52% of the "delayed" intubation group as determined by the *clinical definition* were classified differently with the *temporal definition*. There was no difference in ICU mortality between the "early" and "delayed" intubation groups using the *clinical definition* (52% *vs.* 65%, $p = 0.22$) or the *temporal definition* (54% *vs.* 63%, $p = 0.41$). No cardiac arrest occurred on induction of anesthesia.

In this study, using a *clinical definition* to define "early" and "delayed" intubation yielded a different categorization of patients than using a *temporal definition*. Using solely a temporal criterion as it has been done in recent studies [3] might constitute highly heterogeneous groups in regards to clinical features prior to intubation. Moreover, it is difficult to determine at what point one should "start the clock", since rates of disease progression seem to vary drastically between patients. The *clinical definition*, however, does not depend on this variability of disease progression but still relates to the potential risks of clinically "delayed" intubation, such as patient self-inflicted lung injury or hypoxic cardiac arrest. Using both definitions, there was a trend towards higher ICU mortality in the "delayed" intubation groups which did not reach statistical significance, possibly due to a lack of power. These results must be interpreted with caution, considering that the patients were not randomized and that the groups were significantly different in regards to several characteristics (such as period of admission, dexamethasone therapy, oxygenation device). Nonetheless, one interesting finding is the higher proportion of patients treated with HFNC in the "delayed" intubation group as categorized with the temporal definition. Although the retrospective design of this study impedes definite conclusions, an explanatory hypothesis is that HFNC, by improving respiratory mechanics and oxygenation, might lengthen the time spent breathing spontaneously before a possible intubation. There is conceivably an implication of the oxygenation device on the time-course of the respiratory distress in spontaneously breathing patients. In conclusion, investigating the appropriate timing of intubation of COVID-19 patients is paramount since "early" and "delayed" intubations are both associated with still unclear risk-benefit ratios. In this study, we showed that a categorization based on RR and SpO_2 provides a new approach to explore this issue by classifying patients differently, and we believe in a more suited way, than using a *temporal definition*.

Declarations of Competing Interest

None

CRediT authorship contribution statement

Samuel Chosidow: Conceptualization, Visualization, Formal analysis, Methodology, Writing − original draft, Writing − review & editing. **Damien Contou:** Conceptualization, Visualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Megan Fraissé:** Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Olivier Pajot:** Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Hervé Mentec:** Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Radj Cally:** Conceptualization, Visualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Gaëtan Plantefève:** Conceptualization, Visualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

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Supplementary materials

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