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RESEARCH ARTICLE

Predictive Factors for Intubation in Coronavirus Disease Patients Admitted in the ICU

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Capsule Summary

What is already known

Clinical features have also been described as predictors for poor outcomes: initial fever is associated with an increased risk of hospitalization, but does not seem to be a discriminating factor in the development of critical illness. Initial dyspnea is linked to severe and critical forms and digestive symptoms are associated with severe forms. Only hypoxemia was a predictor for mechanical ventilation in the first 48 hours. Yet many hypoxemic patients show very few signs of respiratory distress, as in « silent hypoxemia ».

What is new in the current study

The clinical assessment of respiratory mechanics is one of the best ways to predict the need for invasive ventilation. Deferring intubation in patients at very high risk of requiring mechanical ventilation could deteriorate respiratory status and lead to increased ventilatory difficulties following intubation.

ABSTRACT

Object: Since it began in Wuhan in December 2019, the Coronavirus Disease pandemic has affected more than 500 million people and caused more than 6 million deaths. Identifying risk factors for severe cases has become a major issue. We evaluated whether patient characteristics upon intensive care unit admission could predict later intubation. We also compared outcomes for patients undergoing early versus delayed intubation.

Methods: This is a retrospective, monocentric study carried out in a medical university intensive care unit between August 2020 and January 2021. Demographic, clinical, biological and imaging data were collected (on arrival and on day 2). We examined intubation timing (before or after 48h hours after intensive care unit admission), ventilatory features and outcomes for intubated patients.

Results: SAPS2, high steroid dosages, pulmonary superinfection, extensive CT pulmonary lesions, polypnea and elevated oxygen requirements were associated with a higher need of intubation. Biological features on admission were non-discriminatory. Delayed intubation seemed to be associated with more severe acute respiratory distress syndrome, but mortality did not vary.

Discussion and conclusion: Intubation can be predicted using a multimodal approach including clinical and imaging features. Early clinical evaluation plays a key role in identifying patients likely to be intubated. Delaying intubation could lead to respiratory worsening.

Keywords: Coronavirus Disease appeared in 2019, severe acute respiratory syndrome, mechanical ventilation, intubation, Non-Invasive Ventilation

INTRODUCTION

Since it began in Wuhan in December 2019, the Coronavirus Disease appeared in 2019 (COVID-19) pandemic has affected more than 500 million people and caused more than 6 million deaths [1]. Identifying predictive factors for negative outcomes became a major issue to adapt patient care and adjust the orientation of these patients. Numerous studies aimed to describe risk factors for severe forms (requiring hospitalization) and critical forms (requiring transfer to an intensive care unit (ICU)). The main features associated with severe forms of COVID often coexist as male gender [2], cardiovascular disease and hypertension [3–5], obesity [6,7], immunodeficiency [3], diabetes [5,8,9], Chronic obstructive pulmonary disease (COPD) [10], interstitial lung disease (ILD) [11], cirrhosis [12,13], chronic kidney disease [3,14] and cancer [15].

Clinical features have also been described as predictors for poor outcomes : initial fever is associated with an increased risk of hospitalization, but does not seem to be a discriminating factor in the development of critical illness [16]. Initial dyspnoea is linked to severe and critical forms [3] and digestive symptoms are associated with severe forms.

Beyond these, clinical criteria helping physicians to predict the occurrence of a severe form of COVID-19 are scarce and non-specific. In a retrospective multicenter study by Carmichael and al. [16], clinical features such as polypnea, fever, impaired general condition and pain were not risk factors for intubation in the first 48 hours after hospital admission. Only hypoxemia was a predictor for mechanical ventilation in the first 48 hours. Yet many hypoxemic patients show very few signs of respiratory distress, as in « silent hypoxemia » [17]. These patients may be stabilized using non-invasive methods, such as High-Flow Nasal canula Oxygen Therapy (HFNOT), Continuous Positive Airway Pressure (CPAP) or Non-Invasive Ventilation (NIV).

The inflammatory storm, raised as the root cause for critical forms of COVID-19, opens the door to using biological markers to assess the severity of patients' conditions. Several biological markers have proven to be associated with severe infections : hyperleukocytosis and lymphopenia [18], elevated d-dimers [4], C-reactive protein (CRP) and ferritin [19,20], low platelet count [4], elevated lactate dehydrogenase (LDH), elevated hepatic transaminases [13] and troponin [3]. Unfortunately, most of these are not pertinent enough as factors for predicting the need for invasive ventilation. Among the numerous biological markers, only hyperleukocytosis, neutrophilia, elevated LDH, CRP and procalcitonin (PCT) levels have been inconstantly linked to intubation [21].

In the early stages of the pandemic, rapid and widespread use of mechanical ventilation was preferred, due to the risk of viral aerosolization and contagion for healthcare professionals. As the pandemic progressed, this strategy had to be revised due to the strain in hospital and ICU beds. A more targeted approach became required to distinguish patients who were going to need invasive mechanical ventilation from those who could be stabilized with non-invasive techniques.

Intubation is classically undertaken only after non-invasive measures prove ineffective, in order to avoid the many complications inherent to invasive ventilation, profound sedation and muscular blockage (infections, critical illness neuromyopathy). However the non-invasive approach has its own downside, as vigorous inspiratory efforts might contribute to lung injury by increasing the mechanical strain incurred by lung parenchyma during the respiratory cycle [22].

- *Stress* (i.e. pulmonary tension) is the end-inspiratory transpulmonary pressure [23]. It is the difference between alveolar pressure and intra-pleural pressure. By generating a very negative intra-pleural pressure, vigorous inspiratory efforts increase pulmonary *stress*.
- *Strain* (i.e., lung deformation) represents the increase of pulmonary volume beyond residual functional capacity. With hypoxia as a stimuli, respiratory centers (mainly medulla chemoreceptors) provoke an increase in tidal volume [24,25]. Also, the discomfort associated with dyspnoea seems partially inhibited by COVID-19, due to a number of evoked mechanisms (neurotoxicity of inflammatory mediators, direct viral attack to the insular and limbic cortex) [17].

Mechanical stress on the lungs and negative intra-thoracic pressure can increase local inflammation and alter venous return, which in turn can promote lung oedema. This is known as "patient self-induced lung injury" (P-SILI).

Ideal timing for intubation remains a controversial issue. Although experimental data may suggest harmful effects of spontaneous breathing, we lack evidence that delaying intubation causes a higher

mortality rate [26]. The physicians' overall assessment plays a key role in deciding if and when to intubate [27].

Our study's primary goal was to define which clinical, biological and radiological features measured or noted on ICU admission were associated with intubation. We then compared the outcomes and treatments in patients who underwent early versus delayed intubation.

MATERIELS AND METHODS

We performed a retrospective, monocenter study in the medical (ICU), in the CHRU of Lille, between August 1st, 2020 and January 31, 2021.

Outcomes

Our main objective was to determine which demographical, clinical, biological and radiological characteristics collected on ICU admission were associated with intubation.

Our secondary aims were:

- To determine which clinical, biological and radiological characteristics, collected 48 hours after ICU admission were associated with intubation
- To compare patients who underwent early (i.e., less than 48 hours after ICU admission) versus delayed intubation (i.e., more than 48 hours after ICU admission) as to:
    - number of days spent in the ICU
    - days in the ICU without mechanical ventilation
    - mortality rates
    - PaO_2/FiO_2 ratios, 24- and 48-hours following intubation
    - lung compliance, 24- and 48-hours following intubation
    - use of prone positioning (PP), nitric oxide (NO) and Extracorporeal membrane oxygenation (ECMO)

Population

We included patients admitted to the medical ICU, CHRU of Lille, with a positive RT-PCR testing for SARS-CoV2 and respiratory symptoms, between August 1st, 2020 and January 31, 2021.

Our exclusion criteria were:

- underage patients and adults under legal protective measures
- refusal to be included, as expressed by the patient or his next of kin
- ICU stay inferior to 48 hours (patients deceased or transferred to another unit)
- patients being transferred from another ICU, because the data regarding the initial admission was not available
- a decision to withhold or withdraw therapy regarding intubation, taken in the first 48 hours after admission
- no respiratory symptoms (asymptomatic SARS-CoV2 infection)
- pregnant and breastfeeding women

Data collection and analysis

Data was collected retrospectively using patients' files (IntelliSpace Critical Care and Anaesthesia, Philips) and entered anonymously onto a spreadsheet (Microsoft Excel software).

This included the following data, as recorded upon admission: age, gender, body mass index (BMI), ethnicity, severity of the illness with sepsis-related organ failure assessment (SOFA) [28] and simplified acute physiology score (SAPS) II [29], comorbidities (COPD, asthma, sleep apnoea syndrome (SAS), chronic respiratory failure requiring oxygen therapy prior to COVID-19, other respiratory comorbidities, hypertension, atrial fibrillation, ischemic heart disease, chronic heart failure, diabetes mellitus, chronic kidney injury with or without dialysis, chronic immunosuppression), time between infection onset and hospital admission / ICU admission. Clinical (temperature, respiratory rate (RR), Saturation level (SpO_2), maximum fraction of inspired oxygen (FiO_2) and biological (lactate, lymphocyte count, platelet count, CRP, PCT, LDH, ferritin, d-dimers) values in the first 24 hours, and between 48- and 72-hours following admission were collected. The following data were recorded during hospitalization: oxygen delivery methods and the drugs used in the first 48 hours, chest CT scan results, intubation (early or delayed), proven or suspected pulmonary superinfection before intubation, length of ICU stay, ICU outcome. For intubated patients, the data on pulmonary compliance (24- and 48-hours following intubation), PaO_2/FiO_2 rate (24- and 48-hours following intubation), use of NO, PP or ECMO were collected.

For quantitative variables, results were expressed in median and interquartile range, because most variables were not normally distributed. Variable distribution was tested using the Kolmogorov-Smirnov test. The groups were compared using the Mann Whitney test. For qualitative variables, results were expressed in numbers and percentages. The groups were compared using Pearson's Khi 2 test or

Fisher's exact test. A p value of under 0.05 was considered significant.
Statistical analyses were performed using SPSS software (version 22.0; SPSS, Chicago, IL).

Ethical considerations

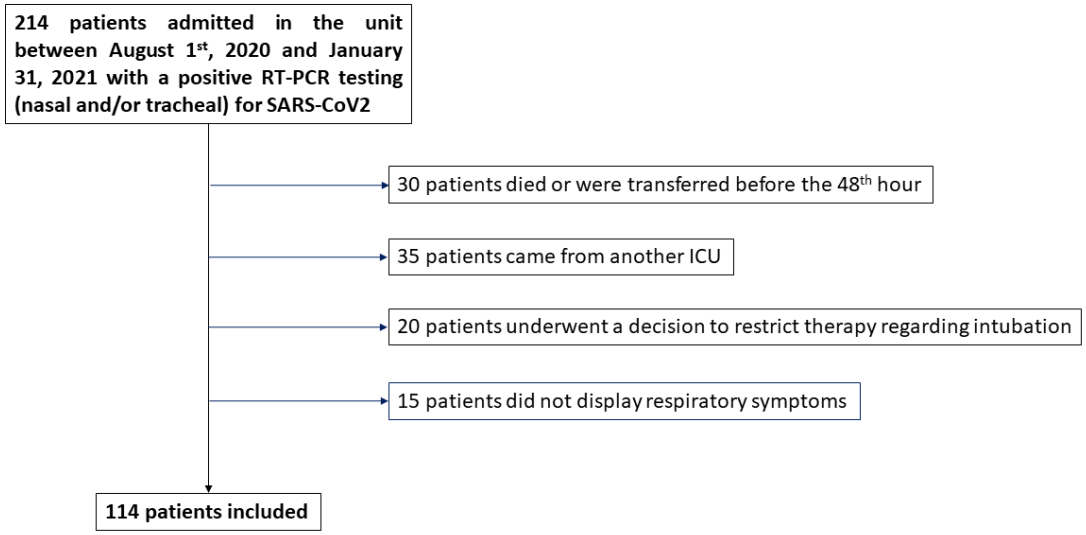
Upon admission, our patients are informed in writing that medical file data can be used for retrospective research projects. Patients or their next of kin can ask not to be included in these studies at any time. Given the retrospective and non-interventional aspect of this study, no extra information was provided to the patients.

Data collection was authorized by the "Comité de Protection des Personnes" under the reference ID-RCB 2020-A00763-36, as an ancillary to the PREDICT study.

RESULTS

Among the 214 patients admitted in the unit between August 1st, 2020 and January 31, 2021 with a positive RT-PCR testing (nasal and/or tracheal) for SARS-CoV2, 114 were included (Fig. 1).

Figure 1: Flow chart



Demographics and comorbidities

There was no statistical difference in demographic characteristics and comorbidities between intubated and non-intubated patients (table 1).

Most of the patients had comorbidities, mainly overweight (85%), hypertension (58%), diabetes (34%) and sleep apnoea (21%). Only 8% of the overall population of patients had no health problem.

	Overall population (n=114)	**Non-intubated patients (n=74; 65%)**	**Intubated patients (n=40; 35%)**	**p**
Age	66 [58-71]	67 [56-73]	65 [58-69]	0.8
Male	87 (76%)	54 (73%)	33 (83%)	0.3
BMI	30 [25-34]	29 [25-34]	30 [26-34]	0.7
Ethnicity				
Caucasian	85 (75%)	54 (73%)	31 (78%)	0.6
Other or unknown	29 (25%)	20 (27%)	9 (22%)	0.6
Respiratory comorbidities				
COPD	12 (11%)	7 (9%)	5 (13%)	0.6
Asthma	7 (6%)	3 (4%)	4 (10%)	0.2
Sleep apnea	24 (21%)	19 (26%)	5 (13%)	0.10
Chronic respiratory failure	1 (1%)	1 (1%)	0 (0%)	0.5
Other	20 (18%)	14 (19%)	6 (15%)	0.6
Cardiovascular comorbidities				
Hypertension	66 (58%)	45 (61%)	21 (53%)	0.4
Atrial fibrillation	15 (13%)	9 (12%)	6 (15%)	0.7
Ischemic heart disease	14 (12%)	7 (10%)	7 (18%)	0.2
Chronic heart failure	11 (10%)	8 (11%)	3 (8%)	0.6
Diabetes	39 (34%)	24 (32%)	15 (38%)	0.6
Chronic kidney injury				
without dialysis	14 (12%)	7 (10%)	7 (18%)	0.2
with dialysis	1 (1%)	1 (1%)	0 (0%)	0.5
Chronic immunosuppression	23 (20%)	12 (16%)	11 (28%)	**0.15**
No comorbidity	9 (9%)	5 (7%)	4 (10%)	**0.5**

Table 1: Demographics characteristics and comorbidities
Qualitative values are expressed in number (%)
Quantitative variables are expressed in median [interquartile range]
BMI : Body Mass Index; COPD: Chronic obstructive pulmonary disease

Time between disease onset and ICU or hospital admission did not vary between the two groups. SOFA did not differ; however, SAPS II was significantly higher in patients who would eventually be intubated (table 2). The use of standard oxygen nasal canulae was associated with no intubation, whereas the use of NIV was significantly associated with later intubation. Patients who received high dose corticosteroids were more likely to be intubated, and a suspected or confirmed infection was also a risk factor.

Extent of pulmonary lesions was correlated to intubation. Ground glass lesions were very frequent and were reported in a large proportion of non-intubated patients. Pulmonary embolism was not associated with a higher intubation rate. Clinical parameters such as SpO_2, RR and FiO_2 were associated to later intubation (table 2). However, at day 1, none of the biological features classically described as risk factors for severe COVID-19 appear to be linked to later intubation.

	Overall population (n=114)	Non-intubated patients (n=74; 65%)	Intubated patients (n=40; 35%)	p
Disease evolution and severity scores				
Days between infection onset and ICU admission	9 [7-12]	9 [7-12]	9 [6-12]	0.5
Days between infection onset and hospital admission	8 [5-10]	8 [5-10]	7 [4-10]	0.6
Days between hospital and ICU admission	1 [0-2]	1 [0-2]	1 [0-2]	0.8
SOFA on ICU admission	2.5 [2-3]	2 [2-2]	3 [2-3]	0.09
SAPS II on ICU admission	36 [29-42]	34 [28-40]	44 [32-53]	0.003
Oxygen administration				
Standard nasal canulae	31 (27%)	29 (94%)	2 (7%)	**<0.001**
High-Flow Nasal canula Oxygen Therapy	100 (89%)	66 (66%)	34 (34%)	0.5
Continuous Positive Airway Pressure	27 (24%)	20 (27%)	7 (10%)	0.3
Non-Invasive Ventilation	57 (50%)	30 (41%)	27 (68%)	**0.006**
Administered drugs				
Corticosteroïds low dose	69/98 (70%)	48/63 (76%)	20/35 (57%)	**0.050**
Corticosteroïds high dose	30/98 (30%)	15/63 (24%)	15/35 (43%)	**0.050**
Anticoagulant therapy preventive	74 (65%)	48 (65%)	27 (68%)	0.8
Anticoagulant therapy full dose	40 (35%)	26 (35%)	13 (32%)	0.8
Antibiotics	104 (91%)	67 (91%)	37 (93%)	0.5
Additional pulmonary infection (before intubation)	38 (33%)	13 (18%)	25 (63%)	**<0.001**
Chest CT scan features at baseline				
CT scan available at baseline	109 (96%)	71 (96%)	38 (95%)	
CT with contrast	84 (74%)	55 (74%)	29 (73%)	
Extent of pulmonary anomalies				
- < 25%	20/109 (18%)	15/71 (21%)	5/38 (13%)	0.009
- 25-50%	40/109 (37%)	28/71 (39%)	12/38 (32%)	0.009
- 50-75%	30/109 (28%)	22/71 (31%)	8/38 (21%)	0.009
- > 75%	19/109 (17%)	6/71 (8%)	13/38 (34%)	0.009
Imaging features				
Ground glass	104/109 (95%)	70/71 (99%)	34/38 (89%)	0.030
Condensations	70/109 (64%)	44/71 (62%)	26/38 (68%)	0.5
Atelectasis	35/109 (32%)	19/71 (27%)	16/38 (42%)	0.10
Pulmonary embolism	9/84 (11%)	7/55 (13%)	1/29 (3%)	0.2
Clinical and biological parameters in the first 24 hours after ICU admission				
Clinical parameters				
Temperature (highest value recorded during the 24 hours)	38 [37.3-38.8]	38.1 [37.3-38.7]	38.1 [37.3-39.1]	0.53
Saturation level (lowest value recorded during the 24 hours)	91 [89-93]	91 [89-93]	88 [87-92]	0.02
Respiratory Rate (average value recorded during the 24 hours)	26 [23-29]	25 [23-28]	28 [26-31]	<0.001

FiO_2 (maximum value recorded during the 24 hours)	60 [50-85]	50 [48-70]	100 [60-100]	<0.001
Laboratory values				
Lactate (mmol/L)	1.2 [0.8-1.6]	1.1 [0.8-1.5]	1.2 [0.95-1.85]	0.10
Lymphocyte count (giga/L)	0.5 [0.4-0.9]	0.6 [0.4-0.9]	0.5 [0.3-0.8]	0.2
Platelet count (giga/L)	227 [186-291]	232 [190-297]	221 [184-282]	0.3
C-Reactive Protein (mg/L)	111 [60-183]	104 [56-175]	120 [64-182]	0.4
Procalcitonin (ng/mL)	0.3 [0.14-0.87]	0.27 [0.14-0.73]	0.43 [0.155-1.41]	0.3
Lactate déshydrogénase (UI/L)	499 [379-556]	482 [375-553]	514 [423-633]	0.3
Fibrinogen (g/L)	7 [5.7-7.9]	7 [5.8-7.9]	7 [5.7-7.7]	0.8
Ferritin (µg/L)	1446 [806-2956]	1470 [775-3282]	1357 [813-2605]	0.6
D-dimers (µg/L)	1295 [700-2340]	1225 [650-2150]	1300 [750-2450]	0.7

Table 2: In the first 24 hours after ICU admission
Quantitative variables are expressed in median [interquartile range]
Qualitative variables are expressed in number (% of known observations)
SOFA: Sepsis-related Organ Failure Assessment; SAPS II: Simplified acute physiology score 2; ICU: Intensive Care Unit; CT: Computed tomography; FiO_2 : Fraction of inspired oxygen

Multivariate analysis

Relevant risk factors for need of intubation with a $p<0.1$ were incorporated into the multivariate analysis. In the multivariate analysis, SAPS II, use of NIV, RR, pulmonary CT involvement > 75% and pulmonary superinfection were independently associated with a higher intubation rate (table 3).

	Non-intubated patients (n=74; 65%)	Intubated patients (n=40; 35%)	P	OR (CI)
SAPS II on ICU admission	34 [28-40]	44 [32-53]	0.04	1.05 [1-1.1]
Non-Invasive Ventilation	30 (41%)	27 (68%)	0.02	3.5 [1.2-9]
Respiratory Rate (average value recorded during the 24 hours)	24.5 [23-28]	28 [26-31]	0.008	1.19 [1.05-1.35]
Saturation level (lowest value recorded during the 24 hours)	91 [89-93]	88 [87-92]	0.2	
Pulmonary involvement > 75% (chest CT)	6 (8%)	13 (32%)	0.05	3.8 [1-14]
Additional pulmonary infection (before intubation)	13 (18%)	25 (63%)	0.008	2.8 [1.3-6]

Table 3: Multivariate analysis
Quantitative variables are expressed in median [interquartile range]
Qualitative variables are expressed in number (%)
SAPS II: Simplified acute physiology score 2; CT: Computed tomography

Secondary outcomes

Clinical and biological parameters between 48- and 72-hours following ICU admission

At day 2 after ICU admission, RR and maximum FiO_2 values remained associated with later intubation (table 4). Higher CRP and PCT levels, as well as lower platelet counts were correlated with intubation. Fibrinogen levels were noted as presenting a small but statistically significant difference.

	Non-intubated patients (n=74; 65%)	Intubated patients (n=40; 35%)	p
Clinical parameters			
Temperature (highest value recorded during the 24 hours)	37 [36.6-37.7]	37.5 [36,9-38]	0.097
Saturation level (lowest value recorded during the 24 hours)	91.5 [89-93]	91 [89-93]	0.7
Respiratory Rate (average value recorded during the 24 hours)	24 [20-26]	28 [26-30]	**<0.001**
FiO_2 (maximum value recorded during the 24 hours)	50 [40-60]	80 [70-100]	**<0.001**
Laboratory values			
Lactate (mmol/L)	1.4 [0.9-1.9]	1.3 [1.1-2.2]	0.5
Platelet count (giga/L)	302 [252-360]	234 [204-282]	**0.003**
C-Reactive Protein (mg/L)	47 [24-77]	80 [57-148]	**<0.001**
Procalcitonin (ng/mL)	0.17 [0-0.4]	0.39 [0.15-0.93]	**0.007**
Lactate déshydrogénase (UI/L)	452 [371-506]	497.5 [460-548]	0.10
Fibrinogen (g/L)	6.1 [5.1-6.9]	6.7 [5.6-7.8]	**0.02**
Ferritin (µg/L)	1228 [718-2699]	1534 [889-2627]	0.4
D-dimers (µg/L)	1040 [462-1658]	1450 [870-2380]	0.07

Table 4: Clinical and biological parameters between 48- and 72-hours following ICU admission
Quantitative variables are expressed in median [interquartile range]
FiO_2 : Fraction of inspired oxygen

Intubated patients (table 5)

		Early intubation (n = 18)	Delayed intubation (n = 22)	p
Management				
Prone positioning		18 (100%)	15 (68%)	0.8
Nitric oxyde		11 (61%)	15 (68%)	**0.041**
ExtraCorporeal Membrane Oxygenation		0 (0%)	7 (32%)	**0.002**
Ventilatory parameters				
At day1 of mechanical ventilation	PaO_2/FiO_2 ratio	131 [94-152]	120 [71-156]	0.119
	Lung compliance (mL/cmH_2O)	33 [25-35]	25 [15-30]	**0.020**
At day2 of mechanical ventilation	PaO_2/FiO_2 ratio	145 [98-223]	109 [80-148]	**0.031**
	Lung compliance (mL/cmH_2O)	32 [25-38]	26 [15-35]	0.053
Outcome				
Days undergoing mechanical ventilation		14 [9-19]	11 [4-21]	0.5
Days spent in the ICU		21 [13-25]	18 [12.5-32.5]	0.6
Mortality rate		6 (33%)	13 (59%)	0.105

Table 5: Management and evolution in intubated patients
Quantitative variables are expressed in median [interquartile range]
Qualitative variables are expressed in number (%)
PaO2: partial pressure of oxygen in arterial blood; FiO_2 : Fraction of inspired oxygen

Among intubated patients, prone positioning was almost always used, with no statistical difference between the two groups. NO and ECMO were more frequently used among patients with delayed intubation (more than 48 hours after ICU admission). Lung compliance at day 1 and PaO_2/FiO_2 ratio at day 2 were lower in patients with delayed intubation. Length of stay, days under mechanical ventilation and mortality rate did not statistically differ.

DISCUSSION

The goal of our study was to look for clinical, biological and imaging features associated with intubation in critical COVID-19 patients. SAPS II, NIV, superinfection, extended CT abnormalities, higher RR were correlated with intubation. Biological features, when collected on day 1, were not linked to intubation. On day 3, CRP, PCT, platelet count and fibrinogen levels differed between patients who would eventually be intubated and those who wouldn't.

Patients who underwent delayed intubation demonstrated a higher rate of NO and ECMO use, and a lower lung compliance on day 1 after intubation and PaO_2/FiO_2 ratio on day 2 than early intubated patients. However, mortality rate did not vary.

Study population

Our population shared the main risk factors for severe COVID previously described in scientific literature namely male gender, obesity, high blood pressure, diabetes [30,31]. Our patients had the same ICU severity as in the other series described with an SAPS II score of 36 [28].

Comorbidities are classically found as predictors for severe forms and ICU admission, but the part they play is less decisive when it comes to intubation. Duration of symptoms on admission did not vary either between intubated and non-intubated patients. We could hypothesize that the emerging of a critical COVID pneumonia is influenced by comorbidities but the evolution towards severe acute respiratory distress syndrome (ARDS) requiring mechanical ventilation also depends on factors other than the patients' background characteristics.

Severity scores in COVID-19

Initial severity, represented by SAPS II, was greater in patients who would eventually require intubation. SAPS II seems to be a good indicator in COVID patients as it was significantly associated with ICU mortality rate in several observational studies [28,29]. Before COVID, SAPS II had already been shown to be associated with NIV failure in patients presenting with respiratory failure [32] and severe acute community-acquired pneumonia [33]. Retrospective studies have also shown an increased rate of HFNOT failure in COVID patients with higher SAPS II on hospital admission [34,35].

SOFA scores appear to be less relevant for COVID patients and their predictive value for intubation or mortality is low. SOFA may not be a pertinent factor for COVID patients for several reasons:

- This score vas originally designed to evaluate patients in septic shock, but stays relatively low in the case of unique organ failure
- The "Respiration" item includes a mechanical ventilation criterion for 3 and 4 pts, whereas COVID patients can be kept spontaneously breathing despite a PaO_2/FiO_2 ratio inferior to 300.

Oxygenation and ventilation strategies

As could be expected, patients provided with standard nasal canulae for oxygenation were less likely to be intubated, as their oxygen demand was lower (up to 6L/min) and/or their respiratory status quickly improved.
In our study, the use of NIV was associated with a higher rate of intubation (OR 3.5). There can be a number of reasons for this:

- there may be a tendency to use NIV in more severe patients in order to avoid intubation when they are showing signs of respiratory fatigue
- NIV could also contribute to higher tidal volume, therefore increase pulmonary strain and causing P-SILI [22].

As we understand more and more about pulmonary damage due to COVID, two phenotypes have been identified (in reality, they represent two edges of a broad spectrum of clinical manifestations): the L-phenotype and the H-phenotype [27].

- The L-phenotype is characterized by a relatively preserved lung compliance, low lung weight, low recruitability, in which hypoxia is mainly due to

ventilation-perfusion mismatch and endothelial dysfunction.
- The H-phenotype represents the "classic" ARDS phenotype, with lowered lung compliance, high lung weight and high lung recruitability.

Patients displaying an L-phenotype can be stabilized using a non-invasive strategy only (HFNOT, CPAP, NIV). However, strenuous respiratory efforts can cause P-SILI, making patients lean towards an H-phenotype, where mechanical ventilation becomes required.

Corticosteroids and superinfection

A higher corticosteroid dose appears to be associated with intubation in univariate analysis. This interaction may be the result of a tendency to prescribe higher doses in severe patients to break down the inflammatory storm, but increasing immunosuppressive therapy could also lead to more bacterial and fungal infections.

Patients with superinfections were more likely to be intubated in our study, but most superinfections were only suspected, based on CRP and PCT increase and radiological progression. Therefore, telling apart an infection and a flare-up of the COVID pneumonia can be difficult. This diagnostic challenge can account for the large percentage of antibiotics usage found in our study (90%).

Chest CT findings: a key indicator

In our study, the extent of CT abnormalities was associated to intubation. CT abnormalities of over 75% of lung parenchyma were linked to intubation (OR 3.8).
Chest CT findings in COVID patients were described at the very beginning of the epidemic [36], when physicians in Wu Han first noticed a typical pattern including sub-pleural ground glass and disseminated condensations (described as "crazy paving"). This typical CT presentation was first used as an element for positive diagnosis [37,38] and later as a severity indicator [39]. In 2020, European Societies of Radiology and Thoracic Imaging launched a recommendation for standardized imaging reports, asking that radiologists systematically report the extent and type of radiological abnormalities [36].

Clinical and biological findings

Among all the clinical and biological findings collected in the first 24 hours, only clinical characteristics were found to be associated with intubation. Oxygen demand was significantly higher for patients who would eventually be intubated (median FiO_2 of 1 vs 0.5). O_2 saturation tended to drop lower for patients who would later be intubated, but this link was not confirmed by multivariate analysis. Low SpO_2 was noted more as an indication of overall severity than as a real risk factor for intubation.

Polypnea was related to intubation, with a median RR of 28 for intubated patients versus 24 for other patients. Respiratory rate is a simple clinical indicator which can be used to detect deteriorated respiratory mechanics.
Experimental studies have shown that even in a healthy human being, hyperventilation (for example during intense physical effort) causes non-hydrostatic pulmonary oedema [22]. Repetitive cycles of alveolar opening and collapse lead to atelectasis, which increases stress applied to aerated lung tissue.
Polypnea is both an indicator of increased oxygen demand and a cause of lung oedema worsening, increasing ARDS severity.

When taken on admission, biological parameters turn out to be disappointing when it comes to predicting intubation. On day 2, inflammatory parameters such as CRP, PCT, thrombopenia and hyperfibrinogenaemia become discriminant.
In studies evaluating the relevance of laboratory values to assess the severity of COVID infections, higher inflammatory protein counts (IL-6, CRP, PCT) were associated with more severe conditions [40,41]. However, in those studies, the biological findings were computed between day 3 and day 5. It is likely that inflammatory markers are not fully informative on ICU admission and become more significant in the days following admission.

At early stages of ICU care, clinical evaluation of respiratory work and hypoxia, as well as chest CT abnormalities are more relevant than biological findings to predict intubation.

Can we predict intubation based on an early evaluation?

In our multivariate analysis, SAPS II, NIV requirement, RR, CT lesions > 75% and proven or suspected infection were significantly associated with intubation.
In previous studies, ROX index (PaO_2/FiO_2/RR ratio) was a good predictor of intubation in COVID patients: in a study including 69 patients in Egypt [42], a ROX index on day 1 < 25.26% was in favour of

intubation with a 90% sensitivity and 75% specificity. More complex models based on artificial intelligence, taking into account dozens of variables, were developed [43]. Their prognostic value is even higher than the ROX index, but the number of variables and the need for an AI self-learning program makes those models difficult to apply in a large scale.
Our results confirm that the clinical examination, however elementary, is the most effective at the patient's bedside.

Parameters at day 2

RR and oxygen requirements remained strongly associated with intubation. We also noted the appearance of biological indicators correlated to intubation (thrombopenia, higher CRP and PCT rates, hyperfibrinogenaemia). Superinfection being associated to intubation, these biological features could be an indication either of sepsis or of a flare up of the inflammatory storm due to COVID.

Outcome among intubated patients

Many studies have tried to determine the impact of early versus delayed intubation strategies. A meta-analysis by Papoutsi and al [26] did not show any difference in mortality between patients intubated within 24h of their ICU admission and patients intubated at later stages. On the contrary, Zirpe and al found a higher mortality rate among patients intubated after more than 48h in the ICU [44]. This could be consistent with a physiological approach suggesting that delayed intubation can concur to P-SILI lesions and aggravate respiratory failure [22].

In our cohort, NO use was wider in patients intubated after 48h. This could indicate more difficulties to achieve oxygenation and decarboxylation goals. Despite the low number of patients receiving ECMO in our study (we had excluded patients coming from other ICUs and transferred to receive ECMO), we noticed that they came exclusively from patients in the "delayed intubation" group. This could support the hypothesis that oxygenation and decarboxylation goals are more difficult to achieve in those patients.

Lung compliance on day 1 following mechanical ventilation was significantly lower (25 vs 33). Once again the part played by P-SILI in ARDS worsening could be noted. This difference became non-significant on day 2, whereas PaO_2/FiO_2 ratio became significantly lower on day 2 in patients intubated later.

Despite the absence of difference in mortality, indirect indicators suggest a higher level of ARDS severity following delayed intubation. Oxygenation and lung compliance seem more impaired, and rescue therapies such as NO and ECMO are undertaken more frequently. Despite it being non-significant, there is a tendency to higher mortality following belated intubation, which should be confirmed by means of a specific study with a larger group of intubated patients.

Strengths and limitations

The main strength of our study lies in its pragmatic nature: the parameters considered are usually collected in standard ICU care. Our aim was to describe a rather simple approach which the ICU physicians can use on a day-to-day basis.
One of the limits is the monocentric dimension of our study. As medical literature on COVID flourishes, medical practices tend towards greater uniformization.
Nevertheless, some aspects of patient care can vary from one hospital to another, especially regarding aspects on which the scientific community hasn't reached a consensus (antibiotic use [45], higher corticosteroid dosages for highly hypoxemic patients [46,47], and timing for intubation).
Our centre is a recourse centre for ECMO implantation, meaning severe patients could be transferred from other ICUs for that purpose. However, we excluded these patients, because the data from their admission was missing and to avoid this recruitment bias.
Despite the retrospective aspect of our study, we were able to have very few missing data due to an effort of uniformity in COVID patient care within our centre.
Lastly, we have to acknowledge the fact that the study was undertaken before the COVID vaccination began, thus the effect of vaccination cannot be measured in our data.

CONCLUSION

In spite of an ever-growing understanding of COVID-19, there are still grey areas around intubation, mostly because profound hypoxemia is sometimes clinically silent. Our study shows that the clinical assessment of respiratory mechanics is one of the best ways to predict the need for invasive ventilation.

Beyond mere oxygen saturation levels, early evaluation of respiratory capabilities, as well as a

close monitoring of the respiratory rate are core elements to consider.

Physicians should not be falsely reassured by a stable saturation level and laboratory values, nor should intubation be delayed where the patient shows polypnea or other signs of respiratory distress, due to the risk of P-SILI. Patients with high oxygen requirements, polypnea, with suspected or confirmed pulmonary superinfection, with extensive pulmonary CT lesions and with elevated SAPS II are at very high risk of requiring intubation during their ICU hospitalization. Even if mortality did not rise in patients who underwent delayed intubation, our data suggests an increased severity of ARDS in this group.

We could hypothesize that deferring intubation in patients at very high risk of requiring mechanical ventilation could deteriorate respiratory status and lead to increased ventilatory difficulties following intubation. Specific studies containing a larger number of intubated patients need to be led to confirm this hypothesis, so the ideal timing for the intubation of critical COVID patients can be determined.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interest.

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