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Predictors of poor prognosis requiring intubation in COVID-19 patients admitted in Intensive Care Unit: a Congolese observational study

Facteurs prédictifs de mauvais pronostic nécessitant une intubation chez les patients COVID-19 admis en unité de soins intensifs : une étude observationnelle congolaise

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Summary

Context and objective

In intensive care units (ICU), clinicians have little information to identify COVID-19 patients at high risk of poor prognosis requiring intubation. Considering the clinical and biological parameters of the patients during their admission to ICU, we determined the incidence of a pejorative evolution requiring intubation, and secondarily we searched among the starting parameters, which were predictors of the intubation during follow-up

Methods

We conducted a monocentric retrospective cohort study of adult patients admitted for moderate, severe or critical COVID-19/WHO clinical classification, during the first two waves of the pandemic in Kinshasa/DR Congo. Our primary end point was the incidence of intubation. Potential predictors of intubation were determined by the Cox regression analysis. The relative risk of death was assessed according to treatment with mechanical ventilation (intubation).

Results

We included 219 patients (average age of 56.8 ±15.2 years; 75 % men), respectively 37 % in the 1st and 63 % in the 2nd wave of the pandemic. Cumulative incidence of intubation was 24% (1st wave: 26% vs 2nd wave: 24%). One-third of intubations were performed on the first 3 days versus two-thirds beyond the third day. The Cox's regression model showed that among data from the 1st day of ICU admission, those predicting intubation were: age (Hazard ratio: 1.025, CI 95%: 1.005-1.044), obesity (HR:

Résumé

Contexte et objectif. Dans les unités de soins intensifs (USI), les cliniciens disposent de peu d'informations pour identifier les patients COVID-19 à haut risque de mauvais pronostic nécessitant une intubation. L'objectif de la présente étude était de rechercher l'incidence d'une évolution péjorative nécessitant une intubation, et les prédicteurs de l'intubation au cours du suivi. *Méthodes.* C'était une étude de cohorte rétrospective monocentrique de patients adultes admis pour une classification clinique COVID-19/OMS modérée, sévère ou critique, durant les deux premières vagues de la pandémie à Kinshasa/RD Congo. Le critère de jugement principal était l'incidence de l'intubation. Les prédicteurs potentiels de l'intubation ont été déterminés par l'analyse de régression de Cox. Le risque relatif de décès a été évalué en fonction du traitement par ventilation mécanique (intubation). *Résultats.* Deux cent dix-neuf patients étaient enrôlés (âge moyen de 56,8 ±15,2 ans ; 75 % d'hommes), respectivement 37 % dans la 1ère et 63 % dans la 2ème vague de la pandémie. L'incidence cumulée de l'intubation était de 24 % (1ère vague : 26 % vs 2ème vague : 24 %). Un tiers des intubations ont été réalisées au cours des 3 premiers jours contre deux tiers au-delà du troisième jour. Les facteurs prédictifs d'intubation en régression de Cox étaient : l'âge (Hazard ratio : 1.025, CI 95% : 1.005-1.044), l'obésité (HR : 4. 808 ; IC 95 % : 2,660-8,696), la corticothérapie (HR : 0,313, IC 95 % : 0,102-0,965), l'indice ROX < 4,88 (HR : 2,024, IC 95 % : 1,003-4,080) et la race noire (HR : 0,502, IC 95 % : 0,272-0,928). Au total, 54 décès

4.808; CI 95%: 2.660-8.696), corticosteroid therapy (HR: 0.313, CI 95%: 0.102-0.965), ROX index < 4.88 (HR: 2.024, CI 95 %: 1.003-4.080) and black race (HR: 0.502, CI 95%: 0.272-0.928). In total, 54 deaths (25 % of patients) were recorded with a higher relative risk (18.8) in intubated patients.

Conclusion

A quarter of COVID-19 patients admitted to ICU could worsen and be intubated. The majority of intubations were performed after the third day of admission and mortality was high. The predictors of intubation that have been identified can help anticipate management by being proactive.

Keywords: COVID-19, Intubation, Incidence, Predictors, Intensive Care Unit

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(25 % des patients) ont été enregistrés avec un risque relatif plus élevé (18,8) chez les patients intubés.

Conclusion

Un quart des patients COVID-19 admis en USI ont vu leur état s'aggraver et être intubés. La majorité d'intubations a été réalisée après le troisième jour d'admission et la mortalité était élevée. Les facteurs prédictifs d'intubation qui ont été identifiés peuvent aider à anticiper la prise en charge en étant proactif.

Mots-clés : COVID-19, Intubation, Incidence, Prédicteurs, Unité de soins intensifs

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Introduction

Until today in sub-Saharan Africa (SSA), fewer than 100 deaths related to COVID-19 per million populations are reported (1). The young african population, cross-immunization thanks to previous local infections and the poor development of means of transportation, are all factors which can explain this situation (2). However, given that systematic screening for the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) infection by the polymerase chain reaction (PCR) tests is not done on a large scale in the population, it must be admitted that the real health statistics are probably underestimated as suggested by anti- SARS CoV-2 IgG serologic tests performed in the population (3-4). Otherwise, some Africa studies have reported high mortality rates among COVID-19 patients admitted to the hospitals especially in the intensive care units (ICU) (5-7). In Zambia, researchers who collected nose and throat swabs from corpses in the capital city of Lusaka's morgue, discovered that COVID-19 related deaths were surprisingly common accounting for the majority of non-hospital deaths between June and September 2020 (8). Apart from these striking examples, it should be noted that at the peaks of the waves of the pandemic in the large cities of SSA, there are reports of saturation of morgues and hospitals and even shortages of oxygen in the ICU (5).

Many controversies have been fueled around the management of COVID-19. Self-medication at home, delay in diagnosis, late transfer to an appropriate hospital, therapeutic inertia, lack of anticipation, are all factors that can explain aggravation of patients. Even if some comorbidities as diabetes, obesity, hypertension and the adulthood, are associated with poor prognosis of the disease, criteria making it possible to know which moderate or severe patients at ICU admission can evolve towards the critical forms requiring an intubation are not clearly defined. Considering the peculiarities inherent in the intubation of a suspected or confirmed COVID-19 patient, including the need to wear personal protective equipment and the preferential use of the rapid sequence, intubation should be done in the most elective possible by an experienced and adequately prepared team. A discussion between the attending physician and the on-call physician in ICU is recommended for all ambiguous or uncertain cases. Clinical judgment prevails because once intubated, the patient placed under an invasive mechanical ventilation (IMV) must be monitored in accordance with the recommendations, otherwise this act will have

been useless. Indeed, several studies report a very high rate of death among COVID-19 patients who have been intubated. For some authors, the delay in deciding to intubate is one of the causes that explain this excess mortality (9-11).

The present study focused on patients admitted to ICU for moderate, severe and critical forms of COVID-19 during the first two waves of pandemic. By the time the study was being conducted, the COVID-19 vaccination had not started in the country. The main objective of the study was to determine the incidence and predictors of progression to critical forms of COVID-19 requiring intubation for IMV. The secondary objective was to evaluate the relative risk of death among intubated versus non-intubated patients.

Methods

Site organization and Study design

This retrospective cohort study covers the period from march 2020 to february 2021, and was conducted at the "Centre Médical de Kinshasa" (CMK), a private hospital located in the western part of the city of Kinshasa/DR Congo. At the time of the study, CMK was one of 10 centers selected to take care of COVID-19 patients in Kinshasa. The CMK ICU has fifteen beds with one multiparameter monitor and one ventilator per bed, five dialysis machine and a nurse to patient ratio of 1:2 during day and night. The medical staff was mixed including internist (cardiologist, pneumologist, nephrologist, endocrinologist), anesthesiologists, emergency and ICU physician. All selected patients were confirmed cases of SARS CoV-2 infection diagnosed by the real time polymerase chain reaction (RT-PCR), performed at the CMK according to World Health Organization (WHO) interim guidance (12). Patients hospitalized for moderate, severe and critical forms of COVID-19 were included in the study and patients with mild and asymptomatic forms were excluded. The different forms of COVID-19 were defined according the WHO clinical classification (13).

All the patients were treated according to the national COVID-19 management protocol (14) and in agreement with the WHO and the "COVID-19 Treatment Guidelines Panel" (13, 15). The chest CT exams were performed on lightspeed 64-detector CT. To quantify the extension of lung lesions, a scoring system was used: each of the five lobes of lungs visually scored from 0 to 5 (0, no involvement; $1, < 5\%$ involvement; 2, 5–25% involvement; 3, 26–49% involvement; 4, 50–75% involvement; $5, > 75\%$ involvement). Then, the total chest CT score was calculated by the sum of each lob's scores, ranging from 0 to 25 (16). The lesions were qualified as severe from more than 25% of the extent of the pulmonary field. Every day, a staff was organized bringing together all the specialists. Once the intubation was decided, it was performed immediately and the patient was put under an IMV machine. For the present study, the data intervals defining the first and second waves of COVID-19 pandemic in Kinshasa were from March 2020 to July 2020 and October 2020 to February 2021, respectively.

Data collection

Age of patient, gender, race, comorbidities, vital signs (temperature, respiratory rate, heart rate), clinical stage of COVID-19 according to the WHO clinical classification (13), laboratory tests (blood gases, blood count, C reactive protein (CRP), procalcitonin, serum creatinine, creatine kinase (CK), D-dimers), thoracic computerized tomography scan (CT), SOFA score and the respiratory oxygenation (ROX) index (defined as the ratio of fraction of inspired oxygen to respiratory rate) were all collected from the time of the ICU admission. In addition, we collected information about medical treatment. The disease outcome was described as discharge, death or transfer to another hospital or abroad.

Data analysis

Analyses were performed using SPSS for Windows version 21.0. Continuous data are presented as median and interquartile range (IQR). Categorical data are expressed as the number of patients (percentage). The Mann-Whitney U test was used to compare non-parametric continuous variables between both groups. Chi-2 or Fisher's exact test was used for categorical variables, as appropriate. All patients were followed up to day 45 to assess their likelihood of intubation and survival. To investigate the predictors of intubation, the Cox regression was performed and the results are expressed as hazard ratios (HR) and 95% confidence interval (95 % CI). All reported p values are two-sided and statistical significance was defined as $p < 0.05$.

Ethical considerations

The investigators agreed to conduct the present study in agreement with the principles of the declaration of Helsinki. The access to patient medical records was granted by the director of the hospital. All data were fully anonymized before they have been accessed.

Results

General characteristics of study population

The study included 219 patients (male to female ratio: 3/1). They had an average age of 56.8 ±15.2 years. Among the comorbidities, hypertension (40 %), obesity (26 %) and diabetes (9 %) were very common. Approximately 72% of patients had lung damage extending to more than 25% of two lung fields and almost all patients received corticosteroid therapy. Generally, 82 patients (37 %) were admitted during the first wave and 137 (63 %) during the second wave. The proportion of white and yellow patients increased during the second wave (12 % vs 23 %; p=0.042) while that of the obese had decreased (34 % vs 22 %; p=0.047) (Table 1).

Table 1. Clinical characteristics of COVID-19 patients on admission to ICU

Variables	Whole group	Wave 1	Wave 2	p
Male/female	164/55	66/16	98/39	0.139
Age, years	46-58-67	48-58-67	45-59-67	0.930
Age ≥ 65/< 65 years	65/154	27/55	38/99	0.416
Blacks/others races	137/82	72/10	105/32	0.042
CTCD use, yes/no	211/8	80/2	131/6	0.713
Diabetes, yes/no	20/199	5/77	15/122	0.228
HTN, yes/no	86/133	34/48	52/85	0.617
Obesity, yes/no	58/161	28/54	30/107	0.047
Lung CT lesions > 25 %, yes/no	158/61	54/28	104/33	0.118

Results are expressed as median, interquartile 25 and 75 or as frequency.
Abbreviations, CTCD: corticosteroids, HTN: hypertension, CT: computed tomography.

Table 2 shows that patients in the first wave more frequently had muscle damage (high CK, p=0.010) and respiratory failure (low PaO2, p < 0.001) on admission. The other parameters studied did not show any difference between the two waves.

Table 2. Biological characteristics of COVID-19 patients on admission to ICU

Variables	Whole group	Wave 1	Wave 2	p
PaO2	63-74-92	61-68-77	67-80-105	<0.001
PaO2/FiO2	171-258-338	184-259-322	165-257-356	0.930
CRP	5-11-22	8-13-22	5-9-22	0.007
Neutrophilsx10^3	3.03-4.47-6.47	2.92-4.48-6.40	3.05-4.44-6.47	0.930
Lymphocytes x10^3	0.84-1.22-1.63	0.99-1.38-1.65	0.76-1.15-1.60	0.015
Platelets x10^3	145-185-241	155-190-242	138-178-236	0.062
Creatine Kinase	79-172-329	92-173-359	76-160-324	0.779
Serum creatinine	74-91-114	74-91-118	74-90-113	0.677
D-dimers	599-1284-3345	749-1581-3311	457-1226-3416	0.137
Sofa score	2-3-4	2-3-3	2-3-4	0.289

Results are expressed as median, interquartile 25 and 75. Abreviations, CRP: C-reactive protein

Cumulative incidence and Predictors of intubation for IMV

Fifty-three patients (24 %) were intubated during the study period; 21 (26%) during the first wave, and 32 (24%) during the second wave. Table 3 shows that a third of intubations had been performed during the first three days of admission. However, some intubations occurred late, particularly on the fifteenth day.

10	44	18	26
15	49	19	30

The Cox's regression analysis shows that among data from the first day of ICU admission, those predicting the poor prognosis requiring patient intubation at follow-up were: the adulthood, obesity, failure to receive corticosteroid therapy, ROX index < 4.88 and the yellow or white race (Table 4).

Table 3. Cumulative number of intubations

Day(s) of follow up	Whole group	Intubation	
		Wave 1	Wave 2
1	4	0	4
3	18	7	11
7	35	15	20

Table 4. Predictors of Intubation by Cox proportional hazard model analysis

Variables	p value	Adjusted HR	95 % CI
Age	0.012	1.025	1.005-1.044
Obesity vs no	< 0.001	4.808	2.660-8.696
Black patients vs other races	0.028	0.502	0.272-0.928
ROX index < 4.88	0.049	2.024	1.003-4.086
Use of corticosteroids vs no	0.043	0.313	0.102-0.965

Variables not entered in the model: sex, hypertension, diabetes, creatinine, creatine kinase, D-dimers, CRP, neutrophils, lymphocytes, platelets. Abbreviations, ROX: ratio of oxygen saturation

Intubation and relative risk of death

A total of 54 deaths (25 % of patients) were reported including 27 in the first wave (33 % of patients) and 27 in the second wave (20 % of patients) (figure 2). Patients who had been intubated had higher mortality, RR: 18.8 (95% CI: 8.4 -41.9; p 0.001).

Discussion

The present ICU study reports a high proportion of COVID-19 patients intubated (24 %), of which nearly a third performed during the first three days. By considering the clinical and biological parameters on admission, we have identified those that were associated with poor prognosis that justified intubation during the follow-up.

We know that previous studies in SSA and particularly in DR Congo have reported a low proportion of COVID-19 intubated patients (6-7, 17-19). These studies concerned global data including patients hospitalized for mild forms of COVID-19. Otherwise, the lack of respirators in the hospitals, qualified personnel available for intensive resuscitation, doubts about the effectiveness of IMV, are all factors that may explain the low proportion of intubated patients in previous studies. The improvement of the CMK hospital's technical platform was an asset that made it possible to refer severe and critical cases requiring the use of IMV.

Regarding the time limit for performing the intubation, the study showed that it could occur from the first days of admission until the 15th day. In the literature, the timing of ICU admission and intubation remains a matter of debate in severe patients (9-10). However, we know that the natural evolution of COVID-19 can be unpredictable, even if the first week seems decisive for patients who will present critical forms. The incubation period of the disease is sometimes difficult to trace in patients. The procedure of intubation also requires additional infection precautions. At the same time, early data in the word suggest that patients who do ultimately require IMV may have worse outcomes when intubation is delayed (11).

If knowing the predictors of intubation may seem important to anticipate care and not to lose the chances of life for patients, these factors are rarely studied. In the present study, adulthood, race other than black, obesity, non-use of corticosteroids on admission, and ROX index < 4.88 were predictive of intubation at the follow-up. Studies have shown that among COVID-19 patients, the ROX index and the PaO2/FiO2 ratio, particularly 24 hours after admission, may be useful tools in identifying patients at high risk of intubation (20-21). Other predictors found in the present study (no use of

corticosteroids and obesity) are consistent with the literature data (22).

In multiracial communities like in the United States of America (USA), black subjects appear to have a poor prognosis when compared to white and hispanic admitted to ICU for COVID-19 (23). Their lower socio-economic level, inequalities in access to health services and a relatively high frequency of obesity were mentioned as factors that could explain this disparity (24). The black patients attending the CMK have a good socio-economic status and easy access to care (private hospital located in one of the richest districts of the city of Kinshasa); this may explain our results, even if it deserves to be confirmed with a more appropriate study. It is not excluded that white or yellow patients came to the hospital only for very severe forms of the disease, preferring to treat themselves at home as long as the situation was manageable.

Although essential in critical forms of COVID-19, mortality in intubated patients was very high.
This mortality was within the range of statistics reported in other ICU in Europe, China and the USA (25-26). The more the pandemic evolved, the fewer deaths we had thanks to several combined factors, especially vaccination and improved treatment protocols (27). Non-invasive respiratory support techniques, including high-flow oxygen and continuous positive airway pressure (CPAP), were little used in patients with severe COVID-19 in the first two waves, as they were not yet formally recommended; These supports could have prevented intubations in some patients, as demonstrated by a few studies later (27-28).

At a distance from the first two waves of the COVID-19 pandemic in Kinshasa, this study makes it possible to learn certain lessons and to understand that the situation was serious in ICU even in SSA and particularly in DR Congo. The monocentric nature of this study as well as the small sample size are limitations. Certain explanatory factors for intubations and/or death have not been studied. For example, the therapeutic inertia, late referral, prone position, viral load or even virus sequencing to determine the type of variant concerned. The evolution dynamics of certain parameters which may evolve over time have not been taken into account. This is the case with creatinine, D-dimers and lung damage.

Conclusion

The study showed that around a quarter of Congolese patients admitted to ICU with moderate to critical COVID-19 during the first two waves of the pandemic could worsen and be intubated. The majority of intubations were performed after the third day of admission and mortality was high. The predictors of intubation that have been identified can help anticipate management by being proactive.

Abbreviations

ARDS: acute respiratory distress syndrome; CK: Creatinin kinase; CMK: Centre Médical de Kinshasa; COVID-19: Coronavirus disease 2019 ; CPAP: continuous positive airway pressure; CRP: C-reactive protein; CT: computer tomography; DRC: Democratic Republic of Congo; FiO2: inspired oxygen fraction; HB: hemoglobin; HR: heart rate; MV: mechanical ventilation; PaO2: arterial oxygen pressure; RR: respiratory rate ; RT-PCR: reverse transcriptase polymerase chain reaction; SARS-Cov-2: 2019 novel coronavirus; WBC: white blood cell ; WHO: World Health Organization.

Declarations

Ethical approval and consent to participate
The investigators agreed to conduct the present study in agreement with the principles of the declaration of Helsinki. The access to patient medical records was granted by the director of the hospital. Our research projects on COVID-19 had been authorized by the Kinshasa School of Public Health, Democratic Republic of Congo (N°ESP/CE/47B/2021). All data were fully anonymized before they have been accessed.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be considered as a potential conflict of interest.

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None

Authors's contribution

PB, MB and JN conceived the idea, designed and supervised the study, had full access to all data and took responsibility for the integrity of the data. JRM analyzed data, performed statistical analysis and drafted the first version of manuscript. YN revised the manuscript. All authors approved the final submitted version for publication and have agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript

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