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Oxygenation Strategy During Acute Respiratory Failure in Critically-Ill Immunocompromised Patients

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Objectives: To assess the response to initial oxygenation strategy according to clinical variables available at admission.

Design: Multicenter cohort study.

Setting: Thirty French and Belgium medical ICU.

Subjects: Immunocompromised patients with hypoxemic acute respiratory failure.

Interventions: None.

Measurements and Main Results: Data were extracted from the Groupe de Recherche en Réanimation Respiratoire du patient d'Onco-Hématologie database. Need for invasive mechanical ventilation was the primary endpoint. Secondary endpoint was day-28 mortality. Six-hundred forty-nine patients were included. First oxygenation strategies included standard oxygen ($n = 245$, 38%), noninvasive ventilation ($n = 285$; 44%), high-flow nasal cannula oxygen ($n = 55$; 8%), and noninvasive ventilation + high-flow nasal cannula oxygen ($n = 64$; 10%). Bilateral alveolar pattern (odds ratio = 1.67

[1.03–2.69]; $p = 0.04$), bacterial (odds ratio = 1.98 [1.07–3.65]; $p = 0.03$) or opportunistic infection (odds ratio = 4.75 [2.23–10.1]; $p < 0.001$), noninvasive ventilation use (odds ratio = 2.85 [1.73–4.70]; $p < 0.001$), Sequential Organ Failure Assessment score (odds ratio = 1.19 [1.10–1.28]; $p < 0.001$), and ratio of PaO_2 and FiO_2 less than 100 at ICU admission (odds ratio = 1.96 [1.27–3.02]; $p = 0.0002$) were independently associated with intubation rate. Day-28 mortality was independently associated with bacterial (odds ratio = 2.34 [1.10–4.97]; $p = 0.03$) or opportunistic infection (odds ratio = 4.96 [2.11–11.6]; $p < 0.001$), noninvasive ventilation use (odds ratio = 2.35 [1.35–4.09]; $p = 0.003$), Sequential Organ Failure Assessment score (odds ratio = 1.19 [1.10–1.28]; $p < 0.001$), and ratio of PaO_2 and FiO_2 less than 100 at ICU admission (odds ratio = 1.97 [1.26–3.09]; $p = 0.003$). High-flow nasal cannula oxygen use was neither associated with intubation nor mortality rates.

Conclusions: Some clinical characteristics at ICU admission including etiology and severity of acute respiratory failure enable to identify patients at high risk for intubation.

Key Words: high-flow oxygen; mechanical ventilation; neutropenia; noninvasive ventilation; radiography

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In immunocompromised patients, acute respiratory failure (ARF) remains associated with high mortality rates, most particularly when invasive mechanical ventilation is required (1, 2). Initial oxygenation and ventilation strategy include standard oxygen, noninvasive ventilation (NIV), or high-flow nasal cannula oxygen (HFNO), which can be used alone or in addition to NIV (2). NIV has been recommended in immunocompromised patients with hypoxemic ARF (3) until a recent multicenter trial failed to report any clinical

benefit from NIV (4). This is also in line with recent observational studies (5–7). HFNO has received particular attention in ARF patients due to the substantial physiologic improvements that include improved comfort, alleviation of dyspnea, and reduction of work of breathing (8). However in immunocompromised patients, pilot randomized controlled trial (RCT) failed to report improvement of comfort or dyspnea in 100 immunocompromised patients with ARF (9). Similarly, despite the impressive survival benefits from HFNO reported in the FLORALI trial that compared NIV, HFNO, and standard oxygen (10), the sub study performed in immunocompromised patients did not identify significant differences between HFNO and standard oxygen (11). Two other studies confirmed these findings. Namely, a post hoc analysis from the trial by Lemiale et al (12) did not report any benefit from HFNO as compared to standard oxygen. Furthermore, in the Efraim cohort that included 1,611 patients from 68 ICUs in 16 countries, HFNO tended to reduce intubation rate but had no impact on survival (7). Last, a proper RCT in this setting that included 776 patients from 32 ICUs compared HFNO and standard oxygen and failed to identify any clinical benefit from HFNO in immunocompromised patients with hypoxemic ARF or in any of the predefined subgroups (9). The search for groups of patients that may benefit from noninvasive management remains a challenge. For instance, it is unknown whether patient's and ARF characteristics should be taken into account when selecting initial oxygen strategy. Patients with different types of immunosuppression, various ARF etiology, or different radiological patterns may respond differently to NIV or HFNO (13). Earlier studies have generated such hypotheses. For instance, ARF etiology has been associated with intubation and mortality rates (14, 15). More particularly, ARF from undetermined etiology was associated with increased rates of adverse outcomes (16). Similarly, radiographic patterns at ICU admission have also been associated with increased intubation rates (17).

To the best of our knowledge, no large multicenter study has assessed the impact of ARF characteristics on intubation rate. Our main hypothesis was that response to initial oxygenation and ventilation strategy would vary according to ARF etiology and initial chest radiograph patterns.

PATIENTS AND METHODS

This study was performed on behalf of the Groupe de Recherche en Réanimation Respiratoire Onco-Hématologique (GRRROH) whose major goals are to improve outcomes in immunocompromised patients. We used the GRRROH database, that included studies for which institutional review board agreement was obtained and in which written informed consent was obtained from each patients or surrogate (1, 4, 15). Inclusion criteria were ARF as defined by tachypnea greater than 30/min, respiratory distress (labored breathing), and SpO_2 less than 90% on room air at ICU admission. Noninclusion criteria were ARF related to isolated cardiogenic pulmonary edema,

invasive mechanical ventilation at ICU admission, and do-not-intubate status.

Initial oxygenation strategy was selected by clinicians in charge, ARF etiology was determined using the appropriate diagnostic strategy, and radiographic patterns at ICU admission were collected for each patient. The other variables recorded are presented in **Table 1**. Primary endpoint was the need for intubation throughout the ICU stay. Secondary endpoint was mortality at day 28.

ARF etiology was classified as bacterial or viral pneumonia, opportunistic infection, lung involvement by the underlying disease, drug-related pulmonary toxicity, other identified cause, or undetermined etiology. Diagnostic strategy and criteria for each diagnosis have been described elsewhere (15). Briefly, bacterial or viral pneumonia was based on clinically or microbiologically documented pneumonia (bacteria or virus); opportunistic infection was defined with pneumonia related to invasive fungal infection (i.e. *Pneumocystis jirovecii*, aspergillosis, mucormycosis, or any other fungi) or cytomegalovirus infection; ARF related to underlying disease was referred to pulmonary infiltration by malignancy, leucostasis, or lymphangitic carcinomatosis; and other identified causes included pulmonary embolism, extrapulmonary acute respiratory distress syndrome, massive pleural effusion, atelectasis. In some patients, the ARF etiology remained undetermined despite a comprehensive diagnostic workup.

Radiologic patterns were classified as follows: 1) focal pulmonary involvement when lesion involved a single quadrant of chest radiograph, 2) bilateral diffuse alveolar lesion (with or without pleural effusion), 3) interstitial uni- or bilateral lesion (with or without pleural effusion), and 4) subnormal chest radiograph. Only the first chest radiograph at ICU admission was analyzed.

Initial oxygenation/ventilation strategy was classified as standard oxygen, NIV only when patient received oxygen between NIV sessions, HFNO only, and HFNO plus NIV when HFNO was used between NIV sessions. ARF related to isolated cardiogenic edema patients were not included in this study, and none of the patients received continuous positive airway pressure as oxygenation strategy. NIV for preoxygenation only in the last hour before intubation was not considered in the database as NIV initial oxygenation strategy.

Statistical Analyses

Results were expressed as median and 25th and 75th quartiles (Q1–Q3) for quantitative data and numbers and percentages for categorical data. Quantitative variables were compared using the Student test or the Wilcoxon test in case of nonnormal distribution. Qualitative variables were compared using chi-square test or Fisher exact test as appropriate. No imputation was made on missing data, and number of patients analyzed was given in each table.

First, a univariate analysis was performed to describe the characteristics and outcomes of the four groups of oxygenation (standard oxygen only, NIV only, HFNO only, NIV and HFNO).

TABLE 1. Characteristics and Outcomes According to First-Oxygenation Strategy at ICU Admission

Variables	Standard O ₂ (n = 245)	NIV Only (n = 285)	HFNC O ₂ Only (n = 55)	NIV and HFNC O ₂ (n = 64)	p
Age (yr), median (IQR)	63 (52–71)	62 (52–70)	65 (55–74)	61.5 (51–69)	0.49
Gender, male, n (%)	121 (49)	152 (53)	37 (67)	39 (61)	0.06
Comorbidities, n (%)					
Cardiovascular	93 (38)	112 (39)	30 (54)	21 (33)	0.08
Pulmonary	55 (22)	86 (30)	14 (25)	18 (28)	0.25
Renal	31 (13)	23 (8)	8 (15)	6 (9)	0.26
Charlson Index, median (IQR)	4 (3–6)	4 (3–6)	5 (3–6)	4 (3–6)	0.70
Underlying disease, n (%)					
Hematologic malignancy	203 (83)	224 (79)	38 (69)	45 (70)	0.04
Allogenic stem cell transplantation	33 (13)	49 (17)	9 (16)	14 (22)	0.38
Performance status > 2, n (%)	27 (11)	38 (13)	10 (18)	13 (20)	0.18
Radiologic pattern at ICU admission					
Subnormal	34/233 (15)	16/269 (6)	5/51 (10)	3/59 (5)	< 0.001
Focal or pleural effusion only	49/233 (21)	57/269 (21)	5/51 (10)	5/59 (9)	
Diffuse alveolar	121/233 (52)	152/269 (57)	34/51 (67)	34/59 (58)	
Interstitial	29/233 (12)	44/269 (16)	7/51 (14)	17/59 (29)	
Number of quadrant involved = 4, n (%)	49/233 (21)	84/269 (31)	20/51 (39)	22/59 (37)	0.006
Etiology of acute respiratory failure, n (%)					
Bacterial or viral pneumonia	88/245 (36)	121/285 (42)	25/55 (45)	26/64 (41)	0.12
Opportunistic infection	30/245 (12)	41/285 (14)	10/55 (18)	14/64 (22)	0.23
Lung involvement by the underlying disease drug-related pulmonary toxicity	29/245 (12)	31/285 (11)	7/55 (13)	12/64 (19)	
Other identified causes	55/245 (22)	48/285 (17)	6/55 (11)	7/64 (11)	
No identified cause	43/245 (18)	44/285 (15)	7/55 (13)	5/64 (8)	
Neutropenia at admission, n (%)	61 (25)	83 (29)	18 (33)	12 (19)	0.23
Maximal respiratory rate at day 1, median (IQR)	31 (26–37)	33 (28–39)	33 (27–37)	33 (28–42)	0.003
Pao ₂ /Fio ₂ at day 1, median (IQR)	192 (121–248)	119 (76–188)	89 (72–146)	103 (80–154)	< 0.001
Pao ₂ /Fio ₂ < 100 at day 1, n (%)	181/224 (81)	147/256 (57)	23/54 (43)	37/64 (58)	< 0.001
Vasopressor at day 1, n (%)	96 (39)	103 (36)	22 (40)	27 (42)	0.79
Kidney failure at day 1 (kidneySOFA > 1), n (%)	102 (42)	107 (38)	17 (31)	16 (25)	0.08
SOFA score at admission, median (IQR)	4 (2–6)	5 (3–7)	5 (4–7)	5 (3–7)	0.021
Length between hospital admission and ICU admission, median (IQR)	1 (0–10)	1 (0–12)	2 (0–12)	2 (0–10)	0.81
Length between ICU admission and intubation	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0.24
Invasive mechanical ventilation during ICU stay, n (%)	61 (25)	137 (48)	26 (47)	27 (42)	< 0.001
Day 28 mortality, n (%)	32 (13)	87 (31)	16 (29)	11 (17)	< 0.001
Length of ICU stay, median (IQR)	4 (2–7)	7 (4–15)	8 (4–16)	8 (5–14)	< 0.001
Length of hospital stay, median (IQR)	15 (8–28)	16 (10–28)	17 (9–27)	19 (11–29)	< 0.001
Hospital mortality, n (%)	36 (15)	97 (34)	18 (33)	16 (25)	< 0.001

HFNC = high-flow nasal cannula, IQR = interquartile range, NIV = noninvasive ventilation, Pao₂/Fio₂ = ratio of Pao₂ and Fio₂, SOFA = Sequential Organ Failure Assessment.

Other identified causes were pulmonary embolism, extrapulmonary acute respiratory distress syndrome, pleural effusion, atelectasis.

Second, factors associated with intubation and day-28 mortality were assessed using multivariate mixed logistic model, taking into account the center as a random variable. Age, sex, variables associated with the severity of acute disease or patient status (Sequential Organ Failure Assessment [SOFA] score without respiratory item, performance status, and ratio of Pao_2 and Fio_2 [Pao_2/Fio_2]), oxygenation strategy, ARF etiology, and radiologic pattern were considered clinically relevant and a priori included in the model as fixed effects. Interactions between variables were assessed. A selection procedure was performed using a backward algorithm with a stopping criteria defined by p values below 0.05 for all variables included in the model. Odds ratios (ORs) of variables present in the final model are given with their 95% CIs. Time effect was assessed and not retained; results with corresponding models are presented in the **supplemental material** (Supplemental Digital Content 1, <http://links.lww.com/CCM/F611>). A sensitivity analysis was performed after excluding patients receiving standard oxygen only.

Analyses were performed with the help of statistical softwares (SAS, version 9.4; SAS Institute; Cary, NC; and R version 3.3.3, R Project for Statistical Computing, Vienna, Austria), and statistical significance was fixed at the 0.05 level.

RESULTS

Description of the Cohort

Six hundred forty-nine patients admitted with ARF were included. Throughout the ICU stay, invasive mechanical ventilation was required for 251 patients (39%). Length of ICU stay was 6 days (3–12 d), length of hospital stay was 16 days (9–28 d). Day 28 and hospital mortality rates were respectively 22% and 26%. Table 1 summarizes patient characteristics at ICU admission, according to the initial oxygenation strategy: patients required standard oxygen ($n = 245$), NIV alone ($n = 285$), HFNO ($n = 55$), or NIV+HFNO ($n = 64$). As shown in Table 1, patients who were receiving standard oxygen had less cardiovascular comorbidities, more often focal lesion on chest radiograph, were less severe hypoxemic with lower SOFA score. Patients receiving other oxygenation strategies were more severe regarding Pao_2/Fio_2 , respiratory rate at ICU admission, and had higher number of quadrant involved on chest radiograph.

Adjusted Relation Between Initial Oxygenation Strategy and Intubation Rate

Table 2 presents the relationship between radiological pattern, ARF etiology at admission and intubation rate after taking into account the initial oxygenation strategy and other confounding factors. Bilateral alveolar pattern (OR = 1.67 [1.03–2.69]; $p = 0.04$), bacterial (OR = 1.98 [1.07–3.65]; $p = 0.03$) or opportunistic infection (OR = 4.75 [2.23–10.1]; $p < 0.001$), NIV use at admission (OR = 2.85 [1.73–4.70]; $p < 0.001$), SOFA score (OR = 1.19 [1.10–1.28]; $p < 0.001$), and Pao_2/Fio_2 less than 100 at ICU admission (OR = 1.96 [1.27–3.02]; $p = 0.0002$) were independently associated with intubation rate.

The adjusted probability of intubation after the multivariate mixed effect logistic model varied according to the method of oxygenation, the SOFA score without the respiratory item (Fig. 1), and Pao_2/Fio_2 (Fig. 2). The higher probability of intubation was in patients with opportunistic infections or bacterial/viral pneumoniae (Fig. 3, A and B; Supplemental Fig. 1, Supplemental Digital Content 2, <http://links.lww.com/CCM/F612> [legend, Supplemental Digital Content 1, <http://links.lww.com/CCM/F611>]; and Supplemental Fig. 2, Supplemental Digital Content 3, <http://links.lww.com/CCM/F613> [legend, Supplemental Digital Content 1, <http://links.lww.com/CCM/F611>]) and with diffuse alveolar consolidation (Fig. 3, C and D; Supplemental Fig. 1, Supplemental Digital Content 2, <http://links.lww.com/CCM/F612>; and Supplemental Fig. 2, Supplemental Digital Content 3, <http://links.lww.com/CCM/F613> [legend, Supplemental Digital Content 1, <http://links.lww.com/CCM/F611>]). Whatever patient's characteristics (ARF etiology and radiological pattern), the SOFA (Fig. 1), and Pao_2/Fio_2 (Fig. 2) were associated with the probability of intubation. The sensitivity analysis performed after excluding patients receiving standard oxygen only is presented in Supplemental Table 1 (Supplemental Digital Content 1, <http://links.lww.com/CCM/F611>).

Adjusted Relation Between Initial Oxygenation Strategy and Mortality Rate

Table 2 describes factors associated with day-28 mortality. Day-28 mortality was independently associated with bacterial (OR = 2.34 [1.10–4.97]; $p = 0.03$) or opportunistic infection (OR = 4.96 [2.11–11.6]; $p < 0.001$), NIV use at admission (OR = 2.35 [1.35–4.09]; $p = 0.003$), SOFA score (OR = 1.19 [1.10–1.28]; $p < 0.001$), and Pao_2/Fio_2 less than 100 at ICU admission (OR = 1.97 [1.26–3.09]; $p = 0.003$). The sensitivity analysis performed after excluding patients receiving standard oxygen only is presented in Supplemental Table 2 (Supplemental Digital Content 1, <http://links.lww.com/CCM/F611>).

Impact of Time Period of ICU Admission on Intubation and Mortality Rates

After adjustment on time effect, according to the following period: 2005 to 2008, 2009 to 2011 and 2012 to 2015, we observed similar results with both significant effects of NIV and HFNC on intubation and mortality rates (Supplemental Tables 3 and 4, Supplemental Digital Content 1, <http://links.lww.com/CCM/F611>).

DISCUSSION

In immunocompromised patients with ARF, NIV use at admission, ARF etiology (i.e., bacterial or opportunistic infections), and bilateral alveolar pattern on chest radiograph were independently associated with intubation rate. The probability of intubation of the sickest patients (elevated SOFA score and $Pao_2/Fio_2 < 100$) was higher in case of NIV or HFNO use, especially when other conditions were also present.

TABLE 2. Relation Between Radiological Pattern at ICU Admission and Acute Respiratory Failure Etiology With Intubation Rate (Mixed Logistic Multivariate Analysis)

Variables	OR	p
Mode of oxygenation		
O ₂ only	1	
NIV only	2.85 (1.73–4.70)	< 0.001
HFNC oxygen only	2.19 (0.99–4.85)	0.05
NIV and HFNC oxygen	1.70 (0.83–3.49)	0.14
Severity of acute respiratory failure		
Sequential Organ Failure Assessment score without respiratory item at admission	1.19 (1.10–1.28)	< 0.001
Ratio of PaO ₂ and FiO ₂ < 100 at ICU admission	1.96 (1.27–3.02)	0.0002
Diagnosis		
Other identified causes	1	
Bacterial or viral pneumonia	1.98 (1.07–3.65)	0.03
Opportunistic infection	4.75 (2.23–10.1)	< 0.001
Lung involvement by the underlying disease or drug-related pulmonary toxicity	2.13 (0.96–4.73)	0.06
No identified cause	1.48 (0.70–3.11)	0.30
Radiologic pattern at ICU admission		
Bilateral alveolar	1.67 (1.03–2.69)	0.04

HFNC = high-flow nasal cannula, NIV = noninvasive ventilation, OR = odds ratio.

Other identified causes were pulmonary embolism, extrapulmonary acute respiratory distress syndrome, pleural effusion, atelectasis.

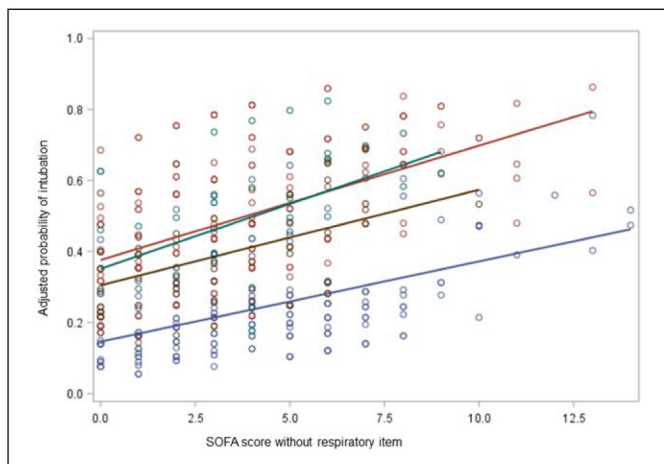


Figure 1. Adjusted probability of intubation according to initial oxygenation/ventilation strategy and the Sequential Organ Failure Assessment (SOFA) score without the respiratory item. The *green line* represents high-flow nasal cannula oxygenation (HFNC) alone, the *red line* noninvasive ventilation (NIV) alone, the *brown line* NIV combined to HFNC, and the *blue line* standard oxygen. The probabilities of intubation presented in y-line are adjusted after the multivariate mixed effect logistic model presented in Table 2.

Optimal oxygenation strategy in immunocompromised patients with acute hypoxemic ARF remains controversial (2, 13, 18). In the present study, NIV was independently associated with higher intubation and day-28 mortality rates. The use of HFNO (alone or with NIV) was not associated with

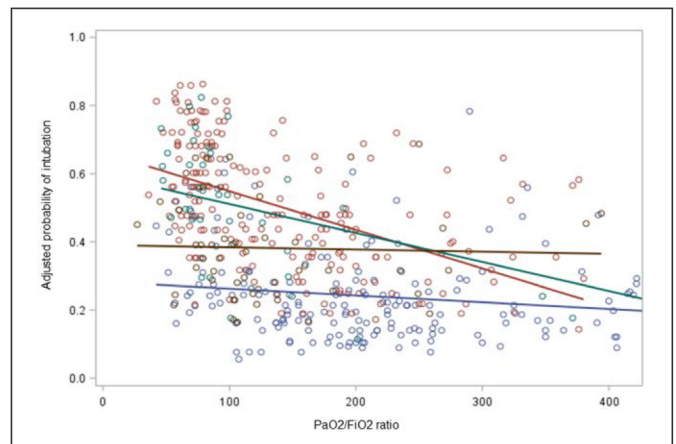


Figure 2. Adjusted probability of intubation according to the method of oxygenation and the ratio of PaO₂ and FiO₂ (PaO₂/FiO₂). The *green line* represents high-flow nasal cannula oxygenation (HFNO) alone, the *red line* noninvasive ventilation (NIV) alone, the *brown line* NIV combined to HFNO, and the *blue line* standard oxygen. The probabilities of intubation presented in y-line are adjusted after the multivariate mixed effect logistic model presented in Table 2.

decreased intubation or day-28 mortality rates compared with standard oxygen. This study is in line with the results of previous studies and of the HIGH randomized trial reporting that HFNO had no impact on outcomes in immunocompromised patients with hypoxemic ARF (4, 7, 9).

The finding that NIV use was associated with worse outcomes has to be carefully discussed. For instance, it is worth noting that

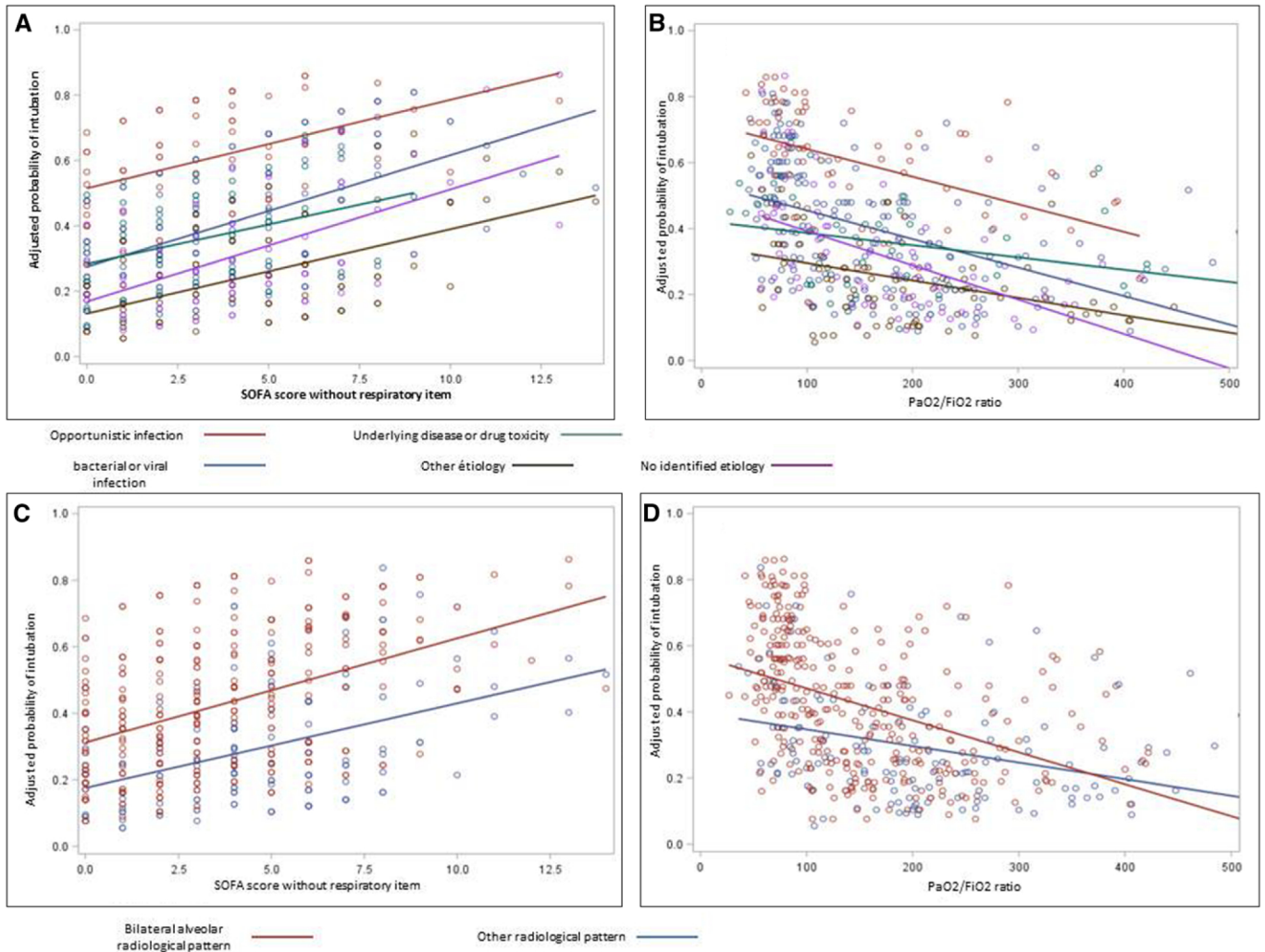


Figure 3. **A**, Adjusted probability of intubation according to the acute respiratory failure (ARF) etiology and the Sequential Organ Failure Assessment (SOFA) score without the respiratory item. The probabilities of intubation presented in y-line are adjusted after the multivariate mixed effect logistic model presented in Table 2. **B**, Adjusted probability of intubation according to the ARF etiology and the ratio of P_{aO_2} and F_{iO_2} (P_{aO_2}/F_{iO_2}). The probabilities of intubation presented in y-line are adjusted after the multivariate mixed effect logistic model presented in Table 2. **C**, Adjusted probability of intubation according to the radiologic pattern at ICU admission and the SOFA score without the respiratory item. The *red line* represents bilateral alveolar pattern, the *blue line* other pattern. Other pattern included interstitial, focal, or subnormal patterns. The probabilities of intubation presented in y-line are adjusted after the multivariate mixed effect logistic model presented in Table 2. **D**, Adjusted probability of intubation according to the radiologic pattern at ICU admission and P_{aO_2}/F_{iO_2} . The *red line* represents bilateral alveolar pattern, the *blue line* other pattern. Other pattern included interstitial, focal, or subnormal patterns. The probabilities of intubation presented in y-line are adjusted after the multivariate mixed effect logistic model presented in Table 2.

patients had severe ARF with respiratory rate at ICU admission of 32 (27–38)/min and estimated P_{aO_2}/F_{iO_2} of 136 (81–204). Furthermore, almost 40% of patients developed another organ failure within the first ICU day. These results actually raise concerns about the appropriate timing of intubation in this setting (13, 18, 19–21). Although well described in the studies, criteria to perform intubation always include a part of subjective and contextual appreciation by the physician in charge (3, 4, 9, 18). This however cannot be captured by any of the collected variables. Objective criteria to assess appropriate time to intubation are scarce particularly when patients received initially NIV and/or HFNO. Only few studies assessed intubation criteria during or after NIV session, and those criteria were mostly related to severity of ARF (hypoxemia and number of quadrant involved on chest radiograph) and associated organ failure (vasopressor or

encephalopathy) (17, 22). In patient receiving HFNO, one single study described risk factors associated with intubation. The most important factor was high respiratory rate after 1-hour HFNO trial (22). A recent study described ratio of oxygen saturation as measured by pulse oximetry/ F_{iO_2} to respiratory rate after 12 hours HFNO, which was associated with intubation rate (23). Further studies should focus on objective and reproducible criteria for intubation including ARF etiology, radiological pattern on initial chest radiograph.

This is the first study to report risk factors for intubation that include clinical characteristics. We report an independent association between bilateral alveolar pattern and intubation rate. In a previous study (17), number of radiological quadrants involved were associated with higher risk of intubation, which may be correlated with a bilateral alveolar radiological pattern. These

results could influence daily clinical practice. Initial radiological pattern at ICU admission or ARF etiology may avoid undermine ARF severity and guide clinicians toward optimal selection of HFNO and NIV, as well as for the timing of intubation. In the current study, the relationship between ARF etiology and mortality was analyzed to deal with the clinical correlation between radiological pattern and etiology of ARF, demonstrated not only in overall immunocompromised patients (24) but also recently in patients with suspected *Pneumocystis pneumonia* (25). These findings suggest that patient with bacterial/viral pneumonia or opportunistic infection who exerted bilateral alveolar infiltration and received NIV or HFNO only did not benefit from the techniques but had maybe underwent delayed intubation. Should these data be validated in large prospective cohorts of immunocompromised patients with hypoxemic ARF, patient's characteristics at ICU admission should then be used to stratify patients at high risk of intubation, and identify those patients that may benefit from early intubation (26, 27)

This study has several limitations. First, patients were included over a 10-year study period. Data have shown that outcomes have changed over the last decade. However, practices also changes substantially with HFNO not used in the first years (15), diagnosis strategy turned to less invasive testing, with bronchoalveolar lavage remaining often performed in the more recent studies (155/604 [25%] in TRIALOH study [1] and 142/374 [38%] in IVNICTUS study [4]). Furthermore, a time effect was assessed in the mixed effect logistic model and not retained.

Second, studies were performed within a research group particularly focused on the management of immunocompromised patient and may not apply to a general ICU. In those ICU, accuracy of ARF diagnosis could be higher than in other ICU leading to higher survival rate.

Third, only characteristics at ICU admission were included in the analysis. Longitudinal patient' status following the first day of admission could not be analyzed. Furthermore, only SOFA score at day 1 and Pao_2/FiO_2 were included in the multivariate analysis. Other prognosis scores as Acute Physiology and Chronic Health Evaluation 2 or Simplified Acute Physiology Score 2 scores were not recorded in the database. In the sensitivity analysis excluding patients receiving only standard oxygen, the oxygenation strategy was no longer associated with intubation and mortality. This result may confirm that in the more severe patients identifying etiology of ARF remains the most important factor to improve survival.

Fourth, patient who received NIV and HFNC had similar results in intubation and mortality rates. This result may be related to the clinician decision to use those devices for the most severe patients. To reduce this bias, all the results were adjusted on the main confounding factors after various multivariate analyses (Table 2; Fig. 1; Supplemental Fig. 1, Supplemental Digital Content 2, <http://links.lww.com/CCM/F612> [legend, Supplemental Digital Content 1, <http://links.lww.com/CCM/F611>]; and Supplemental Tables 1–4, Supplemental Digital Content 1, <http://links.lww.com/CCM/F611>). However, we cannot exclude that some remaining confounding factors not recorded were still present. Using standard oxygen or switch to

NIV or HFNO is commonly based on the clinical appearance of sickness (high respiratory rate, use of accessory muscles, obtundation, severe dyspnea, diaphoresis, cyanosis, lack of ability to manage secretions,...), and these data were not recorded and could not be included in any method of adjustment performed. Furthermore, during that 10 years period, a new device, HFNO, was implemented as an oxygenation strategy. Then, the proportion of HFNO patients was lower than the other oxygenation devices which might have impacted the results.

Fifth, ARF was mostly related to bacterial infection. Although details on infection origin or pathogen could impact the results, they were not available. Although length between hospital and ICU admission was very short (median 1 d) and not different between groups, most of the patients were treated for hematologic diseases and subsequently were exposed to healthcare associated infection.

Last, intubation timing is a crucial element since literature suggests that postpone intubation may represent a high risk for the critically ill patient (28). The decision to intubate patient may waver from the extreme tentative when everything has failed to an immediate decision after a short NIV/HFNC trial. In order to reduce this bias, we did not include patients who were intubated within the first day of ICU admission and patient who received NIV for preoxygenation only before intubation. These most severe patients would have reach intubation criteria without any doubt during the first day (17, 29). It is worth noting that delay between ICU admission and intubation was not different between the groups, that could indicate that none of patients received excessive NIV/HFNO trials, which could have postponed intubation.

In conclusion, in immunocompromised patients with hypoxemic ARF, clinical variables available at ICU admission actually are associated with intubation and mortality rates. Clinicians should consider not only severity of ARF but also radiological pattern and suspected ARF etiology to decide time of intubation. Studies to confirm the impact of first oxygenation strategy on outcomes are still warranted.

Drs. Lemiale, De Jong, Dumas, Jaber, and Azoulay designed the study, performed statistics, and wrote the article. Drs. Lemiale, Mokart, Pène, Kouatchet, Bisbal, Bruneel, Lebert, Vinatier, Benoit, Meert, Demoule, Darmon, and Azoulay included the patients in the database. All the authors reviewed the article and revised it critically for important intellectual content. All authors approved the final version to be published. Dr. Lemiale is the guarantor of the article. Drs. Lemiale and De Jong equally contributed to this work.

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