UNIVERSITÉ DE LILLE

UFR3S-MÉDECINE

Année :2026

THÈSE POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

Predictors of ventilatory supports failure in patients with interstitial lung diseases admitted to Intensive Care Unit

Présentée et soutenue publiquement le 23/01/2026 à 16h

au *Pôle Recherche*

par Charlotte LACOMBE

JURY

Président :

Madame la Professeure Mercé Jourdain

Assesseurs :

Monsieur le Docteur Alexandre Gaudet

Monsieur le Docteur Victor Valentin

Directeur de thèse :

Monsieur le Docteur Laurent Robriquet

AVERTISSEMENT

L’université n’entend donner aucune approbation aux opinions émises dans les thèses : celles-ci sont propres à leurs auteurs

Table of contents

List of Abbreviations

AE-ILD: Acute exacerbation of Interstitial lung diseases

ARDS: Acute Respiratory Distress Syndrome

ARF: Acute respiratory failure

AUC: Area under curve

BMI: Body mass index

C-ILD: Connective tissue-associated ILD and granulomatous diseases

COP: cryptogenic organizing pneumonia

DP: Driving pressure

ETT: Endotracheal intubation

FiO_2: raction of inspired oxygen

HFNO: High-flow nasal oxygen

ICU: Intensive care unit

ILD: Interstitial lung diseases

IPF: Idiopathic pulmonary fibrosis

MP: Mechanical power

MV: Mechanical ventilation

NIV: Noninvasive ventilation

NSIP: nonspecific interstitial pneumonia

OR: Odds ratio

PaO_2: Partial pressure of arterial oxygen

PBW: Predicted body weight

PEEP: Positive end expiratory pressure

Peak: Peak airway pressure

ROC: Receiver Operating Characteristic

ROX: Respiratory rate oxygenation

RR: Respiratory rate

SAPS II: Simplified Acute Physiology Score II

SOFA: Sepsis-related Organ Failure Assessment

SpO_2: Periphéral capillary oxygen saturation

SpO_2/FiO_2: Ratio of pulse oximetry oxygen saturation to the fraction of inspired oxygen

VAP: Ventilator associated pneumonia

VILI: Ventilator induced lung injury

VMm: Measured minute ventilation

Vt: Tidal volume

VR: Ventilatory ratio

Abstract

Background:

Acute respiratory failure (ARF) is a frequent and severe complication in patients with interstitial lung diseases (ILD) admitted to intensive care unit (ICU), and is associated with high short- and long-term mortality. High-flow nasal oxygen (HFNO) and invasive mechanical ventilation (MV) are commonly used and reliable bedside prognostic markers to predict ventilatory supports failure are lacking.

Objectives:

To evaluate the prognostic value of four readily available respiratory indices—the relationship of Respiratory Rate-Oxygenation (ROX index), the ratio of pulse oximetry oxygen saturation to the fraction of inspired oxygen (SpO_2/FiO_2), the ventilatory ratio (VR), and the mechanical power (MP)—to predict ventilatory supports failure in ICU patients with ILD.

Methods:

We conducted a retrospective, single-center observational study including all adult ILD patients admitted to ICU for ARF between January 2013 and November 2024. HFNO failure was defined as a composite endpoint of 30-day mortality or need for invasive MV. MV failure was defined as 30-day mortality among intubated patients. ROX index and SpO_2/FiO_2 ratio were assessed at 0, 24, and 48 hours during HFNO therapy, while VR and MP were evaluated at the same time points during invasive MV. Discriminative performance was assessed using receiver operating characteristic curves with area under the curve (AUC) values, Youden's index, and survival analyses. Multivariable analyses were adjusted for decisions regarding limitations of life-sustaining therapies given sample size constraints.

Results:

A total of 100 ILD patients were included, 71 received HFNO (25 subsequently undergoing tracheal intubation) and 54 required invasive MV. The overall 30-day mortality rate was 41%. Among HFNO patients, 57% experienced failure of HFNO therapy. ROX index ≥ 7.07 at 48 hours was associated with a significantly lower risk of HFNO failure (AUC = 0.81). SpO_2/FiO_2 ratio ≥ 181.9 at 48 hours was significantly associated with a decreased risk of HFNO failure (AUC = 0.79). After adjustment for treatment-limitation decisions, both indices retained independent prognostic value. Among mechanically ventilated patients, VR and MP were significantly higher at 24 hours in the MV failure group. VR at 24 hours showed fair discriminative performance (AUC = 0.72), with a threshold of 1.89 associated with an approximately fourfold increased risk of MV failure. MP at 24 hours demonstrated acceptable discrimination (AUC = 0.73), with a threshold of 31.38 J/min associated with a fourfold increased risk of MV failure. These associations remained robust after adjustment for limitations of life-sustaining therapies.

Conclusions:

In critically ill patients with ILD, simple bedside respiratory indices provided clinically relevant prognostic information. ROX index and SpO_2/FiO_2 ratio at 48 hours could early facilitate and accurate prediction of HFNO therapy failure. In mechanically ventilated patients, VR and MP measurements at 24 hours were significantly associated with 30-day mortality. The study results should be validated in larger prospective studies to assess their clinical uses.

I. Introduction

A. Interstitial lung diseases (ILD)

1. Overview of ILD

ILD encompass a heterogeneous group of chronic lung disorders of different etiologies. ILD include idiopathic diseases such as idiopathic pulmonary fibrosis (IPF), exposure-related disorders such as hypersensitivity pneumonitis (HP), and interstitial lung diseases associated with autoimmune features, including anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (1,2). The diagnosis is based on a combination of clinical, radiological, and, in some cases, histopathological criteria (3). The heterogeneity of ILD makes epidemiological assessment difficult. A multicenter European study reported a heterogeneous epidemiological burden across ILD, with an overall incidence ranging from 20.0 to 42.5 cases per 100 person-years. The incidence of fibrotic ILD ranged from 17.9 to 38.3, while idiopathic pulmonary fibrosis (IPF) showed a lower incidence, between 2.1 and 6.3 cases per 100 person-years. Autoimmune disease–associated ILD displayed variable incidence rates depending on the country, ranging from 0.5 to 1.0 per 100 person-years (4).

Acute exacerbation of ILD (AE-ILD) is defined as a rapid deterioration of dyspnea within 30 days, in the absence of an alternative diagnosis associated with new or worsening abnormalities on chest imaging (5). The etiologies of AE-ILD are diverse, most commonly infectious, pulmonary embolism, alveolar hemorrhage, pneumothorax and cardiovascular disease while idiopathic causes account for approximately 50 % of cases (6,7). The occurrence of an AE-ILD represents a key prognostic factor influencing patients survival (6–9). The literature reports very poor outcomes, with median times to death post-AE-ILD of approximately 2 months for fibrotic form (7,10,11).

2. Prognosis of ILD admitted to Intensive Care Unit (ICU)

A retrospective French study was conducted on 196 patients admitted to ICU with AE-ILD. Among the 108 patients requiring invasive mechanical ventilation (MV), only 21 were discharged alive from the hospital (9). Another recent study showed higher mortality, up to 90% at 90 days after AE-ILD requiring MV (7). Patients admitted to ICU with idiopathic fibrosing ILD showed a worse prognosis than those with ILD associated with autoimmune or connective tissue disorders (12). Thus, an AE-ILD requiring ICU admission constitutes a major prognostic event in the natural history of the disease.

B. High-flow nasal oxygen (HFNO) use in acute respiratory failure (ARF) in patients with ILD

High-flow nasal oxygen (HFNO) provides oxygen at flow rates of 20–60 L/min with an inspired oxygen fraction (FiO_2) from 21% to 100% delivered by nasal cannula. HFNO generates a moderate positive airway pressure (up to 4 cm H_2O), induces alveolar recruitment, limits dead-space effects and decreases respiratory drive (13,14). According to the 2023 international Acute Respiratory Distress Syndrome (ARDS) guidelines, HFNO is recommended over conventional oxygen therapy, as it has been shown to significantly reduce the MV use (15,16). However, HFNO may delay endotracheal intubation (ETT) and be harmful for some patients (17).

Several prognostic factors have been developed to predict HFNO failure, including the ratio of pulse oximetry oxygen saturation (SpO_2) to the FiO_2 (SpO_2/FiO_2) (18–21) and the SpO_2/FiO_2 ratio to the respiratory rate (RR) (ROX index) at a given time (18).

$$ROX\ ratio = \frac{SPO2}{FIO2}/RR$$

Both indices have been validated across various patient populations, with evolving thresholds and timing depending on the clinical context (18,19,21,22). Thus, while the ROX index and the SpO_2/FiO_2 ratio are useful tools to evaluate HFNO failure, their performance requires reassessment in each specific patient population.

HFNO was commonly used in clinical practice for patients with ILD and ARF (23,24). Data from a cohort of 66 patients with AE-ILD suggested that the SpO_2/FiO_2 ratio 24 hours after HFNO initiation was a good predictor of successful treatment (25). To our knowledge, data regarding the prognostic value of the ROX index in critically ill ILD patients treated with HFNO remain rare.

C. MV use in ARF in patients with ILD

1. Monitoring of MV

In cases of noninvasive ventilatory supports failure or most severe forms of ARF, invasive MV may be required. Ventilatory practices have evolved since the early 2000s with the adoption of lung-protective ventilation strategies and these approaches have shown improved survival in patients with ARDS (26,27). During MV, respiratory mechanics can be assessed through parameters derived from pressure–volume curves reflecting resistive and elastic properties of the respiratory system (28). Plateau pressure reflects alveolar pressure at end-inspiration under static conditions, whereas positive end-expiratory pressure (PEEP) represents alveolar pressure at end-expiration. Driving pressure (DP) is defined as the difference between plateau pressure and total PEEP. These are the components of elastic pressure. Resistive pressure is reflected by the difference between peak airway pressure, which corresponds to the pressure in the airways at the beginning of insufflation, and plateau pressure (29).

Lung-protective ventilation is primarily defined by low tidal volumes (Vt), approximately 6 mL/kg of predicted body weight aiming plateau pressure < 30 cm H_2O and DP < 14 cm H_2O (30). DP represents Vt normalized for compliance and is considered as a key component of ventilator induced lung injury (VILI) (31,32). The PaO_2/FiO_2 ratio is another parameter used to assess ARDS severity and is associated with mortality (33).

2. Limits of common monitoring parameters for mechanically ventilated patients with ILD

In cohorts of mechanically ventilated patients with ILD, plateau pressure and DP are frequently reported to exceed recommended targets in ARDS (34–36). Patients with ILD exhibit a distinct physiological profile. *Tonelli et al.* specifically investigated the impact of PEEP and reported that, unlike patients with ARDS, patients with ILD were associated with improved outcomes when managed with lower PEEP levels (34). Moreover, the available literature on the PaO_2/FiO_2 ratio for patients with ILD remains inconclusive concerning its prognostic value, with studies reporting conflicting results (35,37). Thus, in this specific patient population, alternative prognostic factors of MV failure are lacking.

3. Alternative monitoring parameters for mechanically ventilated patients with ILD

Mechanical power (MP) was introduced by *Gattinoni et al.* as an estimate of the risk of VILI, and represents the energy transferred to the respiratory system per unit of time during mechanical inflation (31,38,39). *Paudel et al.* published a simplified MP formula used for bedside measures (40):

$$MP = 0{,}098\ x\ VT\ x\ RR\ x\ (Ppeak - 0{,}5\ x\ DP)$$

MP: Mechanical power (J/min); Vt: tidal volume (ml), RR: Respiratory rate, Ppeak: Peak airway pressure (cmH_2O), DP: Driving pressure (cmH_2O).

Data from the literature suggest that MP may be associated with mortality (41). However, this association has not been consistently reported across all cohorts (42).

The ventilatory ratio (VR) is a bedside parameter used to assess carbon dioxide clearance. It is of particular interest in patients for whom lung-protective ventilation is difficult to achieve, as it often requires tolerance of permissive hypercapnia. VR is also a useful tool in patients with increased dead space (43,44).

$$VR = \frac{VM\mathrm{m}\ x\ PaCO2m}{100xPBWx5}$$

VR: Ventilatory ratio, VMm: Measured minute ventilation (ml), $PaCO_2m$: $PaCO_2$ measured, PBW: predicted body weight

In previous studies, these two parameters were assessed during the first 48 hours of MV (38,40,41,43,44).

To date, MP and VR have been rarely investigated in patients with ILD undergoing MV. However, due to their specific lung architecture, patients with ILD exhibit distinct alterations in respiratory mechanics. In a study by *Nava et al.,* the authors reported increased resistive pressures and moderately elevated levels of capnia in ILD patients (45). These two parameters are assessed respectively in the calculation of MP and VR. The bedside availability and the pathophysiological relevance of MP and VR make them attractive candidates for prognostic assessment in critically ill patients.

D. Study objectives

The study aimed to evaluate the prognostic value of four easily measurable parameters to predict ventilatory supports failure for patients with ILD admitted to ICU. HFNO failure was defined as a composite endpoint including either 30-day mortality or endotracheal intubation (ETT) before day 30. MV failure was defined as 30-day mortality among patients requiring invasive MV. The following parameters were evaluated:

- ROX ratio at H0, H24, H48 during HFNO therapy
- SpO_2/FiO_2 ratio at H0, H24, H48 during HFNO therapy
- VR at H0, H24, H48 during invasive MV
- MP at H0, H24, H48 during invasive MV

H0 corresponds to HFNO initiation for the HFNO analysis, and to start of invasive MV for the MV analysis

II. Materials and Methods

A. Study population and design

A retrospective, observational, single-center cohort study was conducted in the Intensive Care Medicine department of the Lille University Hospital, France. Data were collected from patients hospitalized between January 2013 and November 2024. Patient selection was performed using hospital stay numbers through the Cora coding software, according to the following codes “J70, J848, J990, J991, J998, GLLD002, GLLD004, GLLD007, GLLd008, GLLD012, GLLD015, GLLD003, GLLD013, GLLD017, GLLD019, GLLP001, GLLP004”, and through the IntelliSpace Critical Care and Anesthesia (ICCA, Philips Healthcare, Koninklijke Philips N.V., Netherlands) software.

Inclusion criteria were:

- Age ≥ 18 years
- Ventilatory supports via HFNO or invasive MV
- Diagnosis of ILD, either prior to or during ICU stay
- ILD diagnosis formally established by a senior radiologist or pulmonologist and documented in the clinical file
- ICU Admission for ARF

Exclusion criteria were:

- Patient refusal to participate in data collection
- ICU Admission for reasons other than ARF
- Absence of ILD formally diagnosed by a senior pulmonologist or radiologist and documented in the clinical file
- Age < 18 years

- Lack of ventilatory supports via HFNO or invasive MV during the ICU stay
- Length of stay shorter than 48 hours

Patients were classified into three groups according to the ventilatory strategy implemented during the ICU stay:

1. HFNO
2. HFNO followed by invasive MV (HFNO MV),
3. Direct invasive MV within the first 24 hours of ICU admission.

For analytical purposes, patients initially treated with HFNO who subsequently required invasive MV were included in both analytical populations: in the HFNO cohort for the analysis of HFNO failure, and in the mechanically ventilated cohort for the analysis of MV failure. Patients were included in the descriptive cohort once and could contribute to two distinct analytical datasets addressing different endpoints.

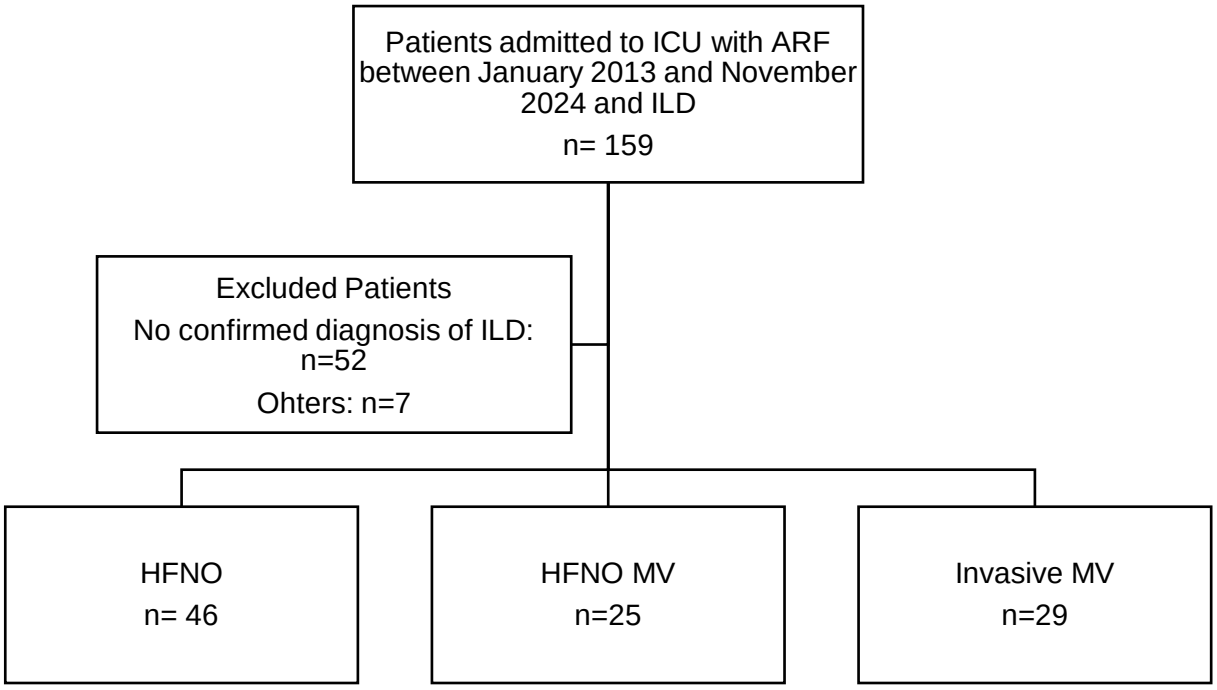

Figure 1: flow chart of patient's selection

A total of 159 patients meeting the inclusion criteria were identified. Fifty-two patients were excluded due to the absence of a formal ILD diagnosis. Others exclusions included: one patient admitted for stroke, three receiving standard oxygen therapy, one on veno-venous ECMO without other ventilatory support, and two patients with ICU length of stay < 48 hours.

100 patients were included during the study period: 46 received HFNO exclusively, 25 HFNO followed by MV and 29 MV exclusivelyARF: Acute respiratory failure, ILD: interstitial lung diseases, HFNO: High-flow nasal oxygen, HFNO MV: High-flow nasal oxygen before mechanical ventilation, MV: Mechanical ventilation

B. Data collection

Data were collected from patient's medical records (source documents) stored at the investigator site. No identifying data were collected. Anonymized data were entered into a password-protected Excel file. Research documents and data will be stored for 15 years following the study's completion.
The study was declared to the Data Protection Department of CHU Lille and obtained a declaration certificate for computerized data processing (No. DEC24-303). Ethical

approval is currently awaiting confirmation from the French Society of Intensive Care Medicine. Data were extracted from medical records using the hospital's software: ICCA and Sillage (SIB, Rennes, France).

All the following characteristics were collected

- Age, sex, main comorbidities for Charlson Comorbidity Index
- Anthropometric data: weight (kg), height (cm), body mass index (BMI, kg/m^2)
- ILD characteristics:
    - ILD type: exclusive ILD such as hypersensitivity pneumonitis, idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), or cryptogenic organizing pneumonia (COP); connective tissue-associated ILD and granulomatous diseases (C-ILD); and others (drug-induced, pneumoconiosis)
    - Fibrosing pattern: Fibrosing phenotype was defined based on radiological findings and clinical course documented in medical records, and classified as rapid (< 3 months) or progressive (> 3 months) according to the timing of fibrosis progression, without applying standardized progressive pulmonary fibrosis criteria
    - Requirement for long term oxygen therapy or noninvasive ventilation (NIV)
    - Disease duration since diagnosis (months)
- Cause of ARF was noted: decompensation factors including infectious episodes, right or left heart failure, iatrogenic cause, pneumothorax, pulmonary embolism, fibrosing flare, AE-ILD (dyspnea onset or worsening < 1 month) or subacute (> 1 month) classified according to the main presumed trigger.

- Severity scores on ICU admission: Simplified Acute Physiology Score II (SAPS II) and Sepsis-related Organ Failure Assessment (SOFA)
- Biological data on ICU admission: white blood cell count (G/L), lymphocytes (G/L), platelets (G/L), hemoglobin (g/L), fibrinogen (g/L), C-reactive protein (CRP, mg/L), procalcitonin (PCT, ng/mL), creatinine (mg/dL), lactate (mmol/L), pH, arterial oxygen pressure (PaO_2, mmHg), arterial carbon dioxide pressure ($PaCO_2$, mmHg), B-type natriuretic peptide (BNP, ng/mL)
- HFNO parameters, respiratory rate (RR, breaths/min), and oxygen saturation (%) for ROX index evaluation at hour 0 (H0), H24 and H48. The ROX index was defined as the ratio of SpO_2 /FiO_2 (%) to RR (breaths/min).
- MV parameters: tidal volume (Vt, mL), RR (cycles/min), positive end-expiratory pressure (PEEP), peak pressure, plateau pressure, DP (cm H_2O) at H0, H24, and H48
- Arterial blood gas data: pH, PaO_2 (mmHg), $PaCO_2$ (mmHg), bicarbonate (mmol/L), lactate level (mmol/L) at H0, H24, and H48
- MP and VR at H0, H24, and H48 for patients requiring invasive MV. MP was defined as (40):

$$MP = 0.098\ x\ VT\ x\ RR\ x\ (Ppeak - 0.5\ x\ Driving\ pressure)$$

MP: Mechanical power (J/min); Vt: tidal volume (ml), RR: Respiratory rate, Ppeak: Peak airway pressure (cmH_2O), DP: Driving pressure (cmH_2O),

- VR was defined as:(43,44)

$$VR = \frac{VM\mathrm{m}\ x\ PaCO2m}{100xPBWx5}$$

VR: Ventilatory ratio, VMm: Measured minute ventilation, $PaCO_2m$: $PaCO_2$ measured, PBW: predicted body weight

- Therapies during invasive MV at H0, H24, and H48: neuromuscular blockers and inhaled nitric oxide (NO).
- Adjunctive ILD therapies: corticosteroids (three dosage categories: 15 mg/kg bolus, 1 mg/kg/day, 2 mg/kg/day), immunomodulators, anti-infectious treatments.
- Occurrence of infectious complications with microbiological evidence: ventilator-associated pneumonia (VAP), bacteremia, fungemia, aspergillosis, pneumocystis.
- Implementation of treatment limitation decisions defined as documented withholding and/or withdrawal of life-sustaining therapies (including do-not-intubate or do-not-resuscitate orders) recorded in the medical chart.
- Duration (days) of ICU stay, invasive MV duration, and total hospital stay.
- Vital status obtained from medical records and the French National Institute of Statistics and Economic Studies (INSEE) death registry.

C. Statistical analysis

Statistical analysis was performed with the assistance of biostatisticians of Lille University Hospital. Statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS

Institute, Cary, NC, USA). Continuous variables are presented as median [interquartile range] and categorical variables as counts and percentages. Comparisons across the three ventilatory strategy groups (HFNO, HFNO followed by MV, and primary invasive MV) were performed using the Kruskal–Wallis test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables, as appropriate. When relevant, post-hoc pairwise comparisons were conducted using Wilcoxon rank-sum tests for continuous variables and pairwise χ^2 or Fisher's exact tests for categorical variables, with Bonferroni correction for multiple comparisons.

To identify factors associated with HFNO failure and MV failure, univariable binary logistic regression models were first fitted, using failure as the dependent variable. Odds ratios (OR) with 95% confidence intervals (95% CI) were reported. Model discrimination was assessed using the c-statistic, equivalent to the area under the receiver operating characteristic curve (AUC). Optimal thresholds for prognostic indices were determined using the Youden index, and the corresponding sensitivity, specificity, and AUC were reported.

Given the limited number of events, fully adjusted multivariable models were not feasible. Therefore, for each time point (H0, H24, and H48), separate parsimonious multivariable logistic regression models were constructed, each including treatment limitation decisions and a single respiratory index (ROX ratio or SpO_2/FiO_2 for HFNO failure; VR or MP for invasive MV failure). This strategy was chosen to limit overfitting while allowing assessment of independent associations.

Survival analyses were performed using Kaplan–Meier curves and compared with the log-rank test. Cox proportional hazards models were used to assess the association

between threshold-based variables and time to failure, with results expressed as hazard ratios (HRs) and 95% confidence intervals.

All tests were two-sided, and a p-value < 0.05 was considered statistically significant.

III. Results

A. Cohort description

One hundred patients with ILD were included during the study period. The cohort was predominantly male (69%), with a median age of 67 years at ICU admission. Most patients had lung-limited ILD (44%) and a fibrosing phenotype (58%). ILD was diagnosed during ICU stay for 23 patients. The 30-day mortality rate was 41% (16 deaths in the HFNO group, 15 in the HFNO MV group, and 10 in the MV group) (Appendix, Table 1).

The distribution by age and sex was similar across groups. Patients in the HFNO MV group had a higher BMI compared to the other groups ($p = 0.046$). Patients in the invasive MV group had a greater severity at ICU admission, as assessed by the SAPS II score ($p = 0.006$) and SOFA score ($p < 0.001$). The distribution of ILD etiologies and a fibrotic phenotype were similar across groups. Patients in the HFNO group presented more acute exacerbations ($p = 0.035$). Causes of exacerbation significantly differed between groups, with infectious triggers being more frequent in the HFNO group ($p = 0.036$).

The most frequently administered immunomodulatory treatments were corticosteroids and cyclophosphamide. Less commonly used immunomodulatory agents included rituximab, JAK inhibitors, and tacrolimus (data not shown). Mortality at 30 days and hospital length of stay were not statistically different between groups. Patients in the HFNO MV group had significantly longer ICU length of stay ($p < 0.001$). Characteristics of these patients during ICU stay were reported in table 1.

Table 1: baseline characteristics of study groups

Variable	HFNO n=46	HFNO MV n=25	MV n=29	p
Patients characteristics				
Sex (Women)	17 (37%)	4 (16%)	10 (34.5%)	0.184
Age	67.5 [56.25-74]	71 [63-74]	64 [48-74]	0.516
BMI	24.25 [20.07-27.13]	26.12[24.49-29.32]	24.92[21.15-27.13]	**0.046**
Charlson Comorbidity index	5 [3-8]	5 [4-7]	5 [3-7]	0.722
Severity at ICU admission				
SAPS II	39 [32.25-45]	39 [35-45]	49 [36-60]	**0.006**
SOFA score	2 [1.25-3]	6 [3-6]	9 [6-11]	**< 0.001**
Type of ILD				
ILD	24 (52.2%)	10 (40%)	10 (34.5%)	0.283
C-ILD	7 (15.2%)	5 (20%)	8 (27.6%)	0.422
Others	15 (32.6%)	10 (40%)	12 (41.4%)	0.698
Fibrosis	27 (58.7%)	17 (68%)	14 (48.3%)	0.333
Rapid Fibrosis	4 (8.7%)	3 (12%)	3 (10.7%)	0.914
Progressive Fibrosis	22 (47.8%)	14 (56%)	10 (35.7%)	0.343
Acute episode characteristics				
Acute exacerbation	29 (63%)	10 (40%)	10 (34.5%)	**0.035**
Subacute exacerbation	9 (19.6%)	4 (16%)	4 (13.8%)	0.890
Diagnosis	8 (17.4%)	4 (16%)	11 (37.9%)	0.100
Infectious disease except Covid	23 (50%)	9 (36%)	6 (20.7%)	**0.036**
Covid	2 (4.3%)	0 (0%)	0(0%)	0.498
Pulmonary embolism	4 (8.7%)	1 (4%)	1 (3.4%)	0.654
Left cardiac Failure	2 (4.3%)	3 (12%)	6 (20.7%)	0.096
Right cardiac Failure	9 (19.6%)	2 (8%)	3 (10.3%)	0.400
Pneumothorax	1 (2.2%)	1 (4%)	1 (3.4%)	1.000
Post bronchoscopy	0 (0%)	1 (4%)	5 (17.2%)	**0.037**

Variable	HFNO n=46	HFNO MV n=25	MV n=29	p
Disease Progression	6 (13%)	5 (20%)	5 (17.2%)	0.783
Adjunctive therapies				
Cyclophosphamide	1 (2.2%)	4 (16%)	3 (10.3%)	0.090
Steroids	20 (43.5%)	14 (56%)	15 (51.7%)	0.576
Outcome				
ICU length of stay	8 [6-10]	14 [7-21]	11 [8-19]	**< 0.001**
Hospital length of stay	17 [13-27]	26 [18-30]	23 [13-47.5]	0.085
30-day mortality	16 (34.8%)	15 (60%)	10 (35.7%)	0.093

Continuous variables are reported as median (IQR), and categorical variables as number (%), excluding missing data.

HFNO: High Flow Nasal Oxygenotherapy, MV: Mechanical ventilation, HFNO-MV: High-Flow nasal Oxygenotherapy before MV ; Acute exacerbation onset : < 3 months from symptom onset, Subacute exacerbation onset : > 3 months from symptom onset, ILD : Ìnterstitial lung disease, C-ILD: Connective tissue-associated ILD and granulomatous diseases; SAPS II: Simplified Acute Physiology Score II; SOFA: Sepsis-related Organ Failure Assessment, ICU: Intensive care unite

B. Prognostic value of the Rox ratio and SpO_2/FiO_2 ratio in the HFNO failure group

1. Factors associated with HFNO failure

The cohort included 71 ILD patients who received HFNO. HFNO failure was defined as a composite endpoint including 30-day mortality or need for MV within 30 days. The HFNO failure rate was 57%. In the HFNO failure group, patients were significantly older (p = 0.009) and had higher Charlson comorbidity index (p = 0.009) compared with patients in the HFNO success group.

Patients with HFNO failure had a delayed ICU admission (p = 0.002). There was no difference between the two groups in oxygen saturation at admission (p = 0.783); patients with HFNO failure had significantly higher SOFA scores (p = 0.018). The

distribution of ILD subtypes was comparable between groups, a higher prevalence of the fibrosing phenotype was observed in the HFNO failure group (p= 0.028). Both the ROX ratio and the SpO_2/FiO_2 ratio were significantly lower in the HFNO failure group at 24 and 48 hours (H24: SpO_2/FiO_2 ratio p = 0.01, ROX ratio p = 0.025; H48: SpO_2/FiO_2 ratio p = 0.001, ROX ratio p = 0.001).

Patients in the HFNO failure group had significantly more treatment limitation decisions (p = 0.002). HFNO duration did not differ between groups. Data were reported on table 2.

Table 2: factors associated with HFNO failure

Variable	HFNO success (n=30)	HFNO failure (n=41)	p
Patient characteristics			
Sex (Women)	43.3%	19.5%	**0.038**
Age	63 [53; 68]	71 [65; 74]	**0.009**
BMI	24.68 [20.16; 27.4]	25.77 [23.28; 27.45]	0.423
Charlson comorbidity index	3.5 [2; 6.5]	6 [4; 8]	**0.009**
ILD subtypes			
ILD	50%	46.3%	0.813
C-ILD	20%	14.6%	0.750
Others	30%	39%	0.463
Fibrosis	46.7%	73.2%	**0.028**
ICU admission			
Delay before ICU admission (days)	0 [0; 3]	4 [2; 9]	**0.002**
SOFA score	2 [1.5; 3]	3 [2; 6]	**0.018**
SAPS II	37 [29.25; 40]	39 [35; 47]	**0.046**
SpO_2	95 [92.25; 97]	95 [91; 97]	0.783
HFNO characteristics			
Flow H0	50 [40; 50]	50 [50; 60]	**0.040**

Fio2 H0	60 [50; 77.5]	70 [50; 80]	0.198
SPO_2/FiO_2 ratio H0	162 [124; 188]	180 [160; 190]	0.314
Rox Ratio H0	6 [5; 9]	5 [4; 7]	0.051
Flow H24	50 [40; 50]	50 [50; 60]	0.121
FiO_2 H24	50 [45; 60]	70 [59; 80]	**0.006**
SpO_2/FiO_2 H24	186 [152; 218]	136 [117; 165]	**0.010**
Rox Ratio H24	8 [6; 10]	6 [4 ; 7]	**0.025**
Flow H48	50 [40; 50]	55 [50; 60]	**0.010**
FiO_2 H48	47.5 [40; 67.5]	75 [57.5; 80]	**0.001**
SpO_2/FiO_2 H48	199 [145; 237]	123 [113; 162]	**0.001**
Rox Ratio H48	9 [7; 12]	5 [4; 6]	**0.001**
HFNO duration	4 [3; 5]	4 [3; 6]	0.947
Decisions to limit life-sustaining treatments			
HFNO-Limit of life-sustaining treatments	20%	58.5%	**0.002**

Continuous variables are reported as median (IQR), and categorical variables as number (%), excluding missing data.

HFNO: High-Flow Nasal Oxygen therapy, BMI: Body mass index, ILD: Interstitial lung diseases, C-ILD: Connective tissue-associated ILD and granulomatous diseases; SAPS II: Simplified Acute Physiology Score II; SOFA: Sepsis-related Organ Failure Assessment

Logistic regression analyses demonstrated that higher ROX ratios were associated with reduced OR of HFNO failure at all time points assessed. Specifically, ROX ratio at 48 hours showed the strongest association (OR = 0.72, 95% CI 0.58–0.89; p = 0.002) and fair model discrimination (AUC = 0.81). ROX ratios at H0 and 24 hours were also inversely associated with HFNO failure (OR = 0.83 and 0.82, respectively), though their ability to discriminate patients at risk was moderate (AUC 0.64–0.66). Data were reported on Table 3.

Table 3: association between Rox ratio and HFNO failure

Variable	OR (95% CI)	p	AUC (c)
Rox ratio H0	0.83 (0.69–0.99)	**0.035**	0.64
Rox ratio H24	0.82 (0.70-0.97)	**0.019**	0.66
Rox ratio H48	0.72 (0.58-0.89)	**0.002**	0.81

Association between ROX ratio and HFNO failure. Logistic regression models were used to assess the relationship between ROX ratio at different time points (H0, H24 and H48) and the risk of HFNO failure. Odds ratio (OR) with 95% confidence intervals (CI) and p-values are reported for each variable. Model discrimination was evaluated using the area under the curve (AUC, c-statistic) with higher values indicating better ability to distinguish patients who experienced HFNO failure from those who did not. OR were expressed per one-unit increase in ROX.

The ROX ratio at 48 hours that provided the best combination of specificity and sensitivity to predict HFNO failure was 7.07. Receiver Operating Characteristic (ROC) curve was reported on figure 2**.** The complete table of Youden index results is included in the Appendix section.

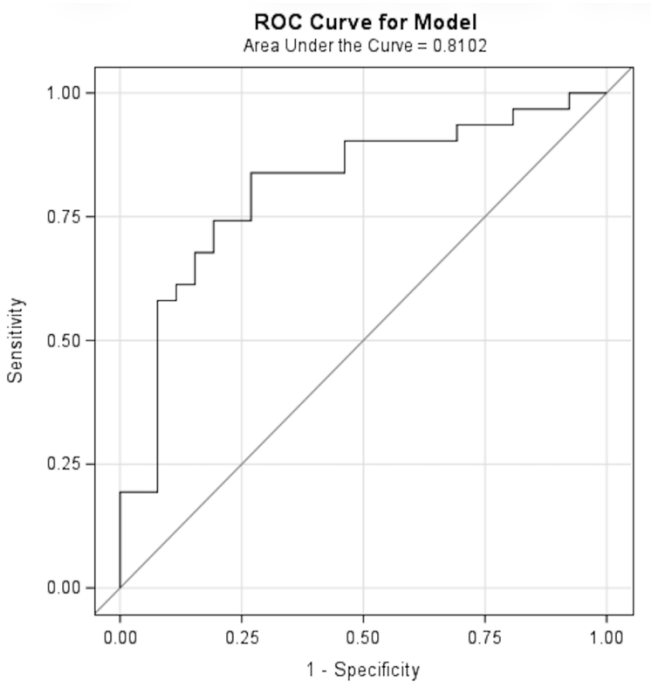

Figure 2: ROC curve for ROX ratio at 48 hours to predict HFNO failure

The ROX ratio at H48 demonstrated fair ability to predict HFNO failure, with an AUC of 0.81. The optimal threshold according to the Youden index was 7.07, corresponding to a sensitivity of 84 % and a specificity of 73 %.

The Cox proportional hazards model showed that a ROX ratio at 48 hours ≥ 7.07 was significantly associated with a decreased risk of HFNO failure.

Patients with a ROX ratio ≥ 7.07 had a hazard ratio of 0.15 (95% CI 0.06–0.40, $p < 0.001$), corresponding to an approximately 85% reduction in the risk of failure compared with patients below the threshold. Survival curves were reported on figure 3.

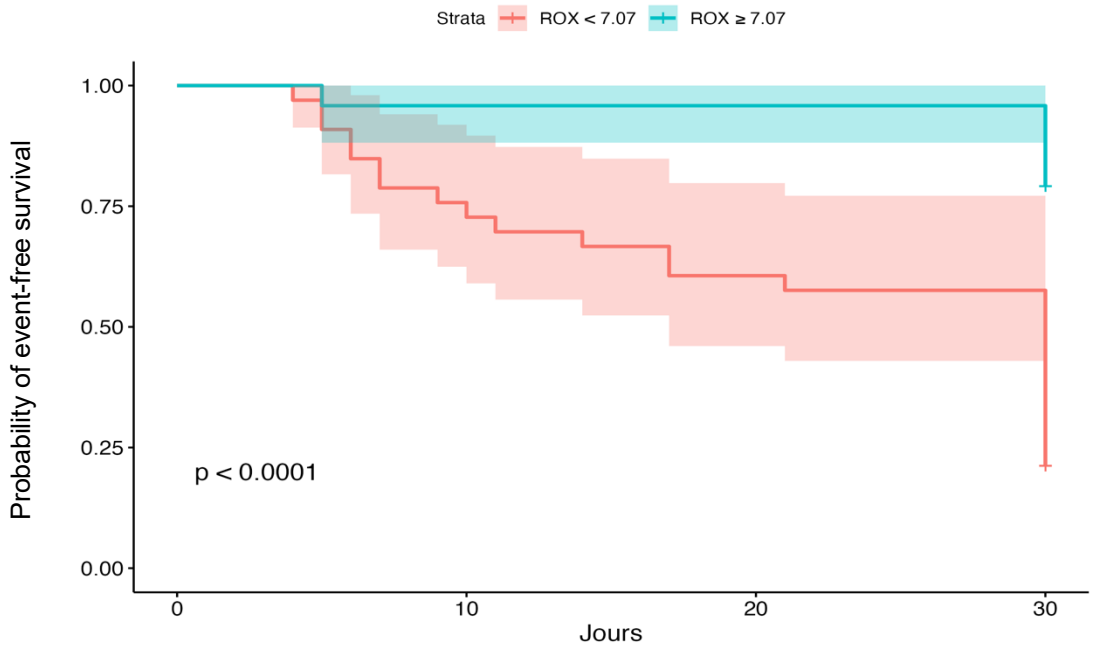

Figure 3: survival analysis based on the Rox ratio at 48 hours

Patients with ROX ≥ 7.07 had a significantly higher event-free survival ($p < 0.001$).

Due to sample size constraints, three separate multivariable models were fitted (H0, H24, and H48), each including treatment limitation decisions and one respiratory index. The presence of a limit of life-sustaining treatment was chosen on its clinical relevance and its significance in the descriptive analysis. After adjustment for treatment limitation decisions, only the ROX ratio at 48 hours remained significantly associated with HFNO failure (OR = 0.796, p = 0.03) with fair discriminative performance (AUC = 0.81). Each one-unit increase in the Rox ratio was approximately associated with 20% reduction in the OR of HFNO failure. Data are reported on table 4.

Table 4: multivariate analyze including limit of life sustaining treatment and association between ROX ratio and HFNO failure

Variable	OR (95% CI)	p	AUC (c)
ROX ratio H0	0.85 (0.70–1.03)	0.1	0.75
Rox ratio H24	0.86 (0.72-1.02)	0.09	0.78
Rox ratio H48	0.796 (0.65-0.98)	**0.03**	0.81

Logistic regression models were used to assess the relationship between ROX ratio at different time points (H0, 24h and 48h) and the risk of HFNO failure. Odds ratio (OR) with 95% confidence intervals (CI) and p-values are reported for each variable. Model discrimination was evaluated using the AUC (c-statistic) with higher values indicating better ability to distinguish patients who experienced HFNO failure from those who did not. OR were expressed per one-unit increase in ROX.

3. Prognostic value of SpO_2/FiO_2 ratio in HFNO failure

Logistic regression analyses revealed that higher SpO_2/FiO_2 ratio were associated with lower OR of HFNO failure at 24 and 48 hours after ICU admission. Specifically, SpO_2/FiO_2 ratio at 48 hours showed the strongest association (OR = 0.16, 95% CI 0.05–0.51; p = 0.002) and fair model discrimination (AUC = 0.79). SpO_2/FiO_2 ratio at 24 hours were also inversely associated with HFNO failure (OR = 0.28), though its

ability to discriminate patients at risk was moderate (AUC 0.69). No significant association was found between SpO_2/FiO_2 ratio at H0 and risk of HFNO failure. Data were reported on table 5.

Table 5: association between SpO_2/ FiO_2 ratio and HFNO failure

Variable	OR (95% CI)	p	AUC (c)
SpO_2/FiO_2 H0	0.45 (0.17–1.21)	0.12	0.57
SpO_2/FiO_2 H24	0.28 (0.09-0.80)	**0.017**	0.69
SpO_2/FiO_2 H48	0.16 (0.05-0.51)	**0.002**	0.79

Association between SpO_2/FiO_2 ratio and HFNO failure. Logistic regression models were used to assess the relationship between SpO_2/ FiO_2 ratio at different time points (H0, H24 and H48) and the risk of HFNO failure. Odds ratio (OR) with 95% confidence intervals (CI) and p-values are reported for each variable. Model discrimination was evaluated using the AUC (c-statistic) with higher values indicating better ability to distinguish patients who experienced HFNO failure from those who did not. Odds ratios for SpO_2/FiO_2 were expressed per one-unit increase in the SpO_2/FiO_2 ratio

The SpO_2/FiO_2 ratio value at 48 hours providing the best combination of specificity and sensitivity to predict HFNO failure was 181.9. ROC curve was reported on figure 4. The complete table of Youden index results is included in the Appendix section.

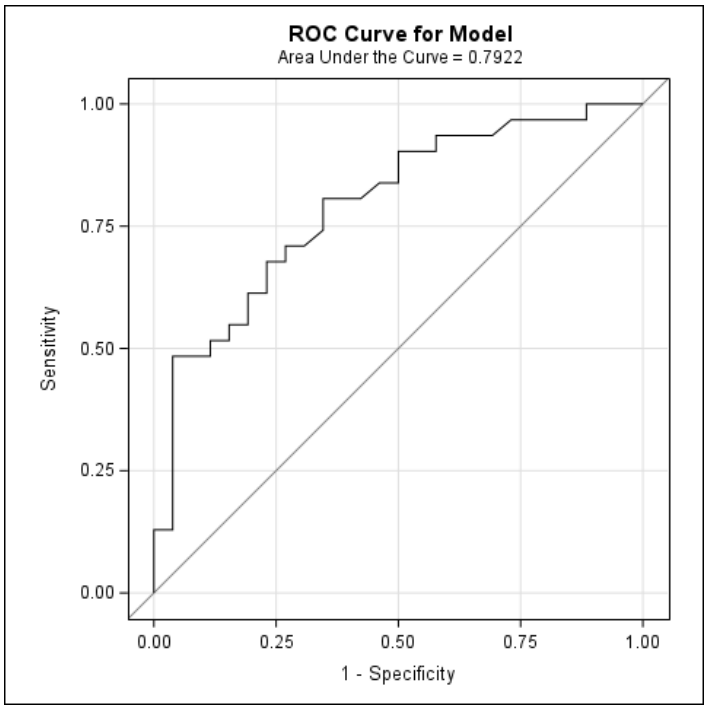

Figure 4.: ROC curve for SpO2/FiO2 ratio at 48 hours to predict HFNO failure

The SpO_2/ FiO_2 ratio at H48 demonstrated fair ability to predict HFNO failure, with an AUC of 0.79. The optimal threshold according to the Youden index was 181,9, corresponding to a sensitivity of 80.6 % and a specificity of 65.4%

The Cox proportional hazards model showed that a SpO_2/FiO_2 ratio at 48 hours ≥ 181.9 was significantly associated with a decreased risk of HFNO failure.

Patients with a SpO_2/FiO_2 ratio ≥ 181.9 had a hazard ratio of 0.25 (95% CI 0.1–0.61, p=0.002), corresponding to an approximately 75% reduction in the OR of HFNO failure compared with patients below the threshold. Survival curves were reported on figure 5.

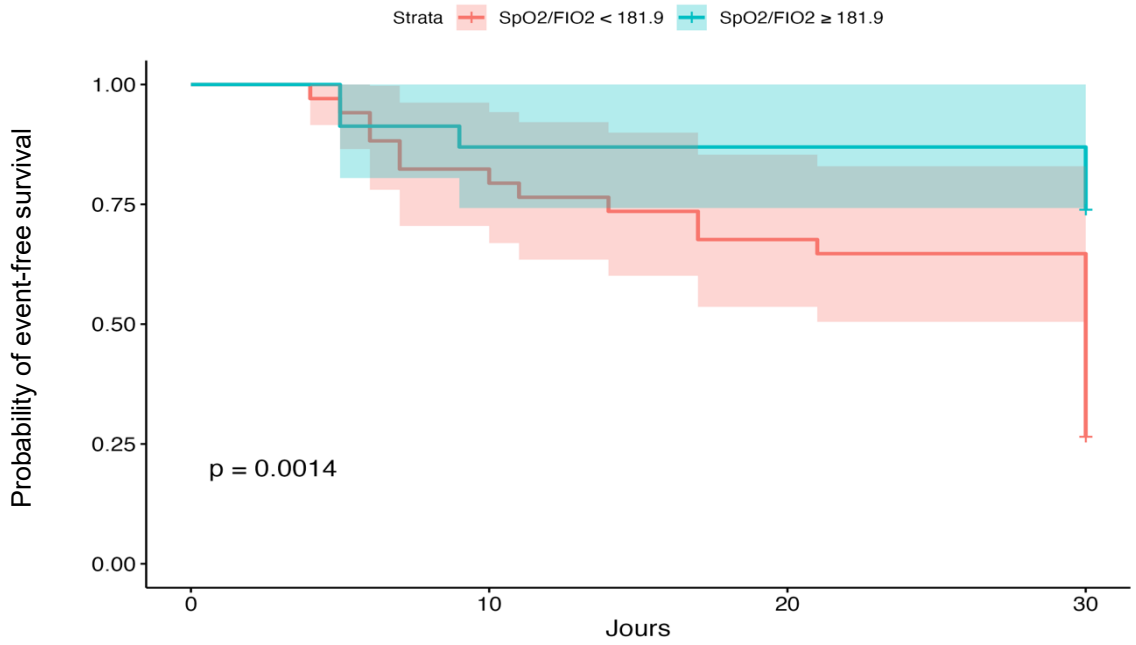

Figure 5: survival analysis based on the SpO2/FiO2 ratio at 48 hours

Patients with SpO2/FiO2 ≥ 181.9 had a significantly higher event-free survival ($p < 0.01$).

After adjustment for treatment limitation decisions, only the SpO_2/FiO_2 measured at 48 hours retained an independent inverse association with HFNO failure (OR = 0.25, p = 0.02) with fair discrimination (AUC = 0.79). Higher SpO_2/FiO_2 values were independently associated with a lower risk of HFNO failure per one-unit increase. Data were reported on table 6.

Table 6: multivariate analysis including limit of life sustaining treatment of association between SpO_2/FiO_2 ratio and HFNO failure

Variable	OR (95% CI)	p	AUC (c)
SpO2/FiO2 H0	0.39 (0.13–1.19)	0.12	0.74
SpO2/FiO2 H24	0.35 (0.12-1.04)	0.06	0.78
SpO2/FiO2 H48	0.25 (0.08-0.79)	**0.02**	0.79

Logistic regression models were used to assess the relationship between SpO2/FiO2 ratio at different time points (H0, 24h and 48h) and the risk of HFNO failure. Odds ratio (OR) with 95% confidence intervals (CI) and p-values are reported for each variable. Model discrimination was evaluated using the AUC (c-statistic) with higher values indicating better ability to distinguish patients who experienced HFNO failure from those who did not. Odds ratios for SpO_2/FiO_2 were expressed per one-unit increase in the SpO_2/FiO_2 ratio

C. Prognosis value of VR and MP in MV failure

1. Factors associated with MV failure

Our cohort included 54 ILD patients requiring MV. MV failure rate was 46%. MV failure was defined as mortality within 30 days from ICU admission. The study population included both the MV cohort and the HFNO before MV group. Baseline characteristics were similar between MV success and MV failure group, including sex (p = 0.371), age (p = 0.285), and the Charlson comorbidity index (p = 0.519). ICU Admission characteristics were similar, especially the delay to ICU admission (p = 0.867) and time from ICU admission to ETT (p = 0.424). There was a significantly higher rate of MV

failure among patients with limitations on life-supportive therapies (p=0.014). The VR and MP were significantly different between MV success and MV failure groups at 24 hours (VR: p=0.006, MP: p=0.005). Data were reported on table 7.

Table 7: factors associated with MV failure

Variable	**MV success**, n = 29	**MV failure** n= 25	**p**
Patients characteristics			
Gender	20.7%	32%	0.371
Age, years	64 [48; 74]	70 [62; 74]	0.285
BMI	25.54 [21.91; 27.55]	26.12 [23.85; 30.1]	0.221
Charlson comorbidity index	5 [3; 7]	5 [4; 7]	0.519
ILD type			
ILD	34.5%	40%	0.780
C-ILD	24.1%	24%	1.00
Others	41.4%	40%	1.00
Fibrosis	51.7%	32%	0.175
ICU admission			
Delay before ICU admission, days	3 [0; 10]	3 [0; 8]	0.867
Time from ICU admission to ETT, days	0.5 [0; 4]	2 [0; 3]	0.424
SpO_2 Admission	97 [91.75; 98]	96 [93; 97]	0.102
SOFA score	7.5 [5; 10.75]	6 [4; 9]	0.577
MV duration	7.5 [3.75; 11]	8.5 [4.75; 15.25]	0.344
Decisions to limit life-sustaining treatments			
MV-Limit of life-sustaining treatments	31%	66.7%	**0.014**
VR			
VR H0	2.17 [1.64; 2.84]	2.33 [2.05; 3.42]	0.233
VR H24	1.84 [1.37; 2.23]	2.44 [2.01; 3.06]	**0.006**
VR H48	1.98 [1.63; 2.27]	2.21 [1.97; 2.82]	0.093

Variable	**MV success**, n = 29	**MV failure** n= 25	**p**
MP			
MP H0	26.75 [23.96; 37.13]	32.18 [25.88; 38.94]	0.435
MP H24	28.25 [22.2; 31.77]	35.7 [30.11; 44.52]	**0.005**
MP H48	30.58 [24.44; 35.03]	34.35 [23.71; 37.43]	0.552

Continuous variables are reported as median (IQR), and categorical variables as number (%), excluding missing data.

MV: Mechanical Ventilation; HFNO: High-Flow Nasal Oxygen therapy, ETT: endotracheal intubation; VR: Ventilatory Ratio; MP: Mechanical Power; ILD: Interstitial lung diseases, C-ILD: Connective tissue-associated ILD and granulomatous diseases: Sepsis-related Organ Failure Assessment

2. Prognostic value of VR in the MV failure group

Logistic regression analyses demonstrated that higher VR was associated with increased OR of MV failure at 24 hours after ICU admission. VR at 24 hours was associated with MV failure (OR = 3.08, 95% CI 1.30–7.32; p = 0.011) with fair model discrimination (AUC = 0.72). No significant association was found between VR at H0, H48 and risk of MV failure. Data were reported on table 8**.**

Table 8: association between VR and MV failure

Variable	OR (95% CI)	p	AUC (c)
VR H0	1.37 (0.78–2.41)	0.278	0.59
VR H24	3.08 (1.30-7.32)	**0.011**	0.72
VR H48	2.14 (0.97-4.71)	0.058	0.65

Association between VR and MV failure. Logistic regression models were used to assess the relationship between ventilatory ratio at different time points (H0, H24 and H48) and the risk mechanical ventilation failure. Odds ratio (OR) with 95% confidence intervals (CI) and p-values are reported for each variable. Model discrimination was evaluated using the AUC (c-statistic) with higher values indicating better ability to distinguish patients who experienced MV failure from those who did not. Odds ratios for ventilatory ratio were expressed per one-unit increase in VR

VR: Ventilatory ratio

The VR value at 24 h that provided the best combination of specificity and sensitivity to predict MV failure was 1.89. ROC curve was reported on figure 6**.** The complete table of Youden index results is included in the Appendix section.

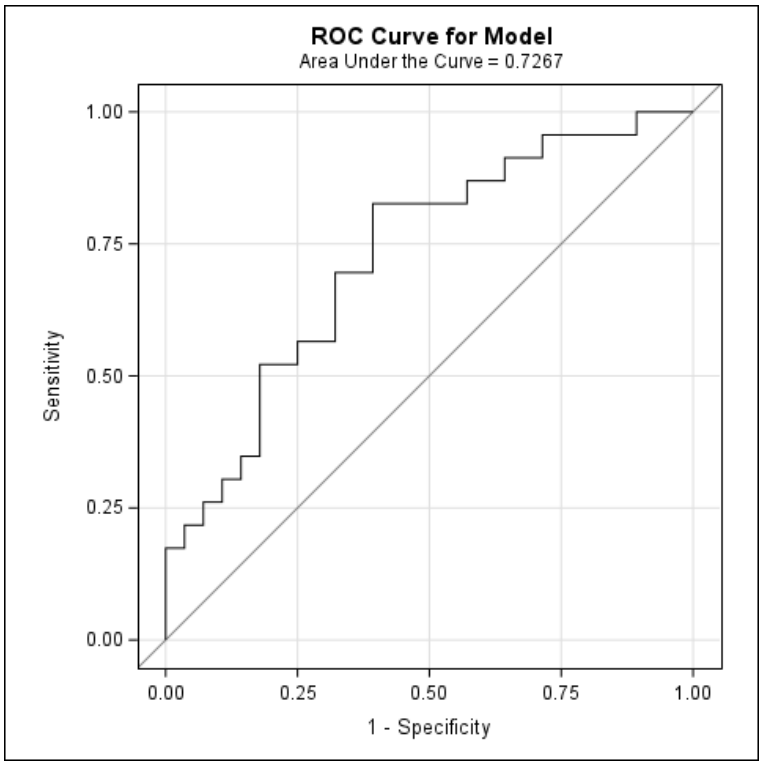

Figure 6: ROC curve for VR at 24 hours to predict MV failure

The ventilatory ratio (VR) at H24 demonstrated fair ability to predict mechanical ventilation (MV) failure, with an AUC of 0.72. The optimal threshold according to the Youden index was 1.89, corresponding to a sensitivity of 82.6 % and a specificity of 60.7%

The Cox proportional hazards model showed that a VR at 24 hours ≥ 1.89 was significantly associated with an increased risk of MV failure.

Patients with a VR ≥ 1.89 had a hazard ratio of 4.16 (95% CI 1.4–12.32, p=0.006), corresponding to an approximately fourfold increase in the risk of failure compared with patients below this threshold. Survival curves were reported on figure 7

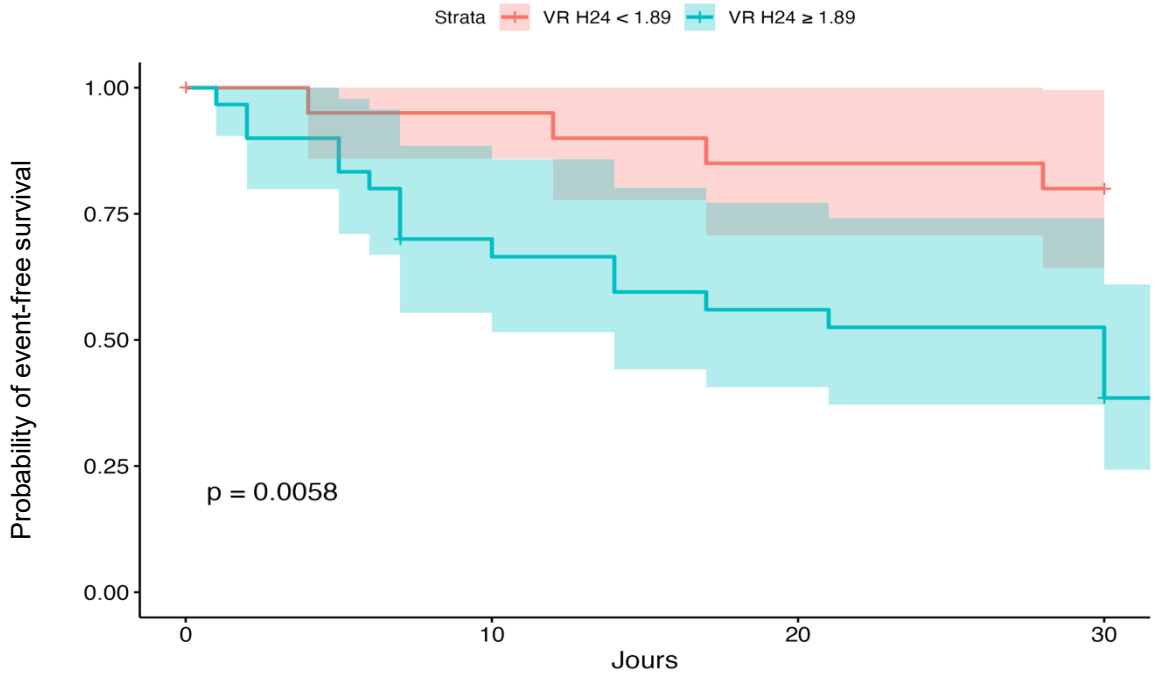

Figure 7: survival analysis based on the VR at 24 hours

Patients with ventilatory ratio (VR) ≥ 1.89 had a significantly lower event-free survival (p < 0.01).

After adjustment for treatment limitation decisions, the VR at 24 hours remained independently associated with MV failure (OR = 3.04, p = 0.015) with fair discrimination (AUC = 0.81). For each one-unit increase in the VR at H24, the OR of MV failure was threefold higher. The VR at 48 hours also became significant after adjustment with MV failure (OR = 2.18, p = 0.048), with a fair discriminative ability (AUC = 0.73). Data were reported on table 9.

Table 9: multivariate analysis including limit of life sustaining treatment of association between VR and MV failure

Variable	OR (95% CI)	p	AUC (c)
VR H0	1.50 (0.81–2.75)	0.196	0.73
VR H24	3.04 (1.25-7.42)	**0.015**	0.81
VR H48	2.18 (1.01-4.74)	**0.048**	0.73

Logistic regression models were used to assess the relationship between ventilatory ratio at H0, H24 and H48) and the risk of MV failure. Odds ratio (OR) with 95% confidence intervals (CI) and p-values are reported for each variable. Model discrimination was evaluated using the AUC (c-statistic) with higher values indicating better ability to distinguish patients who experienced MV failure from those who did not. Odds ratios for ventilatory ratio were expressed per one-unit increase in VR.

VR: Ventilatory ratio, MV : mechanical ventilation

3. Prognostic value of MP in the MV failure group

Logistic regression analyses demonstrated that higher MP was associated with increased OR of MV failure at 24 hours after ICU admission. MP at 24 hours was associated with MV failure (OR = 1.09, 95% CI 1.02–1.16; p = 0.009) with fair model discrimination (AUC = 0.73). No significant association was found between MP at H0, H48 and risk of MV failure. Data were reported on table 10.

Table 10: association between MP and MV failure

Variable	OR (95% CI)	p	AUC (c)
MP H0	1.01 (0.96–1.06)	0.653	0.56
MP H24	1.09 (1.02-1.16)	**0.009**	0.73
MP H48	1.03 (0.96-1.09)	0.434	0.55

Logistic regression models were used to assess the relationship between MP at H0, H24 and H48 and the risk MV failure. Odds ratio (OR) with 95% confidence intervals (CI) and p-values are reported for each variable. Model discrimination was evaluated using the AUC (c-statistic) with higher values indicating better ability to distinguish patients who experienced MV failure from those who did not. Odds ratios for mechanical power were expressed per 1 J/min increase in mechanical power.

MP: Mechanical power, MV: mechanical ventilation

The MP value at 24 hours that provided the best combination of specificity and sensitivity for predicting MV failure was 31.38. ROC curve was reported on figure 8. The complete table of Youden index results is included in the Appendix section.

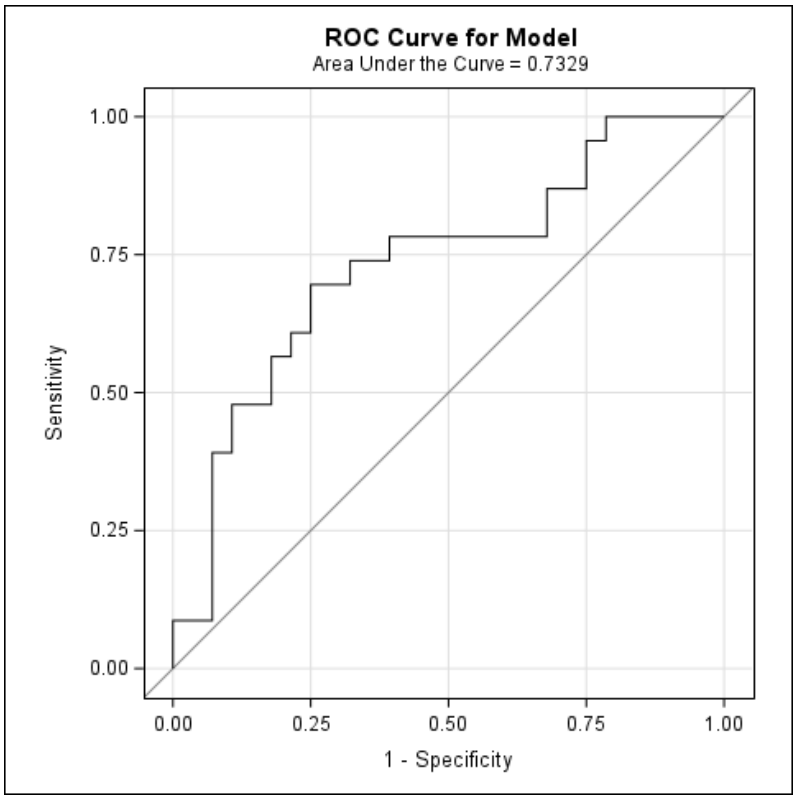

Figure 8: ROC curve for MP at 24 hours to predict MV failure

The mechanical power (MP) at H24 demonstrated fair ability to predict mechanical ventilation (MV) failure, with an AUC of 0.73. The optimal threshold according to the Youden index was 31.38, corresponding to a sensitivity of 69.6 % and a specificity of 75%

The Cox proportional hazards model showed that MP at 24 hours ≥ 31.38 was significantly associated with an increased risk of MV failure.

Patients with a MP ≥ 31.38 had a hazard ratio of 4.14 (95% CI 1.6–10.66, p=0.003), corresponding to an approximately fourfold increase in the risk of failure compared with patients below this threshold. Survival curves were reported on figure 9.

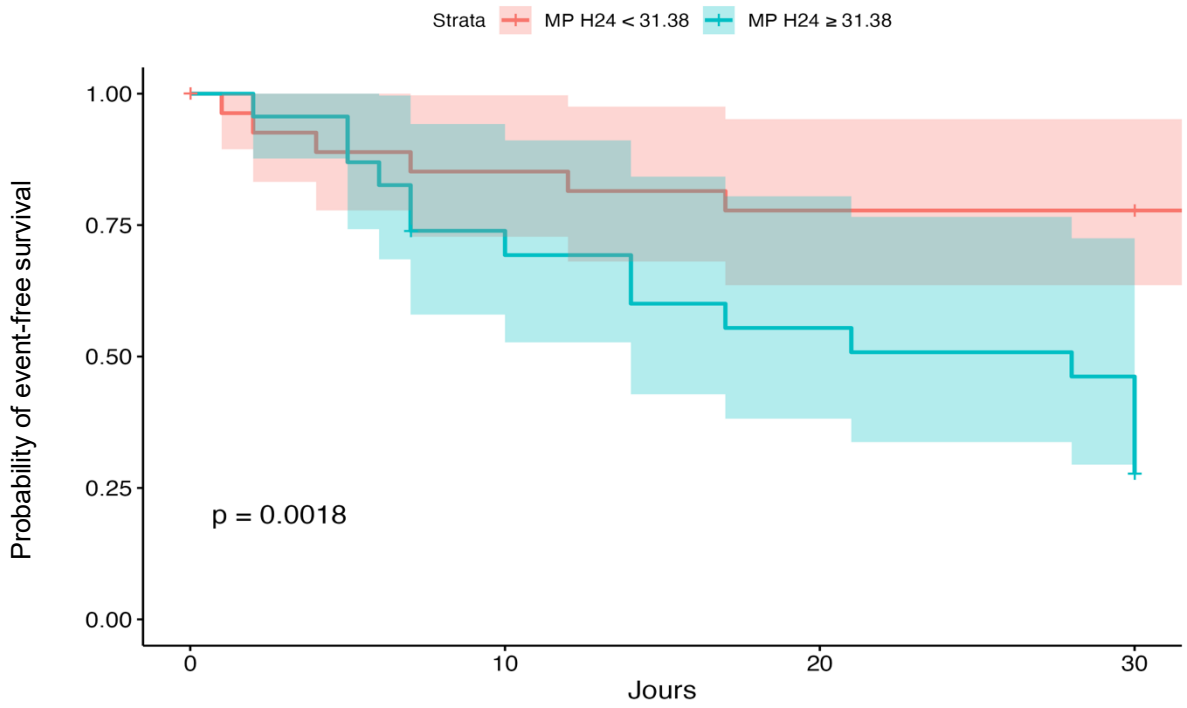

Figure 9: survival analysis based on MP at 24 hours

Patients with mechanical power (MP) ≥ 31.38 had a significantly lower event-free survival ($p < 0.01$).

After treatment limitation decisions adjustment, MP at 24 hours remained significantly associated with MV failure (OR = 1.11, p = 0.008) with fair discrimination (AUC = 0.81). Each one-unit (1 J/min) increase in the MP increased the odds of MV failure by 10%. Data are reported on table 11.

Table 11: multivariate analysis including limit of life sustaining treatment of association between MP and MV failure

Variable	OR (95% CI)	p	AUC (c)
MP H0	1.02 (0.96–1.07)	0.543	0.72
MP H24	1.11 (1.03-1.20)	**0.008**	0.81
MP H48	1.04 (0.97-1.12)	0.292	0.712

Logistic regression models were used to assess the relationship between mechanical power at different time points (H0, H24 and H48) and the risk of MV failure. Odds ratio (OR) with 95% confidence intervals (CI) and p-values are reported for each variable. Model discrimination was evaluated using the AUC (c-statistic) with higher values indicating better ability to distinguish patients who experienced MV from those who did not. Odds ratios for mechanical power were expressed per 1 J/min increase in mechanical power.

MP: Mechanical power, MV : mechanical ventilation

IV. Discussion

In this retrospective single-center cohort of ICU patients with ILD admitted for ARF, we identified several physiological indices associated with ventilatory supports failure. HFNO failure was significantly associated with lower ROX index and lower SpO_2/FiO_2 ratio assessed at 48 hours after HFNO initiation. Optimal discriminative thresholds of 7.07 for the ROX index and 181.9 for the SpO_2/FiO_2 ratio were identified. VR and MP measurements at 24 hours after tracheal intubation were significantly associated with invasive MV failure, with optimal thresholds of 1.89 for VR and 31.38 J/min for MP.

A. Cohort of patients with ILD admitted to ICU

The study included 100 ILD patients admitted to ICU for ARF. The size of the cohort was comparable to other published studies (25,35–37,46–48). Mechanically ventilated patients presented a higher SAPS II and SOFA score, reflecting greater severity at ICU admission. The distribution of ILD subtypes and their fibrotic characteristics was similar across groups. 44% of patients had a lung-limited pulmonary ILD, 20% had ILD associated with a systemic disease, and 36% had other forms, notably toxic-related ILD. The study showed an overrepresentation of specific pulmonary ILD compared with previously published cohorts, which might reflect a center effect (12,35–37). However, in previous studies, ILD subtype was not associated with excess mortality in critically ill patients, which may support the generalizability of our findings (35,36). Accordingly, the majority of patients in our cohort exhibited a fibrotic phenotype (58%).

The study evaluated prognostic factors in patients receiving HFNO or MV therapies. Patients were categorized into three mutually exclusive groups (HFNO, HFNO followed by MV, and primary MV) to reduce classification ambiguity as previously proposed by

Lee et al. (23). Patients receiving HFNO followed by tracheal intubation were included in both analytical populations, as pre-specified.

Two main causes were identified for ICU admission: acute exacerbation and infection. These results were consistent with previous published studies (35,36). In our study, acute exacerbations were overrepresented in the HFNO group which might be associated with in-hospital mortality and influence our results (48).

Significantly longer length of stay in ICU was observed in the HFNO followed by MV group, as also observed by *Lee et al. (*23). In our study, patients managed with HFNO followed by MV presented a higher rate of complications, particularly in-hospital acquired pneumonia. These results could explain a longer ICU length of stay (appendix, table 2).

The overall 30-day mortality in our study was 41%. There was no significant difference in mortality rates according to the type of ventilatory support. These findings were consistent with in-hospital mortality rates reported in other ICU cohorts, which ranged from 30% to 60% following an acute exacerbation, depending on the type of ILD (8,9,12,23,35,37,49). Although in-hospital and 30-day mortality were mostly informative and did not fully assess the impact on survival of patients with ILD requiring ICU stay. The epidemiological data reported very poor outcomes, with median times to death post-acute exacerbation of approximately 2 months for fibrotic ILD (7,10,11). One-year mortality rates among patients with ILD admitted to ICU varied between 60% and 80% (12,37,48). These data were similar to those observed in our cohort (appendix, table 2). The ICU admission of patients with ILD represents a significant evolutionary turning point in the disease.

B. Prognostic value of Rox ratio and SpO_2/FiO_2 ratio

Our study included 71 patients with ILD receiving HFNO. The study presented a relatively small sample size compared with previous studies evaluating the ROX index and the SpO_2/FiO_2 ratio (18,19,22). In contrast, the sample sizes of previous ICU studies evaluating HFNO ventilatory support in patients with ILD were comparable to our study, generally ranging from 30 to 100 patients (25,50–52).

A key methodological aspect concerned the definition of HFNO failure. A composite assessment has been defined. HFNO failure was defined by the requirement of invasive MV or death at 30 days. Several studies, including the original work describing the ROX index, only defined HFNO failure as the use of MV (19,23). However, this approach did not take into account patients with ILD and therapeutics limitations, especially those not receiving MV during the ICU stay. In prior studies of patients with ILD treated with HFNO in ICU, the proportion of patients with treatment limitations varied between 50% and 60% (23,25). The differences observed in the prevalence of treatment limitations might be reflect differences in local practices. In our cohort of patients receiving HFNO, 30 out of 71 (42%) had limitations in therapeutic management. Moreover, patients with treatment limitations were significantly overrepresented in the HFNO failure group.

The prognostic value of the SpO_2/FiO_2 ratio and the ROX index were assessed. The SpO_2/FiO_2 ratio and the ROX index were evaluated at H0, H24, and H48. A previous Japanese study of 60 ILD patients assessed the SpO_2/FiO_2 ratio as a predictor of HFNO failure. The most discriminative value was observed 24 hours after HFNO initiation, compared with measurements obtained at baseline and at 8 hours (25). However, in other studies evaluating the SpO_2/FiO_2 ratio and the ROX index, the

authors reported an earlier discriminative ability, typically between 1 and 12 hours (18,19,21). This difference might be related to variations in initial disease severity between cohorts of patients with ILD and those with pneumonia. In the pneumonia cohort described by *Roca et al.,* in 2016, the HFNO failure group presented a higher SOFA score at ICU admission compared with our cohort of patients with ILD. However, the duration of HFNO use among patients who experienced HFNO failure was similar between the pneumonia cohort and our cohort of patients with ILD (18)Our results showed that ROX ratio assessment at 48 hours provided a useful index to predict HFNO failure, with an optimal threshold of 7.07 with a sensitivity of 84% and specificity of 73%. To the best of our knowledge, this is the first study assessing the prognostic value of the ROX ratio in patients with ILD admitted to ICU. In the study of *Roca et al*. in 2016, conducted on patients with hypoxemic respiratory failure due to pneumonia, the ROX ratio was more discriminating at the thresholds of 2.85, 3.47 and 3.85 at 2, 6 and 12 hours after HFNO initiation.(18) In contrast, in a COVID-19 population, the ROX ratio was found to be discriminant at a threshold of 8.54 one hour after HFNO initiation, with a sensitivity of 59.6% and a specificity of 26.1% to predict HFNO failure (19). In a study evaluating patients with COPD, the optimal ROX ratio threshold to predict HFNO failure was 4.88 at 6 hours after therapy initiation (21). There is therefore considerable heterogeneity in the ROX index thresholds identified as discriminative across the literature, mostly depending on the population studied.

Our results also showed that assessing the SpO2/FIO2 ratio at 48 hours provided a useful prognostic indicator of HFNO failure, with an optimal threshold of 181.9 with a sensitivity of 80,6% and specificity of 65,4%. This is, to our knowledge, the second study to evaluate this index in a cohort specifically composed of patients with ILD. In 2020, *Koyauchi et al.* proposed an evaluation of this index in a Japanese cohort of 64

patients. They selected 30-day mortality as their primary endpoint and reported a mortality rate of 39%. In our cohort, a mortality rate of 43% was observed. However, only two patients (3%) underwent tracheal intubation in their study, whereas the ETT rate reached 35% in our cohort. Conversely, the prevalence of treatment limitations was lower in our cohort (42% vs. 50%). In their study, the SpO_2/FiO_2 ratio demonstrated a strongest predictive performance at 24 hours, with an optimal threshold of 170.9, a sensitivity of 96.2%, and a specificity of 68.4%. Our findings are consistent with previously published data. However, in their analysis, the SpO_2/FiO_2 ratio at 48 hours was also prognostic and even showed a higher AUC (0.856 at 48 hours vs. 0.802 at 24 hours) (25). They nonetheless chose to retain the 24-hour ratio as the preferred marker, referring to a previous study by *Kang et al.* that reported increased mortality among HFNO-treated patients who underwent tracheal intubation after 48 hours. However, in that study, the criteria for ETT were relatively restrictive, requiring a SpO_2 > 90%, respiratory rate > 35 breaths per minute, severe metabolic acidosis, or the presence of shock, which may have contributed to delayed initiation of MV (53).

C. Prognostic value of VR and MP

54 mechanically ventilated patients with ILD were analyzed. The size of the cohort was modest compared to previously ARDS studies analyzing VR and MP (42,43). However, when focusing on critically ill patients with ILD, and more specifically those requiring invasive MV, cohort sizes reported in the literature were highly heterogeneous and ranging from 10 to 100 patients (34,35,37,45). Accordingly, our data were consistent with previously published studies. A 30-days mortality rate of 46% was observed in our study. This mortality rate was in the lower range of hospital

mortality rates reported in the literature. In cohorts of mechanically ventilated patients with ILD, in-hospital mortality rates typically varied between 40% and 100% (12,34,35,37,46). This finding was unexpected because our cohort included an overrepresentation of pulmonary ILD compared with published studies (34–37). 57% of mechanically ventilated patients exhibited a fibrosing phenotype, which is a well-established risk factor for mortality (34,47,54). In contrast, in several previously published cohorts, the presence of fibrotic disease was an inclusion criteria, which may partly explain the wide variability in reported mortality rates (34,36,45). In the present study, we chose to analyze all ILD subtypes together despite their heterogeneous clinical profiles. No significant difference in ILD subtype distribution was observed between MV success and failure groups. These data supported the external validity of our findings.

The VR was significantly higher at 24 hours in the MV failure group compared with the success group. Univariate analysis showed a fair discriminative performance, with an AUC of 0.72. The optimal threshold was 1.89, corresponding to a sensitivity of 82.6 % and a specificity of 60.7%. Patients with a VR ≥ 1.89 had an approximately fourfold increase in the risk of failure compared with patients below this threshold. The VR values observed in our cohort were comparable to those reported in the study by *Sinha et al.* They reported values ranging from 0.7 to 5, with a median of 1.7 in critically ill patients (44). In the study by *Sinha et al.,* the VR measurement 24 hours after MV initiation was associated with ICU mortality, which was consistent with our data (43). A study by *Fu et al.* previously evaluated the prognostic value of the VR as a mortality predictor in intubated patients with ILD admitted to ICU. This retrospective Chinese cohort included 224 patients and reported a higher mortality rate, reaching 80%. The VR was calculated using the same formula as in our study; however, it was derived as

the average of four measurements obtained during the first 24 hours of MV, whereas in our cohort the value was calculated from the arterial blood gas closest to exactly 24 hours after MV initiation. This methodological difference should be considered. However, the high mortality rate in their cohort led to a marked imbalance between groups, with 180 non-survivors compared with only 40 survivors. In contrast, in our study the two groups were of more comparable size, which may reduce extreme imbalance effects. They identified a discriminative threshold close to our study (2.09 versus 1.89). However, the discriminative performance was lower, with an AUC of 0.63 compared with 0.72 in our cohort. Overall, although comparisons are limited by differences in sample size and mortality rates, both studies identified a predictive value of the VR measured at 24 hours for mortality in intubated patients with ILD admitted to ICU, with similar thresholds around 2.0 (46). Taken together, these results suggested that VR assessment 24 hours after MV initiation had prognostic value in patients with ILD.

MP values were significantly higher in non-survivors at 24 hours. An acceptable discriminative performance was observed, with an AUC of 0.73. The threshold was 31.38, yielding a sensitivity of 69.6% and a specificity of 75%. A MP value above this threshold at 24 hours was associated with an approximately fourfold higher risk of MV failure. To our knowledge, this is the first study specifically evaluating MP in mechanically patients with ILD. These patients might be particularly exposed to VILI due to their fibrotic phenotype and reduced lung compliance (45,54). MP, as proposed by *Gattinoni et al.,* was developed as a bedside tool integrating multiple ventilatory parameters to assess the risk of VILI (38,39). However, several studies have already evaluated MP as a prognostic marker of mortality in critically ill patients admitted to ICU (41,42,55,56). The predictive value of MP remains debated, as findings across

studies are conflicting. These discrepancies suggested a population-dependent effect. MP showed a prognostic value in a large retrospective cohort of 8200 patients (41) and this association was not consistently observed in studies specifically focusing on COVID-19 ARDS patients (55). MP values in non-survivors varied between 15 to 20 J/min, which was substantially lower than those observed in our cohort, where MP values were closer to 30 to 35 J/min (41,42,55,56). Differences in ventilator settings, patient populations, and MP computation methods limited direct comparisons. Although no absolute MP threshold has been consistently associated with mortality, an increase in MP has been frequently reported to be associated with worse outcomes, including mortality (38,55,56). The threshold of 31.38 identified in our analyses corresponds to a high MP level, consistent with values previously associated with worse outcomes.

D. Strength and limitations

4. Limits

Our study has several limitations First, the retrospective, single-center design limited the generalization of our findings. In particular, we observed an overrepresentation of patients with specific pulmonary ILD as well as of patients with a fibrotic phenotype, which likely reflects a center effect.

In addition, the size of our cohort remained modest, although comparable to prior ICU studies in patients with ILD, which might reduce statistical power for subgroup analyses and contributed to wider confidence intervals around threshold estimates. This limited sample size reduced statistical power for subgroup analyses and contributed to the impossibility of adjusting multivariable models for all clinically relevant parameters identified in univariable analyses. As a result, residual confounding might not be

excluded, and larger cohorts would be required to more comprehensively account for these potential confounders.

Furthermore, respiratory indices (ROX ratio, SpO_2/FiO_2 ratio, MP and VR) were assessed at predetermined time points, which could not fully reflect the continuous and dynamic evolution of respiratory status during ICU stay.

Due to the retrospective nature of the study, MP was assessed using a simplified formula previously described in the literature (40). Although a significant outcome was observed, these findings should be interpreted with caution. Prospective validation with bedside measurement of MP using the original formula as described by *Gattinoni et al.* would be necessary to allow formal comparison with existing data *(39).*

The prognostic thresholds identified in this study were derived from ROC curves analyses within the same cohort in which their performance was subsequently evaluated. As a result, these cut-off values should be considered exploratory and hypothesis-generating, and their discriminative performance could be subject to optimism bias. External validation in independent cohorts is therefore required before these thresholds can be used for clinical decision-making. Moreover, although the indices evaluated provide valuable prognostic information, they should be interpreted as complementary tools to bedside clinical assessment rather than triggers for therapeutic management. Prospective multicenter studies are warranted to validate these findings, assessed the added value of dynamic trajectories over time, and confirmed their applicability across different clinical settings.

Finally, associations persisted after adjustment for decisions regarding limitations of life-sustaining therapies although residual confounding cannot be excluded. However,

owing to the limited sample size and number of events, multivariable models including all variables significant in univariate analysis could not be constructed due to events-per-variable constraints. This limitation should be considered when interpreting our findings. Although treatment-limitation decisions may influence outcomes, the persistence of associations after adjustment suggests that these indices reflect underlying disease severity rather than decision-making alone.

5. Strengths

This study provides real-world data on critically ill patients with ILD managed with contemporary ventilatory strategies across a long inclusion period. By combining a descriptive three-group classification (HFNO, HFNO followed by MV, and primary invasive MV) with pre-specified prognostic analyses, we were able to evaluate early bedside respiratory indices in clinically relevant settings. Importantly, HFNO failure was defined using a composite endpoint that captures both tracheal intubation and short-term mortality, thereby limiting misclassification in a population where treatment-limitation decisions were frequent. Indices at standardized time points were assessed and reported both discrimination (AUC) and clinically interpretable thresholds derived from the Youden index, complemented by time-to-event analyses (Kaplan–Meier and Cox models). Finally, the consistency of associations after adjustment for treatment limitation decisions supported the clinical relevance of these indices as markers of underlying severity rather than decision-making alone.

V. Conclusion

Early bedside respiratory indices—especially the ROX ratio and SpO_2/FiO_2 ratio 48 hours after HFNO initiation and VR and MP measurements at 24 hours during invasive MV—showed clinically meaningful prognostic value for ventilatory supports failure in

patients with ILD admitted to ICU. These results supported the use of simple, readily available parameters for early risk stratification, while clinical decisions should remain individualized and not rely on a single metric. These indices could help identify patients at high risk of ventilatory supports failure for closer monitoring or earlier reassessment of ventilatory strategy. Prospective multicenter studies are needed to validate these thresholds, evaluate dynamic trajectories, and confirmed performance using standardized bedside measurements, especially MP.

VI. Appendix

Table 1. **Baseline characteristics of the cohort (supplementary data)**

	Total sample size N = 100
Ventilatory support	
HFNO	46 (46)
MV	29 (29)
HFNO MV	25 (25)
Demographics	
Gender	
Women	31 (31)
Age	67 (53 ;74)
Comorbidities	
BMI	25.47 (21.15 ;27.46)
Charlson Index	5 (3.0 ;7.5)
Characteristics of ILD	
ILD	44 (44)
c-ILD	20 (20)
Others	37 (37)
Fibrosis	58 (58)
Progressive fibrosis	46 (46,5)
Rapid fibrosis	10 (10,1)
Mortality (30 days)	41 (41)

Table 1 : Baseline characteristics of the cohort

Continuous variables are reported as median (IQR), and categorical variables as number (%), excluding missing data.

HFNO :High-Flow Nasal Oxygen, MV: Mechanical ventilation, HFNO MV : High-Flow nasal Oxygen before mechanical ventilartion, ILD: hypersensitivity pneumonitis, idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP) ; CILD : connective tissue-associated ILD and granulomatous diseases ; others : drug-induced, pneumoconioses ; progressive fibrosis : > 3 months, rapid fibrosis : < 3 months

Table 2. Characteristics of subgroup (supplementary data)

Variable	HFNO N=46	HFNO MV N=25	MV N=29	p
Year of admission	2023 [2017-2024]	2017 [2015-2023]	2017 [2014-2023]	0.002
Height	174 [166.25-178]	172 [170-177]	175 [166-178]	0.998
Weight	75 [57-85]	77 [73-89]	75 [63-80]	0.194
Long-term oxygen therapy (LTOT)	16 (34.8%)	7 (28%)	6 (20.7%)	0.429
Home noninvasive ventilation	6 (13%)	2 (8%)	2 (6.9%)	0.693
Months since diagnosis	17 [3-54]	10 [0-36]	1.5 [0-29.25]	0.100
Highest Temperature Within First 24h	37.5 [37.1-38.075]	37.7 [37.2-38.7]	37.25 [36.95-37.9]	0.193
Characteristics at ICU admission				
SpO_2	95 [92-97]	95 [91-96]	97 [94-98]	0.038
Heart rate	98.5 [83.5-110.25]	99 [82-105]	92.5 [84-106]	0.871
MAP	76.5 [68-87.5]	81 [75-86]	79.5 [71-86]	0.676
Vasopressor: norepinephrine	4 (8.7%)	1 (4%)	13 (46.4%)	0.001
Vasoppressor : dobutamine	1 (2.2%)	1 (4%)	2 (7.1%)	0.808
Creatinine (mg/dl)	9 [7-14]	8 [8-11]	10 [7-17.5]	0.666
CRP (mg/L)	111.5 [37.25-159.75]	103 [57-159]	109 [59.5-158]	0.901
PCT (ng/ml)	0.2 [0-0.7625]	0.16 [0.115-0.805]	0.485 [0.19-1.4025]	0.167

Variable	HFNO N=46	HFNO MV N=25	MV N=29	p
White cell count ($X10^9$/L)	13.22 [9.515-16.8675]	11.29 [6.87-17.44]	15.555 [10.69-16.705]	0.366
Fibrinogen (g/l)	5.65 [4.5-7.25]	6.1 [5.1-6.7]	6.6 [4.825-7.025]	0.739
Mechanical ventilation characteristics				
Ph H0		7.26 [7.25-7.33]	7.34 [7.27-7.42]	0.013
PCO_2 H0		56.4 [45.6-67.3]	45.7 [36.3-55.6]	0.008
PO_2 H0		104 [71-165]	141 [94-177]	0.252
Blood level lactate H0		1.4 [1.2-2.1]	1.2 [0.9-2.1]	0.492
Nitric oxide (iNo) H0		3 (12%)	1 (3.4%)	0.326
Neuromuscular blocking agents H0		6 (24%)	11 (37.9%)	0.380
FiO_2 H0		80 [70-100]	70 [60-100]	0.175
PaO_2/FiO_2 H0		129.97 [81-255.38]	194 [130-285]	0.093
PEEP H0		8 [5-10]	7 [6-8]	0.455
Peak airway pressure H0		40 [36-46]	39 [33-44]	0.385
Plateau pressure H0		28 [22-32]	24 [20-28]	0.067
Driving pressure H0		21 [14-25]	17 [13-21]	0.173
Ventilatory Ratio H0		2.77 [2.05-3.42]	2.08 [1.44-2.54]	0.003
Mechanical Power H0		32.18 [26.63-40.75]	28.03 [23.96-36.70]	0.228
ARDS H0		19 (76%)	20 (69%)	0.767
Ph H24		7.39 [7.345-7.41]	7.4 [7.3425-7.45]	0.740
Pco_2 H24		46 [40.8-54.6]	43.1 [37.675-46.3]	0.170
Po_2 H24		82 [75-116]	95 [78.75-124]	0.334
Blood level lactate H24		1.3 [1-1.5]	1.5 [0.8-2]	0.453
Neuromuscular blocking agents H24		9 (39.1%)	9 (32.1%)	0.770
Nitric oxide (iNo) H24		4 (17.4%)	2 (7.1%)	0.390
FiO_2 H24		70 [50-80]	50 [40-62.5]	0.085

Variable	HFNO N=46	HFNO MV N=25	MV N=29	p
PaO_2/FiO_2 H24		130 [101.25-185]	192.5 [110-260.75]	0.094
PEEP H24		8 [6-10]	7 [5-8]	0.314
Peak airway pressure H24		37 [31.5-42.5]	36 [31.25-42.25]	0.740
Plateau pressure H24		25 [20.5-29]	23 [20-28.25]	0.460
Driving pressure H24		17 [14-18.5]	16.5 [12.75-20]	0.718
Ventilatory Ratio H24		2.25 [1.92-2.99]	1.89 [1.37-2.43]	0.027
Mechanical Power H24		34.49 [26.00-44.05]	29.25[22.75-33.66]	0.140
ARDS H24		22 (88%)	20 (69%)	0.001
Ph H48		7.395 [7.3525-7.43]	7.4 [7.33-7.41]	0.765
PCO_2 H48		49 [38.7-57.375]	43.8 [36-51.3]	0.150
PO_2 H48		86.5 [78.5-121.5]	117 [92-133]	0.084
Blood level lactate H48		1.2 [1.1-1.8]	1.4 [0.9-1.625]	0.715
Neuromuscular blocking agents H48		11 (50%)	6 (24%)	0.078
Nitric oxide (iNo) H48		8 (36.4%)	1 (4%)	0.001
FiO_2 H48		55 [50-70]	50 [30-60]	0.029
PaO_2/FiO_2 H48		178 [117-226]	266 [222-306]	0.003
PEEP H48		8 [7-10]	6 [5-8]	0.009
Peak airway pressure H48		37.5 [34-43]	36 [32-41]	0.300
Plateau pressure H48		25.5 [21-34.75]	23.5 [17.75-26.5]	0.098
Driving pressure H48		16.5 [13-25.5]	16 [11-18]	0.402
Ventilatory Ratio H48		2.39 [1.99-3.01]	1.89 [1.62-2.21]	0.019
Mechanical Power H48		35.27 [25.26-37.40]	27.59 [22.77-32.36]	0.086
ARDS H48		18 (81.8%)	12 (48%)	0.032
Time to tracheal intubation		3 [2-4.5]	0 [0-1]	0.001
Prone position		11 (44%)	8 (27.6%)	0.017

Variable	HFNO N=46	HFNO MV N=25	MV N=29	p
Number of prone position sessions		0 [0-1]	0 [0-1]	0.047
Fluid balance during first 48h		1179 [-2905.25-5101.5]	1019 [-8-5082]	0.3
Mechanical ventilation duration, days		8 [4-15.25]	7.5 [4.75-11.25]	0.652
Noninvasive ventilation and HFNO characteristics				
Noninvasive ventilation	19 (41.3%)	8 (32%)	2 (6.9%)	0.003
HFNO flow rate H0	50 [40-50]	50 [50-50]		0.062
FiO_2 HFNO H0	60 [50-80]	70 [60-80]		0.202
SpO_2/FiO_2 H0	157 [118,75-190]	136 [119-160]		0.245
HFNO flow rate H24	50 [45-50]	50 [40-60]		0.637
FiO_2 HFNO H24	60 [50-70]	70 [60-80]		0.060
SpO_2/FiO_2 H24	165 [134.29-198]	135,71 [120-161,6]		0.079
HFNO flow rate H48	50 [40-60]	50 [50-60]		0.149
FiO_2 HFNO H48	52.5 [40-76.25]	75 [60-80]		0.005
SpO_2/FiO_2 H48	172.67[122.63-233.13]	125.33 [112.5-148.33]		0.007
HFNO duration	4 [3-6]	3 [2-4.25]		0.001
Rox Ratio H0	6.29 [4.53-8.606]	4.85 [4.05-6.99]		0.236
Rox Ratio H24	7.07 [5.39-10.31]	5.54 [4.37-6.13]		0.022
Rox Ratio H48	7.17 [5.82-11.69]	4.47 [3.57-5.93]		0.001
Fluid balance during first 48H	-1453 [-2779-800]	1051 [-2242-5050]		0.001
Limit of Life sustaining treatments				
Presence	19 (41.3%)	11 (44%)	14 (48.3%)	0.839
Adjuvant treatments				
Beta-blockers	13 (28.3%)	4 (16%)	8 (27.6%)	0.530
Proton pump inhibitors (PPi)	34 (73.9%)	16 (64%)	23 (79.3%)	0.437
Intravenous immunoglobulins (IVIG)	0 (0%)	0 (0%)	1 (3.4%)	0.540

Variable	HFNO N=46	HFNO MV N=25	MV N=29	p
Tacrolimus	0 (0%)	0 (0%)	1 (3.4%)	0.540
JAK-inhibitors	1 (2.2%)	0 (0%)	1 (3.4%)	1.000
Rituximab	1 (2.2%)	0(0%)	0 (0%)	1.000
Cyclophosphamid	1 (2.2%)	4 (16%)	3 (10.3%)	0.090
Antiinfectious therapy	39 (84.8%)	25 (100%)	26 (89.7%);	0.082
Antifungal	11 (23.9%)	21 (84%)	7 (24.1%)	0.001
Antibiotics	40 (87%)	22 (88%)	26 (89.7%)	1.000
Steroids	20 (43.5%)	14 (56%)	15 (51.7%)	0.576
Steroids 1 mg/kg	9 (19.6%)	6 (24%)	7 (24.1%)	0.862
Steroids 2 mg/kg	5 (10.9%)	1 (4%)	0 (0%)	0.134
Steroids Bolus	10 (21.7%)	8 (32%)	11 (37.9%)	0.321
Adverse events				
Bacteriemia	1 (2.2%)	3 (12%)	4 (13.8%)	0.104
Fungemia	0 (0%)	1 (4%)	0 (0%)	0.250
Pneumocystis pneumonia	3 (6.5%)	1 (4%)	0 (0%)	0.368
Aspergillosis	0 (0%)	2 (8%)	1 (3.4%)	0.091
Hospital acquired pneumonia	0 (0%)	7 (28%)	6 (20.7%)	0.001
C. difficile colitis	0 (0%)	0 (0%)	1 (3.4%)	0.540
Outcome				
Length of stay (ICU)	8 [6-10]	14 [7-21]	11 [8-19]	0.001
Length of stay (Hospital)	17 [13-27]	26 [18-30]	23 [13-47.5]	0.085
Mortality rate at 30 days	16 (34.8%)	15 (60%)	10 (35.7%)	0.093
Mortality rate at 90 days	17 (37%);	16 (64%)	12 (41.4%)	0.169
Mortality rate at 1 year	27 (69.2%)	20 (83.3%)	16 (57.1%)	0.122

Table 3. Prognosis factors of HFNO failure

Variable	HFNO success	HFNO failure	p
Long term ILD treaments			
Long term oxigenotheray	33.3%	31.7%	1.000
Noninvasive ventilation at home	13.3%	9.8%	0.714
Month since diagnosis	24 [3; 104]	11 [0; 36]	0.156
Cause of exacerbation			
Infectious Disease Except Covid	53.3%	39%	0.334
Covid	6.7%	0%	0.175
Acute exacerbation	60%	51.2%	0.481
Subacute exacerbation	20%	17.1%	0.766
Diagnosis	16.7%	17.1%	1.000
Pulmonary embolism	10%	4.9%	0.644
Left Cardiac Failure	0%	12.2%	0.069
Right Cardiac Failure	23.3%	9.8%	0.184
Iatrogeny	0%	7.3%	0.258
Pneumothorax	0%	4.9%	0.505
Others	3.3%	4.9%	1.000
Baseline characteristics			
Highest Temperature Within First 24h	37.5 [37.1; 38.1]	37.7 [37.2; 38.3]	0.452
Heart Rate	95 [80; 104.5]	100 [85; 111]	0.200
Mean arterial pressure	74.5 [67; 87.5]	80 [75; 86]	0.139
Norepinephrine	13.3%	2.4%	0.155
Dobutamine	3.3%	2.4%	1.000
Creatinin (mg/ml)	8 [7; 14]	9 [8; 12]	0.755
CRP (mg/L)	116 [32; 159.75]	103 [45; 159]	0.857
PCT (ng/ml)	0.15 [0; 1.05]	0.22 [0.06; 0.72]	0.553
White cell count ($x10^9$/L)	12.77 [9.33; 16.78]	14.18 [7.02; 17.57]	0.762
Fibrinogen (g/l)	6.2 [4.65; 7.48]	5.5 [4.6; 6.9]	0.288
Adjuvant therapeutic			

Variable	HFNO success	HFNO failure	p
Beta-blockers	26.7%	22%	0.780
Proton pump inhibitors	70%	70.7%	1.000
JAK inhibitors	3.3%	0	0.423
Rituximab	3.3%	0	0.423
Cyclophosphamid	3.3%	9.8%	0.388
Anti infectious treatments	90%	90.2%	1.000
Antifungal therapy	16.7%	65.9%	0.000
Antibiotherapy	90%	85.4%	0.724
Steroids	30%	61%	0.016
Steroids 1 mg/kg	16.7%	24.4%	0.560
Steroids 2 mg/kg	3.3%	12.2%	0.390
Steroids Bolus	10%	36.6%	0.013
Adverse events			
Bacteriemia	3.3%	7.3%	0.633
Fungemia	0%	2.4%	1.000
Pneumocystose	3.3%	7.3%	0.633
Aspergillosis	0%	4.9%	0.505
Outcome			
Length of ICU stay	7.5 [6; 9.75]	11 [7; 18]	**0.017**
Length of hospital stay	16 [14; 25]	25 [17; 30]	0.057

Table 4. Determinants of MV failure

Variable	MV success	MV failure	p
Long term ILD treaments			
Long-term oxygen therapy	17.2%	32%	0.339
Home non invasive ventilation	6.9%	8%	1.000
Month since diagnosis	2 [0; 52]	4.5 [0.25; 21.75]	0.893
Cause of exacerbation			
Infectious Disease Except Covid	31%	24%	0.762

Variable	MV success	MV failure	p
Acute exacerbation	34.5%	40%	0.780
Subacute exacerbation	10.3%	20%	0.449
Pulmonary embolism	6.9%	0%	0.493
Left Cardiac Failure	20.7%	12%	0.480
Right Cardiac Failure	13.8%	4%	0.358
Iatrogeny	13.8%	4%	0.358
Pneumothorax	0%	8%	0.210
Others	10.3%	4%	0.615
ICU admission			
SAPS II	42 [34; 54]	45 [35; 57]	0.344
Highest Temperature Within First 24h	37.45 [37.2; 38.02]	37.5 [36.9; 38.6]	0.993
SpO_2	97 [91.75; 98]	96 [93; 97]	0.102
Heart Rate	93.5 [81; 105.25]	96 [85; 103]	0.831
Mean arterial pressure	81 [71; 86.5]	79 [73; 84]	0.894
Norepinephrine	25%	28%	1.000
Dobutamine	3.6%	8%	0.597
Creatinine (mg/dl)	8 [5; 14.75]	10 [8; 13]	0.248
CRP (mg/L)	119 [72; 167.5]	90 [42; 128]	0.156
PCT (ng/ml)	0.34 [0.11; 0.85]	0.32 [0.16; 1.86]	0.534
White blood cell count ($x10^9$/L)	14.09 [8.27; 16]	14.91 [7.02; 20]	0.331
Fibrinogen (g/l)	6.7 [5.75; 7.1]	5.5 [4.9; 6.8]	0.070
Mechanical ventilation parameters			
Ph H0	7.31 [7.26; 7.35]	7.27 [7.25; 7.34]	0.353
PCO_2 H0	49.3 [39.7; 55.6]	56.6 [41.7; 61.5]	0.110
PO_2 H0	141 [102; 177]	94 [71; 168]	0.302
Nitric oxide H0	6.9%	8%	1.000
Neuromuscular blocker H0	31%	32%	1.000
FiO_2 H0	70 [60; 100]	80 [60; 100]	0.410
PaO_2/FiO_2 H0	200.5 [131.46; 264.29]	130 [83; 285]	0.162

Variable	MV success	MV failure	p
PEEP H0	6 [5; 8]	8 [6; 10]	0.272
Peak airway pressure H0	37 [33; 43]	41 [38; 47]	0.052
Plateau pressure H0	24 [20; 27]	28 [24; 32]	**0.015**
Driving pressure H0	15 [13; 21]	22 [16; 24]	0.068
Ventilatory Ratio H0	2.17 [1.64; 2.84]	2.33 [2.05; 3.42]	0.233
Mechanical Power H0	26.75 [23.96; 37.13]	32.18 [25.88; 38.94]	0.435
ARDS H0	75.9%	68%	0.557
Ph H24	7.4 [7.35; 7.45]	7.38 [7.34; 7.41]	0.251
PCO_2 H24	3.6%	4.3%	NA
PO_2 H24	95 [78; 124]	87 [77; 111]	0.538
Neuromuscular blocker H24	17.9%	56.5%	**0.007**
Nitric oxide H24	10.7%	13%	1.000
FiO_2 H24	50 [45; 60]	70 [50; 100]	**0.022**
PaO_2/FiO_2 H24	179 [148.75; 248]	112.86 [95.5; 247]	0.121
PEEP H24	6.75 [5; 8]	8 [6; 10]	0.196
Peak airway pressure H24	33 [28; 41]	41 [34.5; 45]	**0.004**
Plateau pressure H24	3.6%	4.3%	0.140
Driving pressure H24	14 [12; 18.25]	18 [14.5; 21]	**0.030**
Ventilatory Ratio H24	1.84 [1.37; 2.23]	2.44 [2.01; 3.06]	**0.006**
Mechanical Power H24	28.25 [22.2; 31.77]	35.7 [30.11; 44.52]	**0.005**
ARDS H24	79.3%	76%	1.000
Ph H48	7.41 [7.37; 7.43]	7.37 [7.32; 7.42]	0.170
PCO_2 H48	43.75 [35.82; 50.57]	51.2 [41.4; 58.2]	**0.012**
PO_2 H48	117 [96.75; 133]	86 [72; 117]	**0.016**
Curares H48	23.1%	52.4%	0.066
No H48	11.5%	28.6%	0.263
FiO_2 H48	50 [36.25; 50]	60 [50; 70]	**0.008**
PaO_2/FiO_2 H48	267 [220.5; 305.83]	174 [95; 222.86]	**0.001**
PEEP H48	6 [5; 8]	7 [6; 10]	0.075

Variable	MV success	MV failure	p
Peak airway pressure H48	34.5 [31; 39.5]	38 [33; 44]	0.083
Plateau pressure H48	22 [18; 26]	28 [23; 35]	**0.026**
Driving pressure H48	14 [11; 18]	18 [14; 26]	0.083
Ventilatory Ratio H48	1.98 [1.63; 2.27]	2.21 [1.97; 2.82]	0.093
Mechanical Power H48	30.58 [24.44; 35.03]	34.35 [23.71; 37.43]	0.552
ARDS H48	46.2%	85.7%	**0.007**
Prone position	20.7%	52%	**0.023**
Number of prone positions sessions	0 [0; 0]	1 [0; 2]	**0.018**
Fluid balance during first 48 hours	1019 [-1628; 5082]	1308.5 [-462; 5101.5]	0.947
Adjuvent therapies			
Beta-blockers	34.5%	8%	**0.024**
Proton pump inhibitors	79.3%	64%	0.239
Intravenous immunoglobulins	0%	4%	0.463
Tacrolimus	0%	4%	0.463
JAK-inhibitors	0%	4%	0.463
Cyclophosphamid	6.9%	20%	0.229
Anti Infectious therapy	92.9%	100%	0.492
Antifungal	34.5%	72%	**0.007**
Antibiotherapy	86.2%	92%	0.675
Steroids	48.3%	60%	0.425
Steroids 1 g/kg	17.2%	32%	0.339
Steroids 2 mg/kg	0%	4%	0.463
Steroids Bolus	34.5%	36%	1.000
Adverse events			
Bacteriemia	6.9%	20%	0.229
Fungemia	3.4%	0%	1.000
Pneumocystis	3.4%	0%	1.000
Aspergillus	6.9%	4%	1.000
Ventilator acquired pneumonia	20.7%	28%	0.751

Variable	MV success	MV failure	p
Outcome			
Length of stay in ICU	16 [10; 20]	12 [6; 18]	0.082
Length of stay in hospital	32 [20; 56]	18 [13; 29]	**0.002**

Table 5. ROC threshold ROX ratio H48

Threshold	Sensitivity	Specificity	Youden
Inf	1.000	0.000	0.000
20.208	1.000	0.038	0.038
17.812	1.000	0.077	0.077
14.755	0.968	0.077	0.045
13.338	0.968	0.115	0.083
12.750	0.968	0.154	0.122
12.434	0.968	0.192	0.160
12.309	0.935	0.192	0.128
12.051	0.935	0.231	0.166
11.819	0.935	0.269	0.205
11.726	0.935	0.308	0.243
10.833	0.903	0.308	0.211
9.974	0.903	0.385	0.288
9.674	0.903	0.423	0.326
9.224	0.903	0.462	0.365
8.899	0.903	0.500	0.403
8.661	0.903	0.538	0.442
8.373	0.871	0.538	0.409
8.087	0.839	0.538	0.377
7.849	0.839	0.577	0.416

Threshold	Sensitivity	Specificity	Youden
7.448	0.839	0.615	0.454
7.170	0.839	0.654	0.493
7.110	0.839	0.692	0.531
7.068	0.839	0.731	0.569
6.939	0.806	0.731	0.537
6.719	0.774	0.731	0.505
6.600	0.742	0.731	0.473
6.531	0.742	0.769	0.511
6.297	0.742	0.808	0.550
6.108	0.710	0.808	0.517
6.085	0.677	0.808	0.485
6.065	0.677	0.846	0.524
5.998	0.645	0.846	0.491
5.883	0.613	0.846	0.459
5.811	0.613	0.885	0.498
5.774	0.581	0.885	0.465
5.553	0.581	0.923	0.504
5.311	0.548	0.923	0.471
5.251	0.516	0.923	0.439
5.225	0.484	0.923	0.407
5.167	0.452	0.923	0.375
4.925	0.419	0.923	0.342
4.677	0.387	0.923	0.310
4.543	0.355	0.923	0.278
4.378	0.323	0.923	0.246
4.191	0.290	0.923	0.213
3.981	0.258	0.923	0.181

Threshold	Sensitivity	Specificity	Youden
3.848	0.226	0.923	0.149
3.752	0.194	0.923	0.117
3.663	0.194	0.962	0.155
3.614	0.194	1.000	0.194
3.546	0.161	1.000	0.161
3.212	0.129	1.000	0.129
2.812	0.097	1.000	0.097
2.635	0.065	1.000	0.065
2.528	0.032	1.000	0.032
-Inf	0.000	1.000	0.000

Table 6. ROC threshold SpO2/FIO2 H48

Threshold	Sensitivity	Specificity	Youden
Inf	1.000	0.000	0.000
325.000	1.000	0.077	0.077
318.333	1.000	0.115	0.115
280.833	0.968	0.115	0.083
241.250	0.968	0.154	0.122
236.250	0.968	0.269	0.237
233.750	0.935	0.308	0.243
231.250	0.935	0.346	0.282
228.750	0.935	0.385	0.320
226.250	0.935	0.423	0.359
220.278	0.903	0.423	0.326

Threshold	Sensitivity	Specificity	Youden
212.222	0.903	0.462	0.365
201.444	0.903	0.500	0.403
193.000	0.871	0.500	0.371
191.000	0.839	0.500	0.339
189.000	0.839	0.538	0.377
186.000	0.806	0.577	0.383
183.000	0.806	0.615	0.422
181.909	0.806	0.654	0.460
172.576	0.774	0.654	0.428
161.667	0.742	0.654	0.396
155.833	0.710	0.692	0.402
150.000	0.710	0.731	0.440
145.595	0.677	0.731	0.408
140.000	0.677	0.769	0.447
136.429	0.613	0.769	0.382
135.000	0.613	0.808	0.421
132.857	0.581	0.808	0.388
129.048	0.548	0.808	0.356
126.000	0.548	0.846	0.395
125.167	0.516	0.846	0.362
123.833	0.516	0.885	0.401
122.583	0.484	0.885	0.368
121.875	0.484	0.923	0.407
120.625	0.484	0.962	0.445
119.375	0.387	0.962	0.349
117.500	0.355	0.962	0.316
115.625	0.323	0.962	0.284

Threshold	Sensitivity	Specificity	Youden
114.375	0.290	0.962	0.252
113.125	0.258	0.962	0.220
111.544	0.226	0.962	0.187
110.294	0.194	0.962	0.155
106.111	0.129	0.962	0.091
98.611	0.129	1.000	0.129
94.000	0.097	1.000	0.097
92.500	0.065	1.000	0.065
88.500	0.032	1.000	0.032
-Inf	0.000	1.000	0.000

Table 7. ROC threshold ventilatory ratio H24

Threshold	Sensitivity	Specificity	Youden
-Inf	1.000	0.000	0.000
1.111	1.000	0.036	0.036
1.194	1.000	0.071	0.071
1.235	1.000	0.107	0.107
1.263	0.957	0.107	0.064
1.287	0.957	0.143	0.099
1.299	0.957	0.179	0.135
1.302	0.957	0.214	0.171
1.345	0.957	0.250	0.207
1.391	0.957	0.286	0.242
1.431	0.913	0.286	0.199
1.488	0.913	0.321	0.234
1.534	0.913	0.357	0.270

Threshold	Sensitivity	Specificity	Youden
1.625	0.870	0.357	0.227
1.716	0.870	0.393	0.262
1.763	0.870	0.429	0.298
1.799	0.826	0.429	0.255
1.816	0.826	0.464	0.290
1.841	0.826	0.500	0.326
1.874	0.826	0.536	0.362
1.893	0.826	0.607	0.433
1.940	0.783	0.607	0.390
2.012	0.739	0.607	0.346
2.055	0.696	0.607	0.303
2.069	0.696	0.643	0.339
2.110	0.696	0.679	0.374
2.151	0.652	0.679	0.331
2.158	0.609	0.679	0.287
2.187	0.565	0.679	0.244
2.216	0.565	0.714	0.280
2.234	0.565	0.750	0.315
2.262	0.522	0.750	0.272
2.353	0.522	0.786	0.307
2.436	0.522	0.821	0.343
2.537	0.478	0.821	0.300
2.649	0.435	0.821	0.256
2.722	0.391	0.821	0.213
2.783	0.348	0.821	0.169
2.840	0.348	0.857	0.205
2.940	0.304	0.857	0.161

Threshold	Sensitivity	Specificity	Youden
2.990	0.304	0.893	0.197
3.023	0.261	0.893	0.154
3.086	0.261	0.929	0.189
3.164	0.217	0.929	0.146
3.220	0.217	0.964	0.182
3.279	0.174	0.964	0.138
3.362	0.174	1.000	0.174
3.461	0.130	1.000	0.130
4.166	0.087	1.000	0.087
4.895	0.043	1.000	0.043
Inf	0.000	1.000	0.000

Table 8. ROC threshold mechanical power H24

threshold	sensitivity	specificity	youden
-Inf	1.000	0.000	0.000
15.052	1.000	0.036	0.036
16.834	1.000	0.071	0.071
17.484	1.000	0.107	0.107
18.098	1.000	0.143	0.143
18.808	1.000	0.179	0.179
19.828	1.000	0.214	0.214
20.391	0.957	0.214	0.171
21.222	0.957	0.250	0.207
22.308	0.913	0.250	0.163
22.729	0.870	0.250	0.120
23.353	0.870	0.321	0.191

threshold	sensitivity	specificity	youden
24.014	0.826	0.321	0.148
24.387	0.783	0.321	0.104
25.190	0.783	0.357	0.140
26.004	0.783	0.393	0.175
26.616	0.783	0.429	0.211
27.308	0.783	0.464	0.247
28.248	0.783	0.500	0.283
28.888	0.783	0.536	0.318
29.003	0.783	0.571	0.354
29.256	0.783	0.607	0.390
29.538	0.739	0.607	0.346
30.079	0.739	0.643	0.382
30.654	0.739	0.679	0.418
30.960	0.696	0.679	0.374
31.207	0.696	0.714	0.410
31.379	0.696	0.750	0.446
32.181	0.652	0.750	0.402
33.115	0.609	0.750	0.359
33.604	0.609	0.786	0.394
34.152	0.565	0.786	0.351
34.507	0.565	0.821	0.387
35.111	0.522	0.821	0.343
35.930	0.478	0.821	0.300
36.792	0.478	0.857	0.335
38.309	0.478	0.893	0.371
39.818	0.435	0.893	0.328
41.061	0.391	0.893	0.284

threshold	sensitivity	specificity	youden
42.865	0.391	0.929	0.320
44.254	0.304	0.929	0.233
44.523	0.261	0.929	0.189
45.521	0.217	0.929	0.146
47.137	0.174	0.929	0.102
48.702	0.130	0.929	0.059
49.722	0.087	0.929	0.016
51.980	0.087	0.964	0.051
55.978	0.087	1.000	0.087
65.680	0.043	1.000	0.043
Inf	0.000	1.000	0.000

VII. References

1. Wijsenbeek M, Suzuki A, Maher TM. Interstitial lung diseases. The Lancet. sept 2022;400(10354):769-86.

2. Mathai SC, Danoff SK. Management of interstitial lung disease associated with connective tissue disease. BMJ. 24 févr 2016;h6819.

3. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 1 mai 2022;205(9):e18-47.

4. Hilberg O, Hoffmann-Vold AM, Smith V, Bouros D, Kilpeläinen M, Guiot J, et al. Epidemiology of interstitial lung diseases and their progressive-fibrosing behaviour in six European countries. ERJ Open Res. janv 2022;8(1):00597-2021.

5. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. Am J Respir Crit Care Med. 1 août 2016;194(3):265-75.

6. Alhamad EH, Cal JG, Alrajhi NN, AlBoukai AA. Acute exacerbation in interstitial lung disease. Ann Thorac Med. avr 2021;16(2):178-87.

7. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. Eur Respir J. févr 2011;37(2):356-63.

8. Miyashita K, Kono M, Saito G, Koyanagi Y, Tsutsumi A, Kobayashi T, et al. Prognosis after acute exacerbation in patients with interstitial lung disease other than idiopathic pulmonary fibrosis. Clin Respir J. mars 2021;15(3):336-44.

9. Tandjaoui-Lambiotte Y, Gonzalez F, Boubaya M, Freynet O, Clec´h C, Bonnet N, et al. Two-year follow-up of 196 interstitial lung disease patients after ICU stay. Int J Tuberc Lung Dis. 1 mars 2021;25(3):199-205.

10. Salonen J, Purokivi M, Bloigu R, Kaarteenaho R. Prognosis and causes of death of patients with acute exacerbation of fibrosing interstitial lung diseases. BMJ Open Respir Res. avr 2020;7(1):e000563.

11. Arai T, Kagawa T, Sasaki Y, Sugawara R, Sugimoto C, Tachibana K, et al. Heterogeneity of incidence and outcome of acute exacerbation in idiopathic interstitial pneumonia. Respirology. nov 2016;21(8):1431-7.

12. Gannon WD, Lederer DJ, Biscotti M, Javaid A, Patel NM, Brodie D, et al. Outcomes and Mortality Prediction Model of Critically Ill Adults With Acute Respiratory Failure and Interstitial Lung Disease. Chest. juin 2018;153(6):1387-95.

13. Ricard JD, Roca O, Lemiale V, Corley A, Braunlich J, Jones P, et al. Use of nasal high flow oxygen during acute respiratory failure. Intensive Care Med. déc 2020;46(12):2238-47.

14. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure. N Engl J Med. 4 juin 2015;372(23):2185-96.

15. Grasselli G, Calfee CS, Camporota L, Poole D, Amato MBP, Antonelli M, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive Care Med. juill 2023;49(7):727-59.

16. Perkins GD, Ji C, Connolly BA, Couper K, Lall R, Baillie JK, et al. Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients With Acute Hypoxemic Respiratory Failure and COVID-19: The RECOVERY-RS Randomized Clinical Trial. JAMA. 8 févr 2022;327(6):546.

17. Sztrymf B, Messika J, Bertrand F, Hurel D, Leon R, Dreyfuss D, et al. Beneficial effects of humidified high flow nasal oxygen in critical care patients: a prospective pilot study. Intensive Care Med. nov 2011;37(11):1780-6.

18. Roca O, Messika J, Caralt B, García-de-Acilu M, Sztrymf B, Ricard JD, et al. Predicting success of high-flow nasal cannula in pneumonia patients with hypoxemic respiratory failure: The utility of the ROX index. J Crit Care. oct 2016;35:200-5.

19. Kim JH, Baek AR, Lee SI, Kim WY, Na YS, Lee BY, et al. ROX index and SpO2/FiO2 ratio for predicting high-flow nasal cannula failure in hypoxemic COVID-19 patients: A multicenter retrospective study. Hadda V, éditeur. PLOS ONE. 12 mai 2022;17(5):e0268431.

20. Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernández G, et al. An Index Combining Respiratory Rate and Oxygenation to Predict Outcome of Nasal High-Flow Therapy. Am J Respir Crit Care Med. 1 juin 2019;199(11):1368-76.

21. Schaeffer BZ, Fazio SA, Stocking JC, Adams JY, Liu A, Black HB, et al. Using the ROX Index to Predict Treatment Outcome for High-Flow Nasal Cannula and/or Noninvasive Ventilation in Patients With COPD Exacerbations. Respir Care. 1 sept 2024;69(9):1100-7.

22. Azoulay E, Métais M, Lemiale V, Mokart D, Moreau AS, Canet E, et al. Outcomes in immunocompromised patients with acute hypoxemic respiratory failure treated by high-flow nasal oxygen. Intensive Care Med. avr 2025;51(4):731-41.

23. Lee JH, Lim CM, Koh Y, Hong SB, Song JW, Huh JW. High-flow nasal cannula oxygen therapy in idiopathic pulmonary fibrosis patients with respiratory failure. J Thorac Dis. mars 2020;12(3):966-72.

24. Pagliaro R, Aronne L, Fomez R, Ferri V, Montella A, Sanduzzi Zamparelli S, et al. High-Flow Nasal Cannula System in Respiratory Failure Associated with Interstitial Lung Diseases: A Systematic Review and Narrative Synthesis. J Clin Med. 17 mai 2024;13(10):2956.

25. Koyauchi T, Yasui H, Enomoto N, Hasegawa H, Hozumi H, Suzuki Y, et al. Pulse oximetric saturation to fraction of inspired oxygen (SpO_2 /FIO_2) ratio 24

hours after high-flow nasal cannula (HFNC) initiation is a good predictor of HFNC therapy in patients with acute exacerbation of interstitial lung disease. Ther Adv Respir Dis. janv 2020;14:1753466620906327.

26. Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. N Engl J Med. 4 mai 2000;342(18):1301-8.

27. Amato MBP, Meade MO, Slutsky AS, Brochard L, Costa ELV, Schoenfeld DA, et al. Driving Pressure and Survival in the Acute Respiratory Distress Syndrome. N Engl J Med. 19 févr 2015;372(8):747-55.

28. Pham T, Brochard LJ, Slutsky AS. Mechanical Ventilation: State of the Art. Mayo Clin Proc. sept 2017;92(9):1382-400.

29. Mauri T, Lazzeri M, Bellani G, Zanella A, Grasselli G. Respiratory mechanics to understand ARDS and guide mechanical ventilation. Physiol Meas. 30 nov 2017;38(12):R280-H303.

30. Battaglini D, Fazzini B, Silva PL, Cruz FF, Ball L, Robba C, et al. Challenges in ARDS Definition, Management, and Identification of Effective Personalized Therapies. J Clin Med. 9 févr 2023;12(4):1381.

31. Galizia M, Ghidoni V, Catozzi G, Giovanazzi S, Nocera D, Donati B, et al. Predictors of VILI risk: driving pressure, 4DPRR and mechanical power ratio—an experimental study. Intensive Care Med Exp. 11 déc 2024;12(1):116.

32. Beitler JR. Bedside respiratory physiology to detect risk of lung injury in acute respiratory distress syndrome. Curr Opin Crit Care. févr 2019;25(1):3-11.

33. Acute Respiratory Distress Syndrome: The Berlin Definition. JAMA [Internet]. 20 juin 2012 [cité 18 déc 2025];307(23). Disponible sur: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2012.5669

34. Tonelli R, Grasso S, Cortegiani A, Ball L, Castaniere I, Tabbì L, et al. Physiological effects of lung-protective ventilation in patients with lung fibrosis and usual interstitial pneumonia pattern versus primary ARDS: a matched-control study. Crit Care Lond Engl. 18 oct 2023;27(1):398.

35. Zafrani L, Lemiale V, Lapidus N, Lorillon G, Schlemmer B, Azoulay E. Acute Respiratory Failure in Critically Ill Patients with Interstitial Lung Disease. Assassi S, éditeur. PLoS ONE. 12 août 2014;9(8):e104897.

36. Martin MJ, Moua T. Mechanical Ventilation and Predictors of In-Hospital Mortality in Fibrotic Interstitial Lung Disease With Acute Respiratory Failure: A Cohort Analysis Through the Paradigm of Acute Respiratory Distress Syndrome. Crit Care Med. juill 2020;48(7):993-1000.

37. Vahdatpour CA, Pichler A, Palevsky HI, Kallan MJ, Patel NB, Kinniry PA. Interstitial Lung Disease Associated Acute Respiratory Failure Requiring Invasive Mechanical Ventilation: A Retrospective Analysis. Open Respir Med J. 2020;14:67-77.

38. D'Albo R, Pozzi T, Nicolardi RV, Galizia M, Catozzi G, Ghidoni V, et al. Mechanical power ratio threshold for ventilator-induced lung injury. Intensive Care Med Exp. 30 juill 2024;12(1):65.

39. Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, et al. Ventilator-related causes of lung injury: the mechanical power. Intensive Care Med. oct 2016;42(10):1567-75.

40. Paudel R, Trinkle CA, Waters CM, Robinson LE, Cassity E, Sturgill JL, et al. Mechanical Power: A New Concept in Mechanical Ventilation. Am J Med Sci. déc 2021;362(6):537-45.

41. Serpa Neto A, Deliberato RO, Johnson AEW, Bos LD, Amorim P, Pereira SM, et al. Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. Intensive Care Med. nov 2018;44(11):1914-22.

42. Coppola S, Caccioppola A, Froio S, Formenti P, De Giorgis V, Galanti V, et al. Effect of mechanical power on intensive care mortality in ARDS patients. Crit Care. déc 2020;24(1):246.

43. Sinha P, Fauvel NJ, Singh P, Soni N. Analysis of ventilatory ratio as a novel method to monitor ventilatory adequacy at the bedside. Crit Care. 27 févr 2013;17(1):R34.

44. Sinha P, Fauvel NJ, Singh S, Soni N. Ventilatory ratio: a simple bedside measure of ventilation. Br J Anaesth. mai 2009;102(5):692-7.

45. Nava S, Rubini F. Lung and chest wall mechanics in ventilated patients with end stage idiopathic pulmonary fibrosis. Thorax. 1 mai 1999;54(5):390-5.

46. Fu LX, Yu H, Lan L, Luo FM, Ni YN. Association between ventilatory ratio and ICU mortality in interstitial lung disease patients on mechanical ventilation: A retrospective study. Heart Lung. mars 2023;58:223-8.

47. Luo Z, Yang L, Liu S, Hu Y, Cao Z, Zhu J, et al. Mechanical ventilation for acute respiratory failure due to idiopathic pulmonary fibrosis versus connective tissue disease-associated interstitial lung disease: Effectiveness and risk factors for death. Clin Respir J. oct 2020;14(10):918-32.

48. Tandjaoui-Lambiotte Y, Gonzalez F, Boubaya M, Freynet O, Clec´h C, Bonnet N, et al. Two-year follow-up of 196 interstitial lung disease patients after ICU stay. Int J Tuberc Lung Dis. 1 mars 2021;25(3):199-205.

49. Rush B, Wiskar K, Berger L, Griesdale D. The use of mechanical ventilation in patients with idiopathic pulmonary fibrosis in the United States: A nationwide retrospective cohort analysis. Respir Med. févr 2016;111:72-6.

50. Suzuki A, Ando M, Kimura T, Kataoka K, Yokoyama T, Shiroshita E, et al. The impact of high-flow nasal cannula oxygen therapy on exercise capacity in fibrotic interstitial lung disease: a proof-of-concept randomized controlled crossover trial. BMC Pulm Med. déc 2020;20(1):51.

51. Pagliaro R, Aronne L, Fomez R, Ferri V, Montella A, Sanduzzi Zamparelli S, et al. High-Flow Nasal Cannula System in Respiratory Failure Associated with Interstitial Lung Diseases: A Systematic Review and Narrative Synthesis. J Clin Med. 17 mai 2024;13(10):2956.

52. Ruangsomboon O, Dorongthom T, Chakorn T, Monsomboon A, Praphruetkit N, Limsuwat C, et al. High-Flow Nasal Cannula Versus Conventional Oxygen Therapy in Relieving Dyspnea in Emergency Palliative Patients With Do-Not-Intubate Status: A Randomized Crossover Study. Ann Emerg Med. mai 2020;75(5):615-26.

53. Kang BJ, Koh Y, Lim CM, Huh JW, Baek S, Han M, et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. Intensive Care Med. avr 2015;41(4):623-32.

54. Martin C, Papazian L, Payan MJ, Saux P, Gouin F. Pulmonary Fibrosis Correlates With Outcome in Adult Respiratory Distress Syndrome. Chest. janv 1995;107(1):196-200.

55. Azizi BA, Munoz-Acuna R, Suleiman A, Ahrens E, Redaelli S, Tartler TM, et al. Mechanical power and 30-day mortality in mechanically ventilated, critically ill patients with and without Coronavirus Disease-2019: a hospital registry study. J Intensive Care. 6 avr 2023;11(1):14.

56. Jiang X, Zhu Y, Zhen S, Wang L. Mechanical power of ventilation is associated with mortality in neurocritical patients: a cohort study. J Clin Monit Comput. déc 2022;36(6):1621-8.

AUTEUR(E) : Nom : LACOMBE Prénom : Charlotte

Date de soutenance : 23/01/2026

Titre de la thèse : Predictors of ventilatory supports failure in patients with interstitial lung diseases admitted to intensive care unit

Thèse - Médecine – Lille-2026

Cadre de classement : Médecine

DES + FST/option : Médecine intensive et réanimation

Mots-clés : Interstitial lung disease – Intensive care unit – Acute respiratory failure – Ventilatory supports failure – Prognostic bedside indices

Summary: we conducted a retrospective, single-center observational study including 100 patients with interstitial lung diseases (ILD) admitted to intensive care unit (ICU) between 2013 and 2024. High-flow nasal oxygen (HFNO) failure was defined as a composite endpoint including 30-day mortality or the need for invasive mechanical ventilation (MV). MV failure was defined as 30-day mortality among patients undergoing endotracheal intubation. The relationship of respiratory rate-oxygenation (ROX index) and the ratio of pulse oximetry oxygen saturation to the fraction of inspired oxygen (SpO_2/FiO_2) were assessed at HFNO initiation and at 24 and 48 hours. Ventilatory ratio (VR) and mechanical power (MP) were calculated at the same time points during invasive MV.

Among patients treated with HFNO, both ROX index and SpO_2/FiO_2 ratio measurements at 48 hours demonstrated the strongest prognostic performance. A ROX index ≥ 7.07 and a SpO_2/FiO_2 ratio ≥ 181.9 were associated with a significantly lower risk of HFNO failure, and these associations persisted after adjustment for decisions regarding limitations of life-sustaining therapies. In mechanically ventilated patients, VR and MP measured at 24 hours were significantly higher in non-survivors. Thresholds of 1.89 for VR and 31.38 J/min for MP were associated with an approximately fourfold increased risk of mortality at 30 days.

These findings suggested that simple bedside respiratory indices provided clinically meaningful prognostic data in critically ill patients with ILD. Their use may support early risk stratification and help guide clinical decision-making, while remaining complementary to overall clinical assessment. Prospective multicenter studies are needed to validate these thresholds and confirm their clinical utility.

<u>Composition du Jury</u> :

Président : Pr Mercé Jourdain

Assesseurs : Dr Alexandre Gaudet

Dr Victor Valentin

Directeur de thèse : Dr Laurent Robriquet