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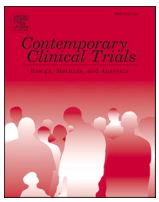

Pirfenidone to prevent fibrosis in acute respiratory distress syndrome: The PIONEER study protocol

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ABSTRACT

Background: Pulmonary fibrosis is a major complication of the Acute Respiratory Distress Syndrome (ARDS). Pirfenidone is an approved treatment for idiopathic pulmonary fibrosis. It may attenuate ARDS-related fibrosis and decrease the need for prolonged ventilation. Accordingly, we aimed to evaluate the effect of pirfenidone on ventilator-free days in patients with ARDS.
Methods: In a multi-center, randomized, double-blind, placebo-controlled trial, we plan to randomly assign 130 adults invasively ventilated for ARDS to receive pirfenidone or placebo for up to 28 days. The primary outcome is days alive and ventilator free at 28 days. Secondary outcomes include ICU-free days, hospital free days all at 28 day, ICU mortality and hospital mortality. We will also assess fibroproliferative changes on high-resolution CT scans at ICU discharge and quality of life. Data analysis will be on an intention-to-treat basis.
Discussion: The trial is ongoing and currently recruiting. It will be the first randomized controlled study to investigate whether, compared to placebo, pirfenidone increases the number of days alive and ventilator-free in patients with ARDS. Its double-blind multicenter design will provide internal validity, minimal bias, and a degree of external validity. If our hypothesis is confirmed, this treatment would justify larger trials of this intervention.
Trial registration: This trial was registered on ClinicalTrials.gov with the trial identification NCT05075161.

1. Background

Acute Respiratory Distress Syndrome (ARDS) is an acute inflammatory lung injury, associated with increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue [1]. Two landmark articles suggest that ARDS can be separated into at least two distinct phenotypes based on unbiased, data-driven analyses of clinical data and several plasma biomarkers of inflammation, coagulation and endothelial activation. One phenotype is characterized by a hyper- inflammatory and hyper-coagulable state, while the other phenotype shows a hypo-inflammatory state with high bicarbonate levels [2,3]. Most hyper–inflammatory ARDS patients survive the acute phase but develop pulmonary fibrosis [4] with a high 1-year mortality (41 %) [5]. Moreover, such patients who survive ARDS show only partial recovery of pulmonary function and continue to have reduced quality of life and persistent exercise limitations [6].

Pharmacological interventions for ARDS are focused on dampening the pro-inflammatory response in the initial phase of ARDS, reducing pulmonary oedema, minimizing ventilator-associated lung injury and improving repair mechanisms. Unfortunately, with the possible but controversial exception of treatment with glucocorticoids [7,8], no pharmacological interventions have achieved a significant reduction in morbidity and/or mortality [9–15]. Pirfenidone is an antifibrotic and anti-inflammatory drug that reduces fibroblast proliferation, inhibits transforming growth factor beta, and reduces the release of tumor necrosis factor alpha and interlukin-1 beta. It is now FDA-approved as an oral anti-fibrotic drug for the treatment of idiopathic pulmonary fibrosis (IPF). Pirfenidone is associated with improved lung function, greater progression-free survival, and better exercise tolerance, in addition to relevant reduction in disease progression in IPF [16]. Its effectiveness in ARDS, however, has never been investigated, apart from a single preclinical study, which demonstrated its ability to reduce pulmonary fibrosis development when administered in the acute phase [17]. Importantly, fibroproliferative changes begin in the early stages of ARDS [18]. However, the above findings in pulmonary fibrosis suggest that pirfenidone might improve clinically relevant outcomes in patients with ARDS. Accordingly, this trial aims to evaluate the efficacy of pirfenidone in ARDS-associated lung injury and fibrosis measured in terms of days alive and ventilator-free.

2. Methods

2.1. Study design

The study is a multicenter randomized double-blind placebo-controlled trial of pirfenidone to reduce pulmonary fibrosis and, thereby, increase days alive and ventilator free in ARDS patient.

The study is registered on ClinicalTrials.gov (NCT05075161) and Ethical Approval was obtained before the beginning of the trial in each participating center. Informed consent expressed is to be obtained from the patient or by his/her legal representative or on Ethical Committee indication.

2.2. Trial population, inclusion and exclusion criteria

The trial aims to enroll 130 adult Intensive Care Unit (ICU) patients with moderate or severe ARDS associated with an hyperinflammatory phenotype.

Patients should have all the following (Berlin criteria [1]):

1) Development within 1 week of a known clinical insult or new or worsening respiratory symptoms,
2) Bilateral opacities on chest X-ray or CT -scan which are not fully explained by effusions, lobar/lung collapse or nodules,
3) Respiratory failure not fully explained by cardiac failure or fluid overload,
4) $PaO_2/FiO_2 < 200$ mmHg with PEEP ≥ 5 cmH_2O while receiving invasive mechanical ventilation.

and at least one of the following markers of a hyperinflammatory state:

1) High plasma levels of an inflammatory biomarker (e.g. IL-6 > 80 pg/ml or CRP > 250 mg/l),
2) Vasopressor dependence (any vasopressor at any dosage for at least 1 h),
3) Low serum bicarbonate (< 18 mmol/l) or increased serum lactate (>4 mmol/l).

Patients are to be excluded if they fulfill at least one of the trial exclusion criteria. The most relevant exclusion criteria include the following and are detailed in Table 1.

1) Moderate or severe ARDS from more than 36 h,
2) Preexistent pulmonary comorbidities requiring home ventilators,
3) Low chance of survival (defined by a Simplified Acute Physiology Score II score higher than 75 points),
4) Contraindication to the administration of the study drug.

2.3. Recruitment and randomization

All eligible patients are screened for inclusion and exclusion criteria, and informed consent will be obtained according to local ethics committee and legal regulations. Randomization will be performed by a computer program, stratified by center and with the use of a permuted block design. Patients will be randomized to pirfenidone versus placebo with a 1:1 allocation.

2.4. Intervention

The experimental group will receive pirfenidone until ICU discharge or to 28 days for a total of 801 mg/day from day 1 to 7, 1602 mg/day from day 8 to 14, and 2403 mg/day from days 15 to 28 or to ICU discharge. The drug will be administered by a nasogastric tube (NG). The total daily dose will be divided into three and administered every eight hours. The control group will receive placebo at the same timepoints.

Tablets will be crushed and diluted in 40–50 ml of water in a syringe for NG administration. The control group will receive equivolume water in the same modalities of the intervention group without the experimental drug. The drug administration will be done by unblinded nurses not included in any phase of the study. The unblinded dosing team will administer the study drug in the absence of treating nurses or physicians by pulling screens as necessary around the patient's bed area and disposing the empty syringe as soon as it is finished.

All patients will receive the best available standard of care for ARDS according to the latest guidelines [19,20], independently of the randomization group (Supplementary eTable 7 and eTable 8).

The drug administration will be paused or interrupted in the presence of any adverse reactions suspected to be due to the trial drug, severe renal failure or hepatic toxicity, or if the treating physician considers it necessary for the safety of the patient (Supplementary eTable 6 and eTable 9).

At randomization, unblinded personnel will receive information about the treatment by email. They will then prepare the correct study drug (either pirfenidone or placebo) for administration. Neither the patient nor the blinded clinicians nor the personnel who perform the data collection or analysis will be aware of treatment assignment.

The unblinded dosing team cannot discuss study drug treatment with research staff or other members of the ICU or hospital staff except for the unblinded pharmacist.

The unblinded dosing team will be independent of the study and independent of direct clinical care of the study patient (PIONEER flowchart in Fig. 1).

2.5. Outcomes and sample size

The primary outcome of the study is days alive and ventilator free (VFD) at day 28.

Since VFD could be influenced by weaning strategies adopted by different centers and by rules of calculations, for the purpose of the study, weaning strategy guidance will be provided (see Table 2) and rules for calculation of VFD will be clearly described (Supplementary eTable 1).

Sample size calculation is based on previously published data [21] with a median of 7 VFD in patients with moderate and severe ARDS. We expect a 3-day increase in VFD in the group of patients treated with Pirfenidone, resulting in 10 VFD, with a standard deviation of 6 days in both groups. To obtain 80 % power to detect this effect at a 5 % alpha level, we plan to enroll 64 subjects per group, which will be rounded to 130 to account for possible dropouts.

Secondary outcomes will be ICU-free days at day 28, hospital length of stay, reduction in fibroproliferative changes on high-resolution CT performed at ICU discharge (Supplementary eTable 3), quality of life evaluated by validated questionnaires (Supplementary eTable 4 and eTable 5), right and left heart dysfunction (determined by echocardiography at ICU discharge, Supplementary eTable 2 for data collected), adverse event rate, use of rescue therapies for severe hypoxemia (Supplementary eTable 2), ICU and hospital mortality.

2.6. Data collection and patient follow up

All data will be stored electronically via a web-based case report form (CRF). Security measures and restricted access will be applied to all data in the electronic case report forms to protect data integrity and patient privacy.

Demographic data and biometric measurements medical history, as well as vital signs, laboratory values, ventilatory status and ventilator settings, and vasopressor drug dosage of patients included in the study will be collected.

At ICU discharge ±48 h, high-resolution CT scan and echocardiography will be performed. A respiratory function test, through spirometry, will be performed according to local standard practice. If additional CT scans are performed for clinical reasons, data will be collected for comprehensive monitoring (See Table 3).

A follow-up examination will be scheduled at 6 months and 1 year to evaluate functional exercise capacity of patients through a 6-min walk test and a health-related quality of life, assessed by SF-36 questionnaire and EQ-5D Health questionnaire (Supplementary eTable 4 and eTable 5).

2.7. Statistical plan

Primary data analysis will be conducted according to the intention-to-treat (ITT) analysis. Per protocol and as treated analyses will be added to primary and secondary outcomes.

The following pre-defined subgroup analyses will examine interactions between treatment and baseline clinical variables, estimating the mean differences between the two groups within each subgroup and calculating the *P* value for interaction:

1) Patient receiving concomitant corticosteroid treatment,
2) Severe versus moderate ARDS according to Berlin's definition,
3) According to baseline SOFA score quartiles,
4) Elderly patients (aged >70 years),
5) Number of "Calfee hyperinflammatory phenotype" criteria satisfied.

Data will also be presented stratified by center.

Dichotomous and categorical variables will be presented as absolute frequencies and percentages. Differences between the two groups (pirfenidone vs. placebo) will be tested using the Chi-square test or Fisher's

Table 1
Inclusion and exclusion criteria.

Inclusion criteria:
Adults of either sex, aged 18 years or older, with the concomitant presence of:

1. ARDS (moderate and severe) based on the Berlin definition: Within 1 week of a known clinical insult or new or worsening respiratory symptoms; bilateral opacities on CXR which are not fully explained by effusions, lobar/lung collapse or nodules; respiratory failure not fully explained by cardiac failure or fluid overload; $PaO_2/FiO_2 < 200$ mmHg with PEEP $\geq$5 cmH_2O (invasive mechanical ventilation)
2. Inflammatory ARDS phenotype as defined by at least one of the following: High plasma levels of inflammatory biomarkers (e.g. IL-6 > 80 pg/ml, CPR > 250 mg/l); vasopressor dependence (any vasoconstrictor at any dosage for at least 1 h); low serum bicarbonate (< 18 mmol/l) or increased serum lactate (>4 mmol/l)
3. Informed consent expressed by the patient or by his/her legal representative or on Ethical Committee indication.

Exclusion criteria:
Patients will be excluded if they meet one or more of the following criteria:

1. ARDS severe or moderate for more than 36 h
2. Untreated pulmonary embolism, pleural effusion or pneumothorax as the primary cause of ARF
3. ARF fully explained by left ventricular failure or fluid overload
4. Consent declined
5. Severe chronic respiratory disease requiring domiciliary ventilation (except for sleep disordered breathing)
6. Clinical suspicion for significant restrictive lung disease
7. Known allergy to pirfenidone
8. Women of childbearing potential
9. Concomitant use of fluvoxamine
10. Known severe hepatic failure either chronic (defined as a Child Plug class C) or acute, defined as: AST/ALT elevation >3 and $\leq$ 5 x ULN and bilirubin >2 mg/dl or clinical signs and symptoms of hepatic damage; or AST/ALT elevation >5 x ULN
11. Known severe renal failure (Clearence-Creatinine less than 30 ml/min) either chronic or at the time of assessment; or necessity of dialysis either chronic or at the time of assessment
12. Little chance of survival, as defined by a SAPSII score more than 75 points
13. Intubated and mechanically ventilated via an endotracheal or tracheostomy tube (>7 days) up to the time of randomization
14. < 18 years of age

Abbreviations: ARDS = acute respiratory distress syndrome; CXR = chest x-ray; PaO_2 = partial arterial pressure of oxygen; FiO_2 = inspiratory fraction of oxygen; PEEP = positive end expiratory pressure; IL-6 = Interleukin-6; CPR = c reactive protein; ARF = acute respiratory failure; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit normal; SAPS = simplified acute physiology score.

exact test, as appropriate. The normality of continuous variables will be assessed using the Shapiro-Wilk test: if normally distributed, data will be reported as mean ± standard deviation and differences between groups will be tested with the *t*-test; if not normally distributed, data will be presented as median and interquartile range, and differences between groups will be tested with the Wilcoxon-Mann-Whitney test.

Between-group differences for the primary and secondary outcomes will be reported as relative risks (RR) or mean differences with their 95 % confidence intervals (CI), for dichotomous and continuous variables respectively.

A Bayesian analysis will be employed to estimate the posterior probability that pirfenidone increases VFD by at least 1 or at least 3 days.

Mortality will be analyzed using a Cox proportional hazards regression model, comparing the pirfenidone group to the placebo group, and differences in survival over time will be assessed using the log-rank test. The results of this comparison will be displayed using Kaplan-Meier survival curves.

An independent safety committee will perform two interim analyses after recruitment of 33 % and 67 % of patients. Data evaluation at each interim analysis will be based on the alpha spending function concept, according to Lan and De Mets', and will employ O'Brien-Fleming *Z*-test boundaries, which are very conservative early in the trial [22]. For the first interim analysis the efficacy stopping rule would require an extremely low *P* value ($P < 0.00065$). For the second interim analysis $P < 0.016$ will be taken as efficacy stopping rule. Investigators will be kept blind to the interim analysis results. The independent safety committee will also perform conditional power analyses in order to evaluate potential interruption for futility issues in the trial.

Statistical significance will be set at $P < 0.05$ for all analyses.

Data will be analyzed by using Stata (Stata Statistical Software: version 18, College Station, TX, USA).

2.8. Handling of missing data

We will not perform missing data imputation for the primary or secondary outcomes in the main analysis. However, as a sensitivity analysis for the primary outcome, we will apply a conservative imputation strategy using the worst-case scenario. Specifically, for patients with missing VFD data, we will assign a VFD of 0, indicating no ventilator-free days or death.

2.9. Safety profile

The safety of Pirfenidone has been extensively evaluated in humans with IPF. Safety outcomes in the pooled population have been consistent with the known safety profile of pirfenidone. Gastrointestinal and skin-related events have been the most reported adverse events in the pirfenidone group and detailed in Supplementary eTable 6; these were typically mild to moderate in severity and rarely led to treatment discontinuation.

Patients with ARDS and admitted in the ICU will experience several abnormal laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard critical medicine therapies. For this reason, such events as listed in the CRF are "expected" to occur and will be considered "disease progression". These will not necessarily constitute an adverse event or serious adverse event unless they are related to study treatment or of concern in the principal investigator's clinical judgement.

2.10. Ethical considerations

The Investigators will conduct the study according to the procedures specified in the study protocol, and in accordance with Good Clinical Practice (GCP). The monitoring of the study will be performed according to international standards and GCP by an independent Contract Research Organization (CRO).

Due to pharmacological sedation necessary for mechanical ventilation, most patients will be unconscious at the time of trial enrollment and not able to provide informed consent. There are widely acknowledged ethical issues in enrolling unconscious patients in research trials,

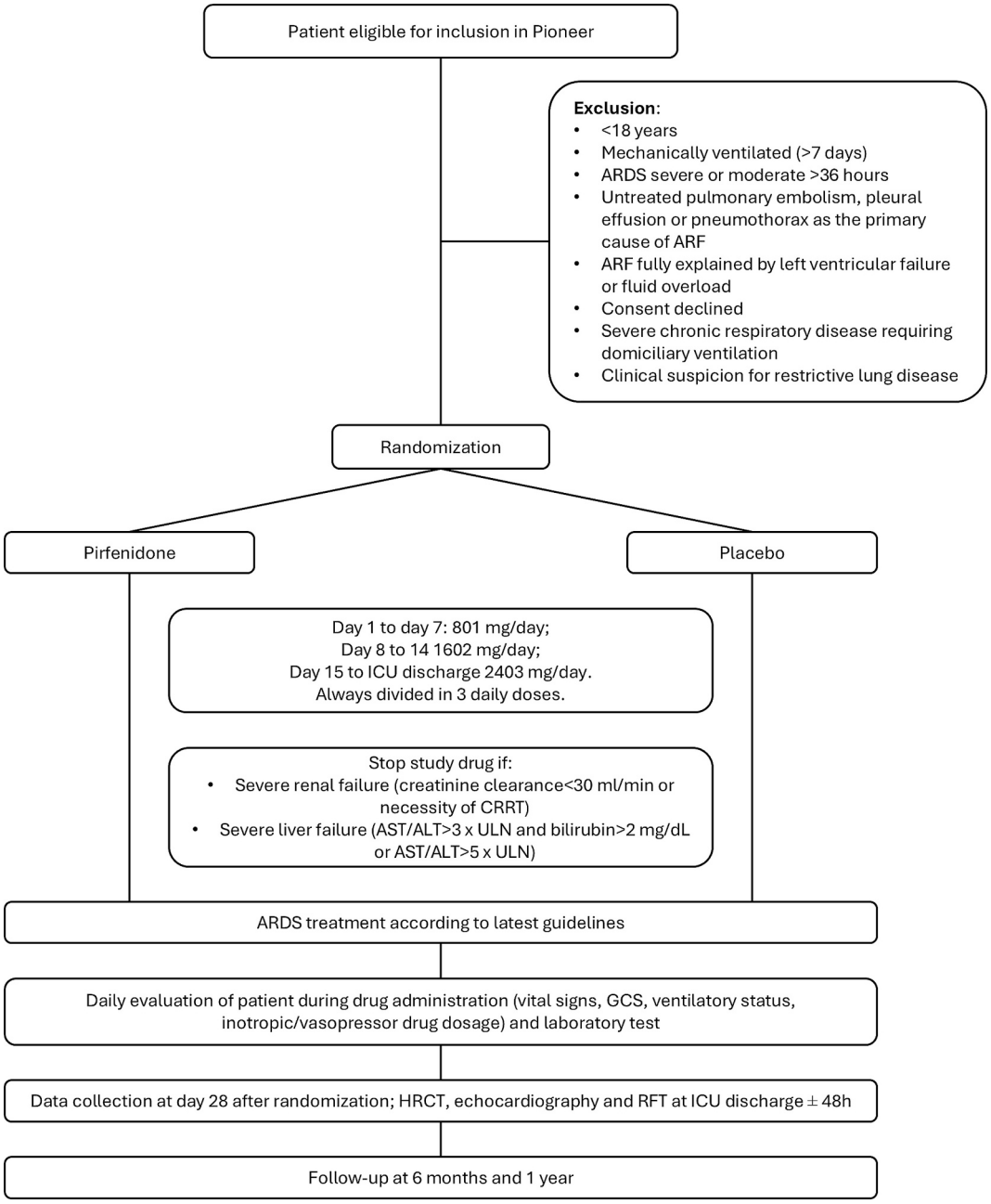

Fig. 1. PIONEER study flowchart.
Abbreviations: ARDS = acute respiratory distress syndrome; ARF = acute respiratory failure; CRRT = continuous renal replacement therapy; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit normal; GCS = Glasgow Coma Scale; HRCT = high resolution computed tomography; RFT = respiratory function test; ICU = intensive care unit.

particularly in intensive care unit (ICU) settings [23].

Thus, Ethical committee instructions and legal requirements in each center and jurisdiction will be followed. We expect that most patients will be enrolled with the "deferred consent" procedure (i.e. the consent to continue to participate to the study when the patient is awake and able to express it).

Table 2
Weaning strategies.

Patients will be considered ready for an unassisted breathing trial when they will meet all of the following criteria:

1. $SaO_2 \geq 90$ % whilst receiving $FiO_2 \leq 0.4$ and PEEP ≤ 10 cmH_2O for ≥ 6 continuous hours
2. Intact airway reflexes and low amount of sputum
3. An acceptable level of consciousness according to the treating clinical team whilst receiving low doses of or no sedative infusions
4. Considered otherwise clinically stable in the opinion of the treating clinical team (e.g. without significant vasopressor or inotropic drugs) and mechanical ventilator liberation is considered appropriate (e.g. there is no imminent procedure requiring ongoing mechanical ventilation)

Abbreviations: SaO_2 = arterial oxygen saturation; FiO_2 = inspiratory fraction of oxygen; PEEP = positive end expiratory pressure.

3. Discussion

ARDS is a syndrome with high mortality rates, representing approximately 10 % of ICU admissions and one in four patients requiring mechanical ventilation [21]. Optimal care for patients with ARDS has changed noticeably over recent years but treatment has not strongly focused on fibrosis occurrence and prevention, because of the absence of potentially effective agents.

Pirfenidone attenuates the fibroblast proliferation and the fibroblast differentiation into myofibroblasts and inhibits the expression of fibrogenic mediators, such as TGF-β, platelet-derived growth factor (PDGF) and IL-1β [24,25]. Furthermore, it can inhibit the production of ROS and pro-inflammatory cytokines [26] and has been associated with a relevant reduction in disease progression in three multinational phase-III trials in patients with IPF [27]. ARDS - induced fibrosis shares some similarities with IPF, but pirfenidone has never been studied in humans with ARDS.

In an experimental study by Li et al. [17], authors constructed a successful LPS-induced mouse model of ARDS that included phases of acute inflammatory injury and pulmonary fibrosis during the repair and re-modelling phase. The administration of pirfenidone significantly ameliorated acute lung injury and fibrosis by suppressing NLRP3 inflammasome activation. These data provide a degree of biological plausibility for the effect of pirfenidone in ARDS.

A potential limitation of our study is the exclusion of patients who initially presented with mild ARDS and progressed to a moderate-severe form after an even long duration of the mild phase. This methodological choice may have led to an underestimation of the antifibrotic activity of the drug in ARDS.

The PIONEER study aims to determine whether pirfenidone, compared to a placebo, can reduce the number of alive and ventilator-free days in ICU patients with ARDS. In addition, it will evaluate other clinical and functional secondary outcomes to assess treatment effectiveness. This trial is important because there is no effective method to prevent fibrosis in ARDS patients.

Trial status

The trial is ongoing, and 51 patients have been randomized in 6 centers.

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Table 3
Study procedures.

	Day 0 Day before randomization	Day 1 Randomization	Days from 2 to 28	ICU discharge	1 month follow up	6 months follow up	1 year follow up
Demographics	✓						
Anthropometry	✓						
Medical history	✓						
COVID-19 status	✓[f]						
Murray Score for ARDS	✓	✓					
SAPS II score	✓						
SOFA score	✓	✓	✓				
Laboratory data collected at baseline[a]	✓[f]						
Laboratory data collected daily[b]	✓	✓	✓				
Ventilatory parameters[c]	✓	✓	✓				
Vital signs[d]	✓	✓	✓				
Mortality		✓	✓	✓	✓	✓	✓
Drugs administered[e]	✓	✓	✓				
ICU-free days			✓[g]				
SOFA-free points			✓[g]				
Pulmonary function test	✓[f]			✓[f,h]			
Echocardiography	✓[f]			✓[h]			
CT scan	✓[f]			✓[h]			
BAL	✓[f]	✓[f]		✓[f,h]			
6MWT						✓[f]	✓[f]
Quality of life questionnaires						✓[f]	✓[f]

Abbreviations: ARDS = acute respiratory distress syndrome; SAPS II = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment; ICU = intensive care unit; CT = computed tomography; BAL = bronchoalveolar lavage; 6MWT = 6-min walking test.

[a] Complete blood count, serum electrolyte panel, albumin, total protein, prothrombin time, activated partial thromboplastin time, total bilirubin, pregnancy test, C-reactive protein, procalcitonin, creatine kinase, troponin, natriuretic peptide, lactate.

[b] Arterial blood gas sample, aspartate aminotransferase, alanine transaminase, creatinine.

[c] Fraction of inspired oxygen, positive end expiratory pressure, maximum pressure, respiratory rate, tidal volume.

[d] Heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, central venous pressure.

[e] Presence of vasopressors, steroids, muscle relaxant drug.

[f] If available.

[g] On day 28.

[h] ±48 h from ICU discharge.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2025.107883.

Data availability

No data was used for the research described in the article.

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