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Outcome of Acute Hypoxaemic Respiratory Failure. Insights from the Lung Safe Study

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Outcome of Acute Hypoxaemic Respiratory Failure. Insights from the Lung Safe Study

Tài Pham; Antonio Pesenti; Giacomo Bellani; Gordon Rubenfeld; Eddy Fan, Guillermo Bugedo; José Angel Lorente; Antero do Vale Fernandes; Frank Van Haren; Alejandro Bruhn; Fernando Rios; Andres Esteban, Luciano Gattinoni; Anders Larsson; Daniel F. McAuley; Marco Ranieri; B. Taylor Thompson; Hermann Wrigge; Laurent J. Brochard* and John G. Laffey* on behalf of the LUNG SAFE Investigators and the European Society of Intensive Care Medicine Trials Group

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Running head: Outcomes of hypoxaemic respiratory failure

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Abstract

Background: The current incidence and outcome of patients with acute hypoxaemic respiratory failure requiring mechanical ventilation in intensive care unit are unknown, especially for patients not meeting criteria for acute respiratory distress syndrome (ARDS).

Methods: An international, multicentre, prospective cohort study of patients presenting with hypoxemia early in the course of mechanical ventilation, conducted during four consecutive weeks in the winter of 2014 in 459 ICUs from 50 countries (LUNG SAFE). Patients were enrolled with $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg, new pulmonary infiltrates and need for mechanical ventilation with a positive end-expiratory pressure (PEEP) of at least 5 cm H_2O . ICU prevalence, causes of hypoxemia, hospital survival, factors associated with hospital mortality were measured. Patients with unilateral versus bilateral opacities were compared.

Findings: 12,906 critically ill patients received mechanical ventilation and 34.9% with hypoxaemia and new infiltrates were enrolled, separated into ARDS (69.0%), unilateral infiltrate (22.7%) and congestive heart failure (8.2%, CHF). The global hospital mortality was 38.6%. CHF patients had a mortality comparable to ARDS (44.1% vs. 40.4%). Patients with unilateral-infiltrate had lower unadjusted mortality but similar adjusted mortality than ARDS. The number of quadrants on chest imaging was associated with an increased risk of death. There was no difference in mortality comparing patients with unilateral-infiltrate and ARDS with only 2 quadrants involved.

Interpretation

More than one third of the patients receiving mechanical ventilation have hypoxaemia and new infiltrates with an hospital mortality of 38.6%. Survival is dependent on the degree of pulmonary involvement whether or not ARDS criteria are reached.

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248 words.

Trial registration

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3 ClinicalTrials.gov Identifier: NCT02010073
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5 Key words: cardiac insufficiency; pneumonia; aspiration;
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9 **Take Home Message**
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12 Patients with hypoxemic respiratory failure represent more than a third of patients
13 requiring mechanical ventilation and their mortality is close to 40%. Mortality is similar for
14 ARDS and for unilateral infiltrate when only two quadrants are involved on the chest X-Ray.
15 This could justify rediscussing the current definition of ARDS.
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Introduction

Acute hypoxaemic respiratory failure is a leading cause of admission and need for mechanical ventilation in Intensive Care Units (ICU). Studies have usually focused on patients meeting the criteria for Acute Respiratory Distress Syndrome (ARDS) [1–3]. There are limited data on hypoxaemic patients who do not fulfil the definition of ARDS [4–6]. A large prospective observational study in Sweden, Denmark, and Iceland, had examined patients with acute respiratory failure requiring mechanical ventilation regardless of the level of FiO_2 , and found more than 20 years ago a mortality rate around 40% with or without ARDS [5].

Hypoxaemic patients without ARDS, can have cardiac failure or fluid overload, or only unilateral infiltrates on chest imaging. These patients are excluded from epidemiological studies addressing ARDS and exploring this population is important. First, the definition of ARDS is subject to variations into clinicians' interpretations such as the relative contribution of heart failure or fluid overload [7], and/or the analysis of chest X-ray for the diagnosis of bilateral pulmonary infiltrates [8–10]. Previous studies have shown that bilateral involvement in community-acquired pneumonia is an independent risk factor for mortality [11, 12]. Understanding the differential impact of unilateral versus bilateral airspace disease is also important because they may overlap with ARDS. In addition it is essential to determine whether these patients can benefit from lung protective approaches like those used for patients with ARDS [13, 14]. Although the underlying biological mechanisms may differ across these different groups, the symptomatic management of the lungs, e.g., ventilator settings, sedation, proning, could be comparable. Therefore, understanding the behaviour of hypoxaemic 'non ARDS' ventilated patients might optimize the management strategy of these acutely hypoxaemic critically ill patients and may help to better understand the limits of the current ARDS definition.

The Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) is the most recent and largest international prospective cohort of hypoxaemic mechanically ventilated patients with new infiltrates [1]. In a pre-specified analysis, we set out to describe the global burden and compare the different sub-groups of hypoxaemic patients with new infiltrates: those who fulfil the criteria for the

Berlin definition of ARDS; patients whose failure was entirely explained by cardiac failure or fluid overload as declared by clinicians; and patients with unilateral infiltrate on the chest imaging.

MATERIALS AND METHODS

Study Design

LUNG SAFE (ClinicalTrials.gov identifier NCT02010073) was a prospective multicentre observational study conducted in 459 ICUs from 50 different countries. All participating ICUs obtained ethics committee approval and patient consent or ethics committee waiver of consent, depending on local regulations. National coordinators and site investigators were responsible for obtaining ethics committee approval and for ensuring data integrity and validity. Participating centres screened all newly admitted patients for four consecutive winter weeks (February-March 2014 in the Northern hemisphere, June-August 2014 in the Southern hemisphere). A total of 4,499 patients had acute hypoxaemic respiratory failure defined by a $\text{PaO}_2/\text{FIO}_2 \leq 300$ mmHg, new pulmonary infiltrates on chest imaging, and requirement of ventilator support with a positive end-expiratory pressure (PEEP) ≥ 5 cm H_2O . The number of quadrants involved (chest X-ray or CT scan) was reported by clinicians. The detailed methods and design of LUNG SAFE have been previously described [1]; some results of this study have been reported in abstract form [15].

Participants and definitions

Patients were divided into 3 groups:

- Acute Respiratory Distress Syndrome (ARDS): patients fulfilling the Berlin criteria for ARDS [4].
- Congestive Heart Failure (CHF): patients in whom respiratory failure was considered by clinicians to be fully explained by cardiac failure or fluid overload.
- Unilateral-infiltrate: patients fulfilling Berlin definition for ARDS criteria except that they presented with only unilateral infiltrates on chest imaging.

To ensure homogeneity in the analysis, we kept patients with early onset (first 48 hours post ICU admission) for meeting criteria, not treated with ECMO in the first 48h, and not admitted to another ICU for >2 days before being transferred to the participating ICU.

Statistical analyses

Continuous variables are reported as mean \pm SD or median (interquartile range [IQR]), and categorical variables as count and proportion. Comparisons of proportions were made using Chi-square and Fisher exact tests. Three groups were compared (unilateral-infiltrate, ARDS and CHF), and continuous variables were compared using ANOVA or Kruskal-Wallis test, as appropriate. We included geo-economic grouping in multivariable analyses, using the 2016 World Bank country classification [16]. When global comparisons were statistically significant, pairwise comparisons adjusting for multiple testing were performed using Tukey or Benjamini and Hochberg method.

Prognostic risk factors from previous literature and variables found to be associated in bivariate analysis with a P value ≤ 0.20 were entered in stepwise (forward and backward) multivariable logistic regression analyses with significance α levels of 0.05 or less for retention.

As basic analysis of chest imaging (quadrants involved) was an important focus, this component was introduced in mortality models using either: 1) considering bilateral opacities as a dichotomous variable; 2) considering the number of quadrants involved as an ordinal variable. To better examine the specific impact of bilateral versus unilateral opacities, mortality analyses were repeated restricting the population to patients having two quadrants involved whether they were unilateral (i.e. non-ARDS) or bilateral (i.e. ARDS).

Multicollinearity was evaluated with variance inflation factors for each variable and ruled out if the variance inflation factor was < 4 (relatively conservative). The results are shown as odds ratios with 95% C. Models' performance was assessed using the Hosmer–Lemeshow goodness-of-fit test statistic. We used a Kaplan–Meier analysis to estimate the likelihood of hospital mortality or invasive ventilation discontinuation within 90 days of onset of acute respiratory failure.

No statistical power calculation was conducted before the study, and sample size was based on available data. For all numerical variables, outliers were assessed and corrected by contacting site investigators if needed. The remaining outliers were plausible values that

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3 were kept in the analysis. No assumptions were made for missing data, and we followed the
4 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)
5 recommendations [17]. Statistical analyses were done with R (version 3.5.5, [http://cran.r-](http://cran.r-project.org)
6 [project.org](http://cran.r-project.org), accessed August 2019). All P values were two-sided, and values <0.05 were
7 deemed statistically significant. Data are presented unadjusted unless specifically stated.
8 We assumed that patients discharged alive from hospital before 90 days were alive on day
9 90.
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RESULTS

Prevalence and outcomes of hypoxaemic patients under Mechanical Ventilation

A total of 29,144 patients were admitted to participating ICUs during the LUNG SAFE study and 12,906 patients received mechanical ventilation. Among them, 4,499 patients (15.5% of the total admissions, and 34.9% of hypoxaemic patients requiring mechanical ventilation) fulfilled our criteria for hypoxaemia. The 4,499 patients with acute hypoxemia under mechanical ventilation represented 0.63 cases/ICU bed over 4 weeks.

N=3,834 (more than 85%) had data available in the two first days (Figure 1). Patients receiving NIV or under early ECMO are shown in Figure 1 but they were not included in the subsequent analysis. Most patients (N=3,176; 83%) received invasive ventilation comprising 2193 (69.0%) who fulfilled all the Berlin criteria for ARDS, 261 (8.2%) with CHF and 722 (22.7%) with only unilateral-infiltrate, of whom 143 (19.8% of the latter group) developed full ARDS criteria (bilateral images) later during their ICU stay. The global hospital mortality of these patients was 38.6%.

Patients with CHF

Patients with congestive heart failure were older, presented more frequent comorbidities such as diabetes, chronic renal failure or chronic cardiac failure (NYHA class 3 or 4), and less frequently chronic obstructive pulmonary disease (COPD) or immunocompromised status compared to patients with ARDS (Table 1 and e-Table 1). Many baseline characteristics were similar to patients with ARDS (SOFA score, arterial pH, PaO₂/FiO₂) but ventilatory parameters indicated lower PaCO₂, PEEP and peak inspiratory pressure (PIP) (Tables 1 and 2). They received higher tidal volumes, lower respiratory rates, and lower standardized minute ventilation (Table 2). Mortality was 44.1 %, not different from mortality of patients with ARDS (40.4%). Survivors from CHF had shorter durations of mechanical ventilation, length of stay in the ICU and in the hospital than ARDS (e-table 1).

Patients with unilateral-infiltrate

Characteristics

Compared to patients with ARDS, the 722 patients with unilateral-infiltrate had many similar characteristics. COPD was more frequent but other comorbidities did not differ

(Table 1 and e-Table 1). The three main risk factors for hypoxemia were similar in patients with unilateral-infiltrate and with ARDS, namely pneumonia, gastric aspiration and extrapulmonary sepsis. Aspiration was more frequent in patients in unilateral-infiltrate while pneumonia and extra-pulmonary sepsis rates were more prevalent in ARDS.

Patients with unilateral-infiltrate had lower baseline respiratory and systemic illness severity than patients with ARDS, lower SOFA and non-pulmonary SOFA scores, and higher arterial pH, PaO₂/FiO₂ ratio and lower PIP (Table 1). Plateau pressure (P_{plat}) and driving pressure (reported in only 31.1% of the patients), were lower in patients with unilateral-infiltrate than in ARDS (Table 2, e-table 1 and Figure 2).

Management

Patients with unilateral-infiltrate received higher tidal volumes but lower PEEP, FiO₂, respiratory rate and standardized minute ventilation than patients with ARDS (Table 2 and figure 2).

'Protective' ventilation, defined as receiving tidal volume lower than 8 mL/kg PBW and a plateau pressure lower than 30 cmH₂O (when available) was delivered at a similar rate in patients with unilateral-infiltrate and in patients with ARDS (63% vs 67%, P=0.250; e-Figure 1). The use of adjunctive therapies was low in the whole population but was higher in patients with ARDS than in unilateral-infiltrate patients (e-Table 2).

Unadjusted outcomes

Overall, unadjusted ICU and hospital mortality were lower in patients with unilateral-infiltrate than in patients with ARDS (26% vs. 35% and 35% vs. 40%) (Table 2, e-Table 1 and Figure 3, panel A) and patients with unilateral-infiltrate had more invasive-ventilation free days than patients with ARDS (Table 2). In an analysis confined to survivors, ICU stay was shorter in patients with unilateral-infiltrate than in patients with ARDS, but hospital length of stay was similar.

Impact of the number of quadrants involved (patients without CHF)

1) Risk factors for death in unilateral-infiltrate and ARDS

Comparison of survivors vs. non-survivors is shown in e-Table 3. Multi-variable analysis of the factors contributing to outcome in these patients with ARDS or unilateral-infiltrate adjusting on main confounders demonstrated that the presence of bilateral opacities on the chest imaging (i.e. ARDS) was an independent risk factor for death (e-Table

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3 4). A similar model adjusting on the same confounders using the number of quadrants
4 involved instead of the bilateral opacities characteristics showed that having 3 or 4 involved
5 quadrants was significantly associated with a higher risk of hospital mortality. Independent
6 risk factors for mortality also included age, immunocompromised status, chronic liver
7 failure, higher extra-pulmonary SOFA score, concomitant cardiac failure, medical indication
8 or trauma, and location in a middle-income country, higher respiratory rate and peak
9 inspiratory pressure and lower pH. Conversely, higher body mass index, higher PEEP, drug
10 overdose as the cause of respiratory failure were associated with better outcomes (e-Table
11 4). The multivariable analysis of factors associated with hospital mortality restricted to
12 patients with unilateral-infiltrate found similar results, although with less significant
13 variables (e-table 5).

23 2) *Patients with infiltrates in only two quadrants of chest X-ray*

24 Of 1094 patients with two quadrant infiltrates on CXR, 172 (16%) had unilateral
25 opacities (unilateral infiltrate), while 922 (84%) had bilateral opacities (ARDS) (Table 3).
26 Unilateral-infiltrate patients had more immunosuppression, gastric aspiration, contusions,
27 and less extra-pulmonary sepsis, but most of other patients' characteristics, gas exchange
28 variables and ventilator management were identical. The unadjusted mortality rates and
29 other outcomes were similar between groups (Figure 3, panel B). In a multivariable analysis
30 adjusting on the same covariates as the model performed for the whole population, the
31 presence of bilateral (vs. unilateral) opacities was not associated with mortality (e-Table 6).

32 3) *Development of ARDS in patients presenting initially with unilateral-infiltrate*

33 Of patients with unilateral-infiltrate on day 1 and 2, 143 (20%) subsequently
34 developed ARDS. Patients who developed bilateral infiltrates were more severely ill than
35 patients who never developed ARDS as evidenced by lower PaO₂/FIO₂ ratio in the first two
36 days; higher hemodynamic SOFA score; lower pH; and higher PIP. Patients who developed
37 ARDS had similar mortality rates but longer stays and duration of MV (e-Table 7). In
38 multivariable analyses adjusting for age, SOFA score, pH and PF ratio, only PIP was
39 associated with the evolution towards ARDS (e-Table 8).

40 Discussion

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3 The LUNG SAFE study shows that slightly more than a third of patients requiring
4 mechanical ventilation in the participating ICU have PaO₂/FIO₂ ratio ≤300 mmHg. Patients
5 with CHF receiving mechanical ventilation have a mortality rate comparable to patients with
6 ARDS. Patients with unilateral-infiltrate have lower severity of illness than patients with
7 ARDS and the extent of the infiltrates on the chest imaging is associated with mortality. The
8 outcome of patients with two quadrant involvement on the chest X-ray is similar whether
9 the distribution is bilateral (i.e. qualifying them for ARDS) or unilateral. Importantly, in
10 patients with unilateral infiltrate, peak pressure is the only independent risk factor for
11 developing ARDS.
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16 More than 15% of all admissions and more than one third of patients who received
17 ventilation in this large international observational study display hypoxaemia with new
18 infiltrates. They have a high mortality rate. This condition as a whole has an important
19 impact on health-care systems worldwide, larger than ARDS alone [1, 18, 19]. While the
20 subgroup with ARDS is well characterized and studied [1, 4], the population not fulfilling
21 ARDS criteria is under-appreciated as a clinical entity and incidence and outcomes have not
22 been often reported to date [5, 6, 20, 21]. The lack of consensual definition and the
23 heterogeneity of this group are potential explanations. In addition, ARDS is considered as an
24 archetypal condition in the critically ill and has dominated the research agenda [22–26].
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29 Few data are available for this category of patients. In a prospective study in
30 Sweden, Denmark, and Iceland Luhr et al examined the prevalence and 90-d mortality of
31 acute respiratory failure (ARF), defined as intubation and mechanical ventilation ≥ 24 h, as
32 well as acute lung injury (ALI) and ARDS based on American-European consensus definition
33 [5]. They did not use any oxygenation criteria for ARF, making comparisons difficult with our
34 data: they included 1231 ARF patients, 287 ALI and 221 ARDS. Ninety-day mortality was 41%
35 for all ARF, 42% for ALI and 41% for ARDS. The severity of illness and any chronic disease
36 (except COPD) was more important for mortality and outcome than the definitions of ARDS
37 if the patient was invasively ventilated more than 24 hours (defined as ARF). Vincent et al
38 reported the results of a substudy to validate the sequential organ failure assessment score
39 looking at patients having PaO₂/FiO₂ below 200 mmHg and mechanical ventilation.[6] They
40 reported a prevalence of 54% with an ICU mortality of 34%. In the present study the number
41 of quadrants seems to be a strong and noteworthy marker of severity of illness independent
42 of whether it is defined as ARDS. This was an unexpected finding given the low
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3 reproducibility of X-Ray imaging in intensive care [27]. The classification based on the
4 number of quadrants with alveolar consolidation is, however, ultra-simple and may have a
5 better reproducibility than more specific description of the type of infiltrates. This
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7 classification was one of the cardinal features of the Lung Injury Score, used for many years
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9 [28]. In our study, patients presenting with ARDS and unilateral-infiltrate had quite similar
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11 profiles.
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14 Comorbidities and main reasons for hypoxemia were comparable, although patients
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16 with aspiration were more frequent in unilateral injury. Patients with unilateral-infiltrate
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18 received slightly higher tidal volumes and lower PEEP than patients with ARDS. After
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20 adjustment, a similarly high mortality in patients with unilateral-infiltrate was observed
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22 compared to patients with ARDS and the same number of quadrants involved. This suggests
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24 that the extent of lung involvement is the predominant factor influencing outcome, rather
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26 than the bilateral characteristic. There was a stepwise increase in mortality when the
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28 number of quadrants involved raised from 2 to 4, and patients with 2 quadrants whether
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30 unilateral or bilateral had the same outcomes. Therefore, a very simple approach using
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32 quadrants confirmed previous findings (such as the general impact of unilateral vs bilateral
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34 on outcome) but also found an association between the number of quadrants and outcome,
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36 which has a biological rationale. The number of quadrants involved may grossly reflect the
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38 amount of non-aerated lung. The important point raised by our study, therefore, is not to
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40 emphasize the importance of the chest X ray, but at the opposite to suggest that it may be
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42 debatable to continue keeping the actual current definition of the need for bilateral
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44 infiltrates for defining ARDS.

45 Regarding the ARDS definition, our data confirm that patients with unilateral-
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47 infiltrate are not fundamentally different in terms of poor outcome from patients with ARDS
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49 [5]. They also have similar underlying risk factors, comorbidity profiles, are managed
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51 similarly. Importantly peak pressure was the only risk factor for developing secondary ARDS
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53 in patients with unilateral infiltrate. This reinforces the need for a protective ventilation in
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55 these patients. The need of subdividing these patients into ARDS and unilateral-infiltrate, at
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57 least based on the current clinical criteria, can be rediscussed depending on what is studied.
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59 Given the lack of knowledge regarding this condition, unilateral patients might be enrolled
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to understand if similar management approaches should be used. The pathophysiology or

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3 biological mechanisms differ but the management may not be so different regarding, for
4 instance, the ventilation of a baby lung. High PIP was the main risk factor for developing
5 ARDS in patients with unilateral-infiltrate. The poor outcomes of this population justify
6 further research.
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10 Physiological studies looking at unilateral versus bilateral injury are needed to
11 understand the impact of ventilator settings. For instance, the respective effects of PEEP or
12 large tidal volumes in the presence of asymmetrical injury is an important question to
13 address. Our data suggest that the same ventilator parameters seem to influence outcome
14 in unilateral or bilateral lung injury. The failure of current clinical criteria to meaningfully
15 subgroup hypoxaemic patients underlines the need to explore alternative classification
16 approaches, including phenotyping based on biologic/immunologic profiles [29, 30], if
17 specific treatments can be applied according to these phenotypes [31]. In our study the
18 basic clinical, though likely imperfect, classification of the number of quadrants involved had
19 a strong prognostic value. Reexamining the impact of the number of quadrants may help to
20 determine whether this parameter could be included as a severity criterion in the ARDS
21 definition or for a definition including all hypoxaemic patients.
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32 Patients with CHF receive a different therapeutic management approach compared
33 to other types of respiratory failure. Although data are scarce, mechanical ventilation has
34 always been associated with a poor prognosis [32, 33]. CHF patients had a shorter duration
35 of support but had a similar mortality than patients with ARDS, again in line with Luhr et al
36 [5]. One study compared outcomes of patients with cardiogenic pulmonary oedema to
37 patients with ARDS [34]. In this retrospective study, authors found a 4 fold-increased risk of
38 hospital mortality for patients with ARDS as compared to patients with cardiogenic
39 pulmonary oedema but definitions differed from ours (limited to need for mechanical
40 ventilation and a PEEP of ≥ 5). This population of patients with cardiac failure may need
41 more specific research attention. One could question the accuracy of the clinical
42 classification of CHF by investigators in Lung SAFE. Differentiating ARDS from pure cardiac
43 failure can be challenging [7, 35, 36] especially since the Berlin definition clearly states that
44 patients could present with ARDS and concomitant heart failure [4] Patients were classified
45 as CHF in the present study when hypoxemia was fully explained by cardiac failure or fluid
46 overload per the treating clinician. This analysis reflects clinical practice and the way
47 patients are enrolled in or excluded from clinical trials.
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3 Our study has the limitations of an observational design with the risk of unmeasured
4 confounding factors. Regarding quality of data collection, all numerical variables were
5 checked, outliers were detected and queries to confirm their values were sent to
6 investigators. This ensured quality of our dataset and explains the low number of missing
7 data, mostly reflecting lack of clinicians' monitoring of certain variables (e.g., plateau
8 pressure). Both the results of chest X rays and CT scans were used by clinicians for the
9 diagnosis of ARDS and the number of quadrants but the images were not systematically
10 validated or reviewed by independent radiologists. For performing the Kaplan Meier curves
11 we considered hospital discharge equal to outcome at 90 days, which is a simplification.
12 Some epidemiological data suggest that hospital outcome and 90-day mortality are very
13 similar for this population. Patients classified in the CHF group were patients for which the
14 clinicians considered that the respiratory failure was fully explained by cardiac failure or
15 fluid overload. Patients with respiratory infection and concomitant fluid overload were
16 considered in the ARDS or the unilateral-infiltrate groups. It is known that chest X ray
17 appearance can worsen after fluid administration. We do not have this granularity of
18 information as this is the case in all trials in ARDS. In general, we don't have systematic
19 validation of the chest X-Ray by independent radiologists.
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37 Conclusion

38 Mechanically ventilated patients with hypoxaemia and new infiltrate represent a
39 high global burden of illness, affecting one third of the patients receiving ventilation in the
40 ICU with a mortality close to 40%. Patients with unilateral-infiltrate have a high mortality
41 comparable to patients with ARDS of similar severity. Regarding outcome, the global extent
42 of lung involvement seems more important than the unilateral vs. bilateral distribution of
43 the lung opacities. These findings emphasize the need for greater attention to patients with
44 unilateral-infiltrate in future studies.
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Collaborators= Lung Safe investigators

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Table 1: Baseline and outcomes of all patients and separated by population category

	ARDS N= 2193	CHF N= 261	Unilateral- Infiltrate N= 722	Overall P value	N
Age, y	61.0±16.8	68.1±13.5*	62.1±17.2	<0.001	3176
Female gender, n(%)	821 (37.4%)	108 (41.4%)	254 (35.2%)	0.056	3012
Weight, kg	77.6±24.0	74.9±17.4	75.8±18.6	0.056	3012
BMI, kg/m ²	27.3±8.6	26.9±5.8	26.5±6.2	0.061	2938
Illness Severity Indices					
SOFA Score	10.0 [7.0;13.0]	10.0 [8.0;12.0]	9.0 [6.0;12.0]*	<0.001	3161
Non-pulmonary SOFA score	6.7 [4.0;10.0]	7.0 [5.0;9.0]	6.0 [3.8;9.0]*	<0.001	3139
CXR quadrants involved				<0.001	2991
1	0 (0.0%)	34 (14.9%)	429 (71.4%)		
2	922 (42.6%)	72 (31.6%)	172 (28.6%)		
3	507 (23.5%)	33 (14.5%)	0 (0.0%)		
4	733 (33.9%)	89 (39.0%)	0 (0.0%)		
Bilateral opacities	2193 (100.0%)	187 (74.8%)*	0 (0.0%)	<0.001	3165
PaCO ₂ , mmHg	45.9±14.9	42.8±14.3*	44.8±15.2*	0.003	3133
pH	7.32±0.12	7.33±0.13	7.34±0.12*	<0.001	3133
PaO ₂ /FiO ₂ , mmHg	161.0±67.9	170.8±67.4	190.0±63.8*	<0.001	3159
Worst PaO ₂ /FiO ₂ in the first 2 days, mmHg	153.2±66.1	159.0±64.3	178.7±62.8*	<0.001	3170
Initial Severity, n(%)		*	*	<0.001	3169
Mild	663 (30.2%)	87 (34.3%)	330 (45.7%)		
Moderate	1024 (46.7%)	120 (47.2%)	313 (43.4%)		
Severe	506 (23.1%)	47 (18.5%)	79 (10.9%)		
Comorbidities, n(%)					
Diabetes	482 (22.0%)	79 (30.3%)*	158 (21.9%)	0.009	3176
COPD	448 (20.4%)	38 (14.6%)*	179 (24.8%)*	0.001	3176
Chronic Renal Failure	210 (9.6%)	51 (19.5%)*	68 (9.4%)	<0.001	3176
Immunosuppression	455 (20.7%)	16 (6.1%)*	133 (18.4%)	<0.001	3176
Chronic Cardiac Failure	211 (9.6%)	106 (40.6%)*	71 (9.8%)	<0.001	3176
Chronic Liver Failure	96 (4.4%)	5 (1.9%)	28 (3.9%)	0.157	3176
At least 1 comorbidity	1287 (58.7%)	181 (69.3%)*	425 (58.9%)	0.004	3176
“Cause of hypoxaemia” (more than 1 cause is possible), n(%)					
Pneumonia	1478 (67.4%)	17 (6.5%)*	453 (62.7%)*	<0.001	3176
Non pulmonary Sepsis	384 (17.5%)	11 (4.2%)*	103 (14.3%)*	<0.001	3176
Gastric aspiration	357 (16.3%)	22 (8.4%)*	149 (20.6%)*	<0.001	3176
Trauma	103 (4.7%)	3 (1.1%)*	47 (6.5%)	0.002	3176
Pancreatitis	47 (2.1%)	0 (0.0%)*	10 (1.4%)	0.013	3176
Pulmonary contusion	74 (3.4%)	3 (1.1%)	34 (4.7%)	0.023	3176
Pulmonary Vasculitis	29 (1.3%)	1 (0.4%)	6 (0.8%)	0.356	3176

Non cardiogenic Shock	184 (8.4%)	6 (2.3%)*	46 (6.4%)	0.001	3176
Overdose	45 (2.1%)	0 (0.0%)*	21 (2.9%)	0.018	3176
TRALI	98 (4.5%)	11 (4.2%)	24 (3.3%)	0.412	3176
CHF	326 (14.9%)	261 (100.0%)*	75 (10.4%)*	<0.001	3176
COPD	218 (9.9%)	0 (0.0%)*	103 (14.3%)*	<0.001	3176
Asthma	30 (1.4%)	0 (0.0%)	11 (1.5%)	0.101	3176
No Cause identified	94 (4.3%)	0 (0.0%)*	34 (4.7%)	0.002	3176

*:P<0.005 vs ARDS

Table 2: Ventilatory Management and Outcomes by population category

	ARDS patients N=2193	CHF N=261	Unilateral- Infiltrate N=722	P value	N
Ventilation Management					
VT, ml/kg PBW	7.7±1.8	8.3±1.8*	7.9±1.9*	<0.001	3009
RR, b/min	20.8±8.7	18.9±5.6*	19.1±5.5*	<0.001	3155
PEEP, cmH2O	8.0 [5.0;10.0]	6.0 [5.0;8.0]*	6.0 [5.0;8.0]*	<0.001	3159
FiO2	0.6 [0.4;0.8]	0.6 [0.4;0.9]	0.5 [0.4;0.6]*	<0.001	3161
Plateau pressure, cmH2O	23.3±6.1	21.8±5.8	20.1±5.2*	<0.001	1002
Driving pressure, cmH2O	14.9±5.6	14.0±5.4	13.1±4.9*	<0.001	999
PIP, cmH2O	26.9±8.2	24.7±8.2*	24.8±8.0*	<0.001	3041
Minute ventilation (standardized), L/min	10.87±4.77	9.95±4.49*	10.20±4.41*	<0.001	3103
Outcomes					
Duration of invasive MV	8.0 [4;15]	4 [2;9]*	6 [3;12]*	<0.001	3003
- in hospital survivors, days	8.0 [4;14]	4.0 [3;10]*	6 [3;12]*	<0.001	1784
VFD, days	11.0 [0;20]	16 [0;24]	18 [0;24]*	<0.001	3003
ICU Length of Stay	10 [5;19]	6 [3;12]*	9 [5;16]*	<0.001	3176
- in ICU survivors, d	11 [6;20]	7 [4;13] *	9 [5;17]*	<0.001	2116
Hospital Length of Stay	17 [8;32]	12 [5;24]*	17 [9;30]*	<0.001	3108
- in hospital survivors, days	23 [13;40]	19 [11;31] *	21 [13;36]*	0.008	1882
ICU mortality, n(%)	774 (35.3%)	98 (37.5%)*	188 (26.0%)*	<0.001	3176
Hospital mortality, n (%)	882 (40.4%)	115 (44.1%)*	229 (31.8%)*	<0.001	3165

PBW : predicted body weight

Table 3: Demographics, illness severity, management and outcomes of patients with unilateral infiltrate and with ARDS with 2 CXR quadrants involved

	Unilateral-infiltrate with 2 quadrants N=172	Bilateral with 2 quadrants(ARDS) N=922	p-value	N
Age, y	61.2±18.0	62.3±16.6	0.452	1094
Female gender, n(%)	63 (36.6%)	356 (38.6%)	0.685	1094
Weight, kg	75.1±20.8	78.2±26.8	0.104	1032
BMI, kg/m ²	25.9±6.5	27.6±10.2	0.008	1008
SOFA	9.6 [7.0;12.0]	9.8 [7.0;12.0]	0.249	1094
Comorbidities, n(%)				
Diabetes	40 (23.3%)	210 (22.8%)	0.969	1094
COPD	36 (20.9%)	201 (21.8%)	0.878	1094
Chronic Renal Failure	15 (8.7%)	96 (10.4%)	0.591	1094
Immunosuppression	43 (25.0%)	157 (17.0%)	0.018	1094
Chronic Cardiac Failure	16 (9.3%)	91 (9.9%)	0.928	1094
Chronic Liver Failure	4 (2.3%)	34 (3.7%)	0.504	1094
At least 1 comorbidity	103 (59.9%)	536 (58.1%)	0.732	1094
“Cause of hypoxaemia” (more than 1 cause is possible), n(%)				
Pneumonia	118 (68.6%)	584 (63.3%)	0.217	1094
Non pulmonary Sepsis	21 (12.2%)	177 (19.2%)	0.038	1094
Gastric aspiration	43 (25.0%)	147 (15.9%)	0.006	1094
Trauma	13 (7.6%)	57 (6.2%)	0.612	1094
Pancreatitis	0 (0.0%)	22 (2.4%)	0.036	1094
Pulmonary contusion	16 (9.3%)	40 (4.3%)	0.012	1094
Oxygenation and Ventilation				
PaO ₂ /FiO ₂ , mmHg	185±63	178±66	0.196	1094
Mild	56 (32.6%)	318 (34.5%)	0.509	1094
Moderate	91 (52.9%)	446 (48.4%)		
Severe	25 (14.5%)	158 (17.1%)		
PaCO ₂ , mmHg	46±15	44±13	0.134	1084
pH	7.33±0.12	7.34±0.11	0.148	1084
FiO ₂	0.5 [0.4;0.8]	0.5 [0.4;0.7]	0.247	1094
Vt, ml/kg PBW	7.6±1.8	7.8±1.7	0.153	1046
RR, b/min	20±6	20±6	0.444	1091
Minute ventilation, L/min	10.33±4.50	10.31±4.62	0.942	1071
PEEP, cmH ₂ O	6.0 [5.0;10.0]	8.0 [5.0;10.0]	0.101	1094
Plateau pressure (n=336), cmH ₂ O	20.8±5.8	21.8±5.4	0.238	336
Driving pressure (n=336), cmH ₂ O	13.1±5.9	14.1±4.9	0.282	336
PIP (n= 1056) , cmH ₂ O	25.9±8.2	25.7±8.0	0.847	1056
Outcomes				
Duration of invasive MV	7 [3;12]	7 [4;14]	0.281	1036
- in hospital survivors, dyas	7 [4;13]	7 [4;14]	0.844	652
VFD28, days	16 [0;23]	15 [0;23]	0.581	1036

ICU LOS	9 [5;16]	10 [5;19]	0.291	1094
- in ICU survivors, days	10 [6;16]	11 [6;20]	0.402	766
Hospital LOS				
- in hospital survivors, days	17 [10;35]	17 [9;33]	0.866	1070
ICU mortality, n(%)	48 (27.9%)	280 (30.4%)	0.578	1094
Hospital mortality, n(%)	58 (33.9%)	328 (35.7%)	0.720	1090

PBW : predicted body weight

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Figure legends

Figure 1: Flowchart of the patients screened and included in the analysis

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; CHF: Congestive Heart Failure; ECMO: ExtraCorporeal Membrane Oxygenation; NIV: Noninvasive Ventilation

Figure 2: Boxplots of respiratory parameters at day 1 according to the population category (Unilateral-infiltrate in blue vs. ARDS in black). P-values are results of Student test comparisons. Outliers appear as dots.

Panel A, B, C: Tidal Volume, PEEP, Peak pressure. Panel D, E: Plateau Pressure and Driving pressure. Data are available for 912 patients (31.2% of the patients). Panel F, G, H:

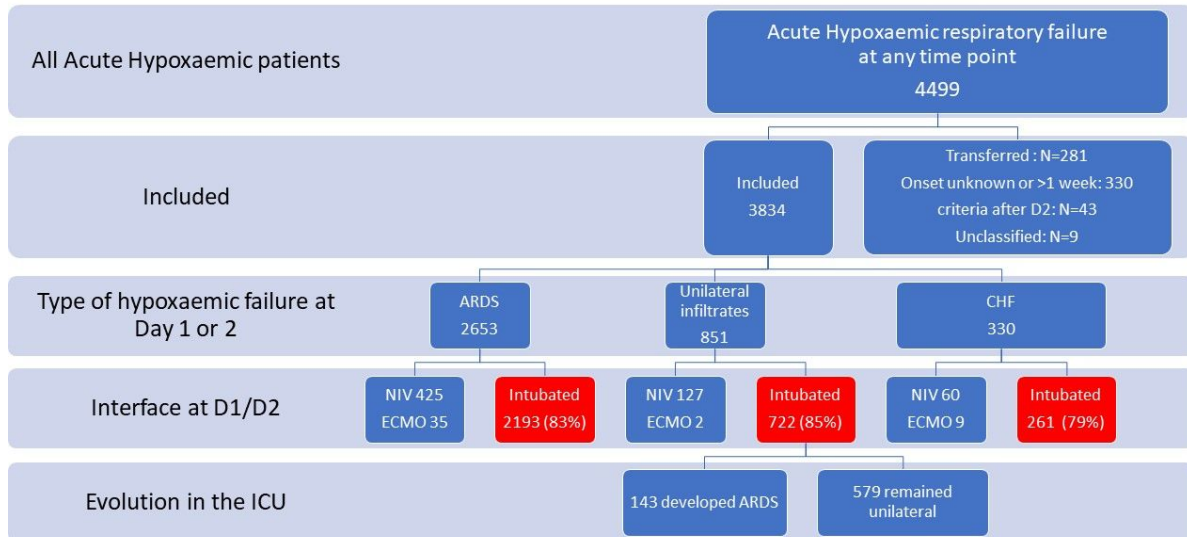
Respiratory Rate, standardized minute ventilation, FiO₂.

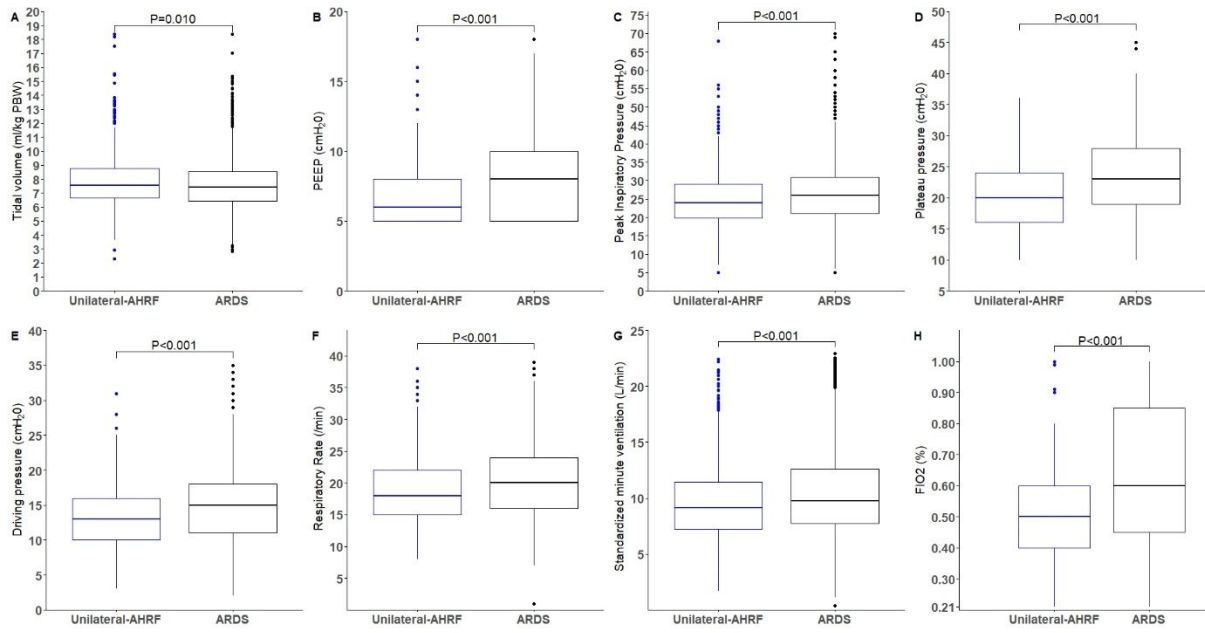
Abbreviations: ARDS: Acute Respiratory Distress Syndrome; mL/kg PBW: millilitre per kilogram of predicted body weight; Pplat: plateau pressure

Figure 3A: Probability of discontinuing mechanical ventilation and of hospital survival in patients with unilateral-infiltrate (Blue) vs ARDS (Black). Solid lines represent the probability of hospital survival and dotted lines, the probability of mechanical ventilation discontinuation. P-values are the results of log-rank tests.

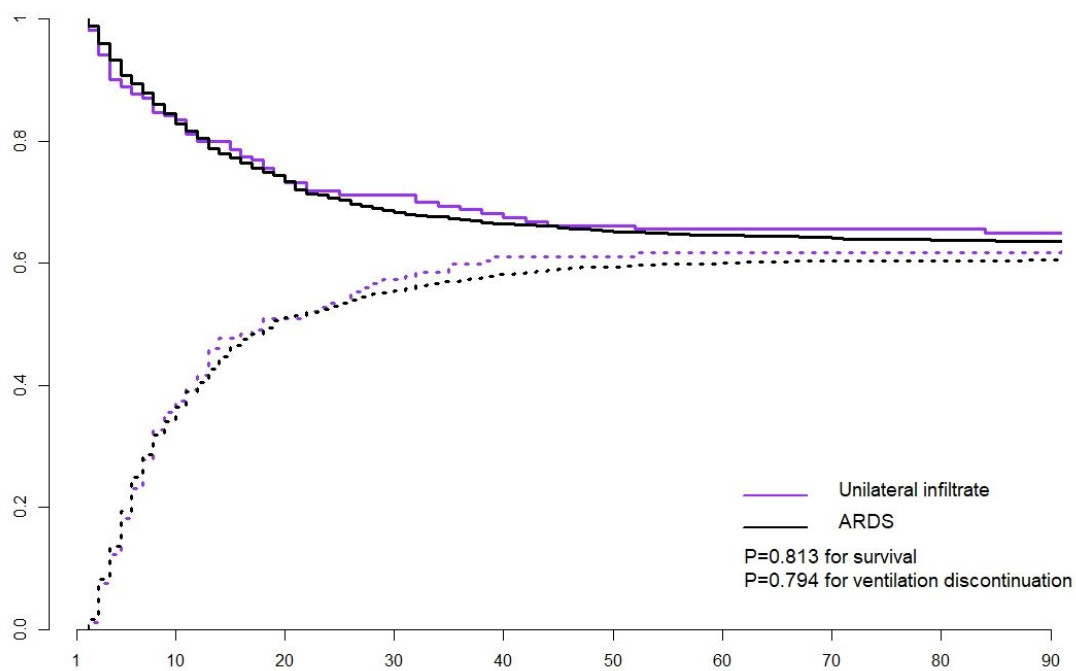
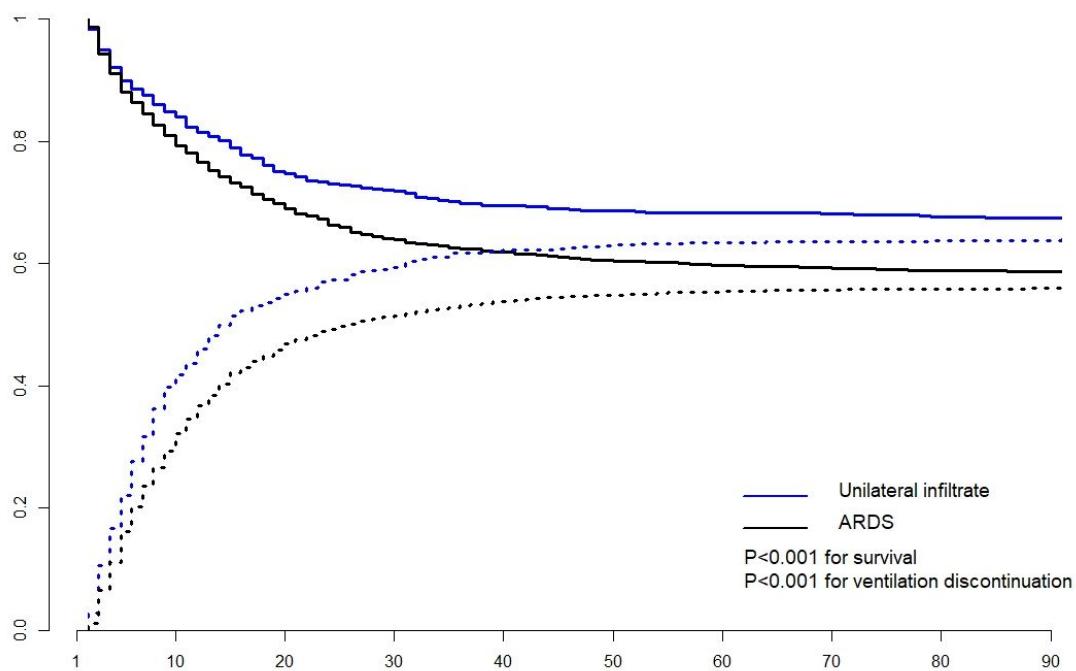
Figure 3B: Probability of discontinuing mechanical ventilation and of hospital survival in patients with 2 quadrants and unilateral-infiltrate (Blue) vs 2 quadrants and ARDS (Black). Solid lines represent the probability of hospital survival and dotted lines, the probability of mechanical ventilation

Figure 1: Flow of patients



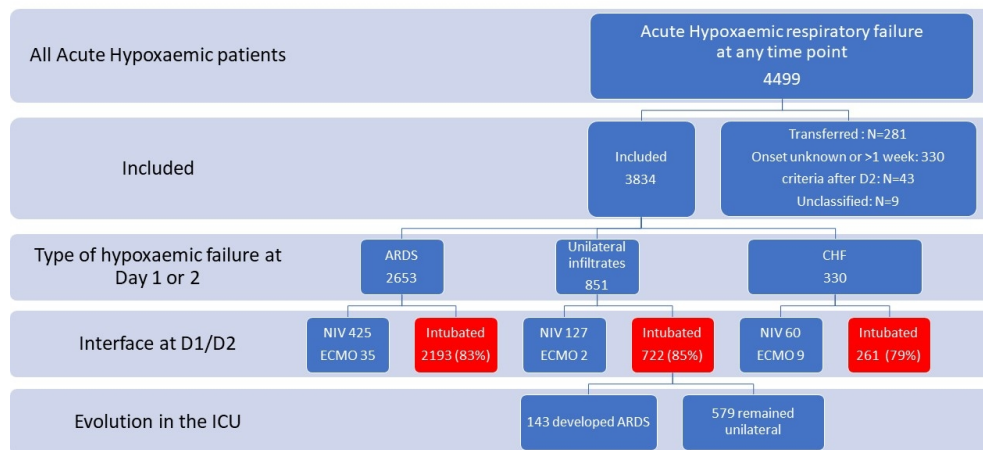


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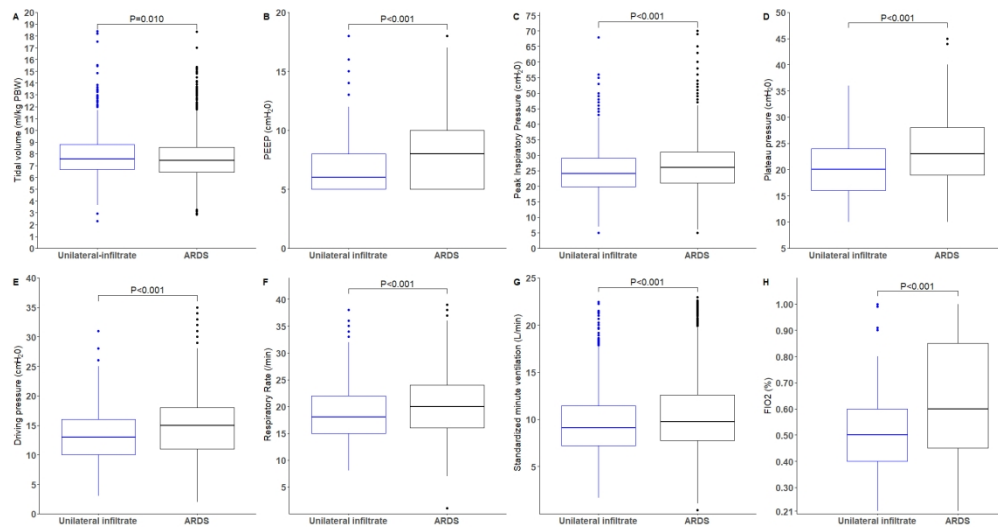
Figure 1: Flow of patients



Flowchart of the patients screened and included in the analysis

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; CHF: Congestive Heart Failure; ECMO: ExtraCorporeal Membrane Oxygenation; NIV: Noninvasive Ventilation

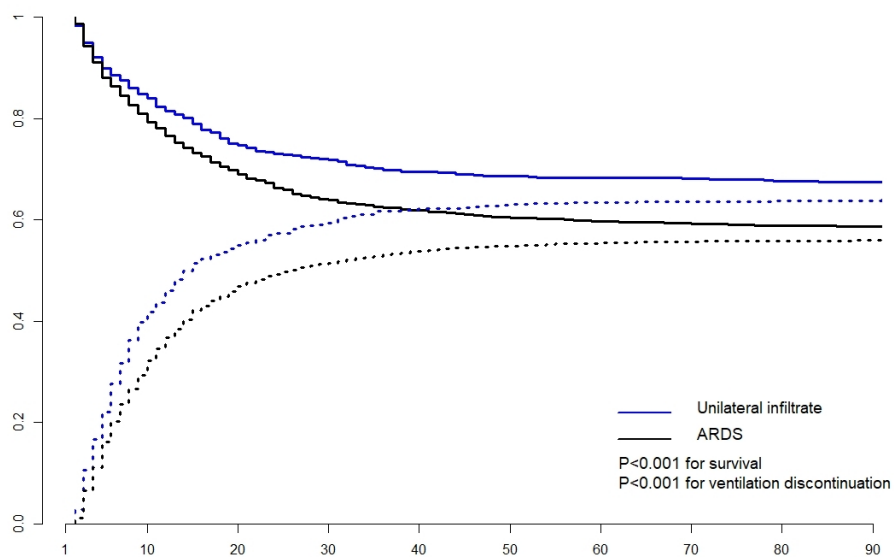
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Boxplots of respiratory parameters at day 1 according to the population category (Unilateral-infiltrate in blue vs. ARDS in black). P-values are results of Student test comparisons. Outliers appear as dots.

Panel A, B, C: Tidal Volume, PEEP, Peak pressure. Panel D, E: Plateau Pressure and Driving pressure. Data are available for 912 patients (31.2% of the patients). Panel F, G, H: Respiratory Rate, standardized minute ventilation, FiO₂.

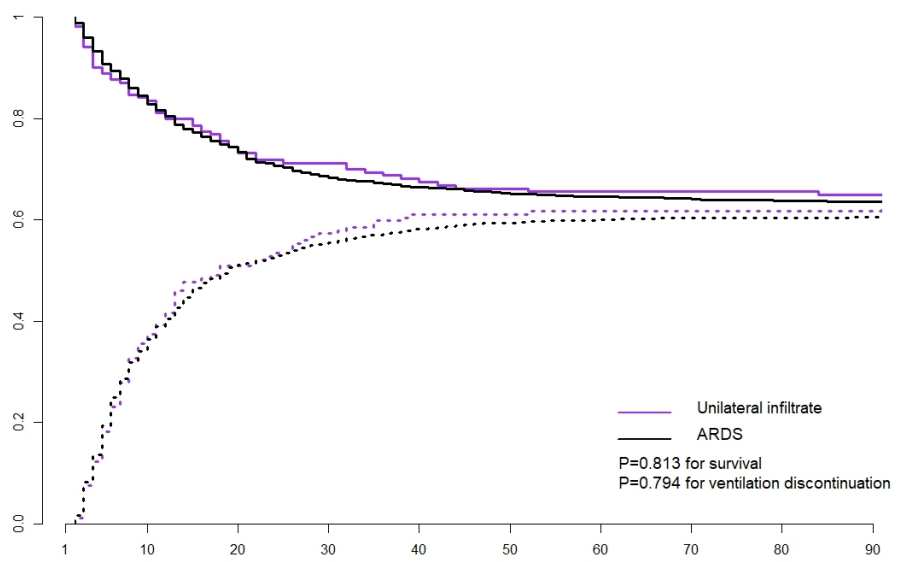
Abbreviations: ARDS: Acute Respiratory Distress Syndrome; mL/kg PBW: millilitre per kilogram of predicted body weight; Pplat: plateau pressure



Probability of discontinuing mechanical ventilation and of hospital survival in patients with unilateral-infiltrate (Blue) vs ARDS (Black). Solid lines represent the probability of hospital survival and dotted lines, the probability of mechanical ventilation discontinuation. P-values are the results of log-rank tests.

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Probability of discontinuing mechanical ventilation and of hospital survival in patients with 2 quadrants and unilateral-infiltrate (Blue) vs 2 quadrants and ARDS (Black). Solid lines represent the probability of hospital survival and dotted lines, the probability of mechanical ventilation

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Outcome of Unilateral and Bilateral Hypoxaemic Respiratory Failure. Insights from the Lung Safe Study

Online supplement

e-Table 1 : global and adjusted p-values for pairwise comparisons.....	2
e-Table 2: Use of adjunct treatments in the 3 groups.....	4
e-Table 3: Characteristics of survivors vs non-survivors.....	5
e-Table 4: multivariable analyses of factors associated with hospital death in patients with unilateral infiltrate or ARDS	7
e-Table 5: Multivariable analysis of variables associated with hospital mortality in patients with unilateral-infiltrate..	8
e-Table 6: Multivariable analysis of variables associated with hospital mortality in unilateral infiltrate patients with 2 quadrants involved.....	9
e-Table 7: Baseline and outcomes of unilateral infiltrate patients according to their evolution.....	10
e-Table 8: Multivariable analysis of factors associated with evolution to ARDS in patients with initial unilateral infiltrate.....	11
e-Figure 1: Distribution of tidal volume vs plateau pressure on day 1 in patients with unilateral infiltrate or with ARDS	12

e-Table 1 : global and adjusted p-values for pairwise comparisons

	Global p-value	ARDS vs CHF	unilateral infiltrate vs ARDS
Age	<0.001	<0.001	0.277
Female gender	0.056	0.296	0.296
BMI	0.061	0.736	0.051
Illness Severity Indices			
SOFA Score	<0.001	0.376	<0.001
Non-pulmonary SOFA score	<0.001	0.146	0.001
Number of CXR quadrants	<0.001	<0.001	0.000
Bilateral opacities	<0.001	<0.001	0.000
PaCO ₂	0.003	0.005	0.165
pH	<0.001	0.657	<0.001
PaO ₂ /FiO ₂	<0.001	0.069	0.000
Worst PF in the 2 first days	<0.001	0.374	0.000
Initial Severity	<0.001	0.190	<0.001
Comorbidities			
Diabetes	0.009	0.010	0.999
COPD	0.001	0.030	0.023
Chronic Renal Failure	<0.001	<0.001	0.958
Immunosuppression	<0.001	<0.001	0.194
Chronic Cardiac Failure	<0.001	<0.001	0.924
Chronic Liver Failure	0.157	0.252	0.638
At least 1 comorbidity	0.004	0.003	0.968
"Cause of hypoxemia"			
Pneumonia	<0.001	<0.001	0.025
Non pulmonary Sepsis	<0.001	<0.001	0.049
Gastric aspiration	<0.001	0.002	0.009
Trauma	0.002	0.018	0.069
Pancreatitis	0.013	0.023	0.262
Pulmonary contusion	0.023	0.117	0.125
Pulmonary Vasculitis	0.356	0.589	0.589

1	Non cardiogenic Shock	0.001	0.002	0.096
2	Overdose	0.018	0.018	0.231
3				
4	TRALI	0.412	0.976	0.662
5				
6	CHF	<0.001	<0.001	0.003
7				
8	COPD	<0.001	0.101	0.900
9				
10	Asthma	0.101	<0.001	<0.001
11				
12				
13	No Cause identified	0.002	0.002	0.707
14				
15	Ventilation Management			
16	VT	<0.001	<0.001	0.010
17				
18	RR	<0.001	0.001	<0.001
19				
20	PEEP	<0.001	<0.001	<0.001
21				
22	FiO2	<0.001	0.668	<0.001
23				
24	Plateau pressure	<0.001	0.061	<0.001
25				
26	Driving pressure	<0.001	0.367	<0.001
27				
28	PIP	<0.001	<0.001	<0.001
29				
30	Minute ventilation	<0.001	0.008	0.002
31				
32	Outcomes			
33	Duration of invasive MV	<0.001	<0.001	<0.001
34				
35	VFD	<0.001	0.064	<0.001
36				
37	ICU Length of Stay	<0.001	<0.001	0.007
38				
39	Hospital Length of Stay	<0.001	<0.001	0.902
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41	ICU mortality	<0.001	0.515	<0.001
42				
43	Hospital mortality	<0.001	0.282	<0.001
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e-Table 2: Use of adjunct treatments in the 3 groups

Var	ALL N=3176	unilateral infiltrate N=722	ARDS N=2193	CHF N=261	Global p-value	p-value unilat vs ARDS	p-value unilat vs CHF	p-value unilat vs CHF	N
Prone	186 (5.9%)	16 (2.2%)	167 (7.6%)	3 (1.1%)	<0.001	<0.001	0.418	<0.001	3176
ECMO	18 (0.6%)	0 (0.0%)	17 (0.8%)	1 (0.4%)	0.026	0.032	0.398	0.713	3176
NMBA	575 (18.1%)	87 (12.0%)	457 (20.8%)	31 (11.9%)	<0.001	<0.001	1.000	0.001	3176
Recruitment Maneuver	575 (18.1%)	90 (12.5%)	455 (20.7%)	30 (11.5%)	<0.001	<0.001	0.764	0.001	3176
Inhaled VD	191 (6.0%)	25 (3.5%)	152 (6.9%)	14 (5.4%)	0.003	0.003	0.367	0.411	3176
HFO	27 (0.9%)	2 (0.3%)	25 (1.1%)	0 (0.0%)	0.022	0.153	1.000	0.153	3176
Any Rescue treatment	1079 (34.0%)	178 (24.7%)	835 (38.1%)	66 (25.3%)	<0.001	<0.001	0.905	<0.001	3176

e-Table 3: Characteristics of survivors vs non-survivors

	ALL N=2904	Survivors N=1793	Deceased N=1111	p-value	N
Age	61±7	59±17	65±17	<0.001	2904
Female gender	1069 (37%)	656 (37%)	413 (37%)	0.780	2904
Weight	77.2±22.8	78.9±24.9	74.5±18.5	<0.001	2758
BMI	27.1±8.1	27.6±9.0	26.5±6.3	<0.001	2691
Illness Severity Indices					
SOFA Score	9.6 [7.0;12.0]	9.0 [6.0;12.0]	11.0 [8.0;14.0]	<0.001	2893
Non-pulmonary SOFA score	6.2 [4.0;9.0]	6.0 [3.8;8.0]	8.0 [5.0;11.0]	<0.001	2872
CXR quadrants involved				<0.001	2752
1	428 (16%)	300 (18%)	128 (12%)		
2	1090 (40%)	704 (42%)	386 (36%)		
3	505 (18%)	289 (17%)	216 (20%)		
4	729 (27%)	399 (24%)	330 (31%)		
Bilateral opacities	2184 (75%)	1302 (73%)	882 (79%)	<0.001	2904
PaCO ₂	46±15	46±14	46±16	0.980	2867
pH	7.33±0.12	7.35±0.11	7.30±0.14	<0.001	2867
PaO ₂ /FiO ₂	168±68	173±68	160±68	<0.001	2893
Initial Severity				<0.001	2904
Mild	988 (34.0)	663 (37%)	325 (29%)		
Moderate	1334 (46%)	817 (46%)	517 (47%)		
Severe	582 (20%)	313 (18%)	269 (24%)		
Comorbidities					
Diabetes	635 (22%)	372 (21%)	263 (24%)	0.071	2904
COPD	623 (22%)	385 (22%)	238 (21%)	1.000	2904
Chronic Renal Failure	277 (9.5%)	152 (8.5%)	125 (11%)	0.016	2904
Immunosuppression	582 (20.0%)	288 (16%)	294 (27%)	<0.001	2904
Chronic Cardiac Failure	280 (10%)	153 (9%)	127 (11%)	0.012	2904
Chronic Liver Failure	124 (4%)	43 (2%)	81 (7%)	<0.001	2904
At least 1 comorbidity	1701 (59%)	955 (53%)	746 (67%)	<0.001	2904
“Cause of hypoxemia” (more than 1 cause is possible)					
Pneumonia	1923 (66%)	1180 (66%)	743 (67%)	0.583	2904
Non pulmonary Sepsis	483 (17%)	259 (14%)	224 (20%)	<0.001	2904
Gastric aspiration	503 (17%)	309 (17%)	194 (18%)	0.914	2904
Trauma	150 (5%)	122 (7%)	28 (3%)	<0.001	2904
Pancreatitis	57 (2%)	29 (2%)	28 (3%)	0.117	2904
Pulmonary contusion	108 (4%)	86 (5%)	22 (2%)	<0.001	2904
Pulmonary Vasculitis	34 (1%)	14 (1%)	20 (2%)	0.021	2904
Non cardiogenic Shock	229 (8%)	114 (6%)	115 (10%)	<0.001	2904
Overdose	66 (2%)	54 (3%)	12 (1%)	0.001	2904
TRALI	122 (4%)	67 (4%)	55 (5%)	0.136	2904
CHF	399 (14%)	206 (12%)	193 (17%)	<0.001	2904
COPD	41 (1%)	29 (2%)	12 (1%)	0.303	2904
Asthma	399 (14%)	206 (12%)	193 (17%)	<0.001	2904
No Cause identified	127 (4%)	90 (5%)	37 (3%)	0.038	2904

1	Ventilation Management					
2	VT	7.7±1.8	7.8±1.8	7.7±1.8	0.215	2758
3	RR	20±8	20±6.2	21±11	<0.001	2887
4	PEEP	8.0 [5.0;10.0]	8.0 [5.0;10.0]	8.0 [5.0;10.0]	0.405	2893
5	FiO2	0.6 [0.4;0.8]	0.5 [0.4;0.8]	0.6 [0.4;0.9]	<0.001	2893
6	Plateau pressure	23±6	22±6	24±6	<0.001	907
7	Driving pressure	15±6	14±5	16±6	<0.001	905
8	PIP	26±8	26±8	28±8	<0.001	2781
9	Minute ventilation	10.7±4.7	10.6±4.5	10.9±5.0	0.113	2839
10	Outcomes					
11	Duration of invasive MV	7.0 [4.0;14.0]	7.0 [4.0;14.0]	7.0 [3.0;15.0]	0.247	2753
12	VFD	14.0 [0.0;22.0]	21.0 [14.0;24.0]	0.0 [0.0;0.0]	<0.001	2753
13	ICU Length of Stay	10.0 [5.0;18.0]	11.0 [6.0;20.0]	8.0 [4.0;16.0]	<0.001	2904
14	Hospital Length of Stay	17.0 [8.0;32.0]	22.0 [13.0;40.0]	9.0 [4.0;19.0]	<0.001	2849
15	ICU mortality	962 (33%)	0 (0%)	962 (87%)	0.000	2904
16	Hospital mortality	1111 (38%)	0 (0%)	1111 (100.0%)	0.000	2904
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e-Table 4: multivariable analyses of factors associated with hospital death in patients with unilateral infiltrate or ARDS

	Model with Bilateral opacities				Model with number of quadrants		
	OR	95%CI	p-value		OR	95%CI	p-value
BILATERAL opacities	1.32	1.06; 1.64	<0.013		-	-	-
Number of quadrants (reference: 1 quadrant)	-	-	-				
2 quadrants	-	-	-		1.17	0.88; 1.56	0.284
3 quadrants	-	-	-		1.53	1.10; 2.11	0.011
4 quadrants	-	-	-		1.76	1.29; 2.41	<0.001
Age (for 1 year)	1.02	1.02; 1.03	<0.001		1.02	1.02; 1.03	<0.001
BMI (for 1 kg/m ²)	0.98	0.97; 1.00	0.011		0.98	0.97; 1.00	0.015
Medical admission	1.98	1.56; 2.51	<0.001		1.86	1.46; 2.38	<0.001
Trauma admission	1.84	1.10; 3.01	0.017		1.81	1.07; 3.00	0.024
Non-pulmonary SOFA	1.13	1.10; 1.16	<0.001		1.13	1.11; 1.16	<0.001
PF (for 10 mmHg decrease)	1.02	1.00; 1.03	0.028		1.01	0.99; 1.02	0.218
pH (for 0.01 increase)	0.98	0.97; 0.99	<0.001		0.98	0.98; 0.99	<0.001
RR (for 1/min)	1.02	1.01; 1.04	0.002		1.02	1.01; 1.04	0.003
PEEP (for 1cmH ₂ O)	0.94	0.91; 0.97	<0.001		0.94	0.91; 0.97	<0.001
PIP (for 1cmH ₂ O)	1.02	1.01; 1.03	0.002		1.02	1.01; 1.03	0.006
immunocompromised	2.19	1.76; 2.72	<0.001		2.19	1.75; 2.74	<0.001
Chronic liver Failure	2.54	1.60; 4.11	<0.001		2.52	1.57; 4.13	<0.001
Extra-pulmonary sepsis	1.32	1.04; 1.69	0.025		1.23	0.95; 1.58	0.109
Drug overdose	0.45	0.21; 0.90	0.031		0.40	0.18; 0.83	0.019
TRALI	1.60	1.03; 2.47	0.034		1.56	1.00; 2.42	0.005
Concomitant Cardiac Failure	1.34	1.04; 1.73	0.025		1.39	1.07; 1.81	0.013
Income area (reference High income Europe)							
Middle Income	1.58	1.26; 1.99	<0.001		1.71	1.35; 2.17	<0.001
High Income non Europe	0.62	0.49; 0.87	<0.001		0.59	0.47; 0.75	<0.001

e-Table 5: Multivariable analysis of variables associated with hospital mortality in patients with unilateral infiltrate

	OR	95%CI	p-value
Age (for 1 year)	1.02	1.01; 1.03	<0.001
Medical admission	2.27	1.51; 3.44	<0.001
Non-pulmonary SOFA	1.19	1.13; 1.25	<0.001
pH (for 0.01 increase)	0.98	0.97; 1.00	0.020
PEEP (for 1cmH2O)	0.88	0.81; 0.95	0.001
Immunocompromised	2.10	1.36; 3.23	<0.001
Income area (reference High income Europe)			
Middle Income	1.94	1.23; 3.07	0.004
High Income non Europe	0.67	0.42; 1.06	0.091

e-Table 6: Multivariable analysis of variables associated with hospital mortality in unilateral infiltrate patients with 2 quadrants involved

	Model for patients with 2 quadrants		
	OR	95%CI	p-value
BILATERAL opacities	1.13	0.76; 1.69	0.56
Age (for 1 year)	1.02	1.01; 1.03	<0.001
BMI (for 1 kg/m ²)	0.99	0.97; 1.01	0.404
Medical admission	2.42	1.67; 3.54	<0.001
Trauma admission	2.57	1.18; 5.40	0.015
Non-pulmonary SOFA	1.08	1.04; 1.13	<0.001
PF (for 10 mmHg decrease)	0.99	0.96; 1.01	0.310
pH (for 0.01 increase)	0.98	0.97; 0.99	0.003
RR (for 1/min)	1.03	1.01; 1.06	0.015
PEEP (for 1cmH ₂ O)	0.94	0.89; 1.00	0.050
PIP (for 1cmH ₂ O)	1.01	0.99; 1.03	0.200
immunocompromised	2.21	1.53; 3.21	<0.001
Chronic liver Failure	2.62	1.14; 6.47	0.026
Extra-pulm sepsis	1.96	1.32; 2.92	<0.001
Drug overdose	2.27	0.03; 0.98	0.080
TRALI	3.11	1.50; 6.47	0.002
Concomitant Cardiac Failure	1.50	1.00; 2.26	0.049
Income area (reference High income Europe)			
Middle Income	1.44	1.00; 2.06	0.049
High Income non Europe	0.67	0.45; 0.99	0.044

e-Table 7: Baseline and outcomes of unilateral infiltrate patients according to their evolution

	Never developed ARDS N=579	Did develop ARDS N=143	p-value	N
Age	61.6±17.5	64.0±16.1	0.126	722
Female gender	214 (37.0%)	40 (28.0%)	0.055	722
Weight	75.2±18.2	78.0±20.2	0.147	691
BMI	26.3±6.1	27.2±6.3	0.135	674
Obese	105 (19.5%)	31 (22.8%)	0.465	674
Comorbidities				
Diabetes	128 (22.1%)	30 (21.0%)	0.858	722
COPD	147 (25.4%)	32 (22.4%)	0.523	722
Chronic Renal Failure	56 (9.7%)	12 (8.4%)	0.757	722
Immunosuppression	111 (19.2%)	22 (15.4%)	0.355	722
Chronic Cardiac Failure	57 (9.8%)	14 (9.8%)	1.000	722
Chronic Liver Failure	23 (4.0%)	5 (3.5%)	0.982	722
At least 1 comorbidity	346 (59.8%)	79 (55.2%)	0.375	722
Risk factor for AHRF				
Pneumonia	271 (46.8%)	77 (53.8%)	0.157	722
Non pulmonary Sepsis	81 (14.0%)	22 (15.4%)	0.769	722
Gastric aspiration	124 (21.4%)	25 (17.5%)	0.355	722
Trauma	34 (5.9%)	13 (9.1%)	0.227	722
Pancreatitis	9 (1.6%)	1 (0.7%)	0.696	722
Pulmonary contusion	24 (4.1%)	10 (7.0%)	0.223	722
Pulmonary Vasculitis	5 (0.9%)	1 (0.7%)	1.000	722
Non cardiogenic Shock	38 (6.6%)	8 (5.6%)	0.815	722
Overdose	17 (2.9%)	4 (2.8%)	1.000	722
TRALI	17 (2.9%)	7 (4.9%)	0.294	722
No Risk Factor identified	58 (10.0%)	15 (10.5%)	0.990	722
Concomitant Cardiac Failure	61 (10.5%)	14 (9.8%)	0.914	722
Concomitant Asthma	8 (1.4%)	3 (2.1%)	0.463	722
Concomitant COPDE	81 (14.0%)	22 (15.4%)	0.769	722
Type of admission			0.336	722
Medical	399 (68.9%)	99 (69.2%)		
Postoperative(elective)	45 (7.8%)	6 (4.2%)		
Surgical	105 (18.1%)	27 (18.9%)		
Trauma	30 (5.2%)	11 (7.7%)		
SOFA	9.0 [6.0;12.0]	9.6 [7.0;12.0]	0.145	711
Non-pulmonary SOFA	6.0 [3.8;9.0]	6.2 [4.0;9.0]	0.247	709
HD SOFA	2.0±1.8	2.4±1.7	0.015	672
Renal SOFA	0.8±1.1	0.9±1.1	0.277	687
Nb quadrants involved			0.218	612
1	351 (72.7%)	86 (66.7%)		
2	132 (27.3%)	43 (33.3%)		
First day with bilateral opacities		62 (43.3%)		

- 5		34 (23.7%)		
- 7		25 (17.4%)		
- 10		9 (6.3%)		
- 14		10 (7.0%)		
- 21		2 (1.4%)		
- 28		1 (0.7%)		
Ventilation and ABG				
PCO ₂	44.5±15.1	45.9±15.6	0.319	707
pH	7.35±0.12	7.33±0.11	0.047	707
FiO ₂	0.5 [0.4;0.6]	0.5 [0.4;0.8]	0.004	711
SpO ₂	97.0 [95.0;99.0]	97.0 [95.0;99.0]	0.705	489
PO ₂	79.2±50.0	84.8±49.2	0.226	711
VT	7.9±1.9	8.0±1.9	0.664	680
PF	191.9±62.9	182.6±67.0	0.138	711
Worst PF in the 2 first days	181.7±62.1	166.5±64.3	0.012	722
Initial Severity			0.031	722
Mild	278 (48.0%)	52 (36.4%)		
Moderate	243 (42.0%)	70 (49.0%)		
Severe	58 (10.0%)	21 (14.7%)		
Worst severity in the 2 first days			0.009	722
Mild	234 (40.4%)	43 (30.1%)		
Moderate	277 (47.8%)	71 (49.7%)		
Severe	68 (11.7%)	29 (20.3%)		
RR	19.1±5.6	19.0±5.4	0.814	711
PEEP	6.0 [5.0;8.0]	6.0 [5.0;8.0]	0.050	711
Plateau pressure	19.8±5.3	20.9±4.9	0.181	210
Driving pressure	12.9±5.0	13.7±4.6	0.291	210
PIP	24.2±7.6	26.9±9.0	0.002	676
Minute ventilation	10.11±4.40	10.55±4.46	0.292	701
Outcomes				
Duration of invasive MV	5.0 [3.0;10.0]	12.0 [8.0;20.0]	<0.001	677
VFD	20.0 [0.0;24.0]	5.5 [0.0;18.0]	<0.001	677
ICU LOS	8.0 [4.0;14.0]	16.0 [10.5;24.5]	<0.001	722
Hosp LOS	15.0 [8.0;28.2]	23.0 [14.0;42.0]	<0.001	705
ICU mortality	146 (25.2%)	42 (29.4%)	0.364	722
Hospital mortality	177 (30.7%)	52 (36.4%)	0.227	720

e-Table 8: Multivariable analysis of factors associated with evolution to ARDS in patients with initial unilateral infiltrate

	Model for patients with 2 quadrants		
	OR	95%CI	p-value
Age (for 1 year)	1.01	1.00; 1.01	0.073
Non-pulmonary SOFA	1.01	0.95; 1.06	0.837
PF (for 10 mmHg decrease)	1.01	0.98; 1.04	0.643
pH (for 0.01 increase)	0.99	0.97; 1.00	0.280

1	PIP (for 1cmH2O)	1.04	1.01; 1.06	0.002
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1 e-Figure 1: Distribution of tidal volume vs plateau pressure on day 1 in patients with unilateral infiltrate or
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Distribution of Tidal Volume versus Plateau Pressure

