# Outcome of acute hypoxaemic respiratory failure: insights from the LUNG SAFE Study

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**Patients with hypoxaemic respiratory failure represent more than one-third of patients requiring mechanical ventilation and their mortality often exceeds 40%. Adjusting for severity, mortality is similar whether it is unilateral or bilateral (as in ARDS).** https://bit.ly/2VshdWc

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ABSTRACT
**Background:** Current incidence and outcome of patients with acute hypoxaemic respiratory failure requiring mechanical ventilation in the intensive care unit (ICU) 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 hypoxaemia 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 arterial oxygen tension/inspiratory oxygen fraction ratio ⩽300 mmHg, new pulmonary infiltrates and need for mechanical ventilation with a positive end-expiratory pressure of ⩾5 $cmH_2O$. ICU prevalence, causes of hypoxaemia, hospital survival and 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 (CHF; 8.2%). The global hospital mortality was 38.6%. CHF patients had a mortality comparable to ARDS (44.1% *versus* 40.4%). Patients with unilateral-infiltrate had lower unadjusted mortality, but similar adjusted mortality compared to those with 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 two quadrants involved.
**Interpretation:** More than one-third of patients receiving mechanical ventilation have hypoxaemia and new infiltrates with a 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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This study is registered as a clinical trial with ClinicalTrials.gov identifier NCT02010073. Requests for data sharing can be submitted to the steering committee of the LUNG SAFE group.

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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 examined patients with acute respiratory failure (ARF) requiring mechanical ventilation regardless of the level of inspiratory oxygen fraction ($F_{iO_2}$), and found a mortality rate ~40% with or without ARDS >20 years ago [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 radiographs 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 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 optimise 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 subgroups 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 upon chest imaging.

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## 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 4499 patients had acute hypoxaemic respiratory failure defined by arterial oxygen tension ($P_{aO_2}$)/$F_{iO_2}$ ratio ⩽300 mmHg, new pulmonary infiltrates on chest imaging and requirement of ventilator support with a positive end-expiratory pressure (PEEP) ⩾5 $cmH_2O$. The number of quadrants involved (chest radiograph or computed tomography (CT) scan) was reported by clinicians. The detailed methods and design of LUNG SAFE have been described previously [1]; some results of this study have been reported in abstract form [15].

### Participants and definitions

Patients were divided into three groups, as follows. 1) ARDS: patients fulfilling the Berlin criteria for ARDS [4]; 2) congestive heart failure (CHF): patients in whom respiratory failure was considered by clinicians to be fully explained by cardiac failure or fluid overload; 3) 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 h post-ICU admission) for meeting criteria, not treated with extracorporeal membrane oxygenation (ECMO) in the first 48 h, and not admitted to another ICU for >2 days before being transferred to the participating ICU.

### Statistical analyses

Continuous variables are reported as mean±SD or median (interquartile range (IQR)), and categorical variables as n (%). Comparisons of proportions were made using Chi-squared 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 the Tukey or Benjamini–Hochberg method.

Prognostic risk factors from prior 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 ⩽0.05 for retention.

As basic analysis of chest imaging (quadrants involved) was an important focus, this component was introduced in mortality models either 1) considering bilateral opacities as a dichotomous variable; or 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% confidence intervals. 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 ARF.

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

## Results

### Prevalence and outcomes of hypoxaemic patients under mechanical ventilation

29 144 patients were admitted to participating ICUs during the LUNG SAFE study and 12 906 patients received mechanical ventilation. Among them, 4499 patients (15.5% of the total admissions, and 34.9% of

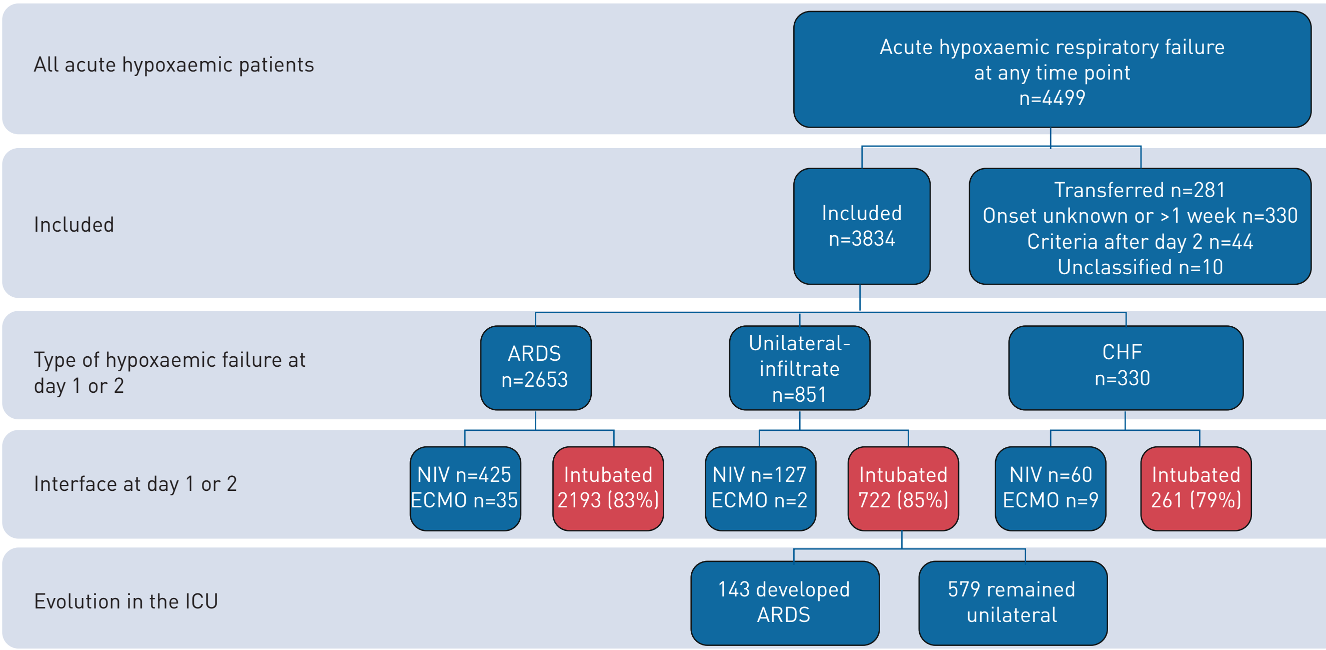


FIGURE 1 Flowchart of the patients screened and included in the analysis. ARDS: acute respiratory distress syndrome; CHF: congestive heart failure; NIV: noninvasive ventilation; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit.

hypoxaemic patients requiring mechanical ventilation) fulfilled our criteria for hypoxaemia. The 4499 patients with acute hypoxaemia under mechanical ventilation represented 0.63 cases per ICU bed over 4 weeks.

3834 (>85%) patients had data available in the first 2 days (figure 1). Patients receiving noninvasive ventilation or under early ECMO are shown in figure 1, but they were not included in the subsequent analysis. Most patients (n=3176; 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 CHF were older, presented more frequent comorbidities such as diabetes, chronic renal failure or chronic cardiac failure (New York Heart Association class 3 or 4), and less frequently COPD or immunocompromised status compared to patients with ARDS (table 1 and supplementary table E1). Many baseline characteristics were similar to patients with ARDS (Sequential Organ Failure Assessment (SOFA) score, arterial pH, $P_{aO_2}/F_{iO_2}$ ratio), but ventilatory parameters indicated lower arterial carbon dioxide tension, PEEP and peak inspiratory pressure (PIP) (tables 1 and 2). They received higher tidal volumes, lower respiratory rates and lower standardised minute ventilation (table 2). Mortality was 44.1%, not different from mortality of patients with ARDS (40.4%). Survivors of CHF had shorter durations of mechanical ventilation, length of stay in the ICU and in the hospital than ARDS (supplementary table E1).

### 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 supplementary table E1). The three main risk factors for hypoxaemia 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 extrapulmonary 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 nonpulmonary SOFA scores, and higher arterial pH, $P_{aO_2}/F_{iO_2}$ ratio and lower PIP (table 1). Plateau pressure and driving pressure (reported in only 31.1% of the patients) were lower in patients with unilateral-infiltrate than in ARDS (table 2, supplementary table E1 and figure 2).

TABLE 1 Baseline and outcomes of all patients and separated by population category

| | Patients | ARDS | CHF | Unilateral-infiltrate | Overall p-value |
|---|---|---|---|---|---|
| **Patients** | | 2193 | 261 | 722 | |
| **Age years** | 3176 | 61.0±16.8 | 68.1±13.5* | 62.1±17.2 | <0.001 |
| **Female** | 3012 | 821 (37.4) | 108 (41.4) | 254 (35.2) | 0.056 |
| **Weight kg** | 3012 | 77.6±24.0 | 74.9±17.4 | 75.8±18.6 | 0.056 |
| **BMI kg·m$^{-2}$** | 2938 | 27.3±8.6 | 26.9±5.8 | 26.5±6.2 | 0.061 |
| **Illness severity indices** | | | | | |
| SOFA score | 3161 | 10.0 (7.0–13.0) | 10.0 (8.0–12.0) | 9.0 (6.0–12.0)* | <0.001 |
| Nonpulmonary SOFA score | 3139 | 6.7 (4.0–10.0) | 7.0 (5.0–9.0) | 6.0 (3.8–9.0)* | <0.001 |
| Chest radiography quadrants involved | 2991 | | | | <0.001 |
| 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 | 3165 | 2193 (100.0) | 187 (74.8)* | 0 (0.0) | <0.001 |
| $P_{aCO_2}$ mmHg | 3133 | 45.9±14.9 | 42.8±14.3* | 44.8±15.2* | 0.003 |
| pH | 3133 | 7.32±0.12 | 7.33±0.13 | 7.34±0.12* | <0.001 |
| $P_{aO_2}/F_{iO_2}$ mmHg | 3159 | 161.0±67.9 | 170.8±67.4 | 190.0±63.8* | <0.001 |
| Worst $P_{aO_2}/F_{iO_2}$ in the first 2 days mmHg | 3170 | 153.2±66.1 | 159.0±64.3 | 178.7±62.8* | <0.001 |
| Initial severity | 3169 | | * | * | <0.001 |
| 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** | | | | | |
| Diabetes | 3176 | 482 (22.0) | 79 (30.3)* | 158 (21.9) | 0.009 |
| COPD | 3176 | 448 (20.4) | 38 (14.6)* | 179 (24.8)* | 0.001 |
| Chronic renal failure | 3176 | 210 (9.6) | 51 (19.5)* | 68 (9.4) | <0.001 |
| Immunosuppression | 3176 | 455 (20.7) | 16 (6.1)* | 133 (18.4) | <0.001 |
| Chronic cardiac failure | 3176 | 211 (9.6) | 106 (40.6)* | 71 (9.8) | <0.001 |
| Chronic liver failure | 3176 | 96 (4.4) | 5 (1.9) | 28 (3.9) | 0.157 |
| ⩾1 comorbidity | 3176 | 1287 (58.7) | 181 (69.3)* | 425 (58.9) | 0.004 |
| **Cause of hypoxaemia (⩾1 cause is possible)** | | | | | |
| Pneumonia | 3176 | 1478 (67.4) | 17 (6.5)* | 453 (62.7)* | <0.001 |
| Nonpulmonary sepsis | 3176 | 384 (17.5) | 11 (4.2)* | 103 (14.3)* | <0.001 |
| Gastric aspiration | 3176 | 357 (16.3) | 22 (8.4)* | 149 (20.6)* | <0.001 |
| Trauma | 3176 | 103 (4.7) | 3 (1.1)* | 47 (6.5) | 0.002 |
| Pancreatitis | 3176 | 47 (2.1) | 0 (0.0)* | 10 (1.4) | 0.013 |
| Pulmonary contusion | 3176 | 74 (3.4) | 3 (1.1) | 34 (4.7) | 0.023 |
| Pulmonary vasculitis | 3176 | 29 (1.3) | 1 (0.4) | 6 (0.8) | 0.356 |
| Noncardiogenic shock | 3176 | 184 (8.4) | 6 (2.3)* | 46 (6.4) | 0.001 |
| Overdose | 3176 | 45 (2.1) | 0 (0.0)* | 21 (2.9) | 0.018 |
| TRALI | 3176 | 98 (4.5) | 11 (4.2) | 24 (3.3) | 0.412 |
| CHF | 3176 | 326 (14.9) | 261 (100.0)* | 75 (10.4)* | <0.001 |
| COPD | 3176 | 218 (9.9) | 0 (0.0)* | 103 (14.3)* | <0.001 |
| Asthma | 3176 | 30 (1.4) | 0 (0.0) | 11 (1.5) | 0.101 |
| **No cause identified** | 3176 | 94 (4.3) | 0 (0.0)* | 34 (4.7) | 0.002 |

Data are presented as n, mean±SD, n (%) or median (interquartile range), unless otherwise stated. ARDS: acute respiratory distress syndrome; CHF: congestive heart failure; BMI: body mass index; SOFA: Sequential Organ Failure Assessment; $P_{aCO_2}$: arterial carbon dioxide tension; $P_{aO_2}$: arterial oxygen tension; $F_{iO_2}$: inspiratory oxygen fraction; TRALI: transfusion-related acute lung injury. *: p<0.05 *versus* ARDS.

*Management*

Patients with unilateral-infiltrate received higher tidal volumes, but lower PEEP, $F_{iO_2}$, respiratory rate and standardised minute ventilation than patients with ARDS (table 2 and figure 2).

"Protective" ventilation, defined as receiving tidal volume <8 mL·kg$^{-1}$ predicted body weight and a plateau pressure <30 cmH$_2$O (when available) was delivered at a similar rate in patients with unilateral-infiltrate and in patients with ARDS (63% *versus* 67%, p=0.250; supplementary figure E1). The use of adjunctive therapies was low in the whole population, but was higher in patients with ARDS than in unilateral-infiltrate patients (supplementary table E2).

TABLE 2 Ventilatory management and outcomes by population category

| | Patients | ARDS patients | CHF | Unilateral-infiltrate | p-value |
|---|---|---|---|---|---|
| **Patients** | | 2193 | 261 | 722 | |
| **Ventilation management** | | | | | |
| Tidal volume $mL \cdot kg^{-1}$ PBW | 3009 | 7.7±1.8 | 8.3±1.8* | 7.9±1.9* | <0.001 |
| Respiratory rate $breaths \cdot min^{-1}$ | 3155 | 20.8±8.7 | 18.9±5.6* | 19.1±5.5* | <0.001 |
| PEEP $cmH_2O$ | 3159 | 8.0 (5.0–10.0) | 6.0 (5.0–8.0)* | 6.0 (5.0–8.0)* | <0.001 |
| $F_{iO_2}$ | 3161 | 0.6 (0.4–0.8) | 0.6 (0.4–0.9) | 0.5 (0.4–0.6)* | <0.001 |
| Plateau pressure $cmH_2O$ | 1002 | 23.3±6.1 | 21.8±5.8 | 20.1±5.2* | <0.001 |
| Driving pressure $cmH_2O$ | 999 | 14.9±5.6 | 14.0±5.4 | 13.1±4.9* | <0.001 |
| PIP $cmH_2O$ | 3041 | 26.9±8.2 | 24.7±8.2* | 24.8±8.0* | <0.001 |
| Minute ventilation (standardised) $L \cdot min^{-1}$ | 3103 | 10.87±4.77 | 9.95±4.49* | 10.20±4.41* | <0.001 |
| **Outcomes** | | | | | |
| Duration of invasive mechanical ventilation days | 3003 | 8.0 (4–15) | 4 (2–9)* | 6 (3–12)* | <0.001 |
| In hospital survivors days | 1784 | 8.0 (4–14) | 4.0 (3–10)* | 6 (3–12)* | <0.001 |
| Ventilation-free days | 3003 | 11.0 (0–20) | 16 (0–24) | 18 (0–24)* | <0.001 |
| ICU length of stay days | 3176 | 10 (5–19) | 6 (3–12)* | 9 (5–16)* | <0.001 |
| In ICU survivors days | 2116 | 11 (6–20) | 7 (4–13)* | 9 (5–17)* | <0.001 |
| Hospital length of stay days | 3108 | 17 (8–32) | 12 (5–24)* | 17 (9–30)* | <0.001 |
| In hospital survivors days | 1882 | 23 (13–40) | 19 (11–31)* | 21 (13–36)* | 0.008 |
| ICU mortality | 3176 | 774 (35.3) | 98 (37.5)* | 188 (26.0)* | <0.001 |
| Hospital mortality | 3165 | 882 (40.4) | 115 (44.1)* | 229 (31.8)* | <0.001 |

Data are presented as n, mean±SD median (interquartile range) or n (%), unless otherwise stated. ARDS: acute respiratory distress syndrome; CHF: congestive heart failure; PBW: predicted body weight; PEEP: positive end-expiratory pressure; $F_{iO_2}$: inspiratory oxygen fraction; PIP: peak inspiratory pressure; ICU: intensive care unit. *: p<0.05 *versus* ARDS.

*Unadjusted outcomes*

Overall, unadjusted ICU and hospital mortality were lower in patients with unilateral-infiltrate than in patients with ARDS (26% *versus* 35% and 35% *versus* 40%) (table 2, supplementary table E1 and figure 3a) 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)***

*Risk factors for death in unilateral-infiltrate and ARDS*

Comparison of survivors *versus* nonsurvivors is shown in supplementary table E3. Multivariable 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 (supplementary table E4). A similar model adjusting on the same confounders using the number of quadrants involved instead of the bilateral opacities characteristics showed that having three or four involved quadrants was significantly associated with a higher risk of hospital mortality. Independent risk factors for mortality included age, immunocompromised status, chronic liver failure, higher extrapulmonary SOFA score, concomitant cardiac failure, medical indication or trauma, location in a middle-income country, higher respiratory rate and peak inspiratory pressure and lower pH. Conversely, higher body mass index, higher PEEP and drug overdose as the cause of respiratory failure were associated with better outcomes (supplementary table E4). The multivariable analysis of factors associated with hospital mortality restricted to patients with unilateral-infiltrate found similar results, although with less significant variables (supplementary table E5).

*Patients with infiltrates in only two quadrants of chest radiograph*

Out of 1094 patients with two quadrant infiltrates on chest radiography, 172 (16%) had unilateral opacities (unilateral-infiltrate), while 922 (84%) had bilateral opacities (ARDS) (table 3). Unilateral-infiltrate patients had more immunosuppression, gastric aspiration and contusions and less extrapulmonary sepsis, but most of other patients' characteristics, gas exchange variables and ventilator management were identical. The unadjusted mortality rates and other outcomes were similar between groups (figure 3b). In a multivariable analysis adjusting on the same covariates as the model performed for the whole population, the presence of bilateral (*versus* unilateral) opacities was not associated with mortality (supplementary table E6).

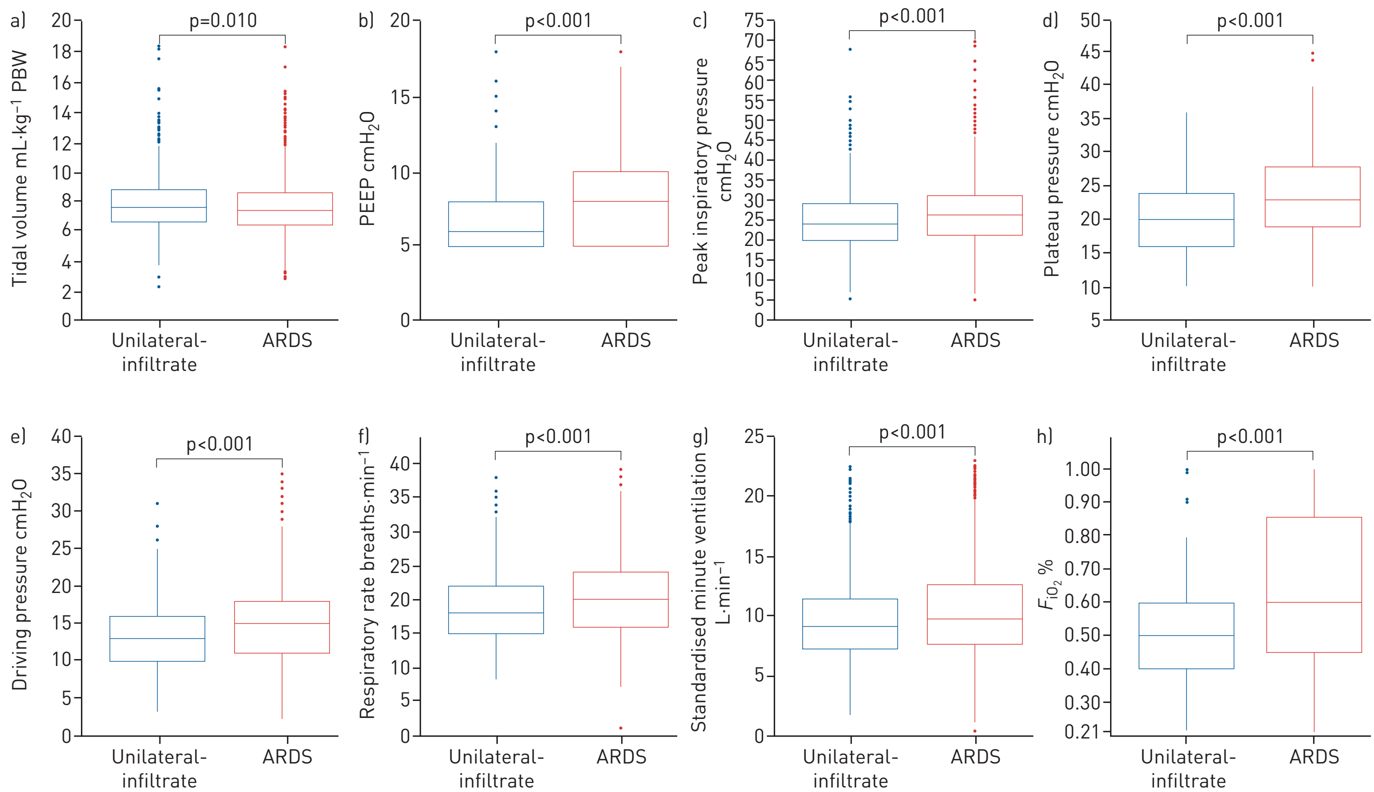


FIGURE 2 Boxplots of respiratory parameters at day 1 according to the population category (unilateral-infiltrate *versus* acute respiratory distress syndrome (ARDS)). p-values are results of t-test comparisons. Outliers appear as dots. a) Tidal volume; b) positive end-expiratory pressure (PEEP); c) peak inspiratory pressure; d) plateau pressure; e) driving pressure. Data available for 912 (31.2%) patients in d) and e); f) respiratory rate; g) standardised minute ventilation; h) inspiratory oxygen fraction ($F_{iO_2}$). PBW: predicted body weight.

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

Of patients with unilateral-infiltrate on day 1 and 2, 143 (20%) subsequently developed ARDS. Patients who developed bilateral infiltrates were more severely ill than patients who never developed ARDS as evidenced by lower $P_{aO_2}/F_{iO_2}$ ratio in the first 2 days, higher haemodynamic SOFA score, lower pH and higher PIP. Patients who developed ARDS had similar mortality rates, but longer stays and duration of mechanical ventilation (supplementary table E7). In multivariable analyses adjusting for age, SOFA score, pH and $P_{aO_2}/F_{iO_2}$ ratio, only PIP was associated with the evolution towards ARDS (supplementary table E8).

## Discussion

The LUNG SAFE study shows that slightly more than a third of patients requiring mechanical ventilation in the participating ICU have $P_{aO_2}/F_{iO_2}$ ratio ⩽300 mmHg. Patients with CHF receiving mechanical ventilation have a mortality rate comparable to patients with ARDS. Patients with unilateral-infiltrate have lower severity of illness than patients with ARDS and the extent of the infiltrates on the chest imaging is associated with mortality. The outcome of patients with two-quadrant involvement on the chest radiograph is similar whether the distribution is bilateral (*i.e.* qualifying them for ARDS) or unilateral. Importantly, in patients with unilateral-infiltrate, peak pressure is the only independent risk factor for developing ARDS.

More than 15% of all admissions and more than one-third of patients who received ventilation in this large international observational study display hypoxaemia with new infiltrates. They have a high mortality rate. This condition as a whole has an important impact on healthcare systems worldwide, greater than ARDS alone [1, 18, 19]. While the subgroup with ARDS is well characterised and studied [1, 4], the population not fulfilling ARDS criteria is underappreciated as a clinical entity, and incidence and outcomes have not been often reported to date [5, 6, 20, 21]. The lack of consensual definition and the heterogeneity of this group are potential explanations. In addition, ARDS is considered as an archetypal condition in the critically ill and has dominated the research agenda [22–26].

Few data are available for this category of patients. In a prospective study in Sweden, Denmark, and Iceland, Luhr *et al.* [5] examined the prevalence and 90-day mortality of ARF, defined as intubation and

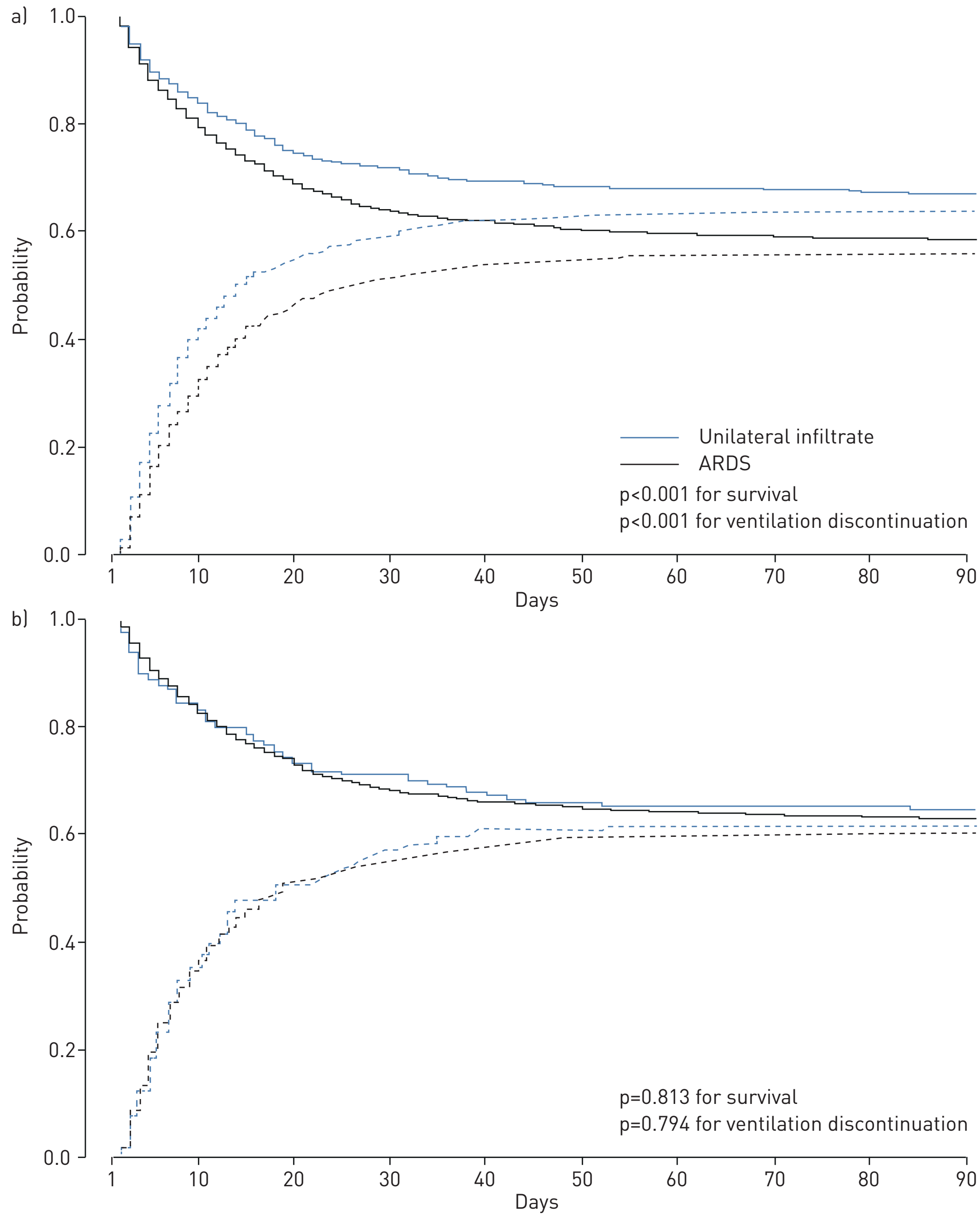


FIGURE 3 a) Probability of discontinuing mechanical ventilation and of hospital survival in patients with unilateral-infiltrate *versus* acute respiratory distress syndrome (ARDS); b) probability of discontinuing mechanical ventilation and of hospital survival in patients with two quadrants and unilateral-infiltrate *versus* two quadrants and ARDS. Solid lines represent the probability of hospital survival and dotted lines represent the probability of mechanical ventilation discontinuation. p-values are the results of log-rank tests.

mechanical ventilation ⩾24 h, as well as acute lung injury (ALI) and ARDS based on American–European consensus definition [5]. They did not use any oxygenation criteria for ARF, making comparisons difficult with our data: they included 1231 ARF patients, 287 ALI patients and 221 ARDS patients. 90-day mortality was 41% for all ARF, 42% for ALI and 41% for ARDS. The severity of illness and any chronic disease (except COPD) was more important for mortality and outcome than the definitions of ARDS if the patient was invasively ventilated >24 h (defined as ARF). VINCENT *et al.* [6] reported the results of a sub-study to validate the sequential organ failure assessment score looking at patients having $P_{aO_2}/F_{iO_2}$ <200 mmHg and mechanical ventilation. They reported a prevalence of 54% with an ICU mortality of 34%. In the present study the number of quadrants seems to be a strong and noteworthy marker of severity of illness independent of whether it is defined as ARDS. This was an unexpected finding given the low reproducibility of radiographic imaging in intensive care [27]. However, the classification based on the number of quadrants with alveolar consolidation is ultra-simple and may have a better reproducibility

TABLE 3 Demographics, illness severity, management and outcomes of patients with unilateral infiltrate and with acute respiratory distress syndrome (ARDS) with two quadrants involved on chest radiography

| | Patients | Unilateral-infiltrate with two quadrants | Bilateral with two quadrants (ARDS) | p-value |
|---|---|---|---|---|
| **Patients** | | 172 | 922 | |
| **Age years** | 1094 | 61.2±18.0 | 62.3±16.6 | 0.452 |
| **Female** | 1094 | 63 (36.6) | 356 (38.6) | 0.685 |
| **Weight kg** | 1032 | 75.1±20.8 | 78.2±26.8 | 0.104 |
| **BMI kg·m$^{-2}$** | 1008 | 25.9±6.5 | 27.6±10.2 | 0.008 |
| **SOFA** | 1094 | 9.6 (7.0–12.0) | 9.8 (7.0–12.0) | 0.249 |
| **Comorbidities** | | | | |
| Diabetes | 1094 | 40 (23.3) | 210 (22.8) | 0.969 |
| COPD | 1094 | 36 (20.9) | 201 (21.8) | 0.878 |
| Chronic renal failure | 1094 | 15 (8.7) | 96 (10.4) | 0.591 |
| Immunosuppression | 1094 | 43 (25.0) | 157 (17.0) | 0.018 |
| Chronic cardiac failure | 1094 | 16 (9.3) | 91 (9.9) | 0.928 |
| Chronic liver failure | 1094 | 4 (2.3) | 34 (3.7) | 0.504 |
| ⩾1 comorbidity | 1094 | 103 (59.9) | 536 (58.1) | 0.732 |
| **Cause of hypoxaemia (⩾1 cause is possible)** | | | | |
| Pneumonia | 1094 | 118 (68.6) | 584 (63.3) | 0.217 |
| Nonpulmonary sepsis | 1094 | 21 (12.2) | 177 (19.2) | 0.038 |
| Gastric aspiration | 1094 | 43 (25.0) | 147 (15.9) | 0.006 |
| Trauma | 1094 | 13 (7.6) | 57 (6.2) | 0.612 |
| Pancreatitis | 1094 | 0 (0.0) | 22 (2.4) | 0.036 |
| Pulmonary contusion | 1094 | 16 (9.3) | 40 (4.3) | 0.012 |
| **Oxygenation and ventilation** | | | | |
| $P_{aO_2}/F_{iO_2}$ mmHg | 1094 | 185±63 | 178±66 | 0.196 |
| Mild | 1094 | 56 (32.6) | 318 (34.5) | 0.509 |
| Moderate | | 91 (52.9) | 446 (48.4) | |
| Severe | | 25 (14.5) | 158 (17.1) | |
| $P_{aO_2}$ mmHg | 1084 | 46±15 | 44±13 | 0.134 |
| pH | 1084 | 7.33±0.12 | 7.34±0.11 | 0.148 |
| $F_{iO_2}$ | 1094 | 0.5 (0.4–0.8) | 0.5 (0.4–0.7) | 0.247 |
| Tidal volume mL·kg$^{-1}$ PBW | 1046 | 7.6±1.8 | 7.8±1.7 | 0.153 |
| Respiratory rate breaths·min$^{-1}$ | 1091 | 20±6 | 20±6 | 0.444 |
| Minute ventilation L·min$^{-1}$ | 1071 | 10.33±4.50 | 10.31±4.62 | 0.942 |
| PEEP cm$H_2O$ | 1094 | 6.0 (5.0–10.0) | 8.0 (5.0–10.0) | 0.101 |
| Plateau pressure cm$H_2O$ | 336 | 20.8±5.8 | 21.8±5.4 | 0.238 |
| Driving pressure cm$H_2O$ | 336 | 13.1±5.9 | 14.1±4.9 | 0.282 |
| PIP cm$H_2O$ | 1056 | 25.9±8.2 | 25.7±8.0 | 0.847 |
| **Outcomes** | | | | |
| Duration of invasive mechanical ventilation days | 1036 | 7 (3–12) | 7 (4–14) | 0.281 |
| In hospital survivors days | 652 | 7 (4–13) | 7 (4–14) | 0.844 |
| Ventilation-free for 28 days | 1036 | 16 (0–23) | 15 (0–23) | 0.581 |
| ICU length of stay days | 1094 | 9 (5–16) | 10 (5–19) | 0.291 |
| In ICU survivors days | 766 | 10 (6–16) | 11 (6–20) | 0.402 |
| Hospital length of stay days | | | | |
| In hospital survivors days | 1070 | 17 (10–35) | 17 (9–33) | 0.866 |
| ICU mortality | 1094 | 48 (27.9) | 280 (30.4) | 0.578 |
| Hospital mortality | 1090 | 58 (33.9) | 328 (35.7) | 0.720 |

Data are presented as n, mean±SD median (interquartile range) or n (%), unless otherwise stated. BMI: body mass index; SOFA: Sequential Organ Failure Assessment; $P_{aO_2}$: arterial oxygen tension; $F_{iO_2}$: inspiratory oxygen fraction; PBW: predicted body weight; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure; ICU: intensive care unit.

than more specific description of the type of infiltrates. This classification was one of the cardinal features of the Lung Injury Score, used for many years [28]. In our study, patients presenting with ARDS and unilateral-infiltrate had quite similar profiles.

Comorbidities and main reasons for hypoxaemia were comparable, although patients with aspiration were more frequent in unilateral injury. Patients with unilateral-infiltrate received slightly higher tidal volumes and lower PEEP than patients with ARDS. After adjustment, a similarly high mortality in patients with unilateral-infiltrate was observed compared to patients with ARDS and the same number of quadrants involved. This suggests that the extent of lung involvement is the predominant factor influencing outcome, rather than the bilateral characteristic. There was a stepwise increase in mortality when the number of quadrants involved increased from two to four, and patients with two quadrants, whether unilateral or bilateral, had the same outcomes. Therefore, a very simple approach using quadrants confirmed previous findings (such as the general impact of unilateral *versus* bilateral on outcome), but also found an association between the number of quadrants and outcome, which has a biological rationale. The number of quadrants involved may grossly reflect the amount of nonaerated lung. Therefore, the important point raised by our study is not to emphasise the importance of the chest radiograph, but conversely to suggest that it may be debatable to continue keeping the current definition of the need for bilateral infiltrates for defining ARDS.

Regarding the ARDS definition, our data confirm that patients with unilateral-infiltrate are not fundamentally different in terms of poor outcome from patients with ARDS [5]. They also have similar underlying risk factors, comorbidity profiles and are managed similarly. Importantly, peak pressure was the only risk factor for developing secondary ARDS in patients with unilateral-infiltrate. This reinforces the need for a protective ventilation in these patients. The need of subdividing these patients into ARDS and unilateral-infiltrate, at least based on the current clinical criteria, can be re-discussed depending on what is studied. Given the lack of knowledge regarding this condition, unilateral patients might be enrolled in studies of ARDS, perhaps with stratification based on the number of quadrants involved to understand if similar management approaches should be used. The pathophysiology or biological mechanisms differ, but the management may not be so different regarding, for instance, the ventilation of a baby lung. High PIP was the main risk factor for developing ARDS in patients with unilateral-infiltrate. The poor outcomes of this population justify further research.

Physiological studies looking at unilateral *versus* bilateral injury are needed to understand the impact of ventilator settings. For instance, the respective effects of PEEP or large tidal volumes in the presence of asymmetrical injury is an important question to address. Our data suggest that the same ventilator parameters seem to influence outcome in unilateral or bilateral lung injury. The failure of current clinical criteria to meaningfully subgroup hypoxaemic patients underlines the need to explore alternative classification approaches, including phenotyping based on biological/immunological profiles [29, 30], if specific treatments can be applied according to these phenotypes [31]. In our study, the basic clinical classification of the number of quadrants involved, although probably imperfect, had a strong prognostic value. Re-examining the impact of the number of quadrants may help to determine whether this parameter could be included as a severity criterion in the ARDS definition or for a definition including all hypoxaemic patients.

Patients with CHF receive a different therapeutic management approach compared to other types of respiratory failure. Although data are scarce, mechanical ventilation has always been associated with a poor prognosis [32, 33]. CHF patients had a shorter duration of support but a similar mortality to patients with ARDS, again in line with LUHR *et al.* [5]. One study compared outcomes of patients with cardiogenic pulmonary oedema to patients with ARDS [34]. In this retrospective study, authors found a four-fold increased risk of hospital mortality for patients with ARDS as compared to patients with cardiogenic pulmonary oedema, but definitions differed from ours (limited to need for mechanical ventilation and a PEEP of $\geqslant$5 $cmH_2O$). This population of patients with cardiac failure may need more specific research attention. One could question the accuracy of the clinical classification of CHF by investigators in LUNG SAFE. Differentiating ARDS from pure cardiac failure can be challenging [7, 35, 36], especially since the Berlin definition clearly states that patients could present with ARDS and concomitant heart failure [4]. Patients were classified as CHF in the present study when hypoxaemia was fully explained by cardiac failure or fluid overload per the treating clinician. This analysis reflects clinical practice and the way patients are enrolled in or excluded from clinical trials.

Our study has the limitations of an observational design with the risk of unmeasured confounding factors. Regarding quality of data collection, all numerical variables were checked, outliers were detected and queries to confirm their values were sent to investigators. This ensured quality of our dataset and explains the low numbers of missing data, mostly reflecting lack of clinicians' monitoring of certain variables (*e.g.* plateau pressure). Both the results of chest radiographs and CT scans were used by clinicians for the diagnosis of ARDS and the number of quadrants, but the images were not systematically validated or reviewed by independent radiologists. For performing the Kaplan–Meier curves, we considered hospital discharge to be equal to outcome at 90 days, which is a simplification. Some epidemiological data suggest that hospital outcome and 90-day mortality are very similar for this population. Patients classified in the CHF group were patients for which the clinicians considered that the respiratory failure was fully explained by cardiac failure or fluid overload. Patients with respiratory infection and concomitant fluid overload were considered in the ARDS or the unilateral-infiltrate groups. It is known that chest radiography appearance can worsen after fluid administration. We do not have this granularity of information as this is the case in all trials in ARDS. In general, we don't have systematic validation of the chest radiograph by independent radiologists.

### Conclusion

Mechanically ventilated patients with hypoxaemia and new infiltrate represent a high global burden of illness, affecting one-third of the patients receiving ventilation in the ICU with a mortality close to 40%. Patients with unilateral-infiltrate have a high mortality comparable to patients with ARDS of similar severity. Regarding outcome, the global extent of lung involvement seems more important than the unilateral *versus* bilateral distribution of the lung opacities. These findings emphasise the need for greater attention to patients with unilateral-infiltrate in future studies.

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