Death in Hospital Following ICU Discharge: Insights from the LUNG SAFE Study

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Abstract

**Background:** To determine the frequency of, and factors associated with, death in hospital following ICU discharge.

**Methods:** The Large observational study to UNderstand the Global impact of Severe Acute respiratory Failure (LUNG SAFE) study was an international, multicenter, prospective cohort study of patients with severe respiratory failure, conducted across 459 ICUs from 50 countries globally. This current study aimed to understand the frequency and factors associated with death in hospital in patients who survived their ICU sta. We examined outcomes in the subpopulation discharged with no limitations of life sustaining treatments ('treatment limitations'), and the subpopulations with treatment limitations.

**Results:** 2,186 (94%) patients with no treatment limitations discharged from ICU survived, while 142 (6%) died in hospital. 118 (61%) of patients with treatment limitations survived while 77 (39%) patients died in hospital. Patients without treatment limitations that died in hospital after ICU discharge were older, more likely to have COPD, immunocompromise or chronic renal failure, less likely to have trauma as a risk factor for ARDS. Patients that died post ICU discharge were less likely to receive neuromuscular blockade, or to receive any adjunctive measure, and had a higher pre- ICU discharge non-pulmonary SOFA score. A similar pattern was seen in patients with treatment limitations that died in hospital following ICU discharge.

**Conclusions:** A significant proportion of patients die in hospital following discharge from ICU, with higher mortality in patients with limitations of life-sustaining treatments in place. Non-survivors had higher systemic illness severity scores at ICU discharge than survivors.

**Trial Registration:** ClinicalTrials.gov NCT02010073

**Background**

Patients that are discharged alive from the ICU are often considered to have ‘survived’ their critical illness, and to be in the recovery phase. However, this is now understood that these patients suffer ongoing increased morbidity and mortality following the acute phase of their critical illness. Indeed, one might view ICU survival as one – albeit major – of a series of hurdles in a recovery process from critical illness that can take several years. Elegant long-term follow-up studies, such as those conducted by Herridge and colleagues, show substantial ongoing functional limitations that persist up to 5 years following ARDS [1].

One group about which less is known about is the subgroup of patients that are discharged from the ICU, but subsequently die in hospital prior to discharge. Of particular interest is the identification of potentially modifiable factors associated with in-hospital death in these patients. Patients discharged from ICU can be considered to fall into 2 groups, depending on whether limitations regarding life-sustaining treatments (referred to as ‘treatment limitations’) were placed at the time of discharge [2, 3]. Patients in whom
treatment limitations were in place are generally considered to have a more guarded prognosis, while patients without such treatment limitations are thought to have a better prognosis [2, 3].

Given these issues, we wished to examine the frequency and factors associated with death in hospital following ICU discharge in patients enrolled into The Large observational study to UNderstand the Global impact of Severe Acute respiratory Failure (LUNG SAFE) study, a prospective cohort study undertaken in 459 Intensive Care Units (ICUs) in 50 countries across 5 continents [4]. LUNG SAFE constitutes the largest cohort available of patients with acute hypoxaemic respiratory failure requiring ventilatory support. The wide geographic spread of participating ICUs, and the large patient sample size are important strengths of this study [4]. Our primary objective was to determine the percentage of patients dying in hospital following ICU discharge, in patients with and without treatment limitation decisions in place. Secondary objectives included identification of factors associated with death in both patient subgroups, with a particular focus on identifying potentially modifiable risk factors, particularly issues relating to patient management.

Methods And Materials

Study Design

The detailed methods and protocol have been published elsewhere [4]. In brief, LUNG SAFE was an international, multicenter, prospective cohort study, with a 4-week enrollment window in the winter season [4]. The study, funded by the European Society of Intensive Care Medicine (ESICM), was endorsed by multiple national societies/networks (Appendix 1). All participating ICUs obtained ethics committee approval, and either patient consent or ethics committee waiver of consent. National coordinators (Appendix 1) and site investigators (Appendix 2) were responsible for obtaining ethics committee approval and for ensuring data integrity and validity.

Study Population

The study inclusion criteria for acute respiratory hypoxemic failure (AHRF) were: a PaO₂/FIO₂ of 300 mmHg or less; new pulmonary infiltrates on chest imaging, and requirement of ventilatory support with a positive end-expiratory pressure (PEEP) of 5 cm H2O or more. Exclusion criteria were: age < 16 years or inability to obtain informed consent, where required. The study population consisted of patients fulfilling criteria for AHRF that survived their ICU stay and were discharged to a hospital ward within 90 days of ICU admission. The study population was divided into 2 groups, depending on whether or not the patient has a decision to limit life-sustaining measures [Figure 1].

Data Definitions

Our data definitions have been previously reported [4]. In the present study, ICU and hospital survival were evaluated at ICU or hospital discharge, or at day 90, whichever occurred first.

Data management and Statistical analyses
Descriptive statistics included proportions for categorical and mean (standard deviation) or median (interquartile range) for continuous variables. The amount of missing data was low as previously reported [4], and no assumptions were made for missing data. Statistical differences in proportions observed in the groups (treatment limitation, no treatment limitation) were assessed with chi-square test, or Fisher exact test according to number of expected cases. Continuous variables were compared using T-test or Wilcoxon rank sum test, according to Normal data distribution. Shapiro-Wilks test was used to assess normality in data distribution.

Logistic regression models were applied in order to identify predictors of hospital mortality in patients without treatment limitation. A stepwise approach was used to detect predictor of hospital mortality after ICU discharge. This approach combines forward and backward selection methods in an iterative procedure (significance level of 0.05 both for entry and retention). Potential independent predictors were: patient characteristics at baseline (age, sex, BMI, geoeconomic area), chronic disease (chronic obstructive pulmonary disease (COPD), diabetes mellitus, immuno-incompetence, cardiac failure, renal failure, liver failure), presence of ARDS risk factors, ICU characteristics (number of beds, proportion of ICU beds in hospital, number of beds per physician and per nurse, academic ICU), illness severity parameters evaluated at last available day in ICU (PaO2/FiO2, PaCO2, pH, SOFA score adjusted for missing values). Results were reported as odds ratio with 95% confidence interval. Same approach was used on patients on invasive mechanical ventilation for at least two days during ICU stay in order to assess the possible association between ventilator parameters and hospital mortality (after ICU discharge). The list of possible independent variables used in stepwise approach also included ventilator setting observed during the last available day of IMV. Same analysis was performed on patients with a treatment limitation during ICU stay.

The Kaplan-Meier approach was applied to assess the probability of hospital survival after ICU discharge, considering censored those patients discharged alive from hospital, as well as those patients with a hospital discharge after 60 days from ICU discharge. The log-rank test was used to compare survival curves estimated in patients with or without treatment limitation. Same approach was used to assess probability of hospital survival in study population stratified in 3 groups: patients with a treatment limitation, patients without a treatment limitation and adjunctive measures used during ICU stay, patients without a treatment limitation and no adjunctive measures.

All p-values were two-sided, with p-values < 0.05 considered as statistically significant. Statistical analyses were performed with Rstudio, version 1.2.5042 (RStudio: Integrated Development for R. RStudio, PBC, Boston, M)) and SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

**Results**

A total of 4,499 patients had AHRF defined by a PaO2/FiO2 of 300 mmHg or less, new pulmonary infiltrates on chest imaging, and requirement of ventilator support with a PEEP of 5 cm H2O or more.
[Figure 1]. Of these, 3,058 (68%) survived to ICU discharge. Of these, 2,814 (92%) did not have any treatment limitations in place, while 244 patients (8%) did have limitations in place.

**Death in hospital post-ICU discharge**

2,186 (94%) of patients without treatment limitations survived to hospital discharge, while 142 (6.1%) died in hospital [Figure 1]. 118 (61%) of patients with treatment limitations survived, while 77 (39%) patients died in hospital. Of the 39 patients (20%) with treatment limitations placed on (36 patients) or before (3 patients) ICU admission, 12 died (32%). Of the 145 patients (74%) that had treatment limitations in place after the day of ICU admission, 62 (43%) died in hospital following ICU discharge. 11 patients had date of limitation not available, of whom 3 died (27%). There were no significant differences in hospital mortality rates (P = 0.18).

Patients that died in hospital after ICU discharge differed in a number of potentially important respects from those that survived [Tables 1–2] being older, more likely to have COPD, immunocompromise or chronic renal failure and less likely to have trauma as a risk factor for ARDS.
Table 1
Characteristics of study subpopulation with no treatment limitations at ICU discharge according to vital status at hospital discharge.

| Characteristic                                      | Alive N = 2,186 | Dead N = 142 | Total N = 2,328 | p-value |
|-----------------------------------------------------|-----------------|-------------|-----------------|---------|
| Male, n (%)                                         | 1,363 (62.35)   | 93 (65.49)  | 1,456 (62.49)   | 0.4536  |
| Age (years), mean ± SD                              | 60.03 ± 16.34   | 68.70 ± 15.71 | 60.56 ± 16.43   | < .0001 |
| Geographic area                                      |                 |             |                 | 0.2086  |
| European high income countries                      | 1,207 (55.22)   | 88 (61.97)  | 1,295 (55.63)   |         |
| Non-European high income countries                  | 655 (29.96)     | 33 (23.24)  | 688 (29.55)     |         |
| Middle income countries                             | 324 (14.82)     | 21 (14.79)  | 345 (14.82)     |         |
| BMI (kg/m²), mean ± SD                              | 27.92 ± 7.72    | 26.57 ± 6.03 | 27.84 ± 7.63    | 0.1389  |
| Length of ICU stay (days) from AHRF onset, median [IQR] | 8.00 [5.00–16.00] | 10.00 [6.00–16.00] | 9.00 [5.00–16.00] | 0.1162  |
| Length of ICU stay > 28 days from AHRF onset, n (%)  | 226 (10.34)     | 8 (5.63)   | 234 (10.05)     | 0.0708  |
| Length of ICU stay (days) from admission, median [IQR] | 10.00 [5.00–18.00] | 10.50 [7.00–18.00] | 10.00 [6.00–18.00] | 0.0984  |
| ARDS during ICU stay, n (%)                         | 1,414 (64.68)   | 93 (65.49)  | 1,507 (64.73)   | 0.8451  |
| Clinical recognition of ARDS during ICU stay, n (%) | 925 (42.31)     | 61 (42.96)  | 986 (42.35)     | 0.8806  |
| Chronic disease§, n (%)                             |                 |             |                 |         |
| COPD                                                | 492 (22.51)     | 43 (30.28)  | 535 (22.98)     | 0.0328  |
| Diabetes mellitus                                   | 501 (22.92)     | 36 (25.35)  | 537 (23.07)     | 0.5047  |
| Immune-incompetence (all-types)                     | 344 (15.74)     | 40 (28.17)  | 384 (16.49)     | 0.0001  |
| Chronic cardiac failure                             | 241 (11.02)     | 19 (13.38)  | 260 (11.17)     | 0.3878  |
| Chronic renal failure                               | 229 (10.48)     | 23 (16.10)  | 252 (10.82)     | 0.0335  |
| Chronic liver failure                               | 42 (1.92)       | 5 (3.52)    | 47 (2.02)       | 0.2054  |

Abbreviations: ARDS: acute respiratory distress syndrome; BMI: body mass index; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; IQR: interquartile range [first and third quartile]; SD: standard deviation.

§ Sum of percentages is greater than 100%, because patient could have more than one chronic disease/risk factor.
| Risk factors for ARDS, n (%) | Alive N = 2,186 | Dead N = 142 | Total N = 2,328 | p-value |
|-----------------------------|----------------|-------------|-----------------|---------|
| None                        | 373 (17.06)    | 22 (15.49)  | 385 (16.97)     | 0.3586  |
| Only non-pulmonary          | 448 (20.49)    | 36 (25.35)  | 484 (20.79)     |         |
| Only pulmonary              | 1,110 (50.32)  | 72 (50.70)  | 1,172 (50.34)   |         |
| Both                        | 265 (12.12)    | 12 (8.45)   | 277 (11.90)     |         |

Risk factors for ARDS§, n (%)

| Risk factor                           | Alive N = 2,186 | Dead N = 142 | Total N = 2,328 | p-value |
|---------------------------------------|----------------|-------------|-----------------|---------|
| Pneumonia                             | 1,089 (49.82)  | 78 (54.93)  | 1,167 (50.13)   | 0.2377  |
| Extra-pulmonary sepsis                | 301 (13.77)    | 16 (18.31)  | 327 (14.05)     | 0.1313  |
| Aspiration of gastric contents         | 289 (13.22)    | 13 (9.15)   | 302 (12.97)     | 0.1624  |
| Pancreatitis                          | 30 (1.78)      | 4 (2.82)    | 43 (1.85)       | 0.3304  |

**Trauma or pulmonary contusion**

| Risk factor                           | Alive N = 2,186 | Dead N = 142 | Total N = 2,328 | p-value |
|---------------------------------------|----------------|-------------|-----------------|---------|
| Inhalation                            | 37 (1.69)      | 4 (2.82)    | 41 (1.76)       | 0.3120  |
| Non cardiogenic shock                 | 124 (5.67)     | 11 (7.75)   | 135 (5.80)      | 0.3055  |
| Drowning                              | 0 (0.00)       | 0 (0.00)    | 0 (0.00)        | -       |
| Drug overdose                         | 55 (2.52)      | 3 (2.11)    | 58 (2.49)       | 1.0000  |
| Blood transfusion                     | 77 (3.52)      | 6 (4.23)    | 83 (3.57)       | 0.6616  |
| Other risk factors                    | 101 (4.62)     | 5 (3.52)    | 106 (4.55)      | 0.5426  |

ICU characteristics

| ICU characteristic                      | Alive N = 2,186 | Dead N = 142 | Total N = 2,328 | p-value |
|-----------------------------------------|----------------|-------------|-----------------|---------|
| Academic hospital, n (%)                | 1,660 (78.01)  | 106 (75.71) | 1,766 (77.87)   | 0.5267  |
| % of ICU on hospital beds, median [IQR] | 2.60 [1.56–4.17] | 2.61 [1.56–4.35] | 2.60 [1.56–4.22] | 0.7886  |
| Beds per physician, median [IQR]       | 4.83 [2.67–10.00] | 4.67 [2.67–9.00] | 4.83 [2.67–10.00] | 0.4145  |
| Beds per nurse, median [IQR]           | 1.50 [1.00–2.00] | 1.31 [1.00–2.00] | 1.50 [1.00–2.00] | 0.0511  |

**Abbreviations:** ARDS: acute respiratory distress syndrome; BMI: body mass index; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; IQR: interquartile range [first and third quartile]; SD: standard deviation.

§ Sum of percentages is greater than 100%, because patient could have more than one chronic disease/risk factor.
### Table 2
Illness severity in study subpopulation with no treatment limitations at ICU discharge stratified by vital status at hospital discharge.

| Parameter                                      | Alive | Dead  | Total   | \(p\)-value |
|------------------------------------------------|-------|-------|---------|--------------|
| **Alive** \((N = 2,186)\)                      |       |       |         |              |
| **Dead** \((N = 142)\)                        |       |       |         |              |
| **Total** \((N = 2,328)\)                     |       |       |         |              |
| **Illness severity at 1st day of AHRF**        |       |       |         |              |
| ARDS, n (%)                                    | 1,242 | 76    | 1,318   | 0.4427       |
| Gas exchange                                   |       |       |         |              |
| \(P_{aO_2}/FiO_2\) (mmHg), mean ± SD          | 173.81 ± 66.30 | 182.49 ± 63.28 | 174.34 ± 66.14 | 0.1032       |
| \(SpO_2\) (%), median [IQR]                   | 96.0 [94.0–98.0] | 96.0 [94.0–98.0] | 96.0 [94.0–98.0] | 0.7613       |
| \(P_{aCO_2}\) (mmHg), mean ± SD               | 45.34 ± 14.88 | 44.80 ± 14.40 | 45.31 ± 14.85 | 0.8351       |
| \(pH\), mean ± SD                             | 7.35 ± 0.10 | 7.35 ± 0.10 | 7.35 ± 0.10 | 0.9699       |
| Adjusted SOFA scores, mean ± SD               | 8.33 ± 3.72 | 9.30 ± 3.58 | 8.39 ± 3.72 | 0.0010       |
| **Illness severity at last available day in ICU** |       |       |         |              |
| ARDS, n (%)                                    | 132   | 8     | 140     | 0.8452       |
| Gas exchange                                   |       |       |         |              |
| \(P_{aO_2}/FiO_2\) (mmHg)                     |       |       |         |              |
| Mean ± SD                                      | 259.00 ± 91.83 | 252.83 ± 86.61 | 258.58 ± 91.47 | 0.7798       |
| Available data, n (%)                          | 1,163 | 85    | 1,248   | 0.1232       |
| \(SpO_2\) (%)                                  |       |       |         |              |
| Median [IQR]                                   | 97.0 [95.0–98.0] | 97.0 [95.0–99.0] | 97.0 [95.0–98.0] | 0.7263       |
| Available data, n (%)                          | 1,381 | 89    | 1,470   | 0.9050       |
| \(P_{aCO_2}\) (mmHg)                          |       |       |         |              |

**Abbreviations:** ARDS: acute respiratory distress syndrome; \(FiO_2\): fraction of inspired oxygen; IBW: ideal body weight; ICU: intensive care unit; IQR: interquartile range [first and third quartile]; \(P_{aCO_2}\): partial pressure arterial carbon dioxide; \(P_{aO_2}\): partial pressure arterial oxygen; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure; SD: standard deviation; SOFA: sequential organ failure assessment.
### Parameter

| Parameter                                      | Alive | Dead | Total | p-value |
|-----------------------------------------------|-------|------|-------|---------|
|                                               | N = 2,186 | N = 142 | N = 2,328 |         |
| Mean ± SD                                     | 42.40 ± 10.97 | 42.01 ± 11.49 | 42.38 ± 10.99 | 0.6008  |
| Available data, n (%)                         | 1,265 (57.87) | 90 (63.38) | 1,355 (58.20) | 0.1969  |
| pH (unit)                                     |       |      |       |         |
| Mean ± SD                                     | 7.43 ± 0.05 | 7.43 ± 0.06 | 7.43 ± 0.06 | 0.4129  |
| Available data, n (%)                         | 1,271 (58.14) | 90 (63.38) | 1,361 (58.46) | 0.2197  |
| Adjusted non-pulmonary SOFA scores, mean ± SD |       |      |       |         |
| Mean ± SD                                     | 2.49 ± 2.75 | 4.08 ± 3.37 | 2.59 ± 2.82 | < .0001 |
| Available data, n (%)                         | 1,337 (61.16) | 97 (68.31) | 1,434 (61.60) | 0.0897  |
| Adjusted SOFA scores, mean ± SD              |       |      |       |         |
| Mean ± SD                                     | 3.87 ± 3.16 | 5.62 ± 3.71 | 3.99 ± 3.60 | < .0001 |
| Available data, n (%)                         | 1,341 (61.34) | 97 (68.31) | 1,438 (61.77) | 0.0979  |

**Abbreviations:** ARDS: acute respiratory distress syndrome; FiO₂: fraction of inspired oxygen; IBW: ideal body weight; ICU: intensive care unit; IQR: interquartile range [first and third quartile]; PₐCO₂: partial pressure arterial carbon dioxide; PₐO₂: partial pressure arterial oxygen; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure; SD: standard deviation; SOFA: sequential organ failure assessment.

### Illness severity Factors

Patients with no treatment limitations who died in hospital following ICU discharge had higher non-pulmonary organ injury severity scores [Figure 2A] compared to survivors, at both ICU admission and at ICU discharge. SOFA scores at first day of AHRF and at last available day in ICU were higher in patients that died in hospital after ICU discharge. This seemed to be driven by the non-pulmonary components of the SOFA score [Figure 2B], as pulmonary organ injury severity scores did not differ between survivors and non-survivors in those without treatment limitations. Specifically, there was no difference in P/F or PaCO2 on initial or last day between survivors and non-survivors [Figure 2C-D]. In addition, there was no difference in the proportion of patient with ARDS in patients that survived versus those that died following ICU discharge [Table 1].

In contrast, patients with treatment limitations who die in hospital following ICU discharge had higher pulmonary organ injury severity scores [Figure e1A-B] but comparable systemic organ injury severity scores [Figure e1C-D] compared to survivors, at both ICU admission and at ICU discharge.
Patient management Factors

Patients with no treatment limitations that survived to hospital discharge received higher levels of PEEP on the first day of invasive MV [Table 3]. In contrast, on the last day of assisted ventilation in the ICU, both surviving and non-surviving patients with no treatment limitations required similar levels of ventilatory support [Table 3]. Specifically, last day FiO\textsubscript{2} [Figure 3A] and peak initiatory pressures [Figure 3C] were lower, while tidal volume, respiratory rates, dynamic compliance and minute volumes [Figure 3B, D-F] were similar, in comparison to hospital survivors. Furthermore, there were no differences in the length of ICU stay between survivors and non-survivors, while the proportion of patients with long ICU stays was significantly higher in patients that survived post-ICU discharge [Table 1].
Table 3
Ventilator setting in patients with no treatment limitations at ICU discharge who received invasive MV for at least 2 days (from AHRF onset) stratified by vital status at hospital discharge.

| Parameter                                                                 | Alive                     | Dead                      | Total                    | p-value |
|---------------------------------------------------------------------------|---------------------------|---------------------------|--------------------------|---------|
| Patients on IMV at 1st and 2nd day, n (%)                                 | 1,545 (70.68)             | 111 (78.17)               | 1,656 (71.13)            | 0.0562  |
| Last day on IMV (with collected data), median [IQR]                       | 7 [3–20]                  | 7 [3–10]                  | 7 [3–10]                 | 0.7307  |
| Non-Invasive Mechanical Ventilation after IMV, n (%)                      | 144 (9.32)                | 7 (6.31)                  | 151 (9.12)               | 0.2866  |
| Ventilator setting at 1st day of Invasive MV                              |                           |                           |                          |         |
| Controlled ventilation, n (%)                                            | 1,081 (71.21)             | 76 (69.72)                | 1,157 (71.11)            | 0.7407  |
| FiO₂, median [IQR]                                                       | 0.60 [0.40–0.80]          | 0.50 [0.40–0.70]          | 0.57 [0.40–0.80]         | 0.1899  |
| Set respiratory rate (breaths/min), mean ± SD                            | 17.92 ± 5.83              | 17.66 ± 5.38              | 17.90 ± 5.80             | 0.7580  |
| Total respiratory rate (breaths/min), mean ± SD                          | 19.74 ± 6.14              | 19.51 ± 5.84              | 19.73 ± 6.12             | 0.7573  |
| Tidal volume (ml/kg IBW), mean ± SD                                      | 7.77 ± 1.83               | 7.78 ± 1.88               | 7.77 ± 1.84              | 0.6565  |
| High tidal volume (> 8 ml/kg IBW), n (%)                                 | 543 (36.86)               | 42 (40.00)                | 585 (37.07)              | 0.5203  |
| Dynamic compliance (ml/cmH₂O), mean ± SD                                | 33.35 ± 23.96             | 32.23 ± 23.04             | 33.27 ± 23.89            | 0.2753  |
| PEEP (cmH₂O), mean ± SD                                                 | 8.12 ± 3.21               | 7.40 ± 2.85               | 8.07 ± 3.19              | 0.0095  |
| PIP (cmH₂O), mean ± SD                                                  | 26.04 ± 7.99              | 25.50 ± 8.02              | 26.01 ± 7.99             | 0.5395  |
| Plateau pressure measured, n (%)                                         | 489 (31.65)               | 33 (29.73)                | 522 (31.52)              | 0.6740  |
| Plateau pressure (cmH₂O), mean ± SD                                     | 21.50 ± 5.62              | 21.73 ± 6.27              | 21.52 ± 5.66             | 0.9205  |
| Driving pressure (cmH₂O), mean ± SD                                     | 13.19 ± 5.03              | 14.64 ± 5.81              | 13.28 ± 5.09             | 0.1699  |
| Minute ventilation (l/min), mean ± SD                                    | 9.32 ± 2.87               | 9.06 ± 3.07               | 9.30 ± 2.89              | 0.1545  |

Abbreviations: FiO₂: fraction of inspired oxygen; IBW: ideal body weight; IMV: invasive mechanical ventilation; IQR: interquartile range [first and third quartile]; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure; SD: standard deviation.
| Parameter                                                                 | Alive (N=2,186) | Dead (N=142) | Total (N=2,328) | p-value |
|--------------------------------------------------------------------------|-----------------|--------------|-----------------|---------|
| **Standardized minute ventilation (l/min), mean ± SD**                  | 10.43 ± 4.45    | 9.96 ± 3.94  | 10.40 ± 4.42    | 0.4408  |
| **Ventilator setting at last available day of Invasive MV in ICU**       |                 |              |                 |         |
| Controlled ventilation, n (%)                                           | 384 (25.35)     | 25 (23.15)   | 409 (25.20)     | 0.6112  |
| FiO₂                                                                     |                 |              |                 |         |
| median [IQR]                                                            | 0.40 [0.35–0.45]| 0.40 [0.30–0.40] | 0.40 [0.35–0.45] | 0.0309  |
| Available data, n (%)                                                   | 1,501 (97.15)   | 107 (96.40)  | 1,608 (97.10)   | 0.5586  |
| **Total respiratory rate (breaths/min)**                                |                 |              |                 |         |
| Mean ± SD                                                               | 20.21 ± 12.15   | 20.91 ± 6.76 | 20.26 ± 11.86   | 0.1920  |
| Available data, n (%)                                                   | 1,499 (97.02)   | 109 (98.20)  | 1,608 (97.10)   | 0.7674  |
| **Tidal volume (ml/kg IBW)**                                            |                 |              |                 |         |
| High tidal volume (>8 ml/kg IBW), n (%)                                  | 602 (42.82)     | 42 (42.00)   | 644 (42.76)     | 0.8733  |
| Mean ± SD                                                               | 7.95 ± 2.06     | 7.89 ± 2.04  | 7.95 ± 2.06     | 0.9763  |
| Available data, n (%)                                                   | 1,406 (91.00)   | 100 (90.09)  | 1,506 (90.94)   | 0.7461  |
| **Dynamic compliance (ml/cmH₂O)**                                       |                 |              |                 |         |
| Mean ± SD                                                               | 49.39 ± 45.70   | 48.72 ± 30.39| 49.35 ± 44.84   | 0.1701  |
| Available data, n (%)                                                   | 1,344 (86.99)   | 96 (86.49)   | 1,440 (86.96)   | 0.8790  |
| PEEP (cmH₂O)                                                            |                 |              |                 |         |
| Mean ± SD                                                               | 6.66 ± 2.43     | 6.26 ± 1.95  | 6.63 ± 2.40     | 0.0597  |
| Available data, n (%)                                                   | 1,496 (96.83)   | 106 (95.50)  | 1,602 (96.74)   | 0.4043  |

**Abbreviations:** FiO₂: fraction of inspired oxygen; IBW: ideal body weight; IMV: invasive mechanical ventilation; IQR: interquartile range [first and third quartile]; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure; SD: standard deviation.
| Parameter                        | Alive          | Dead           | Total           |  \( p \)-value |
|--------------------------------|----------------|----------------|-----------------|---------------|
|                                | \( N = 2,186 \) | \( N = 142 \)  | \( N = 2,328 \) |               |
| PIP (cmH\(_2\)O)              |                |                |                 |               |
| Mean ± SD                      | 20.17 ± 7.16   | 18.51 ± 7.01   | 20.06 ± 7.16    | 0.0079        |
| Available data, n (%)          | 1,395 (90.29)  | 99 (89.19)     | 1,494 (90.22)   | 0.7058        |
| Minute ventilation (l/min)     |                |                |                 |               |
| Mean ± SD                      | 9.65 ± 4.08    | 9.56 ± 3.25    | 9.64 ± 4.03     | 0.9026        |
| Available data, n (%)          | 1,447 (93.66)  | 103 (92.79)    | 1,550 (93.60)   | 0.7194        |
| Standardized minute ventilation (l/min) |          |                |                 |               |
| Mean ± SD                      | 10.11 ± 4.93   | 10.04 ± 4.00   | 10.10 ± 4.87    | 0.7355        |
| Available data, n (%)          | 1,257 (81.36)  | 92 (82.88)     | 1,349 (81.46)   | 0.6899        |

**Abbreviations:** FiO\(_2\): fraction of inspired oxygen; IBW: ideal body weight; IMV: invasive mechanical ventilation; IQR: interquartile range [first and third quartile]; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure; SD: standard deviation.

Similar patterns were seen in patients with treatment limitations who died in hospital [Figure e2A-F]. Patients with treatment limitations who died post ICU discharge had shorter ICU stays compared to those that survived [Table S1].

**Impact of Adjunctive Therapies**

The frequency of neuromuscular blockade use, and of any adjunctive treatment was reduced in patients who died in hospital following ICU discharge [Table 4]. Use adjunctive measures was independently associated with reduced hospital mortality in a multivariate logistic regression model [Table 5].
Table 4
Adjunctive measures performed during ICU stay in study subpopulation with no treatment limitations at ICU discharge stratified by vital status at hospital discharge.

| Parameter                        | Alive (N = 2,186) | Dead (N = 142) | Total (N = 2,328) | p-value |
|----------------------------------|-------------------|----------------|-------------------|---------|
| Neuromuscular blockade, n (%)    | 304 (13.91)       | 8 (5.63)       | 312 (13.40)       | 0.0050  |
| Recruitment maneuvers, n (%)     | 305 (13.95)       | 14 (9.86)      | 319 (13.70)       | 0.1693  |
| Prone positioning, n (%)         | 100 (4.57)        | 2 (1.41)       | 102 (4.38)        | 0.0741  |
| ECMO, n (%)                      | 30 (1.37)         | 0 (0.00)       | 30 (1.29)         | 0.1600  |
| Inhaled vasodilators, n (%)      | 126 (5.76)        | 7 (4.93)       | 133 (5.71)        | 0.6781  |
| HFOV, n (%)                      | 27 (1.24)         | 0 (0.00)       | 27 (1.16)         | 0.1828  |
| None of above adjunctive measures, n (%) | 1,571 (71.87) | 116 (81.69)  | 1,687 (72.47)     | 0.0111  |

**Abbreviations**: ECMO: extra corporeal membrane oxygenation; HFOV: high frequency oscillatory ventilation.

Table 5
Factors associated with hospital mortality in patients with no treatment limitations at ICU discharge

| Model | OR (95% CI) | p-value |
|-------|-------------|---------|
| Multivariable logistic regression model 1 (n = 1,438 on 2,328) | | |
| Age (years) | 1.044 (1.028–1.061) | < .0001 |
| Adjusted SOFA score at last available day in ICU | 1.154 (1.090–1.222) | < .0001 |
| Immune-incompetence (ref. No) | 2.086 (1.281–3.397) | 0.0031 |
| Adjunctive measures during ICU stay (ref. No) | 0.574 (0.340–0.970) | 0.0383 |

Multivariable logistic regression model on patients on MV for at least 2 days (from AHRF onset) (n = 1,043 on 1,656)

| Model | OR (95% CI) | p-value |
|-------|-------------|---------|
| Age (years) | 1.048 (1.029–1.067) | < .0001 |
| Adjusted SOFA score at last available day in ICU | 1.167 (1.091–1.248) | < .0001 |
| Immune-incompetence (ref. No) | 1.938 (1.071–3.509) | 0.0288 |
| BMI (kg/m²) | 0.954 (0.911–0.999) | 0.0469 |

**Abbreviations**: CI: confidence interval; ICU: intensive care unit; OR: odds ratio; SOFA: sequential organ failure assessment.
Length of ICU stay was similar in patients who survived to hospital discharge and those that died, both with and without treatment limitations [Figure 4A]. Hospital survival rates post ICU discharge were significantly lower in patients that had treatment limitations, compared to those with no limitations [Figure 4B]. In patients without treatment limitations, there were more deaths post ICU discharge in patients who received no adjunctive treatment as part of their ARDS management [Figure 4C]. The majority deaths for patients with limitations in life-sustaining therapies occurred within 10 days of discharge from the ICU [Figure 4B].

In a multivariate logistic regression model Factors associated with increased hospital mortality in patients with no limitations of life sustaining measures included age, adjusted SOFA score on the last available day in ICU, and immune-incompetence. Duration of ICU stay was also associated with hospital mortality post ICU discharge in patients that received at least 2 days of invasive mechanical ventilation [Table 5].

**Discussion**

In the current study, we found that 94% of patients without limitations of life sustaining therapy that were discharged from ICU stay survived to hospital discharge, while 61% of patients who had treatment limitations in place also survived to hospital discharge. Patients without treatment limitations that died in hospital after ICU discharge were older, and more likely to have COPD, immunocompromise or chronic renal failure. They were less likely to have trauma as a risk factor for ARDS, or to receive neuromuscular blockade or any adjunctive measure. Of importance non-survivors had a higher ICU pre-discharge non-pulmonary SOFA score. Understanding the factors associated with death in hospital following ICU discharge may allow us to focus efforts on these issues in order to improve outcomes.

**Factors contributing to Death post ICU discharge**

Our finding of a 6% mortality post ICU discharge in patients with acute hypoxaemic respiratory failure is at the lower end of a range of 6–25% hospital mortality rates reported in ICU survivors in earlier studies [5–7]. However, it remains higher than other studies of ICU survivors where it has ranged from 3% in patients at risk for ARDS to 4% in all ICU patients without limitations in life sustaining therapies [8, 9]. In this regard it is important to remember that the LUNG SAFE population constitutes a more severely ill patient cohort, with patients all fulfilling criteria for severe hypoxaemia requiring assisted ventilation.

Identifying potentially modifiable factors in patients who are likely to die in hospital following ICU discharge may allow us to focus efforts on these factors in order to improve outcomes, either prior to or following ICU discharge. In this study, we found that patients dying post ICU discharge were systemically sicker as indicated by non-pulmonary SOFA at ICU discharge. Sepsis is a frequent cause of later deaths in patients with ARDS [10], which may be consistent with our finding of a higher non-pulmonary SOFA score for patients that died post ICU discharge. In contrast, pulmonary factors, including initial ARDS severity or
respiratory status at weaning from invasive ventilation, were not associated with hospital mortality post ICU discharge.

In regard to patient management, patients that received either neuromuscular blockade use or the use of any adjunct, were more likely to survive post ICU discharge. However, this finding needs to be balanced against our prior findings showing that ICU survival in patient receiving adjunctive therapies was lower [11], raising the potential that this finding may reflect an alteration in the pattern of patients dying in the ICU versus the wards, rather than a true association with improved patient outcome.

The duration of ICU stay was similar in patients that survived following ICU discharge compared to those that died in-hospital, with the proportion of longer ICU stay patients significantly higher in survivors. In patients with treatment limitations, non-survivors actually had shorter ICU stays compared to survivors. This finding appears to rule out the potential for patients that die post ICU discharge to have had longer durations of critical illness compared to patients that survive to hospital discharge.

Impact of Limitation of Care

Our findings suggest that the likelihood of hospital survival post-ICU discharge varies greatly depending on whether or not treatment limitations are in place. This finding is consistent with previous studies showing that the presence of limitations of life sustaining therapies is the most important factor in predicting death post ICU admission [2].

The majority of decisions to limit of life sustaining therapies were made after development of AHRF. Interestingly, hospital survival post ICU discharge in patient with a treatment limitation decision was encouragingly high at 61%, while the timing of placement of treatment limitations didn't significantly affect the mortality rate.

Increased age and the presence of active or hematologic neoplasm, immune suppression, chronic liver failure and indices of greater illness severity were associated with limitation of care, consistent with prior findings [9]. Overall, there were similarities between the factors associated with patient outcome, and those associated with limitation of care. This may be consistent with the fact that death in the ICU frequently occurs in the context of decisions to limit life sustaining therapy due to perceived futility [12, 13].

Encouragingly, the majority of patients with treatment limitations survived their hospital stay in this cohort. This finding is consistent with reports of improved outcomes for patients with limitations of life sustaining therapies in other recent studies. In a prospective observational study of 22 European ICUs, significantly more patients had limitations in life-sustaining therapies occurred significantly, while death without limitations in life-sustaining therapies occurred significantly less frequently, in 2015–2016 compared with 1999–2000 [3]. Consistent with our findings, overall survival in patients with treatment limitations was better in the 2015-6 cohort (20.4%) compared to the 1999–2000 cohort (5.5%). Our
findings further suggest that, in the patient cohort with treatment limitations that survive to ICU discharge, the chances of survival to hospital discharge are quite favourable.

**Study Limitations**

There are limitations to this study. Our study focused on identifying factors during the ICU stay, and did not examine factors following ICU discharge, that were associated with death in this population. This is not to negate the impact of events following ICU discharge on patient outcomes. In this regard, recent findings that adverse events occur commonly following ICU discharge, and can contribute to death in hospital are of particular relevance [14]. We do not have data on whether care-providers instituted treatment limitations in some patients once discharged from the ICU, nor do we have information on where patients were discharged to such as home or nursing home. Additionally, as this is an observational study, we cannot ascribe causation to factors that were associated with better outcomes including adjunctive measure use.

Similar to other epidemiologic studies, we did not have access to the source data for the patients in the enrolling ICUs, and it is possible that some patients with hypoxemia, and thus ARDS, in participating centres were missed. It is important to stress, however, that ICUs were participating whether or not they identified any patient having ARDS and that the diagnosis of ARDS was not based on chart records. In addition, enrolment of patients with ARDS from participating ICUs met expectations based on their recorded 2013 admission rates, while data from lower recruiting ICUs were not different from higher enrolling ICUs, suggesting the absence of reporting biases. To ensure data quality, we instituted a robust data quality control program in which all centres were requested to verify data that appeared inconsistent or erroneous. The absence of data on other aspects of ICU management, e.g. fluid therapy, may limit the conclusions that can be drawn.

**Conclusions**

This is the first study to our knowledge examining factors associated with mortality post ICU discharge in patients with ARDS. Encouragingly, survival rates to hospital discharge following ICU discharge are high, with survival rates in patients with limitations of life sustaining therapy higher than expected. Of importance, greater severity of systemic illness prior to ICU discharge, and the lack of adjunctive therapy use, both independently increased the risk of death in hospital following ICU discharge. Focusing attention on this and other factors associated with death in hospital following ICU discharge may allow us to further improve outcomes in these patients.

**List Of Abbreviations**

Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE)
Intensive Care Units (ICUs)

European Society of Intensive Care Medicine (ESICM)

Acute hypoxemic respiratory failure (AHRF)

Positive end-expiratory pressure (PEEP)

Declarations

Ethics approval and consent to participate

This study is an ancillary analysis of the LUNG SAFE database. All ICUs participating in LUNG SAFE obtained ethical approval, patient consent or ethics committee waiver of consent [4]. No further data was collected for this ancillary analysis.

Consent for publication

Not applicable.

Availability of data and material

The data that support the findings of this study were made available by the European Society of Intensive Care Medicine. Restrictions apply to the availability of these data, which were used after approval was granted by the executive committee for the OPEN-LUNG SAFE initiative. Further details about accessing these data can be found online (https://www.esicm.org/research/trials/trials-group-2/lung-safe/).

Competing Interests:

Prof Laffey reports personal fees from consultancy for Baxter and Cala Medical, and funds to his institution from grants from Science Foundation Ireland, the Health Research Board and others.

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**Figures**
Figure 1

Flowchart of study population subdivided into the patient groups with and without treatment limitations.
Patients with no treatment limitations who die in hospital following ICU discharge have higher systemic organ injury severity scores (Panels A and B) but comparable pulmonary organ injury severity scores (Panels C and D) compared to survivors, at both ICU admission and at ICU discharge.
Patients with no treatment limitations who die in hospital require comparable or lower degrees of ventilatory support on the last day of assisted ventilation in the ICU compared to survivors at ICU discharge. Specifically, last day FiO2 (Panel A) and peak initiatory pressures (Panel B) were lower, while tidal volume, respiratory rates, dynamic compliance and minute volumes (Panels C-F) were similar, in comparison to hospital survivors.
Figure 4

Outcomes of patients that survive to hospital discharge. In panel A length of ICU stay was similar in patients who survived to hospital discharge and those that died, both with and without treatment limitations. In panel B, hospital survival rates post ICU discharge were significantly lower in patients that had treatment limitations, compared to those with no limitations. In panel C in patients with no limitations, survival was significantly higher in those that received adjunctive therapies.

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