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RESEARCH ARTICLE



Patient characteristics, management and outcomes in a Nordic subset of the “large observational study to understand the global impact of severe acute respiratory failure” (LUNG SAFE) study

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Abstract

Background: The “Large observational study to understand the global impact of severe acute respiratory failure” (LUNG SAFE) study described the worldwide epidemiology and management of patients with acute hypoxaemic respiratory failure (AHRF). Here, we present the Nordic subset of data from the LUNG SAFE cohort.

Methods: We extracted LUNG SAFE data for adults fulfilling criteria for AHRF in intensive care units (ICU) in Denmark, Norway and Sweden, including demographics, co-morbidities, clinical assessment and management characteristics, 90-day survival and length-of-stay (LOS). We analysed ICU LOS with linear regression, and associations between risk factors and mortality were quantified using Cox regression.

Results: We included 192 patients, with a median age of 64 years (IQR 55, 72), and a male-to-female ratio of 2:1. The majority had one or more co-morbidities, and

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clinicians identified pneumonia as the primary cause of respiratory failure in 56% and acute respiratory distress syndrome (ARDS) in 21%.

Median ICU LOS and duration of invasive mechanical ventilation (IMV) were 5 and 3 days. Tidal volumes (TV) were frequently larger than that supported by evidence and IMV allowing for spontaneous ventilation was common. Younger age, co-morbidity, surgical admission and ARDS were associated with ICU LOS. Sixty-one patients (32%) were dead at 90 days. Age and a non-surgical cause of admission were associated with death.

Conclusions: In this subset of LUNG SAFE, ARDS was often not recognised in patients with AHRF and management frequently deviated from evidence-based practices. ICU LOS was generally short, and mortality was attributable to known risk factors.

Editorial Comment

The LUNG SAFE study has been important for understanding epidemiology, patterns of care and outcomes of ARDS. That primary report however did not present specific information about epidemiology and practices present in the Nordic countries. This paper fills the gap, showing that at that time also in the Nordic countries, ARDS was often not promptly recognised, and that its management frequently deviated from evidence-based practices. These findings illustrate the approach to ARDS by the community of Nordic intensivists before Covid-19, where there is recognition that lessons learned during the pandemic might change promptness and preparedness to identify the acute respiratory diseases.

1 | INTRODUCTION

Acute hypoxaemic respiratory failure (AHRF) may present as acute respiratory distress syndrome (ARDS), a common but underrecognised cause of admission to the intensive care unit (ICU) that is highly lethal and associated with significant morbidity in survivors.^{1–4} There are no specific therapies for ARDS and supportive therapy, including invasive mechanical ventilation (IMV), remains a mainstay in the management of these patients.⁵ Over the last 20 years, a number of randomised clinical trials (RCTs) have improved our understanding of how patients with ARDS can best be managed, with the potential for an improvement in outcome.⁶

ARDS was first defined by American–European consensus in 1994.⁷ The current “Berlin-definition” was published in 2012.¹ These two definitions correspond broadly in that “acute lung injury” and ARDS (1994) are now lumped together and subdivided into three categories, mild, moderate and severe ARDS (2012), based on the ratio of arterial oxygen partial pressure (PaO₂, in kPa or mmHg) to fractional inspired oxygen (FiO₂); (i.e., PaO₂-FiO₂ ratio).

The Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) was undertaken to understand the impact of the “Berlin-definition” on the epidemiology, patterns of care and outcomes of ARDS. LUNG SAFE collected data from >450 ICUs and 50 countries and revealed that crude mortality

rates in ARDS remain at approximately 40 percent, that ARDS is often not recognised by clinical staff and that clinical practice regarding mechanical ventilation often does *not* correspond to evidence from randomised controlled trials.^{2,8} Although Nordic ICUs participated in LUNG SAFE, there is a little specific information about current Nordic practices available. Practice variation across major geo-economic regions was reported, but not specifically for the Nordic countries.⁹

The Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI) published guidelines for the management of patients with ARDS in 2015–16^{10,11} and transatlantic guidelines were issued by the American Thoracic Society, the Society of Critical Care Medicine and the European Society of Intensive Care Medicine in 2017.¹² Following publication of these guidelines, the evidence-base for some interventions has been modified or strengthened by the results of recent randomised controlled trials; for example, neuromuscular blockade,^{13,14} oxygenation targets¹⁵ and in Covid-19, corticosteroids.¹⁶ There is currently very little data available on Nordic clinicians’ adherence to guidelines and more recent evidence.

Nordic practices regarding the management and outcome of patients with ARDS were last surveyed in 1999, that is, before recommendations based on empirical studies were available to clinicians.¹⁷ Mortality rates of more than 40% were found for patients fulfilling the criteria for ARDS and “acute lung injury” (that is, “mild ARDS” according to the “Berlin definition”).^{1,7} In this observational study, we

present the Nordic subset of data derived from the LUNG SAFE cohort.² The aim was to describe the epidemiological characteristics of patients with AHRF in Scandinavia at the time of the conduct of the LUNG SAFE study, as well as common management practices and mortality rates.

2 | METHODS

2.1 | Study design, patients and data collection

LUNG SAFE was a prospective, observational, international cohort study conducted during 4 consecutive winter-weeks in 2014. The study, funded by the European Society of Intensive Care Medicine (ESICM), was endorsed by multiple national societies/networks (Appendix 1 and 2). All participating ICUs obtained ethics 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. For this study, we extracted data obtained from Denmark, Norway and Sweden. Two Nordic countries, Finland and Iceland, did not participate in the LUNG SAFE study.

Detailed methods have been published elsewhere,² and are available in Appendix 3. In Nordic countries, patients were enrolled in February–March 2014. Any patient acutely admitted to a participating ICU and receiving IMV or non-invasive ventilation (NIV) was eligible for screening and enrolment in the database. Exclusion criteria were age less than 16 years or inability to obtain informed consent where no waiver of consent was provided by regulatory authorities. In this study, a waiver for consent was obtained at all sites.

Following enrolment, patients were evaluated daily for AHRF, defined as a $\text{PaO}_2\text{-FIO}_2$ ratio less than or equal to 40 kPa (300 mm Hg) while simultaneously receiving IMV or NIV with end-expiratory pressure greater than or equal to 5 cm H_2O , and new radiologic pulmonary parenchymal abnormalities.² For patients fulfilling AHRF criteria, a more detailed set of data was recorded, to determine whether they fulfilled the Berlin criteria for ARDS.¹

In patients fulfilling AHRF criteria, data were extracted on 9 selected days (until ICU-discharge) within a 28 day-period (days 1, 2, 3, 5, 7, 10, 14, 21 and 28). Data collection included *inter alia* arterial blood gas-data, type of ventilatory support/settings, and Sequential Organ Failure Assessment (SOFA) score.² Data were collected once per day, as close as possible to 10:00 A.M. Data on ventilatory settings were recorded simultaneously with arterial blood gas analysis and without any intervening procedures (e.g., end-expiratory occlusion). Clinician recognition of ARDS was assessed at two time points: on Day 1 of study entry, and when patients exited the study. ARDS was deemed to have been clinician-recognised if either question was answered positively. Decisions to withhold or withdraw life-sustaining treatments, and their timing, were recorded. ICU and hospital survival were collected at the time of discharge, censored at 90 days after enrolment. In patients transferred to other ICUs follow-up was limited to vital status.

In this paper, we briefly describe the screening cohort, and our data analysis is restricted to the subset of patients fulfilling criteria for AHRF and/or ARDS.

2.2 | Statistical analyses

Data are presented using descriptive statistics, with categorical variables reported as frequencies (percentages) and continuous variables as medians (with interquartile ranges [IQRs]) and means (with standard deviation [SD]), as appropriate.

Vital status was assessed at hospital discharge or at follow-up at day 90. Kaplan–Meier survival estimates and Cox proportional hazards models were used to assess the strength of association between clinically relevant patient characteristics and mortality. Demographics and the most frequent co-morbidities, as well as measures of severity of illness at baseline, were included in the analysis. Follow-up was computed in days and defined as time from fulfilment of AHRF criteria (inclusion) to death (event) or at 90-day follow-up (censoring), whatever happened first.

We generally did not include patient management data (e.g., ventilator mode) in survival analysis due to the risk of time-dependent bias (e.g., immortal time bias) and lack of statistical power to model this with enough precision. As a proxy for kidney injury, we, however, investigated the association between renal replacement therapy (RRT) and mortality. RRT was treated as a time-dependent covariate.

ICU length of stay (LOS) was log transformed to ensure a good enough model fit and analysed with multiple linear regression using demographic data and severity of illness measures (selected for clinical relevance) as independent variables. Lack of statistical power precluded the fitting of a more complex model.

To investigate possible associations between the type of ventilatory support and ICU LOS, we fitted generalised linear models (GLM) for repeated measures to model the odds for continued hospitalisation. The outcome (ICU LOS) was log-transformed, and the model was adjusted for type of ventilatory support (group 1, no IMV; group 2, IMV with spontaneous breathing efforts; group 3, IMV without spontaneous breathing efforts), day of follow-up and the interaction term (day of follow-up * type of ventilatory support), in addition to anticipated confounders (gender, fulfilment of ARDS-criteria and severity of AHRF). As the interaction term was statistically significant, that is, the size of the effect of type of ventilatory support on odds for continued hospitalisation, was dependent on the day of follow-up the support was given, the results are presented stratified by type of ventilatory support. The regression coefficients estimated with the GLM were back transformed and the results are expressed as odds ratios (OR) with 95% confidence intervals (CI). The OR express the odds for being hospitalised one extra day given continued stayed in the ICU until the indicated day of follow up, with the day of inclusion used as reference.

All tests were two-sided and p -values $<.05$ were considered statistically significant. No corrections for multiple testing were done as our study is considered exploratory.

Data were analysed using Stata, version 16.1, (StataCorp LLC, College Station, TX, USA), SPSS version 27.0, (IBM Corp, NY, USA) and Excel for Office (Microsoft Corp, CA, USA).

3 | RESULTS

3.1 | Patient characteristics

Five-hundred and sixteen patients were screened for development of AHRF (Figure 1). The median age of screened patients was 62 years (IQR 53, 73) and 184 (36%) were women. Patients were broadly categorised as medical ($n = 230$ [44%]), surgical non-elective (133 [26%]), planned postoperative (122 [24%]) and trauma (31 [6%]). Of these, 192 fulfilled the criteria for AHRF after a median hospital stay of 2 days (IQR 0–5 days).

Table 1 details the demographical and baseline characteristics of patients included for further follow-up after development of AHRF. Patients were predominantly male, elderly and most were admitted

for a non-surgical diagnosis. The most common comorbidities were obesity, (27%); chronic obstructive pulmonary disease (COPD; 17%), diabetes mellitus (13%) and heart failure (12%). Sixty patients (31%) had no documented comorbidities.

3.2 | Clinical assessment

Pneumonia was recognised as both the most frequently occurring risk factor for ARDS (Table 2) and was identified by clinicians as the direct cause of AHRF in a majority of cases (Table 2). ARDS was identified as the direct cause of AHRF at baseline in 41 patients (21%) and at any stage in 76 patients (40%). In contrast, using the Berlin definition, we identified 141 patients (73%) who fulfilled all ARDS-criteria at some point during follow-up (Figures 1 and 2A). At inclusion, hypoxaemia was classified as severe ($\text{PaO}_2\text{-FIO}_2$ ratio ≤ 13.3 kPa) in 26%, moderate ($\text{PaO}_2\text{-FIO}_2$ ratio > 13.3 and ≤ 26.6 kPa) in 43% and mild ($\text{PaO}_2\text{-FIO}_2$ ratio > 26.6 and ≤ 40 kPa) in 31% (Table 1, Appendix 4, Table A1).

Six patients died on the first day of fulfilling AHRF criteria, and by day 1 of follow-up, one patient was no longer classified as hypoxaemic ($\text{PaO}_2\text{-FIO}_2$ ratio > 40.0 kPa). (Figure 2B).

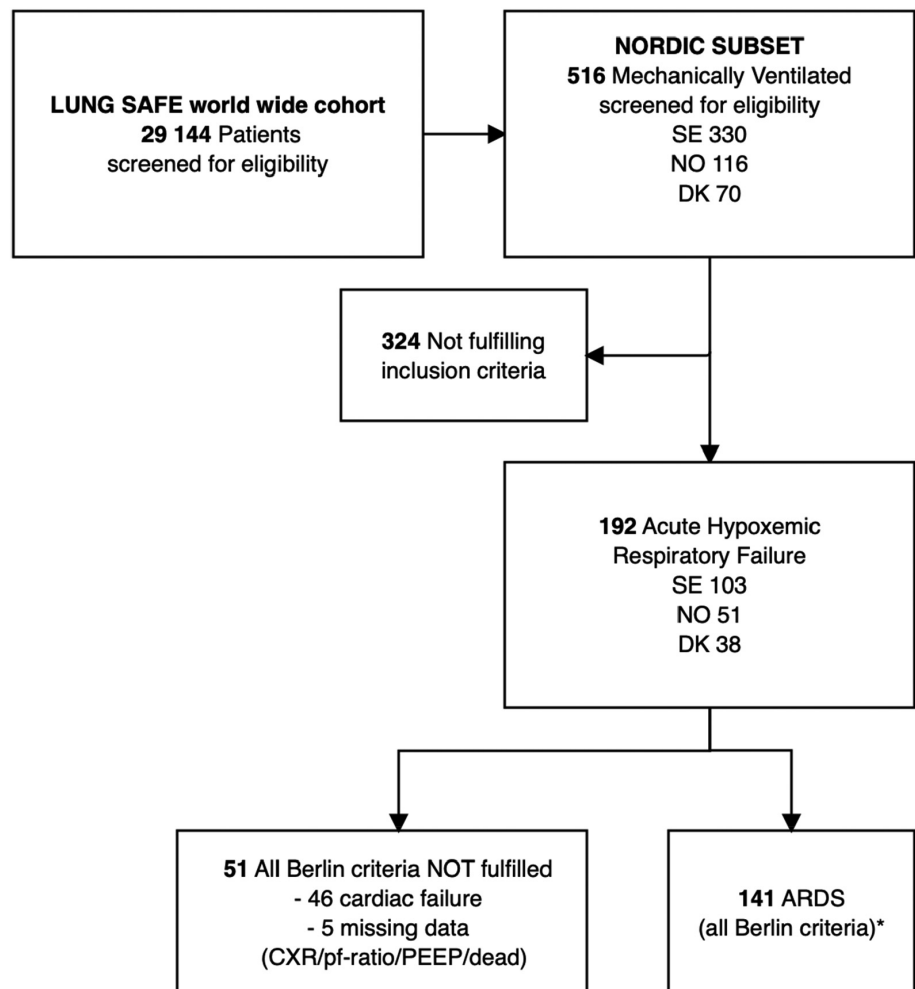


FIGURE 1 Flow of patient screening and enrolment. The median age of screened patients was 62 years (IQR 53, 73) and 184 (36%) were women. Patients were broadly categorised as non-surgical ($n = 230$ [44%]), surgical non-elective (133 [26%]), planned postoperative (122 [24%]) and trauma (31 [6%]). ARDS, acute respiratory distress syndrome; CXR, chest x-ray; pf-ratio; ratio of arterial oxygen partial pressure (PaO_2 , in kPa or mmHg) to fractional inspired oxygen (FIO_2); PEEP, positive end-expiratory pressure; DK, Denmark; NO, Norway; SE, Sweden

TABLE 1 Baseline characteristics

N (country)	192 (DK 38 / N 51 / SE 103)
Female; n (%)	65 (33.9)
Male, n (%)	127 (66.1)
Age (years) median, IQR (n = 192)	64 (55; 72)
Women (n = 65)	65 (57; 72)
Men (n = 127)	64 (53; 72)
Height (cm) median, IQR (n = 185)	175 (167; 180)
Women (n = 62)	165 (160; 168)
Men (n = 123)	180 (175; 184)
Weight (kg), median, IQR (n = 189)	80 (68; 94)
Women (n = 63)	70 (60; 82)
Men (n = 126)	85 (75; 98)
Body mass index, median, IQR (n = 185)	25.7 (22.8; 29.5)
Women (n = 62)	25.1 (22.1; 28.6)
Men (n = 123)	26.2 (23.6; 29.8)
Predicted body weight, median, IQR (n = 185)	70.6 (59.7; 75.1)
Women (n = 62)	57.0 (52.4; 59.7)
Men (n = 123)	75.1 (70.6; 78.8)
Cause of admission	
Medical (n, %)	123 (64.1)
Surgical non-elective (n, %)	50 (26.0)
Postoperative (n, %)	16 (8.3)
Trauma (n, %)	3 (1.5)
Co-morbidities (n, %)	
None	60 (31.3)
1	78 (40.6)
2	41 (21.3)
3 or more	13 (6.8)
Obesity (BMI ≥30)	52 (27.1)
COPD	33 (17.2)
Diabetes mellitus	25 (13.0)
Heart failure NYHA II-IV	23 (12.0)
Active neoplasm	18 (9.4)
Immunosuppression	18 (9.4)
Chronic renal failure	17 (8.9)
Haematological neoplasm	12 (6.3)
Home ventilation	4 (2.1)
Chronic liver failure (Child-Pugh Class C)	2 (1.0)
Severity of AHRF at inclusion, n (%)	
Mild (pf-ratio > 26.6 and ≤ 40 kPa)	60 (31.4)
Moderate (pf-ratio > 13.3 and ≤ 26.6 kPa)	82 (42.9)
Severe (pf-ratio ≤ 13.3 kPa)	49 (25.6)

3.3 | Management

Median LOS in ICU following inclusion was longer in survivors than in non-survivors. However, median time on MV was similar in survivors

TABLE 2A Risk factors for acute respiratory distress syndrome*

	n (%)
<i>Direct</i>	
Pneumonia	97 (50.5)
Gastric aspiration	20 (10.4)
Inhalation injury	0 (0.0)
Lung contusion	1 (0.5)
Drowning	0 (0.0)
Pulmonary vasculitis	1 (0.5)
<i>Indirect</i>	
Non-pulmonary sepsis	30 (15.6)
Transfusion-related acute lung injury (TRALI)	8 (4.2)
Non-cardiogenic shock	6 (3.1)
Major trauma	3 (1.6)
Drug overdose	3 (1.6)
Pancreatitis	2 (1.0)
Burn injury	0 (0.0)
Other	14 (7.3)

TABLE 2B Physicians' assessment of the direct cause(s) of the patients' acute hypoxemic respiratory failure*

Cause of AHRF	N (%)
Pneumonia	107 (55.7)
Cardiac failure	46 (24.0)
ARDS	41 (21.4)
COPD	15 (7.8)
Unknown	12 (6.3)
Asthma	2 (1.0)
Other	47 (24.5)

*Any combination of risk factors and causes could be entered.

and non-survivors. Overall, survivors consumed nearly four times as many ICU bed-days and more than 8 times as many hospital bed-days compared to decedents (Table 3, Appendix 4, Table A2a).

3.3.1 | Mechanical ventilation

A majority of patients (72%) were managed with invasive mechanical ventilation (IMV) at day 1 of follow-up (Figure 2C), with 48% ventilated in a controlled mode and 26% in modes that allowed for spontaneous breaths (Figure 2D). Non-invasive techniques were used in 27% at day 1. There were no apparent differences in choice of ventilator modes in ARDS and non-ARDS patients; controlled modes of ventilation were most commonly used during the first 3 days of MV in both groups, with supported ventilation becoming more prevalent at day 5 (Figure 2D). In patients ventilated in controlled modes, a majority (65% of records) were managed with pressure-controlled

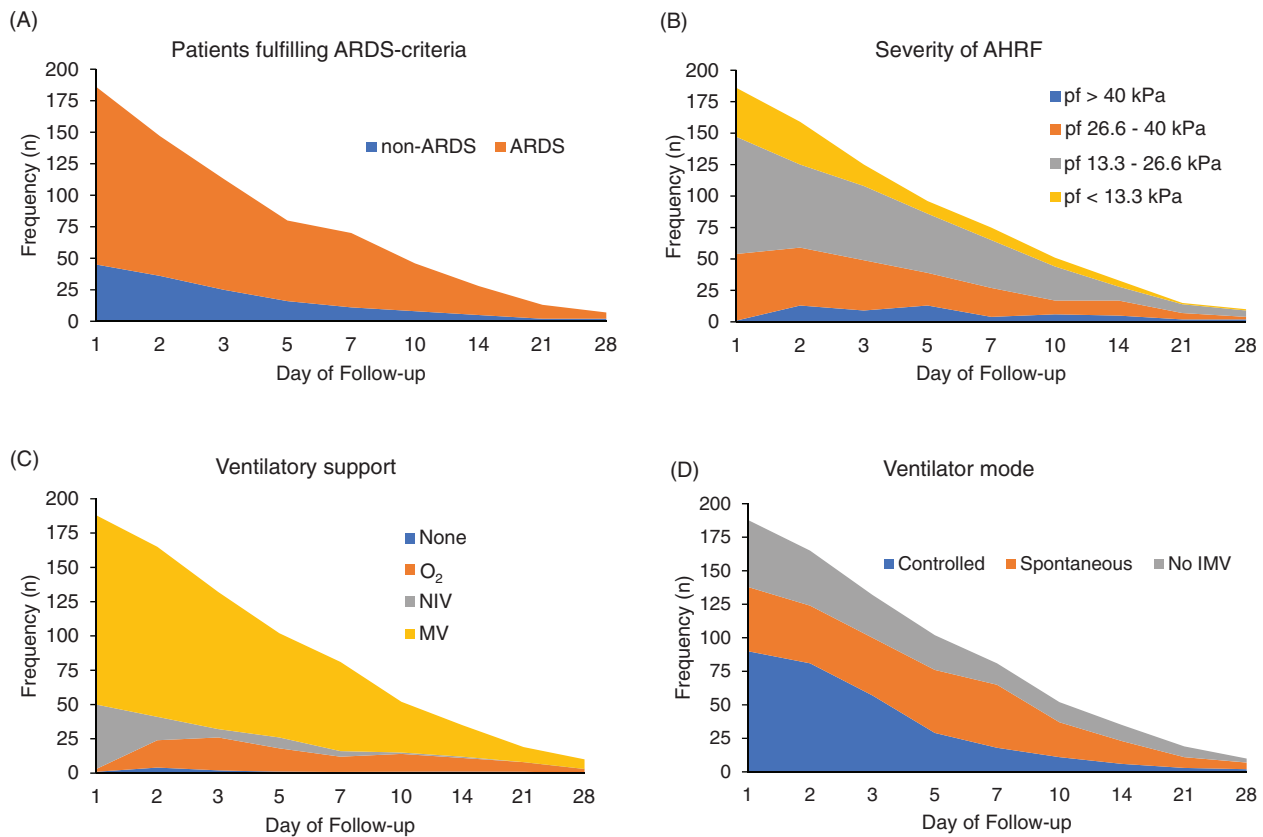


FIGURE 2 Frequencies of patients by day of follow-up and characterised by (A) fulfilment of ARDS-criteria (Berlin definition¹). (B) Severity of acute hypoxaemic respiratory failure (AHRF) according to PaO₂-FIO₂ ratio. (C) Method of ventilatory support. (D) ventilator mode. NIV, non-invasive ventilation; MV, invasive mechanical ventilation; O₂, oxygen therapy only; ARDS, acute respiratory distress syndrome; AHRF, acute hypoxaemic respiratory failure; Controlled, invasive mechanical ventilation with no spontaneous ventilatory efforts; Spontaneous, invasive mechanical ventilation with spontaneous ventilatory efforts; No IMV, no invasive mechanical ventilation (NIV or oxygen therapy only); pf, PaO₂-FIO₂ ratio; Mild, PaO₂-FIO₂ ratio > 26.6 and ≤ 40 kPa; Moderate, PaO₂-FIO₂ ratio > 13.3 and ≤ 26.6 kPa; Severe, PaO₂-FIO₂ ratio ≤ 13.3 kPa; Non-AHRF, PaO₂-FIO₂ ratio > 40 kPa

TABLE 3 ICU length of stay (LOSicu*) and duration of invasive mechanical ventilation (dIMV)

	N	Mean (SD)	Median (IQR)	Sum
<i>LOSicu (days)</i>				
All	192	8.2 (12.0)	5.0 (2.0; 9.0)	1575.0
Alive	131	9.5 (13.7)	5.0 (2.0; 11.0)	1240.0
Dead	61	5.5 (6.3)	3.0 (1.0; 8.0)	335.0
<i>dIMV (days)</i>				
All	138	7.2 (10.5)	3.0 (1.0; 9.0)	989
Alive	99	7.9 (11.7)	3.0 (1.0; 10.0)	779
Dead	39	5.4 (6.3)	3.0 (1.0; 8.0)	210

*LOSicu = ICU length of stay following development of acute hypoxaemic respiratory failure; dIMV = duration of invasive mechanical ventilation

ventilation and only 9% were managed with conventional volume-controlled ventilation. In patients with spontaneous breaths, 50% were managed with pressure support and 38% with pressure-controlled ventilation (allowing for spontaneous efforts). Various hybrid modes typically found on modern ventilators were used in the rest of the records.

Ventilator settings are shown in Table 4. Actual and predicted body weight correlated poorly in both men and women (Appendix 4, Figure A1). Tidal volumes corrected for predicted body weight (PBW) were highly variable (Figure 3A,C), but were not associated with age, clinicians' recognition of ARDS (or per Berlin-criteria), severity of AHRF or mode of ventilation (spontaneous or controlled). Notably, male patients were ventilated with significantly smaller tidal volumes (mean difference 0.9 ml per kg predicted body weight) and lower peak inspiratory pressures (PiP) than female patients (Appendix 4, Table A3; Figure A2). Plateau pressures were too infrequently reported to be included in the analysis.

PiP was higher in patients with severe AHRF, in patients ventilated in a controlled mode (Figure 3B,D) and in patients with ARDS recognised by clinicians (or by objective criteria). Higher positive end-expiratory pressure (PEEP) was associated with severity of AHRF and presence of ARDS (as above). Respiratory rates (RR) were higher in severe AHRF and in patients breathing spontaneously. (Appendix 4, Table A3).

In invasively ventilated patients, spontaneous ventilatory efforts, defined as actual respiratory rate larger than the set rate, was observed in 35% at day 1 and this changed to 62% by day 5 (Figure 2D). Varieties of pressure support ventilation (PSV) were

	Mode of support	No of observations	Median IQR
VT (pbw)	All (n)	630	7.4 (6.2; 8.9)
	No IMV (n)	78	7.7 (6.4; 9.9)
	Spontaneous (n)	267	7.4 (6.1; 8.9)
	Controlled (n)	285	7.3 (6.2; 8.6)
Respiratory rate	All (n)	655	20 (15; 25)
	No IMV (n)	86	24 (20; 31)
	Spontaneous (n)	275	21 (17; 27)
	Controlled (n)	294	17 (14; 20)
Peak inspiratory pressure	All (n)	635	22 (18; 26)
	No IMV (n)	81	12 (10; 16)
	Spontaneous (n)	267	22 (19; 26)
	Controlled (n)	287	25 (21; 29)
PEEP	All (n)	649	8 (6; 10)
	No IMV (n)	83	7 (5; 8)
	Spontaneous (n)	275	9 (7; 10)
	Controlled (n)	291	10 (7; 10)

TABLE 4 Ventilatory metrics

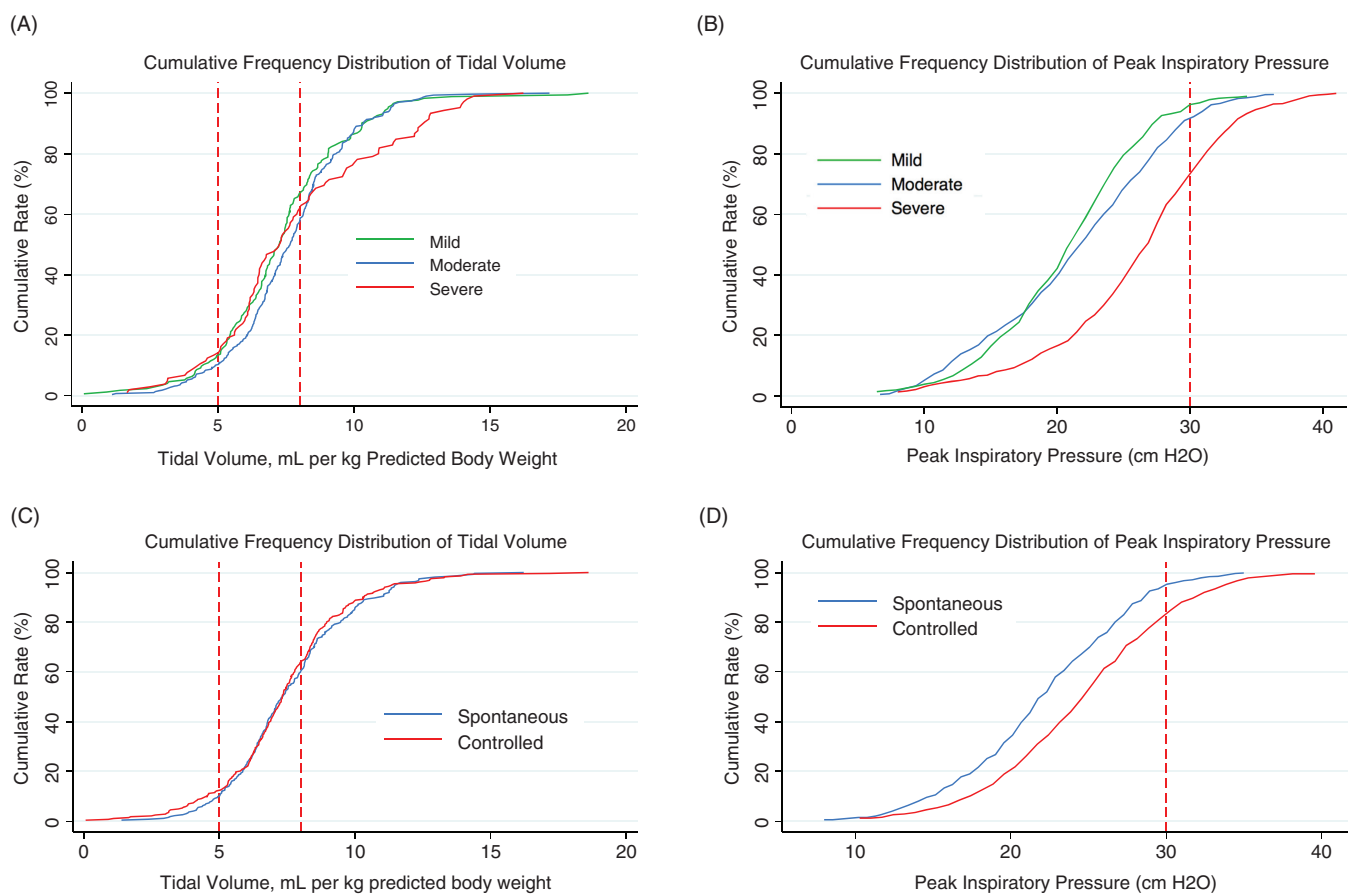


FIGURE 3 Cumulative frequency distribution of tidal volumes (A, C) and peak inspiratory pressures (B, D) in patients with or mild, moderate or severe AHRF, according to severity of hypoxaemia ($\text{PaO}_2\text{-FIO}_2$ ratio)* and mode of ventilatory support. Dashed red lines illustrate traditional limits for lung-protective ventilation. AHRF-severity: Mild, $\text{PaO}_2\text{-FIO}_2$ ratio > 26.6 and ≤ 40 kPa; Moderate, $\text{PaO}_2\text{-FIO}_2$ ratio > 13.3 and ≤ 26.6 kPa; Severe, $\text{PaO}_2\text{-FIO}_2$ ratio ≤ 13.3 kPa; Spontaneous, invasive mechanical ventilation with spontaneous ventilatory efforts; Controlled, invasive mechanical ventilation with no spontaneous ventilatory efforts

frequently employed in this group of patients. In patients with spontaneous breathing, tidal volumes were similar, and PiP was significantly lower (mean difference 2 cm H₂O) than in patients managed with fully controlled ventilation. RR was higher in spontaneously breathing patients (mean difference 4 breaths/min) and increased by day of follow-up. (Appendix 4, Table A3).

3.3.2 | Adjunctive therapies

Fifteen patients (8%) received an inhaled vasodilator (nitric oxide, epoprostenol) and twenty patients (10%) received a neuromuscular blocking agent at some point during their ICU stay. Seven patients (8%) were ventilated in the prone position for a median duration of 12 days. Fourteen patients (7%) were managed with extracorporeal membrane oxygenation (ECMO) for a total of 161 days during the 28-day observation period (ARDS and non-ARDS patients combined). Eight patients were managed with venovenous ECMO, five with venoarterial ECMO and one switched from venoarterial to venovenous ECMO.

3.3.3 | Other supportive therapies

Vasoactive agents were used in 142 patients (74%) and fifty-nine patients (31%) were managed with renal replacement therapy at any time point during their ICU stay (Figure 6A, Appendix 4, Figure A4).

3.4 | Outcomes

Length of stay in the ICU (ICU LOS) was associated with younger age, co-morbidity and fulfilment of ARDS criteria. A non-surgical cause of admission (as opposed to trauma or any surgical cause) was associated with shorter ICU LOS (Appendix 4, Table A2b). The odds for further hospitalisation (i.e., continued ICU stay) were low in patients who did not receive invasive ventilatory support and were roughly equal in patients ventilated in controlled vs. spontaneous modes, and declined from day 2 until follow-up day 10, when the odds for continued hospitalisation increased in patients ventilated in controlled modes. This effect was not confounded by other analysed factors. (Figure 4).

At day 90, a total of 61 deaths (32%) were recorded after a median ICU LOS of 3 days (IQR 1, 8) and median time on MV of 3 days (IQR 1, 8) following inclusion. One death was reported after last day of detailed follow-up, at day 37. Treatment limitations (withhold or withdraw) were noted in 55 patients, 11 of whom survived until end of follow-up. Thus, 72% of decedents had some form of treatment limitation. Age and non-surgical admission were associated with a higher risk of death, and body-mass index (BMI) ≥ 30 kg/m² was associated with a lower risk of death (Figure 5, Table 5, Appendix 4, Table A4). Initial hypoxaemia severity (as determined by the PaO₂-

FIO₂ ratio at follow-up day 1) was not associated with mortality. (Appendix 4, Figure A3).

Provision of renal replacement therapy (RRT) was associated with a three-fold increase in the risk of death compared to patients who did not receive any RRT (Figure 6B). In elderly patients (>65 years), this effect was more pronounced following

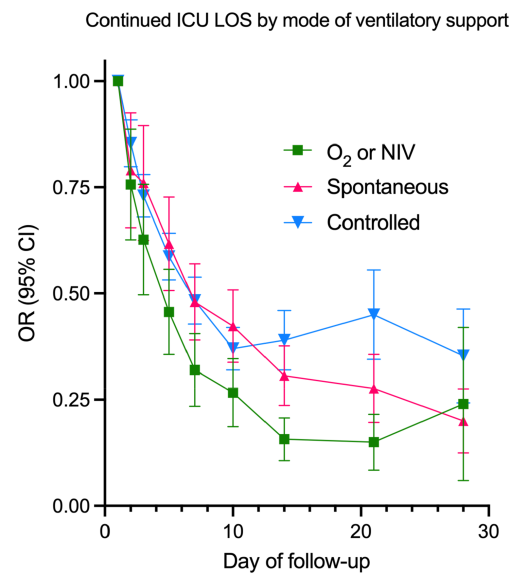


FIGURE 4 Odds for continued length of stay (95% CI) in ICU in patients supported by oxygen-therapy only or non-invasive ventilation, invasive mechanical ventilation with spontaneous ventilatory efforts or invasive mechanical ventilation with no spontaneous ventilatory efforts. The odds ratio (OR) depicted for each patient group was estimated separately (fit of three separate generalised linear models). Thus, we estimate the odds for staying one more day in the ICU at a given day compared to the reference (day of inclusion). O₂ or NIV, non-invasive ventilation or oxygen therapy only; Spontaneous, invasive mechanical ventilation with spontaneous ventilatory efforts; Controlled, invasive mechanical ventilation with no spontaneous ventilatory efforts

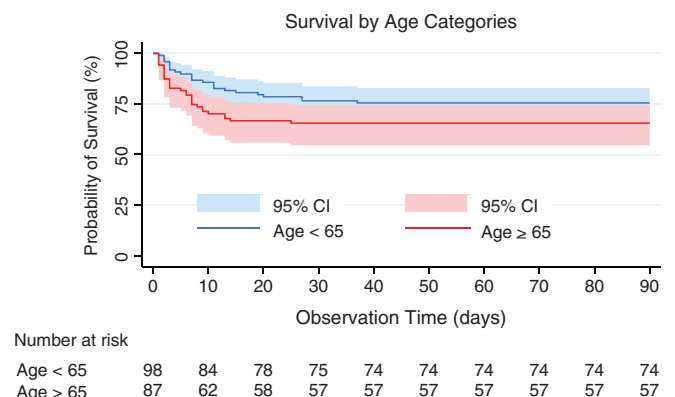


FIGURE 5 Kaplan–Meier estimates of the probability of survival by categories of age (<65 years and ≥ 65 years). Overall mortality was 32% by day 90. CI, confidence interval

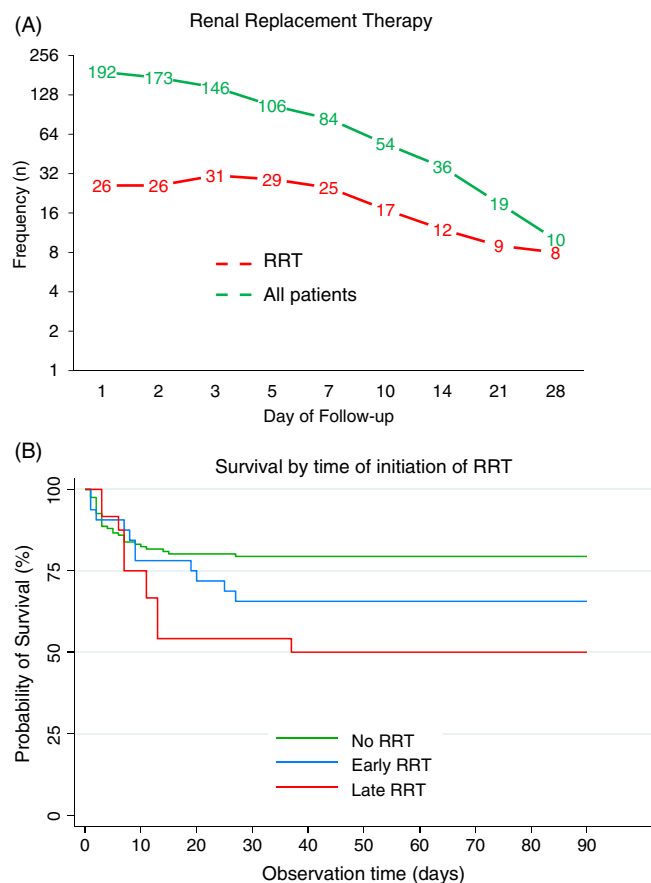


FIGURE 6 (A) Frequencies of patients managed with renal replacement therapy (RRT) by day of follow-up. (B) Crude estimates of the probability of survival according to requirement for renal replacement therapy (none, early initiation [1–2 days follow-up] and late initiation [>2 days of follow-up]). A patient was treated as “not on RRT treatment” until it was provided. Thus, some patients were included two times into the analysis.³⁶ To model mortality risk for the different RRT categories, we fitted Cox proportional hazards model adjusted for age and gender

TABLE 5 Multivariate analysis of non-modifiable risk factors and mortality

	HR (95% CI)	p
Male sex	1.07 (0.59; 1.93)	.83
Age > 65	1.93 (1.09; 3.42)	.02
Non-surgical cause of admission	2.76 (1.33; 5.73)	.01
BMI ≥ 30 kg/m ²	0.43 (0.21; 0.88)	.02
COPD	0.61 (0.25; 1.47)	.27
Diabetes	1.47 (0.69; 3.16)	.32
Cardiovascular	1.40 (0.59; 3.32)	.45
Active neoplasm	1.53 (0.57; 4.10)	.40
Immunodeficiency	1.83 (0.83; 4.03)	.13
Chronic renal failure	1.51 (0.63; 3.58)	.35
Hematologic neoplasm	1.64 (0.65; 4.13)	.30
Home ventilation	1.59 (0.31; 8.05)	.57
Chronic liver disease	-	-

Note: Significant values are highlighted in bold text.

late initiation of RRT (≥ 3 days following inclusion) than early initiation (<3 days after inclusion); however, this effect was not observed in younger patients (<65 years old). (Appendix 4, Table A5).

4 | DISCUSSION

The LUNG SAFE study was a worldwide collaboration including 450 intensive care units in 50 countries.² The data collected have allowed a detailed description of patients, management and outcomes in patients with severe respiratory failure in more than twenty publications to date. The Nordic sample represents a small subset of the LUNG SAFE data. Thus, the analyses presented here cannot emulate what has previously been published and we therefore refrained from making statistical comparisons.

Our data show that in Nordic patients with AHRF, pneumonia was identified as the direct cause of respiratory failure in a majority of patients, and that ARDS was underrecognised. Evidence-based management of ARDS dictates that patients are ventilated with volume and pressure limitation, moderate to high PEEP and, in moderate to severe cases, prone ventilation and neuromuscular blockade.^{10,12} This study indicates that adherence to such practices was low at the time the LUNG SAFE study was conducted: Tidal volumes were frequently higher than recommended, and prone ventilation and neuromuscular blockade may have been underutilised. Nordic registry data from the first wave of the SARS-CoV-2 pandemic (spring 2020) serve to illustrate that practices have evolved; 38%–48% of ICU-patients with Covid-19 were ventilated in the prone position, as compared to only 8% in this LUNG SAFE subset.¹⁸ Under-recognition of ARDS does, however, does not appear to have made a differential impact on the management of these patients or their outcomes. Overall, 90-day mortality was 32 percent and associated with age, a non-surgical cause of admission, as well as extrapulmonary and late organ failure.

Patients were frequently managed with modes of mechanical ventilation allowing spontaneous breathing efforts. Current ARDS guidelines do not make specific recommendations regarding ventilator modes and strict adherence to the principles of low tidal volume ventilation may come into conflict with other evidence-based practices, such as light sedation and early mobilisation.¹⁹ Lightly sedated or awake patients may not tolerate controlled ventilation with small tidal volumes and mechanical ventilation in the prone position. To many clinicians, a reasonable trade-off appears to be allowing light sedation if tolerated by the patient and, consequently, to accept spontaneous ventilatory efforts as well as larger tidal volumes than recommended.

Measured airway pressures and blood-gas findings may reinforce clinicians' decisions to allow mechanically ventilated patients to breathe spontaneously. Ventilatory efforts by the patient will result in lower PiP, and blood-gas measurements may normalise with larger tidal volumes. If oxygenation also improves, this may be interpreted as a general improvement of the patient's condition.

This can be deceptive, however. If measured, plateau pressures will often exceed PIP, and lower PEEP may result in higher transpulmonary and driving pressures. Spontaneous ventilation may also increase transvascular pulmonary pressures (difference between intravascular pressure and pressure outside the vessels) and blood flow due to negative pleural pressure during spontaneous breathing. This may in turn exacerbate pulmonary oedema in the injured lung and contribute to “ventilator induced lung injury.”^{20,21}

Previously published LUNG SAFE data suggest that more than half of patients with ARDS are ventilated with techniques allowing spontaneous breaths during the first two days after inclusion, and that this is associated with more ventilator-free days without any negative impact on mortality.²² In our Nordic subset, we found that both non-invasive ventilation and invasive mechanical ventilation allowing spontaneous breaths were common at day one of inclusion and became the dominant mode by day 5 of follow-up. (Figure 2) Moreover, spontaneous breathing was not associated with larger tidal volumes but was instead associated with significantly lower peak inspiratory pressures. In this study, the impact of the mode of ventilation on ICU LOS was limited to the last day of follow-up when continued ventilation in controlled mode was associated with continued ICU LOS. To which extent choice of ventilator mode impacts survival remains an unanswered question.²³

Mechanical ventilation and ICU LOS was generally of short duration (median 3 and 5 days, respectively) when compared with global data,⁹ Hospital LOS was considerably longer (median 11 days). Conversely, Nordic registry data suggest that critically ill patients with Covid-19 were characterised by prolonged mechanical ventilation and ICU LOS.¹⁸ Case-mix, admission and discharge policies, need for isolation, adjunctive measures (proning and neuromuscular blockade) and bed capacities may explain such differences.²⁴ Overall mortality in this dataset was 32%. This corresponds with the mortality rates observed in high-income countries in the complete LUNG SAFE dataset,⁹ and is lower than what was found in an earlier Nordic survey.¹⁷ A small sample size limits the precision of our estimate, however, and this limitation also applies to quantification of any association of patient and management characteristics with risk of death. However, increasing age, a non-surgical cause of admission, as well as provision of renal replacement therapy were strongly associated with an increased risk of death. In contrast, a higher body mass (BMI ≥ 30 kg/m²) was associated with survival, as previously reported.²⁵ Notably, 29% of patients (72% of decedents) had some form of treatment limitation. This corresponds with practices common in high-income countries in Europe.²⁶

Management of respiratory failure during the SARS-CoV-2 pandemic has been described for most Nordic countries.²⁷⁻³⁰ The singular aetiology and homogenous presentation in critically ill patients with COVID-19 contrast with the heterogenous patient population in, for example, LUNG SAFE. Thus, risk factors and disease trajectories are more precisely described in the pandemic literature.³¹ There are many similarities, however, (age, co-morbidities) and the main differences

between patients described here and patients with COVID-19 appear to be longer duration of mechanical ventilation and use of prone ventilation in the latter group.

4.1 | Strengths and limitations

The main strength of this study is its association with the LUNG SAFE dataset that included a large number of patients sharing the characteristics of AHRF, and with sufficient power to address important associations between the characteristics of patients, their management and outcomes, for further study. Thus, when the analyses presented here correspond with what has been found in world-wide data, it reinforces the idea that the LUNG SAFE papers provide relevant insights in a Nordic context.

The main weaknesses of this study are the small sample size and that these data were collected in 2014. Moreover, ICUs in Finland and Iceland did not participate in the LUNG SAFE study. The observational nature of our study precludes any inference of causality where statistically significant associations was observed.

Nordic and trans-Atlantic clinical practice guidelines for the management of ARDS were published in 2015 and 2017,¹⁰⁻¹² and these have been reinforced because of the COVID-19 pandemic.³² We may therefore assume that practices have evolved, and this is indeed indicated by recent publications detailing the management of severely ill covid-19-patients.^{18,27-29,33}

5 | CONCLUSION

In this Nordic subset, ICU LOS was generally of short duration, and mortality was attributable to known risk factors. At the time of the conduct of the LUNG SAFE study, ARDS was frequently not recognised in ICU-patients with AHRF, and incomplete adherence to evidence-based practises was common. Although management of critically ill patients with severe respiratory failure may have evolved, several practices, including frequent use of ventilator-modes allowing for spontaneous ventilatory efforts, remain largely unsupported by data from randomised trials.^{34,35} Thus, the LUNG SAFE dataset remains a valuable source for clinical researchers looking for relevant problems to investigate in clinical trials.

AUTHOR CONTRIBUTIONS

JGL, GB, EF and TP were responsible for the overall design of the LUNG SAFE study. All authors contributed to the design of the Nordic sub-study. AL, MHL and JHL acted as national co-ordinators or representatives for Sweden, Denmark and Norway. JHL and MCS analysed the data. JHL, MCS, TNA and KH wrote the manuscript and other authors all revised and approved the manuscript.

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