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Patterns of use of adjunctive therapies in patients with early moderate- severe Acute Respiratory Distress syndrome: Insights from the LUNG SAFE Study

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Abbreviation List: AHRF: Acute Hypoxemic Respiratory failure; ARDS: Acute Respiratory Distress Syndrome; ECMO: Extracorporeal membrane oxygenation; HFOV: high frequency oscillatory ventilation; iVD: inhaled vasodilators; ICU: Intensive Care Units; NMBA: neuromuscular blocking agent; PP: prone positioning; P/F ratio: PaO_2/FiO_2; PEEP: Positive End Expiratory Pressure

Abstract

Background: Adjunctive strategies are an important part of the management of acute respiratory distress syndrome (ARDS). However, their application in clinical practice remains inconsistent.

Research Question*:* We wished to determine the frequency and patterns of use of adjunctive strategies in patients with moderate-severe ARDS (P/F ratio < 150) enrolled into the Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) study.

Study Design and Methods**:** The LUNG SAFE study was an international, multicenter, prospective cohort study of patients with severe respiratory failure, conducted in 2014 in 459 ICUs from 50 countries. The primary objective of this substudy was to determine the frequency of use of widely available (neuromuscular blockade, prone position) adjuncts versus adjuncts requiring specialized equipment (ECMO, Inhaled vasodilators, HFOV) in patients in the first 48 hours of moderate-severe ARDS (P/F ratio < 150).

Results**:** Of 1,151 invasively ventilated patients with moderate-severe ARDS, 818 pts (71%) received no adjunct within 48h of ARDS onset. Of 335 (29%) that received adjunctive strategies, 248 (75%) received a single strategy, and 85 (26%) receiving more than one adjunct. Of ARDS non-survivors, 67% did not receive any adjunctive strategy in the first 48 hours. Most patients (63%) receiving specialized adjuncts did not receive prone positioning or neuromuscular blockade. Patients that received adjuncts were more likely to have their ARDS recognized, be younger and sicker, have pneumonia, and be more difficult to ventilate, and be in a European high income country than those that did not receive adjuncts.

Interpretation**:** Three in ten patients with moderate-severe ARDS, and only one third of non-survivors, received adjunctive strategies over the first 48 hours of ARDS. A more consistent and evidence driven approach to adjunct use may reduce costs and improve outcomes in patients with moderate-severe ARDS.

Trial Registration: ClinicalTrials.gov NCT02010073

Introduction

Adjunctive therapies constitute an important part of the management of early moderate to severe acute respiratory distress syndrome (ARDS). However their application in clinical practice appears variable and inconsistent [1,2]. Underlying reasons for this heterogeneity may include the availability of adjuncts, which varies from widely available adjuncts such as prone positioning (PP) and neuromuscular blockade (NMB) to those which require more specialized equipment and expertise, including extracorporeal membrane oxygenation (ECMO), inhaled vasodilators (iVD) and high frequency ventilation (HFOV). A second issue may be the variable level of scientific evidence that underpins the use of different adjunctive strategies, which varies from robust evidence for PP [3], to potential benefits for NMB [4] and for ECMO [5,6], to little evidence for inhaled vasodilators [7] to potential for harm with HFOV [8,9].

The Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) study was undertaken in 459 Intensive Care Units (ICUs) in 50 countries across 5 continents [10]. One key finding was that the use of contemporary evidence-based ventilatory strategies and adjunctive strategies was lower than expected [10]. The primary objective of this secondary study was to determine the frequency of use of adjunctive strategies in patients in the first 48 hours of moderate-severe ARDS (P/F ratio < 150) in the LUNG SAFE Cohort. Key secondary objectives included understanding patterns of use of adjuncts, the approach to using adjunctive

strategies, the relationship between adjunct use and their supporting evidence base, and factors associated with the use of adjunctive strategies in early ARDS.

Methods

Study Design

The detailed methods and protocol have been published elsewhere [10]. In brief, LUNG SAFE was an international, multicenter, prospective cohort study, which recruited 3,033 patients with ARDS from 459 Intensive Care Units (ICUs) in 50 countries across 5 continents [10]. 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 and site investigators (***Appendix 1***) were responsible for obtaining ethics committee approval and for ensuring data integrity and validity.

Patient Selection, Study Design and data collection

Inclusion criteria for the present study included: development of ARDS within 48 hours of the diagnosis of Acute Hypoxemic Respiratory failure (AHRF); a P/F ratio <150 within 48 h of ARDS diagnosis; in patients undergoing invasive mechanical ventilation.

Exclusion criteria included patients transferred from an external ICU and unknown admission source, as these patients may have received adjunctive strategies before inclusion into the study.

Adjunctive therapies were defined as the use of prone positioning (PP), continuous neuromuscular blocking agents (NMBA), inhaled vasodilators, extracorporeal membrane oxygenation (ECMO), and high frequency oscillatory ventilation (HFOV). We did not

include recruitment maneuvers (RM) as LUNG SAFE data did not collect information on the number and type of recruitment maneuvers used. We divided the adjunctive strategies into adjuncts that were widely available (PP, NMBA) versus adjuncts that required specialized equipment (inhaled vasodilators, ECMO, HFOV). We examined use of adjuncts in the first 48 hours of ARDS, because this is where the evidence base for adjunct use exists.

We also studied the variability and patterns of use of the adjunctive therapies in different geo-economic regions enrolling in the LUNG SAFE cohort. The 2016 World Bank countries classification was used to define three major geo-economic groupings: high-income countries in Europe, high-income countries in the rest of the world, and middle-income countries [11].

Statistical Analysis

Continuous variables were described by medians (interquartile ranges), and compared using unpaired Student's t-test or Mann-Whitney U test, and one-way analysis of variance (ANOVA) or the Kruskal-Wallis H test, as appropriate. Bonferroni's correction was used for multiple comparison. Proportions were used for categorical variables, and compared using $\chi 2$ or Fisher's exact test. 95% Confidence Interval was reported for estimated proportions of patients who were treated with different patterns of adjunctive measures. We explored the presence of variables that could be associated with the use of adjunctive therapies by a univariate logistic regression analysis. Variables with a p-value<0.20 were included into a multivariable logistic regression model using a

stepwise selection approach. Statistical significance was considered with a p-value<0.05 (two-tailed). Statistical analyses and graphs were performed using STATA-14/MP (StataCorp LP, College Station, TX, USA) and GraphPad Prism 7a (GraphPad Software, San Diego, CA, USA), respectively.

Results

2,129 patients developed ARDS within 48 hours of AHRF onset, and received invasive MV, of whom 1,146 (54%) had moderate-severe ARDS (i.e. P/F ratio < 150) within the first 48 hours of ARDS.

Frequency of adjunctive strategy use

Adjuncts were used in the first 48 hours in 335 (29%) of patients with moderate-severe ARDS [***Figure 1***]. Of patients with ARDS that did not survive, 33% received an adjunct. Of these patients, 252 (75%) received a single adjunct, while 83 (25%) received two or more adjuncts [***Figure 1***]. Adjunct use at any time over the 28 day period following development of ARDS increased somewhat, with 37% of patients receiving an adjunct. Neuromuscular blockade was used in less than one third of patients (29%), prone positioning and inhaled vasodilators in 1 out of 10 patients and HFOV and ECMO in less than 2% of patients [***Supplemental Table 1***].

Patients receiving an adjunctive strategy were younger, and were more likely to have their ARDS recognized on day 1, be a medical admission, and have pneumonia [***Table 1, Supplemental Tables 2-4***]. Patients receiving adjuncts had more severe ARDS (i.e. lower P/F ratios), and were more difficult to ventilate (lower tidal volumes, higher PEEP, higher peak and plateau airway pressures) compared to patients treated only with conventional therapy [***Table 1***]. Furthermore, patients receiving adjunctive strategies had fewer nurses and more physicians per ICU bed in ICU [***Table 1***].

Widely available versus specialized adjuncts

Of patients that received adjunctive strategies, the majority (n=249/335, 70%) received 1 or more widely available adjuncts, while 30% received at least 1 specialized adjunct. Patients receiving specialized adjuncts were not different from patients receiving solely widely available adjuncts, apart from having a lower percentage of pulmonary risk factors, lower pH, more post-elective surgery [***Table 1, Supplemental Tables 2-4***]. Of interest, ARDS severity and ventilator settings were not different in patients that

received widely available adjuncts alone compared to those that received specialized adjuncts [***Table 1, Supplemental Tables 2-4***].

Patterns of adjunctive measure use

Neuromuscular blocking agent (NMBA) infusion was the most frequently (255 patients, 22%) used adjunct. It was used as a sole adjunct in 177 (69%) of these patients [***Table 2***]. PP was the second most frequently used adjunct, used in 79 patients (7%), of whom 57 (72%) received concomitant NMBA infusions. Inhaled vasodilator therapy was administered to 74 (6%) patients. ECMO was initiated in 11 patients within the first 48 hours, 5 (46%) of whom did not receive any other adjunctive therapies. HFOV was rarely used (0.5%) in this population. In patients that received multiple adjunctive therapies, there was significant variability in the combinations of adjuncts used. NMBA infusion and PP was the most frequent combination used [***Table 2***]. There was no difference in the frequency or pattern of adjunct use in surviving versus non-surviving patients over the first 48 hours of ARDS [***Figure 2***].

There was no clear pattern of use for adjunctive strategies. Most patients receiving ECMO (6 of 11, 55%) and inhaled vasodilators (47 of 74, 64%) did not receive a more widely available adjunct strategy. Only 7 of 91 patients (8%) receiving specialized interventions received PP [***Table 2***].

Geo-economic variability in adjunct use

European high income countries had the highest utilization of adjunctive strategies**.** The use of both NMBA and PP was significantly higher in European ICU's when compared to the other geo-economic areas. Prone positioning was used less often in high income non- European countries. Use of other high resource intensive therapies were not different across different geo-economic areas [***Table 3***].

Factors associated with adjunct use

The use of adjuncts was independently associated with younger age and more severe ARDS (lower P/F ratio). These patients received lower tidal volumes, higher levels of PEEP, and had higher peak inspiratory pressures. Early clinician recognition of ARDS, a higher physician to bed ratio and a lower nurse to bed ratio were associated with early adjunct use. Geo-economic location was important, with adjunct use associated with high income European countries [***Table 4***].

Outcomes in patients receiving adjunctive strategies

Crude ICU – but not hospital - mortality was greater in patients that received adjunctive strategies [***Supplemental Table 5***]. However, patients receiving adjunctive strategies had more severe ARDS, and were more difficult to ventilate [***Supplemental Table 6***]. There was no independent association between adjunct use and outcome in multivariate analyses [***Supplemental Table 6***].

Discussion

One-third of patients with moderate-severe ARDS received adjunctive strategies over the first 48 hours of ARDS in this study. Patients that received adjuncts were more likely to have their ARDS recognized, be younger and sicker, have pneumonia, and be more difficult to ventilate than those that did not receive adjuncts. They were more likely to receive treatment in a European high income country. There was no clear pattern in regard to the use of adjuncts in terms of their supporting evidence base or their resource requirements. Most patients receiving more specialized and expensive adjuncts did not also receive the more widely available adjuncts. ARDS severity did not appear to play a key role. In contrast geographical factors did appear important with markedly greater adjunct use in Europe.

Frequency of adjunctive strategy use: A key finding of the study is the under use of adjuncts in patients with moderate-severe ARDS, which is of significant concern. Most patients with moderate-severe ARDS that died in ICU did not receive any adjunct in the first 48 hours, or at any time up to 28 days after developing ARDS. This low frequency of adjunct use is of concern.

Patterns of adjunctive measure use: Illness severity appeared to play a role in the decision to use adjuncts, with factors related to ARDS severity and difficulty in ventilatory management both associated with adjunct use. The factors underlying the specific type of adjunct used were unclear. Most patients receiving specialized adjuncts did not also receive a more widely available adjunct. ARDS severity and mechanical ventilation indices were largely similar between patients receiving widely available versus specialized adjuncts.

We did not find evidence for a sequential approach to use of adjunctive strategies, commencing with more widely available adjunctive strategies and progressing to more specialized and expensive adjuncts in patients that remain severely hypoxaemic. This approach has been used effectively in EOLIA, a recent large scale

clinical trial of ECMO [6], where 92 % of the patients received neuromuscular blocking agents, while 56% underwent PP before they were considered for extracorporeal support [6]. Similarly in the ACURASYS trial of NM blockade, 45% of the patients received other adjunctive therapies (PP, Inhaled vasodilators or a combination) during the course of their ICU stay [4]. In the PROSEVA trial 87% of the patients that underwent PP also received neuromuscular blocking agents, while 13 % also received inhaled vasodilators [3]. Our findings support the proposal from Bein et al. for the use of protocols to guide the sequential application of adjunctive strategies based on the severity of hypoxemia [12].

Factors influencing Adjunct Use: Understanding the barriers to the use of adjunctive strategies in patients with moderate-severe ARDS is an important step towards addressing this issue. The strength of the evidence base supporting the use of adjunctive strategies does not appear to be an important factor. Prone positioning has been clearly demonstrated to improve patient outcome [3], and is recommended in evidence-based guidelines for the management of ARDS [13]. Despite this, only 7% of eligible patients received prone positioning, which is comparable to the frequency of inhaled vasodilator therapy use, an adjunct with a scant supporting evidence base. Prone positioning was rarely used in patients that received other, more specialized and costly adjunctive strategies such as ECMO. This confirms and extends the prior findings of Li and colleagues who found that most patients enrolled in older studies of ECMO did not first have a trial of PP [14], although this was improved in the more recent EOLIA study [6].

ARDS remains an under-recognized condition [15], and this appears to have important implications for the management of these patients. Early recognition of ARDS by clinicians was independently associated with the use of adjunctive strategies. These findings are similar to a recent multicentre prospective study by Duan et al that showed that recognition of ARDS is associated with a higher use of adjunctive therapies [16].

Geo-economic factors also appeared to play an important role, with patients in European high income countries more likely to receive adjunctive strategies, independent of other important covariates such as ARDS severity. Patients in high

income countries outside Europe were less likely to receive adjuncts, suggesting that resource constraints may not be the key issue. The evidence base for both neuromuscular blockade and prone positioning was developed largely in Europe [3,4]. As a consequence, physicians in these counties may be more experienced and familiar with these approaches. On the other hand, under use of adjuncts, particularly prone positioning, might be a result of ineffective knowledge translation and perhaps, a resistance to change by clinicians, as has been shown to be the case for other interventions such as low tidal volume ventilation [17]. In any case, these findings support prior studies [1,2], providing evidence that adjunctive strategy usage may depend more on clinician or health system factors than patient need. Further studies are needed to further dissect these important issues.

Study Limitations: This study has a number of strengths. This study population is derived from the largest cohort of patients with ARDS in the era of the Berlin definition of ARDS. To our knowledge, this is the first global patient cohort study that has addressed the issue of adjunct use. Our study also has a number of limitations. First, given the prospective cohort design, all inferences are associative, and causality cannot be inferred. Second, we lacked the available data to determine the sequence of adjunct use on patients that received more than 1 adjunct. Third, we did not have access to the source data for the patients in the enrolling ICUs, and it is possible that not all patients with ARDS in participating centres were enrolled. However, enrolment of patients with ARDS from participating ICUs met expectations based on their recorded 2013 admission rates, while data from lower recruiting ICUs was not different from that from higher enrolling ICUs, suggesting the absence of reporting biases. We instituted a robust data quality control program in which all centres were requested to verify data that appeared inconsistent or erroneous. Fourth, the LUNG SAFE study was performed in 2014, and focused on adjuncts in clinical use at that time. Data reported by Duan et al in 2017 [16] and the recently published ROSE trial [18], suggest little change in the use of adjuncts such as prone positioning since then. However, extra-corporeal CO_2 removal, a niche

technique in 2014, may have significantly increased in use since then as a result of advances in device technology [19].

Conclusions: One-third of all patients with moderate-severe ARDS, while less than one third of non-survivors, received adjunctive strategies over the first 48 hours of ARDS. Patients that received adjuncts were more likely to have their ARDS recognized, be younger and sicker, have pneumonia, and be more difficult to ventilate than those that did not receive adjuncts. They were more likely to receive treatment in a European high income country. Clinician and system based factors such as ARDS recognition, the availability of particular adjunctive therapies, and the local expertise available may be more important factors than patient requirement or cost in driving the frequency and type of adjunct used. A more consistent and evidence driven approach to the use of adjuncts may reduce costs and improve outcomes in patients with moderate-severe ARDS.

Author Contributions: AD, ER, TP, GB, and JGL conceived the study. ER and TP performed analyses for the study. AD, ER and JGL wrote the first draft of the manuscript. All authors provided critical input into manuscript drafting, and revisions. JGL is the guarantor of the paper.

Figure Legends

Figure 1: Study population regarding the use of adjunctive strategies in all patients with moderate-severe Acute Respiratory Distress Syndrome (PaO_2/FiO_2<150) who required invasive ventilation over the first 48 hours

Figure 2: Pattern of adjunctive therapy use over the first 48h of ARDS stratified by hospital survival.
Abbreviations. NMBA: neuro muscular blocking agents; ECMO: extracorporeal membrane oxygenation; VD: vasodilators; HFOV: high frequency oscillatory ventilation.

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Table 1: Demographics, illness severity and ventilatory management data for patients with moderate-severe ARDS (i.e. PaO_2/FiO_2<150 in the first 48 hours of ARDS onset (n=1146)).

	Conventional Therapy	**Any Adjunct**	**≥ 1 widely available Adjunct**	**≥ 1 Specialized Adjunct**
Number of Patients, (%) [95% CI]	811 (71%) [68-73%]	335 (29%) [27-32%]	249 (22%) [19-24%]	86 (8%) [6-9%]
Age, years, median (IQR)	64 (51-73)	59 (46-72)*	58 (45-72)*	62 (48-71)
Female	295 (36.4)	126 (37.6)	92 (36.9)	34 (39.5)
BMI, median (IQR)	26.0 (22.8-30.2)	26.8 (23.4-30.9)*	27.1 (23.4-30.9)	26.2 (23.5-30.9)
Clinical recognition of ARDS at baseline	265 (32.7)	152 (45.4)*	119 (47.8)*	33 (38.4)
ARDS less than 24 h	104 (12.8)	37 (11.0)	28 (11.2)	9 (10.5)
Illness severity (worst during 48h)				
Adjusted SOFA	11 (8.4-14)	12 (9.6-15)*	12 (10-15.6)*	12 (9.6-14.4)
Adjusted Non-Pulmonary SOFA	7.5 (5-10)	8.9 (6-11.3)*	9 (6-11.3)*	8.8 (6.3-11)
pH	7.31 (7.22-7.39)	7.26 (7.17-7.34)*	7.25 (7.16-7.33)*	7.27 (7.19-7.38)†
PaO_2/FiO_2	105 (80-129)	89 (68-114)*	89 (69-112)*	93 (66-118)*
FiO_2, median (IQR)	0.5 (0.4-0.7)	0.6 (0.5-0.8)*	0.6 (0.5-0.8)*	0.6 (0.5-0.8)*
Ventilator Settings (worst during 48h)				
$PaCO_2$	46 (40-58)	52 (44-61)*	53 (45-62)*	47 (41-59)
Tidal volume (ml/ kg predicted body weight)	8.0 (7.0-9.3)	7.3 (6.5-8.6)*	7.4 (6.5-8.5)*	7.3 (6.5-9.2)*
PEEP	10 (7-10)	10 (8-14)*	12 (8-14)*	10 (10-13)*
Peak Inspiratory Pressure	28 (24-33)	32 (28-38)*	33 (28-38)*	31 (26-37)*†
Plateau Pressure	23 (19-28)	27 (24-30)*	27 (24-30)*	25 (20-29)
Total respiratory rate	22 (18-27)	25 (20-30)*	26 (20-30)*	24 (20-29)
ICU variables				
Number of beds	2.6 (1.5-4.5)	2.3 (1.5-3.8)	2.5 (1.6-4.0)	2.0 (1.4-3.1)
Physicians per bed, median (IQR)	0.21 (0.10-0.35)	0.25 (0.12-0.42)*	0.27 (0.12-0.42)	0.25 (0.11-0.44)
Nurses per bed, median (IQR)	0.76 (0.5-1.0)	0.58 (0.42-0.90)*	0.50 (0.42-0.75)*	0.83 (0.50-1.04)
Academic	607 (76.8)	239 (74.2)	175 (73.5)	64 (76.2)

* Any adjunct statistically different than Conventional therapy

† Value statistically different from those observed in the widely available adjunct therapy

Note: In patients in whom both widely available and specialized adjuncts were used, the patient was classified based on the use of the specialized adjunct.
Ventilator settings – data available:
Worst parameter during 48h: Adjusted SOFA (n=1146); Adjusted non respiratory SOFA (n=1144); pH (n=1135); PaO_2/FiO_2 (n=1146); paCO2 (n=1135); Tidal volume/predicted body weight (n=1095); PEEP (n=1146); Peak inspiratory pressure (n=1116); Plateau pressure (n=575); Total respiratory rate total (n=1146).

Table 2: Patterns of adjunctive measures use in the first 48 h of patients with moderate-severe ARDS (n=1146) stratified by ICU survival.

	Patients receiving measure n (%) [95%CI]	Concomitant NMBA n (%) [95%CI]	Concomitant Prone Position n (%) [95%CI]	Concomitant ECMO n (%) [95%CI]	Concomitant Inhaled Vasodilator n (%) [95%CI]	Concomitant HFOV n (%) [95%CI]	No other Adjuncts n (%) [95%CI]
NMBA							
All patients, n=1146	255 (22.3) [19.9-24.8]		57/255 (22.4) [17.4-28.0]	4/255 (1.6) [0.4-4.0]	21/255 (8.2) [5.2-12.3]	3/255 (1.2) [0.2-3.4]	177/255 (69.4) [63.3-75.0]
ARDS non-survivors, n=458	116 (25.3) [21.4-29.6]		23/116 (19.8) [13.0-28.3]	2/116 (1.7) [0.2-6.1]	6/116 (5.2) [1.9-10.9]	2/116 (1.7) [0.2-6.1]	86/116 (74.1) [65.2-81.8]
Prone position							
All patients, n=1146	79/1146(6.9) [5.5-8.5]	57/79 (72.2) [60.9-81.7]		1/79 (1.3) [0.0-6.8]	6/79 (7.6) [2.8-15.8]	0/79 (0) [0-4.6]	20/79 (25.3) [16.2-36.4]
ARDS non-survivors, n=458	31/458 (6.8) [4.6-9.5]	23/31 (74.2) [55.4-88.1]		0/31 (0) [0-11.2]	2/31 (6.5) [0.8-21.4]	0/31 (0) [0-11.2]	7/31 (22.6) [9.6-41.1]
ECMO							
All patients, n=1146	11/1146 (1.0) [0.5-1.7]	4/11 (36.4) [10.9-69.2]	1/11 (9.1) [0.2-41.3]		3/11 (27.3) [6.0-61.0]	0/11 (0) [0-28.5]	5/11 (45.5) [16.7-76.6]
ARDS non-survivors, n=458	6/458 (1.3) [0.5-2.8]	2/6 (33.3) [4.3-77.7]	0/6 (0) [0-45.9]		3/6 (50.0) [11.8-88.2]	0/6 (0) [0-45.9]	2/6 (33.3) [4.3-77.7]
Inhaled vasodilators							
All patients, n=1146	74/1146 (6.5) [5.1-8.0]	21/74 (28.4) [18.5-40.1]	6/74 (8.1) [3.0-16.8]	3/74 (4.1) [0.8-11.4]		2/74 (2.7) [0.3-9.4]	48/74 (64.9) [52.9-75.6]
ARDS non-survivors, n=458	30/458 (6.6) [4.4-9.2]	6/30 (20.0) [7.7-38.6]	2/30 (6.7) [0.8-22.1]	3/30 (10.0) [2.1-26.5]		2/30 (6.7) [0.8-22.1]	20/30 (66.7) [47.2-82.7]
HFOV							
All patients, n=1146	6/1146 (0.5) [0.2-1.1]	3/6 (50.0) [11.8-88.2]	0/6 (0) [0-45.9]	0/6 (0) [0-45.9]	2/6 (33.3) [4.3-77.7]		2/6 (33) [4.3-77.7]
ARDS non-survivors, n=458	4/458 (0.9) [0.2-2.2]	2/4 (50.0) [6.8-93.2]	0/4 (0) [0-60.2]	0/4 (0) [0-60.2]	2/4 (50.0) [6.8-93.2]		1/4 (25.0) [0.6-80.6]
None of the Above							
All patients, n=1146	811/1146 (70.8) [68.0-73.4]						
ARDS non-survivors, n=458	308/458 (67.2) [62.7-71.5]						

Abbreviations. ARDS: Acute Respiratory Distress Syndrome; NMBA: neuro muscular blocking agents; HFOV: high frequency oscillatory ventilation; ECMO: Extracorporeal Membrane Oxygenation

Table 3: Geo-economic distribution of adjunctive measures use in the first 48 h of patients with moderate-severe ARDS (n=1146).

Adjunctive therapy within 48h of ARDS	All patients (n=1146)	High income Europe (n=638)	High income Non-European (n=269)	Middle income Countries (n=239)	P-value (between groups)
Adjunct Use					
Any, n (%) [95% CI]	335 (29.2) [26.6-32.0]	230 (36.1) [32.3-39.9]	64 (23.8) [18.8-29.3]*	41 (17.2) [12.6-22.5]*	<0.001
None, n (%) [95% CI]	811 (70.8) [68.0-73.4]	408 (63.9) [60.1-67.7]	205 (76.2) [70.7-81.2]*	198 (82.8) [77.5-87.4]*	
Neuromuscular blockade n (%) [95% CI]	255 (22.3) [19.9-24.8]	183 (28.7) [25.2-32.4]	48 (17.8) [13.5-23.0]*	24 (10.0) [6.5-14.6]*†	<0.001
Prone Positioning, n (%) [95% CI]	79 (6.9) [5.5-8.5]	67 (10.5) [8.2-13.1]	2 (0.7) [0.1-2.7]*	10 (4.2) [2.0-7.6]*†	<0.001
ECMO, n (%) [95% CI]	11 (1.0) [0.5-1.7]	7 (1.1) [0.4-2.2]	4 (1.5) [0.4-3.8]	0 (0) [0-1.5]	0.200
Inhaled vasodilators, n (%) [95% CI]	74 (6.5) [5.1-8.0]	43 (6.7) [4.9-9.0]	18 (6.7) [4.0-10.4]	13 (5.4) [2.9-9.1]	0.772
High Frequency Oscillation, n (%) [95% CI]	6 (0.5) [0.2-1.1]	2 (0.3) [0.0-1.1]	4 (1.5) [0.4-3.8]	0 (0) [0-1.5]	0.052

* Value statistically different from those observed in European countries with high income.

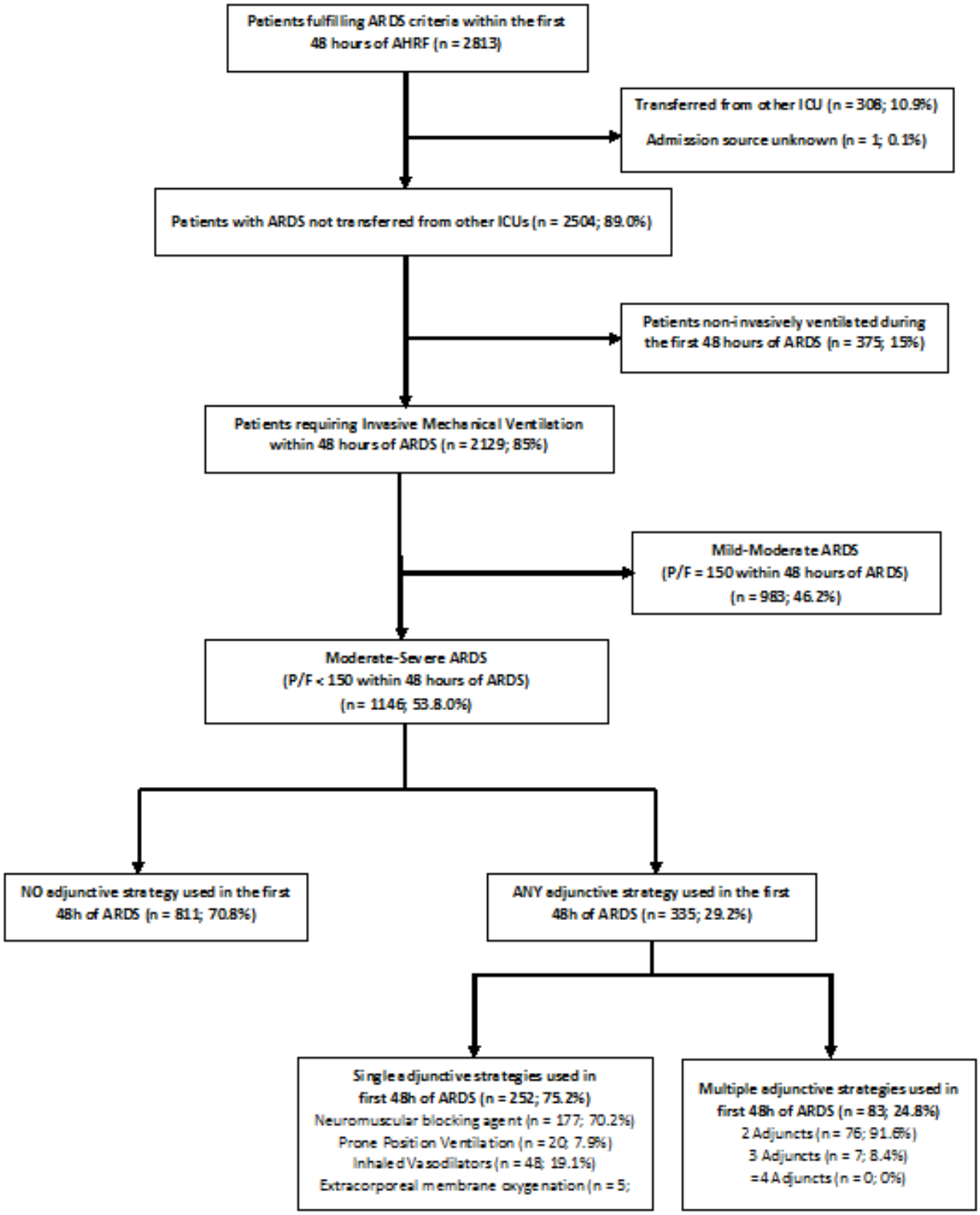
† Value statistically different from those observed in non-European countries with high income.

Abbreviations. ARDS: Acute Respiratory Distress Syndrome, ECMO: Extracorporeal Membrane Oxygenation

Table 4. Multivariate logistic regression analysis of factors associated with the use of any adjunct strategies in patients with moderate-severe ARDS within the first 48 hours.

Variable	OR	95% CI	p
Age	0.98	0.98-0.99	0.003
BMI	1.02	1.00-1.05	0.034
Pneumonia (Ref: No)	1.45	1.03-2.02	0.031
Inhalation (Ref: No)	3.32	1.08-10.18	0.036
Adjusted non respiratory SOFA	1.07	1.03-1.12	0.001
PaO_2/FiO_2 Ratio	0.99	0.99-1.00	0.021
Tidal Volume (ml/kg PBW)	0.80	0.73-0.88	<0.001
PIP	1.03	1.01-1.05	0.007
PEEP	1.13	1.08-1.19	<0.001
Nurses per bed	0.56	0.38-0.82	0.003
Physicians per bed	2.42	1.33-4.40	0.004
Clinician recognition at baseline	1.53	1.10-2.12	0.012
High income RW (Ref: High income Europe)	0.62	0.40-0.96	0.033
Middle income countries (Ref: High income Europe)	0.24	0.14-0.39	<0.001

Sample size n=956


Patients fulfilling ARDS criteria within the first 48 hours of AHRF (n = 2813)
Transferred from other ICU (n = 308; 10.9%)
Admission source unknown (n = 1; 0.1%)
Patients with ARDS not transferred from other ICUs (n = 2504; 89.0%)
Patients non-invasively ventilated during the first 48 hours of ARDS (n = 375; 15%)
Patients requiring Invasive Mechanical Ventilation within 48 hours of ARDS (n = 2129; 85%)
Mild-Moderate ARDS (P/F = 150 within 48 hours of ARDS) (n = 983; 46.2%)
Moderate-Severe ARDS (P/F < 150 within 48 hours of ARDS) (n = 1146; 53.8.0%)
NO adjunctive strategy used in the first 48h of ARDS (n = 811; 70.8%)
ANY adjunctive strategy used in the first 48h of ARDS (n = 335; 29.2%)
Single adjunctive strategies used in first 48h of ARDS (n = 252; 75.2%)
Neuromuscular blocking agent (n = 177; 70.2%)
Prone Position Ventilation (n = 20; 7.9%)
Inhaled Vasodilators (n = 48; 19.1%)
Extracorporeal membrane oxygenation (n = 5;
Multiple adjunctive strategies used in first 48h of ARDS (n = 83; 24.8%)
2 Adjuncts (n = 76; 91.6%)
3 Adjuncts (n = 7; 8.4%)
=4 Adjuncts (n = 0; 0%)