Geo-economic variations in epidemiology, patterns of care, and outcomes in patients with acute respiratory distress syndrome: insights from the LUNG SAFE prospective cohort study

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Summary

Background **Little information is available about the geo-economic variations in demographics, management, and outcomes of patients with acute respiratory distress syndrome (ARDS). We aimed to characterise the effect of these geo-economic variations in patients enrolled in the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE).**

Methods **LUNG SAFE was done during 4 consecutive weeks in winter, 2014, in a convenience sample of 459 intensive-care units in 50 countries across six continents. Inclusion criteria were admission to a participating intensive-care unit (including transfers) within the enrolment window and receipt of invasive or non-invasive ventilation. One of the trial's secondary aims was to characterise variations in the demographics, management, and outcome of patients with ARDS. We used the 2016 World Bank countries classification to define three major geo-economic groupings, namely European high-income countries (Europe-High), high-income countries in the rest of the world (rWORLD-High), and middle-income countries (Middle). We compared patient outcomes across these three groupings. LUNG SAFE is registered with ClinicalTrials.gov, number NCT02010073.**

Findings **Of the 2813 patients enrolled in LUNG SAFE who fulfilled ARDS criteria on day 1 or 2, 1521 (54%) were recruited from Europe-High, 746 (27%) from rWORLD-High, and 546 (19%) from Middle countries. We noted significant geographical variations in demographics, risk factors for ARDS, and comorbid diseases. The proportion of patients with severe ARDS or with ratios of the partial pressure of arterial oxygen (PaO_2) to the fractional concentration of oxygen in inspired air (F_IO_2) less than 150 was significantly lower in rWORLD-High countries than in the two other regions. Use of prone positioning and neuromuscular blockade was significantly more common in Europe-High countries than in the other two regions. Adjusted duration of invasive mechanical ventilation and length of stay in the intensive-care unit were significantly shorter in patients in rWORLD-High countries than in Europe-High or Middle countries. High gross national income per person was associated with increased survival in ARDS; hospital survival was significantly lower in Middle countries than in Europe-High or rWORLD-High countries.**

Interpretation **Important geo-economic differences exist in the severity, clinician recognition, and management of ARDS, and in patients' outcomes. Income per person and outcomes in ARDS are independently associated.**

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Introduction

Important geographical and economic variations in epidemiology and patterns of care have been described for diseases including diabetes,[1] asthma,[2] myocardial infarction,[3,4] heart failure,[5] atrial fibrillation,[6] chronic obstructive pulmonary disease (COPD),[7] end-stage kidney disease,[8] and breast cancer.[9] Furthermore, use of interventions such as blood transfusion,[10] amputation,[11] aneurysm repair,[12] and carotid revascularisation[13]—and outcomes after interventions such as coronary artery bypass grafting[14]—also vary by region or socioeconomic status, or both. Thus, geo-economic variations in the epidemiology and management of patients with acute respiratory distress syndrome (ARDS) could have important effects on patient outcomes, but the extent and implications of these variations have not been characterised.

The Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE)[15] in 459 intensive-care units (ICUs) in 50 countries on six continents showed a two-fold variation in the incidence of ARDS per ICU bed across the continents, which was independent of clinician recognition. ARDS was under-recognised by clinicians, and the use of evidence-based ventilatory strategies and adjuncts was less common than expected. Of most

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Research in context

Evidence before this study

We searched PubMed with the terms "respiratory distress syndrome, adult" [MeSH terms] OR ("respiratory" [all fields] AND "distress" [all fields] AND "syndrome" [all fields] AND "adult" [all fields]) OR "adult respiratory distress syndrome" [all fields] OR ("acute" [all fields] AND "respiratory" [all fields] AND "distress" [all fields] AND "syndrome" [all fields]) OR "acute respiratory distress syndrome" [all fields]) AND "geographic" [all fields] OR "country" [all fields] for articles published in any language between Jan 1, 1990, and Dec 31, 2016, the date of our final search. We also reviewed the reference lists of publications identified by our search strategy. We found some studies of the epidemiology of acute respiratory distress syndrome (ARDS) within regions or small groups of countries (eg, Europe), but no data for ARDS across major geo-economic groupings. We also identified studies showing important geo-economic variations in diseases such as diabetes, asthma, chronic obstructive pulmonary disease, and myocardial infarction.

Added value of this study

Significant variations exist in demographics, risk factors for ARDS, and comorbid diseases across the three major geo-economic groupings included in our study—namely, high-income countries in Europe, high-income countries in the rest of the world, and middle-income countries. Severity of ARDS was less overall in high-income countries in the rest of the world than in high-income European or middle-income countries. In terms of patterns of care, use of prone positioning, neuromuscular blockade, and recruitment manoeuvres were more common in high-income European countries than in the other two geo-economic groups. Length of stay in intensive-care units was shorter, and unassisted ventilation to day 28 was more common, in high-income countries in the rest of the world than in high-income European or middle-income countries. Lower gross national product was associated with poorer hospital survival in patients with ARDS. Outcomes in middle-income countries were worse than those in either high-income country grouping.

Implications of all the available evidence

Important regional differences exist in the demographics, management, and outcomes of patients with ARDS. Our data show opportunities to increase implementation of evidence-based interventions that improve outcomes for patients.

concern, ARDS had high mortality, with 40% of patients dying in hospital.[15]

A key secondary aim of LUNG SAFE was to characterise geo-economic variations in demographics, management, and outcomes of patients with ARDS. We compared patients across three major geo-economic groupings.

Methods

Study design and participants

Detailed methods for LUNG SAFE have been published elsewhere.[15] Briefly, LUNG SAFE was an international, multicentre, prospective cohort study, with a 4-week enrolment window during the winter in each hemisphere.[15] The study, which was conceived by the Acute Respiratory Failure Section of the European Society of Intensive Care Medicine, was endorsed by several national societies and networks (appendix). Its primary outcomes were to determine the incidence of ARDS in ICUs, and management of ARDS and patient outcomes in the era of the Berlin definition. All participating ICUs obtained ethics committee approval. Patients either provided informed consent, or the need for consent was waived by ethics committees. National coordinators and site investigators were responsible for obtaining ethics approval and ensuring the integrity and validity of data.

Inclusion criteria were admission to a participating ICU (including ICU transfers) within the enrolment window and receipt of invasive or non-invasive ventilation. An extended dataset was composed of all patients receiving continuous positive airway pressure therapy of 5 cm H_2O, or assisted ventilation (invasive or non-invasive) with positive end-expiratory pressure continuous positive airway pressure therapy of 5 cm or more H_2O and a ratio of the partial pressure of arterial oxygen (PaO_2) to the fractional concentration of oxygen in inspired air (F_IO_2) of less than 300. Exclusion criteria were age younger than 16 years or inability to obtain informed consent (when required). Patients were classified as having ARDS on the basis of the Berlin criteria.[16] To ensure a homogenous dataset, we restricted subsequent analyses in this Article to the large subset (2813 [93%] of 3022 patients) fulfilling the criteria for ARDS on day 1 or day 2 after the onset of acute hypoxaemic respiratory failure. Data from the first day of fulfilment of ARDS criteria were used in these analyses.

Data definitions

We used the 2016 World Bank countries classification, which includes data for gross national income per person, to define three major geo-economic groupings: high-income countries in Europe (Europe-High), high-income countries in the rest of the world (rWORLD-High), and middle-income countries (Middle).

Duration of invasive ventilation was calculated as the number of days that the patient required invasive mechanical ventilation up to day 28. Driving pressure was defined as plateau pressure minus positive-end expiratory pressure. Plateau and driving-pressure analyses were confined to patients (n=742) in whom plateau pressure was measured and in whom no evidence of spontaneous ventilation was detected (ie, when set and measured respiratory rates were equal). All modes other than volume and pressure control modes were judged to permit spontaneous breathing. Mortality was assessed on day 28, at discharge from ICU, and at discharge from hospital (or on day 90, whichever came first).

Statistical analysis

Descriptive statistics included proportions for categorical variables and mean (SD) for continuous variables. No assumptions were made for missing data, which were rare.[15] Data were unadjusted unless specifically stated otherwise. We used the χ^2 test and ANOVA or Kruskal-Wallis test (as appropriate) to assess differences among geo-economic groupings. We used the Shapiro-Wilk test to assess normality in data distribution. Bonferroni correction was applied to determine significance in the setting of multiple comparisons. We did Kaplan-Meier analysis to estimate the likelihood of liberation from invasive mechanical ventilation and of hospital mortality within 28 days of onset of acute hypoxaemic respiratory failure. We assumed that patients discharged alive from hospital before 28 days were alive on day 28. In the survival analysis, we used the log-rank test to compare survival curves among geo-economic groups.

We used mixed-effect logistic regression to assess the association between mortality and ICU-level predictors. We used a two-level random intercept model for binary responses: the first level was represented by individuals and the second level by ICUs. Demographic, risk, illness severity, and management factors were included in the first level; gross national income per person, geographical area, and ICU characteristics (number of beds, academic or non-academic ICU, beds per nurse, beds per doctor, and proportion of the total number of beds in a hospital that ICU beds account for) were included on the second level. Because some ICUs had too few observations to support the normal assumptions of the model, we applied the bootstrap method (1000 samples randomly extracted) to estimate the model parameters, odds ratio (ORs), and CIs. The individual predictors (ie, level one) were identified through the stepwise approach (forward and backward selection combined with a significance level of 0·05 both for entry and retention) and applied to a logistic regression. We included these predictors in a mixed-effect logistic regression model and then, one by one, we assessed the significance of each ICU variable (ie, level two). Analogously, we applied the mixed-effect

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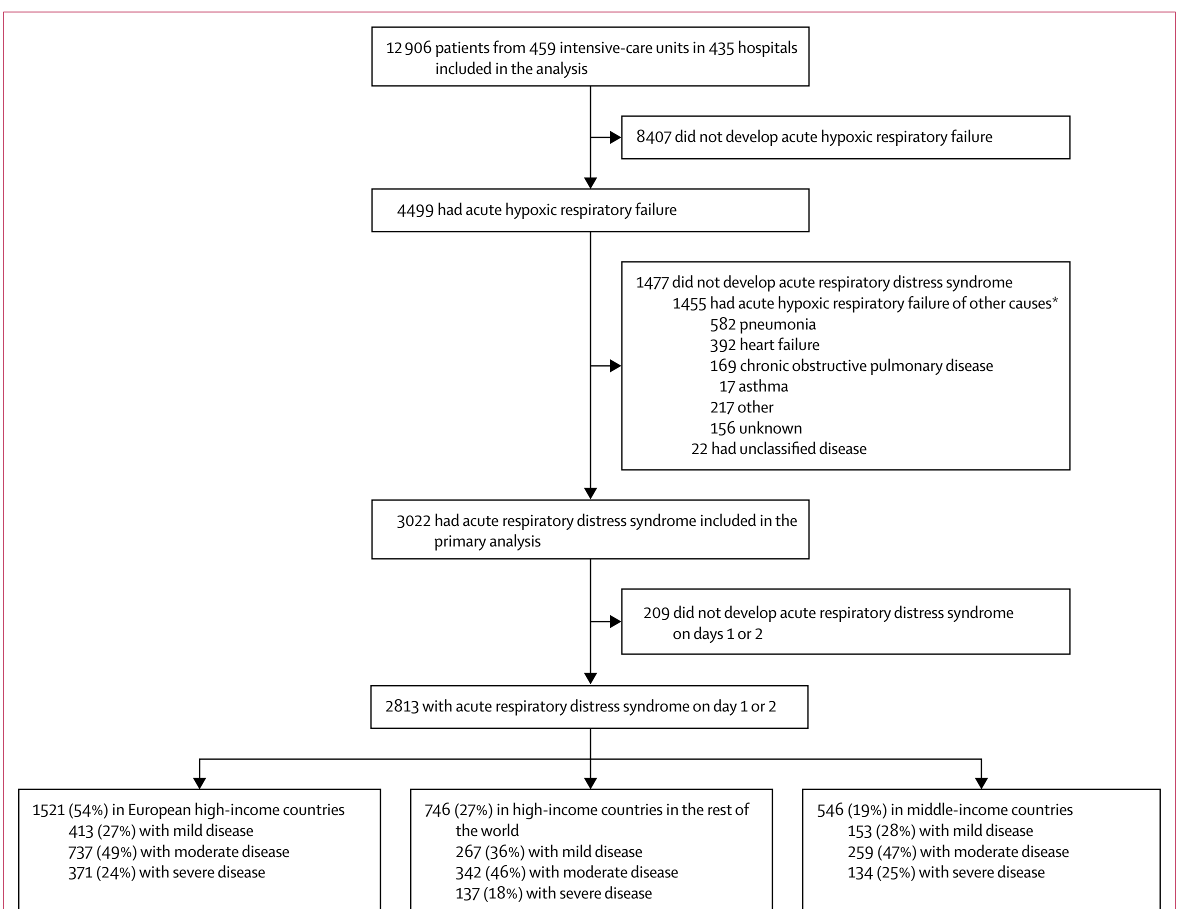

***Figure 1*: Flowchart of study population**
*Patients could have more than one cause for acute hypoxic respiratory failure.

See Online for appendix

For the **2016 World Bank countries classification** see http://databank.worldbank.org/data/home.aspx

	Participating ICUs	Academic ICUs	Enrolled patients	Patients with acute respiratory distress syndrome on day 1 or 2	ICU beds	Percentage of ICU beds in hospital	Nurse-to-bed ratio (daytime)	Physician-to-bed ratio (daytime)
High-income European countries	229	145 (63%)	6717	1521 (23%)	12 (9–17)	2·1% (1·4–3·2)	0·6 (0·4–0·9)	0·3 (0·2–0·4)
Austria	1	1 (100%)	18	3 (17%)	8 (8–8)	0·4% (0·4–0·4)	0·9 (0·9–0·9)	0·5 (0·5–0·5)
Belgium	6	5 (84%)	145	36 (25%)	15 (14–22)	1·8% (1·3–5·4)	0·5 (0·5–0·5)	0·1 (0·1–0·1)
Czech Republic	1	1 (100%)	24	2 (8%)	23 (23–23)	1·8% (1·8–1·8)	0·2 (0·2–0·2)	0·1 (0·1–0·1)
Denmark	2	2 (100%)	70	22 (31%)	19 (14–23)	2·5% (1·9–3·1)	1·0 (1·0–1·1)	0·3 (0·2–0·3)
France	41	21 (51%)	1312	347 (26%)	15 (12–17)	1·7% (1·3–2·5)	0·4 (0·4–0·5)	0·3 (0·2–0·4)
Germany	6	2 (33%)	275	17/275 (6%)	11 (10–14)	3·2% (2·2–3·8)	0·4 (0·3–0·4)	0·3 (0·2–0·4)
Greece	5	3 (60%)	100	18 (18%)	7 (7–9)	1·3% (1·0–1·6)	0·7 (0·7–0·8)	0·7 (0·6–0·7)
Ireland	8	8 (100%)	277	101 (36%)	13 (8–17)	2·1% (1·4–2·6)	1·2 (1·2–1·3)	0·1 (0·1–0·1)
Italy	32	16 (50%)	752	125 (17%)	8 (8–10)	1·4% (1·1–2·0)	0·5 (0·5–0·6)	0·3 (0·2–0·4)
Latvia	1	1 (100%)	19	5 (26%)	19 (19–19)	4·8% (4·8–4·8)	0·4 (0·4–0·4)	0·2 (0·2–0·2)
Netherlands	7	3 (43)	412	59 (14%)	27 (15–32)	3·7% (2·7–4·2)	0·8 (0·7–0·9)	0·1 (0·1–0·1)
Norway	4	3 (75%)	116	33 (28%)	11 (10–21)	2·8% (1·3–4·5)	1·0 (0·9–1·1)	0·3 (0·2–0·3)
Poland	1	1 (100%)	13	5 (38%)	8 (8–8)	0·7% (0·7–0·7)	1·0 (1·0–1·0)	0·3 (0·3–0·3)
Portugal	11	5 (46%)	247	80 (32%)	8 (6–14)	1·9% (1·7–2·2)	0·7 (0·6–0·8)	0·5 (0·5–0·6)
Spain	45	39 (87%)	1030	259 (25%)	17 (12–20)	3·0% (2·7–4·3)	0·5 (0·4–0·5)	0·4 (0·4–0·6)
Sweden	10	8 (80%)	330	65 (20%)	9 (7–10)	1·4% (1·2–1·9)	0·7 (0·7–0·8)	0·4 (0·3–0·5)
Switzerland	2	1 (50%)	136	22 (16%)	21 (6–35)	3·2% (2·4–4·0)	0·8 (0·7–0·9)	0·3 (0·2–0·3)
UK	46	25 (54%)	1441	322 (22%)	12 (9–19)	2·2% (1·6–3·2)	1·0 (0·8–1·1)	0·1 (0·1–0·2)
High-income countries (rest of world)	110	79 (72%)	3615	746 (21%)	16 (10–22)	3·1% (2·0–6·1)	0·8 (0·5–1·0)	0·1 (0·1–0·3)
Australia	12	12 (100%)	695	125 (18%)	17 (13–24)	3·3% (2·7–4·9)	1·2 (1·0–1·3)	0·1 (0·1–0·2)
Brunei	1	1 (100%)	21	5 (24%)	26 (26–26)	4·7% (4·7–4·7)	0·5 (0·5–0·5)	0·1 (0·1–0·1)
Canada	8	8 (88%)	380	88 (23%)	24 (18–26)	5·8% (4·3–9·6)	1·0 (0·9–1·1)	0·1 (0·1–0·1)
Chile	7	4 (57%)	116	37 (32%)	9 (8–16)	2·6% (2·3–7·5)	0·3 (0·3–0·4)	0·1 (0·1–0·4)
Japan	28	15 (54%)	643	81 (13%)	10 (8–15)	2·0% (1·2–3·0)	1·0 (0·8–1·2)	0·3 (0·2–0·3)
New Zealand	6	3 (50%)	142	27 (19%)	9 (6–16)	2·2% (2·0–2·8)	0·9 (0·8–1·1)	0·2 (0·2–0·2)
Saudi Arabia	7	5 (71%)	120	57 (48%)	9 (8–20)	1·7% (0·8–3·4)	1·1 (1·0–2·8)	0·2 (0·1–0·5)
USA	35	31 (89%)	1421	306 (22%)	20 (12–25)	4·1% (2·0–6·4)	0·7 (0·5–0·8)	0·1 (0·1–0·1)
Uruguay	6	1 (17%)	77	20 (26%)	10 (10–14)	8·3% (5·6–14·0)	0·3 (0·3–0·6)	0·3 (0·3–0·4)
Middle-income countries	120	76 (63%)	2574	546 (21%)	15 (10–23)	2·7% (1·5–6·7)	0·6 (0·5–0·9)	0·3 (0·1–0·4)
Albania	2	2 (100%)	32	3 (9%)	15 (15–15)	1·1% (1·1–1·1)	0·3 (0·3–0·3)	0·3 (0·3–0·3)
Argentina	18	12 (67%)	280	77 (28%)	12 (8–16)	6·0% (3·8–10·0)	0·5 (0·5–0·6)	0·4 (0·3–0·4)
Brazil	8	2 (25%)	47	18 (38%)	10 (8–10)	10·8% (5·0–11·3)	0·2 (0·1–0·3)	0·2 (0·1–0·2)
China	35	21 (60%)	1181	189 (16%)	20 (16–30)	1·5% (0·9–1·8)	0·8 (0·6–1·2)	0·3 (0·2–0·5)
Colombia	1	1 (100%)	89	39 (44%)	80 (80–80)	..	..	0·1 (0·1–0·1)
Costa Rica	2	2 (100%)	30	13 (43%)	12 (8–16)	1·8% (1·0–2·6)	0·5 (0·5–0·5)	0·1 (0·1–0·1)
Ecuador	2	1 (50%)	2	1 (50%)	12 (12–12)	4·8% (4·8–4·8)	0·3 (0·3–0·3)	0·3 (0·3–0·3)
Guatemala	2	2 (100%)	25	2 (8%)	10 (10–10)	16·7% (16·7–16·7)	0·6 (0·4–0·8)	0·4 (0·1–0·6)
India	10	4 (40%)	206	56 (27%)	19 (14–29)	4·7% (2·4–10·8)	0·8 (0·6–1·0)	0·1 (0·1–0·2)
Iran	2	1 (50%)	61	9 (15%)	28 (26–30)	5·8% (3·0–8·7)	1·2 (0·6–1·9)	0·1 (0·1–0·2)
Lebanon	1	0 (0%)	1	1 (100%)	..	..	..	..
Malaysia	1	0 (0%)	6	0 (0%)	3 (3–3)	1·5% (1·5–1·5)	0·7 (0·7–0·7)	0·3 (0·3–0·3)
Mexico	10	8 (80%)	118	40 (34%)	9 (6–11)	4·4% (2·7–6·9)	0·8 (0·7–1·0)	0·3 (0·3–0·5)
Morocco	5	4 (80%)	48	12 (25%)	10 (7–21)	1·7% (1·1–2·3)	0·8 (0·6–1·5)	0·4 (0·2–0·6)
Peru	2	1 (50%)	51	5 (9%)	20 (15–24)	4·4% (1·6–7·1)	0·5 (0·4–0·5)	0·2 (0·1–0·3)
Philippines	2	1 (50%)	18	5 (28%)	16 (12–20)	2·8% (1·7–3·9)	0·9 (0·7–1·0)	0·1 (0·0–0·1)

(Table 1 continues on next page)

	Participating ICUs	Academic ICUs	Enrolled patients	Patients with acute respiratory distress syndrome on day 1 or 2	ICU beds	Percentage of ICU beds in hospital	Nurse-to-bed ratio (daytime)	Physician-to-bed ratio (daytime)
(Continued from previous page)								
Romania	3	3 (100%)	106	19 (18%)	28 (18–38)	3·1% (2·3–3·5)	0·3 (0·2–0·5)	0·1 (0·1–0·2)
Russia	2	2 (100%)	11	3 (27%)	78 (78–78)	7·1% (7·1–7·1)	0·3 (0·3–0·3)	0·2 (0·2–0·2)
Serbia	3	2 (67%)	56	5 (9%)	25 (25–25)	2·0% (2·0–2·0)	0·5 (0·5–0·5)	0·1 (0·1–0·1)
South Africa	1	1 (100%)	70	19 (27%)	10 (10–10)	1·3% (1·3–1·3)	1·3 (1·3–1·3)	0·1 (0·1–0·1)
Tunisia	4	2 (50%)	51	15 (29%)	12 (10–13)	2·9% (1·3–4·5)	0·5 (0·5–0·5)	0·2 (0·2–0·2)
Turkey	4	4 (100%)	85	15 (18%)	19 (17–20)	1·5% (1·3–5·0)	0·4 (0·4–0·6)	0·2 (0·1–0·2)

Data are n, n (%), or median (IQR). ICU=intensive-care unit.

***Table 1*: Geographical distribution of participating ICUs, enrolled patients, and organisational differences**

Poisson regression to assess the association between ICU-level predictors and length of stay in the ICU and duration of invasive mechanical ventilation.

Statistical analyses were done with R (version 3.0.2) and SAS (version 9.4). All p values were two-sided, and values less than 0·05 were deemed significant. The study protocol, case-report form, and full statistical analysis plan are in the appendix.

Role of the funding source

The study funders had no role in study design; data collection, analysis, or interpretation; or writing of the Article. JGL, FM, GB, TP, and EF had access to the raw data. The corresponding author had full access to all data and final responsibility for the decision to submit for publication.

Results

Of the 12 906 patients screened for the LUNG SAFE study, 2813 (22%) fulfilled ARDS criteria on day 1 or 2 after enrolment. Of these 2813 participants, 1521 (54%) were recruited from Europe-High, 746 (27%) from rWORLD-High, and 546 (19%) from Middle countries (figure 1). In Europe-High countries, 23% of screened patients had ARDS, compared with 21% in both rWORLD-High and Middle countries (table 1). Overall 300 (65%) of the 459 participating ICUs were in academic hospitals, with a median of 14 beds (IQR 9–20) per ICU, a median nurse-to-bed daytime ratio of 0·6 (0·5–1·0), and a median physician-to-bed daytime ratio of 0·3 (0·1–0·4).

Patients from Europe-High countries were significantly older (p<0·01 *vs* r-WORLD-High; p<0·0001 *vs* Middle; table 2). Body-mass index was signicantly higher in patients in rWORLD-High countries than in those in Europe-High countries (p=0·0076), who in turn had significantly higher body-mass indices than those in Middle countries (p<0·0001; table 2). Diabetes mellitus, chronic renal failure, and liver disease were significantly more frequent pre-existing comorbidities in rWORLD-High countries than in Europe-High or Middle countries, whereas congestive heart failure was more common in patients from Middle countries than in those from rWorld-High countries (appendix). Pneumonia was the dominant risk factor for ARDS across each group (appendix). Extra-pulmonary sepsis was significantly more common in Middle countries than in Europe-High or rWORLD-High countries, and differences were also noted in the frequency of trauma, inhalational injury, pancreatitis, and the presence of no risk factors in patients with ARDS (appendix).

Severity of ARDS varied by region, with mild disease significantly more common, and severe disease significantly less common in rWORLD-High countries than in Europe-High or Middle countries (table 2; appendix). The proportions of patients with a PaO_2:F_IO_2 ratio of less than 150 and patients with persistent severe ARDS were significantly lower in rWORLD-High countries than in Europe-High countries (table 2). Mean PaO_2:F_IO_2 ratios were significantly higher in rWORLD-High countries than in Europe-High and Middle countries (p<0·0001 for both comparisons; table 2). Worst non-pulmonary sepsis-related organ failure assessment (SOFA) scores were significantly lower in Europe-High countries than in rWorld-High (p=0·0163) or Middle (p=0·0004) countries (table 2).

Clinician recognition of ARDS was significantly less common in rWORLD-High than in Europe-High or Middle countries (p<0·0001 for both comparisons; table 3). Significantly more patients (67%) received lower tidal volumes (≤8 mL/kg of predicted bodyweight) in rWORLD-High countries than in Europe-High (62%; p=0·02) and Middle countries (61%; p=0·02; figure 2A). The proportion of patients in whom plateau pressure was measured was highest in patients from Middle countries (table 3). The distributions of driving pressures were similar acrosss the three regions (figure 2C). Over 50% of patients in Middle countries had a positive end expiratory pressure of less than 7·5 cm H_2O, compared with 44% of participants in Europe-High (p=0·0011) and 40% in rWORLD-High countries (p<0·0001; figure 2D).

	All (n=2813)	European high-income countries (n=1521)	High-income countries (rest of world) (n=746)	Middle-income countries (n=546)	p value (among groups)
Demographic data					
Mean age (years)	61·3 (16·8)	62·6 (15·7)	60·7 (17·0)*	58·5 (18·8)*	<0·0001
Male	1729 (61·5)	962 (63·2)	443 (59·4)	324 (59·3)	0·11
Men:women	1·6:1·0	1·7:1·0	1·5:1·0	1·5:1·0	
Body-mass index	27·5 (8·7)	27·5 (7·3)	29·1 (12·1)*	25·5 (6·2)*†	<0·0001
Acute respiratory distress syndrome severity (day 1)					
Mild disease	833 (30%)	413 (27%)	267 (36%)*	153 (28%)†	<0·0001
Moderate disease	1338 (48%)	737 (48%)	342 (46%)	259 (47%)	0·50
Severe disease	642 (23%)	371 (24%)	137 (18%)*	134 (25%)†	0·0032
PaO_2:F_IO_2 <150 mm Hg	1361 (48%)	791 (52%)	309 (41%)*	261 (48%)	<0·0001
Persistent severe disease‡	197/2659 (7%)	126/1439 (9%)	26/702 (4%)*	45/518 (9%)†	<0·0001
No longer fulfilling disease criteria after 24 h	486 (17%)	247 (16%)	143 (19%)	96 (18%)	0·22
Gas exchange (day 1)					
PaO_2:F_IO_2 at disease onset (mm Hg)	160·4 (67·3)	155·5 (65·8)	171·8 (68·7)*	158·5 (67·7)†	<0·0001
SpO_2	94·7 (5·2)	94·5 (5·0)	95·2 (5·0)*	94·4 (6·1)	0·0096
$PaCO_2$ (mm Hg)	46·0 (15·4)	47·2 (14·9)	45·7 (15·6)*	43·4 (16·2)*†	<0·0001
pH	7·33 (0·12)	7·32 (0·12)	7·34 (0·11)*	7·35 (0·12)*	0·0002
SOFA scores§					
Day 1	9·5 (4·1)	9·3 (4·0)	9·8 (4·2)	9·8 (4·5)	0·11
Day 1 non-pulmonary score	6·3 (4·1)	6·1 (3·9)	6·7 (4·2)*	6·4 (4·4)	0·0397
Worst score	11·1 (4·4)	10·8 (4·1)	11·2 (4·5)	11·9 (4·7)*†	0·0002
Worst non-pulmonary score	8·0 (4·2)	7·7 (4·0)	8·3 (4·3)*	8·6 (4·6)*	0·0007

Data are mean (SD), n (%), or n/N (%), unless otherwise specified. Among groups p values refer to a comparison across the three geo-economic regions. p values for between-group comparisons are in the appendix. LUNG SAFE=Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure. PaO_2=partial pressure of arterial oxygen. F_IO_2=fraction of inspired oxygen. SpO_2=peripheral capillary oxygen saturation. $PaCO_2$=partial pressure of arterial carbon dioxide. SOFA=sepsis-related organ failure assessment. *Significantly different from European high-income countries. †Significantly different from high-income countries in the rest of the world. ‡Defined as PaO_2:F_IO_2 ≤100 mm Hg for greater than 48 h from onset of acute respiratory distress syndrome. Prevalence was calculated in patients in the intensive-care unit for at least 48 h. §Adjusted for missing items.

***Table 2*: Demographic and illness severity data in patients with acute respiratory distress enrolled in LUNG SAFE**

The proportion of patients receiving protective ventilation (defined as a tidal volume ≤8 mL/kg of predicted bodyweight and plateau pressure of ≤30 cm H_2O) did not differ significantly between geo-economic groupings (table 3). Spontaneous ventilation in early ARDS was significantly more frequent in patients from rWORLD-High countries than in those from Europe-High countries (table 3). Inspired oxygen use differed by region: low FiO_2 (ie, $FiO_2 \leq 0 \cdot 4$) was significantly more common in rWORLD-High countries than in Europe-High countries ($p<0 \cdot 0001$), and high FiO_2 (ie, >0·6) was significantly more frequent in Europe-High than in rWORLD-High ($p=0 \cdot 0070$) or Middle ($p=0 \cdot 0060$) countries (figure 2E). Hypercapnia (defined as a partial pressure of carbon dioxide in arterial blood [$PaCO_2$] ≥45 mm Hg) was significantly more frequent in patients from Europe-High countries than in those from rWORLD-High countries ($p=0 \cdot 124$), whereas hypocapnia was significantly more frequent in patients from Middle countries than in those from Europe-High ($p<0 \cdot 0001$) or rWORLD countries ($p<0 \cdot 0001$; appendix). Modes of ventilation differed by region; use of pressure support was significantly less common—and use of synchronised intermittent mandatory ventilation significantly more common—in Middle countries than in Europe-High or rWORLD-High countries (appendix). Use of volume and pressure-control ventilation modes, and non-invasive ventilation did not differ by geo-economic group (figure 2; appendix).

Use of neuromuscular blockade and prone positioning in all patients, and in the subgroup with a PaO_2:F_IO_2 ratio of less than 150, were significantly more common in patients from Europe-High countries than in those from Middle ($p<0 \cdot 0001$ and $p=0 \cdot 002$, respectively) or rWORLD-High countries ($p<0 \cdot 0001$ for both comparisons; figure 2; appendix). Use of extracorporeal membrane oxygenation was significantly less common in Middle countries than in both other regions (figure 2; appendix). Use of recruitment manoeuvres was lower in rWORLD-High countries than in Middle or Europe-High countries (figure 2; appendix). Adjustment for severity of ARDS did not account for the regional differences in the use of adjunctive measures (data not shown).

	All	European high-income countries	High-income countries (rest of world)	Middle-income countries	p value (among groups)
Clinical recognition of acute respiratory distress syndrome					
All patients	1735/2813 (62%)	967/1521 (64%)	406/746 (54%)*	362/546 (66%)†	<0·0001
Mild disease	407/833 (49%)	217/413 (53%)	113/267 (42%)*	77/153 (50%)	0·0311
Moderate disease	844/1338 (63%)	468/737 (64%)	199/342 (58%)	177/259 (68%)†	0·0360
Severe disease	484/642 (75%)	282/371 (76%)	94/137 (69%)	108/134 (81%)	0·07
Tidal volume >8 mL/kg of predicted bodyweight					
All patients	937/2553 (37%)	533/1407 (38%)	210/644 (33%)*	194/502 (39%)†	0·0428
Receiving invasive mechanical ventilation	792/2255 (35%)	435/1210 (36%)	187/599 (31%)	170/446 (38%)†	0·0468
Airway plateau pressure measured					
Invasively ventilated patients	954/2377 (40%)	487/1263 (39%)	214/649 (33%)*	253/465 (54%)*†	<0·0001
Patients with controlled ventilation	762/1628 (47%)	413/954 (43%)	166/399 (42%)	183/275 (67%)*†	<0·0001
Plateau pressure (cm H_2O)‡	23·20 (6·12)	23·60 (5·65)	23·30 (5·86)	22·19 (7·17)*	0·0229
Plateau pressure >30 cm H_2O‡	72/742 (10%)	34/395 (9%)	17/166 (10%)	21/181 (12%)	0·51
Positive end-expiratory pressure (cm H_2O)	8·22 (3·21)	8·30 (3·18)	8·42 (3·48)	7·70 (2·82)*†	0·0010
Driving pressure (cm H_2O)	14·73 (5·54)	15·16 (5·44)	14·36 (5·20)	14·12 (6·00)	0·08
F_IO_2	0·64 (0·23)	0·65 (0·23)	0·62 (0·24)*	0·63 (0·22)	0·0113
Receiving protective ventilation§	607/957 (63%)	309/490 (63%)	143/206 (69%)	155/261 (59%)	0·08
Standardised minute ventilation (L/min)¶	11·3 (5·3)	11·7 (5·6)	11·0 (5·2)*	10·2 (4·6)*†	<0·0001
Spontaneous ventilation in first 48 h from disease onset					
All	1478/2769 (53%)	737/1492 (49%)	445/739 (60%)*	296/538 (55%)	<0·0001
PaO_2:F_IO_2 <150 mm Hg	647/1342 (48%)	343/780 (44%)	174/304 (57%)*	130/258 (50%)	0·0003

Data are n/N (%) or mean (SD). Driving pressure and plateau pressure were assessed in patients in whom no evidence of spontaneous ventilation was noted. Among groups p values refer to a comparison across the three geo-economic regions. p values for between-group comparisons are in the appendix. LUNG SAFE=Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure. F_IO_2=fraction of inspired oxygen. PaO_2=partial pressure of arterial oxygen. *Significantly different from European high-income countries. †Significantly different from high-income countries in the rest of the world. ‡Plateau pressure values were limited to patients in whom this value was reported and in whom either an assist control mode or a mode permitting spontaneous ventilation was used. The set and total respiratory rates were equal. Patients receiving high-frequency oscillatory ventilation or extracorporeal membrane oxygenation were also excluded. §Tidal volume ≤8 mL/kg and plateau pressure ≤30 cm H_2O. ¶Standardised minute ventilation=minute ventilation x partial pressure of arterial carbon dioxide/40 mm Hg.

***Table 3*: Management of patients with acute respiratory distress syndrome enrolled in LUNG SAFE**

Unadjusted duration of invasive ventilation and length of stay in ICUs were significantly shorter in rWORLD-High countries than in Europe-High (p=0·0001 and p=0·002, respectively) or Middle countries (p=0·0002 and p<0·0001, respectively; appendix). Kaplan-Meier analyses showed significant differences in the probability of weaning from invasive ventilation at each level of severity of ARDS (figure 3; appendix). Probability of weaning was significantly greater in patients from rWORLD-High countries than in those from Europe-high or Middle countries (p<0·0001 for both; figure 3A). Multivariate analyses showed that the adjusted incidence rate ratios for duration of invasive mechanical ventilation and length of ICU stay were significantly higher in Europe-High countries than in rWORLD-High countries (figure 4; appendix).

Unadjusted ICU and hospital mortality were both significantly lower in rWORLD-High countries than in Europe-High (p=0·0006) or Middle countries (p<0·0001; appendix). 28-day survival was highest in rWORLD-High countries and lowest in Middle countries (figure 3). The adjusted odds ratios for ICU and hospital survival were significantly higher in rWORLD-High and Europe-High countries than in Middle countries (figure 4; appendix). Differences in approaches to mechanical ventilation did not result in significant geo-economic variations in ICU or hospital mortality (appendix). Patient-level variables associated with hospital mortality included age, active or haematological neoplasm, chronic liver failure, acidosis, PaO_2:F_IO_2, non-pulmonary SOFA score, and respiratory rate (table 4; appendix). We noted no independent association between ICU-level variables and hospital mortality (table 4; appendix).

In a separate multivariate analysis across all countries (ie, without any grouping) in which gross domestic product per person was a continuous variable, all-cause mortality in ARDS was independently associated with gross domestic product (table 4). Respiratory (42%) and cardiovascular failure (37%) were the most common factors leading to death in ICUs, and we noted no significant geographical variations (appendix). Decisions

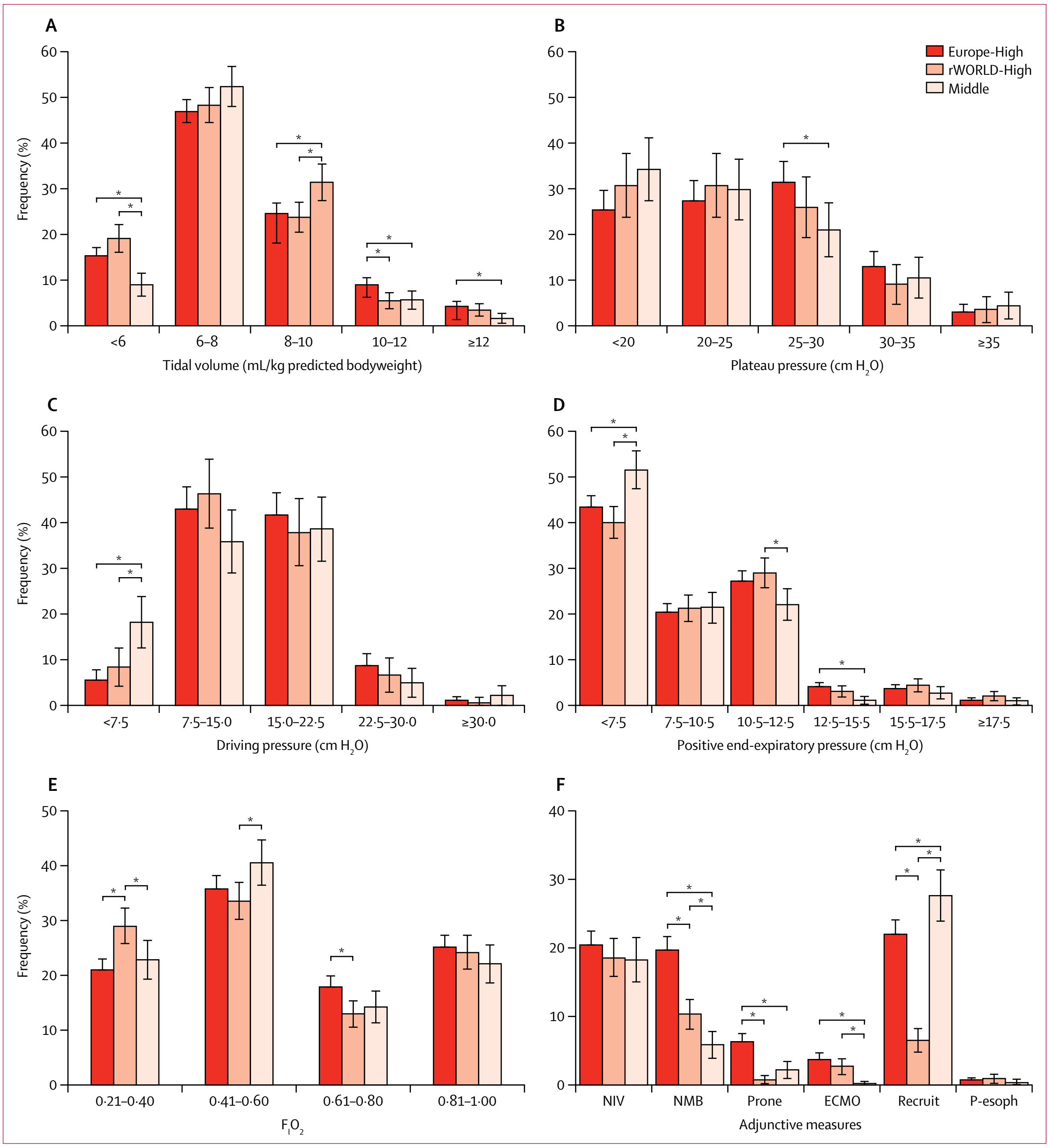

***Figure 2*: Tidal volume (A), plateau pressure (B), driving pressure (C), positive end-expiratory pressure (D), F_IO_2 (E), and adjunctive measures (F), by geo-economic region**

Error bars represent 95% CIs. p values for between-group comparisons are in the appendix. F_IO_2=fractional concentration of oxygen in inspired air. Europe-High=high-income European countries. rWORLD-High=high-income countries in the rest of the world. Middle=middle-income countries. NIV=non-invasive ventilation. NMB=neuromuscular blockade. ECMO=extracorporeal membrane oxygenation. Recruit=recruitment manoeuvres. P-esoph=oesophageal pressure. *Shows significant between-region differences.

about limitation of life-sustaining measures were less frequent in Middle (17%) than in Europe-High (27%) or rWORLD (26%) countries (appendix).

Discussion

In this prospective observational cohort study, we noted important differences in severity patterns, extent of clinician recognition, and approaches to management of ARDS across geo-economic regions. Patients from Europe-High countries had longer durations of mechanical ventilation and ICU stays than did patients from rWORLD-High countries. We show for the first time (to our knowledge) that indices of national socioeconomic status are associated with survival in ARDS.

Although the patients from the three regions differed significantly in terms of their demographics, the effect of these differences on outcomes seems small. The older age of patients from Europe-High countries could partly explain the higher unadjusted mortality in this region compared with rWORLD-High and Middle countries, because age was independently associated with hospital mortality in this and previous studies.[17–19] Of the pre-existing comorbidities associated with poor outcomes, only chronic liver failure differed significantly in frequency: it was more common in rWORLD-High countries than in Middle countries. The pattern of critical illnesses seemed to differ between regions: patients from Europe-High countries had greater severity of ARDS and were more likely to have persistent severe disease than those from rWORLD-High countries, whereas those from rWORLD-High countries had more severe systemic illness than those from Europe-High countries. As has previously been shown, both severity of ARDS and non-pulmonary SOFA scores were independently associated with hospital mortality.[19]

The greater use in Europe-High countries of neuromuscular blockade and prone positioning in patients with a PaO_2:F_IO_2 ratio of less than 150 could reflect the fact that these approaches were largely developed in Europe-High countries,[20,21] and might have penetrated to a lesser extent to the rest of the world. Other possible explanations include the unavailability of cisatracurium in some countries or lack of hands-on experience with prone positioning. Even in Europe-High countries, however, prone positioning was used in less than 10% of patients with a PaO_2:F_IO_2 ratio of less than 150, the population in which proning improves outcomes.[20] A large clinical trial is being done in the USA by the PETAL network (NCT02509078) to address uncertainty about the efficacy of neuromuscular blockade in ARDS. Variations in the use of adjunctive measures cannot be explained by differences in severity profile, economic differences (with the possible exception of extracorporeal membrane oxygenation, which was used less often in Middle countries), or by differences in recognition of ARDS. The absence of regional variation in the use of non-invasive ventilation suggests that barriers to the use of adjuncts can be addressed.[22] Understanding and addressing local barriers to, and facilitators of, implementation of simple and inexpensive adjunctive measures, such as prone positioning and neuromuscular blockade, should be prioritised, in view of the potential to improve survival.

Patients from Europe-High countries had longer durations of mechanical ventilation and ICU stays than did those from rWORLD-High countries. These differences persisted after adjustment for disease severity and other covariates. Importantly, we found no associations between ICU-level variables and outcomes from ARDS, suggesting that differences in ICU organisation or staffing do not explain the effect of income. This finding implies that differences in approaches to management of ARDS could have important implications for these highly patient-centred outcomes. Potential explanations include that the proportion of patients who received large tidal volumes was lowest in rWORLD-High countries and highest in Europe-High countries, a concern because high tidal volumes have been associated with poor outcomes.[23] The greater use of higher oxygen concentrations (ie, F_IO_2 >0·6) in patients from Europe-High countries is of concern, because use of high FiO_2 in critically ill patients could be harmful.[24] Other potential explanations include differences in practices for weaning from ventilation, but we do not have any data to examine this issue.

Clinician recognition of ARDS was significantly lower in rWORLD-High countries than in Europe-High countries, although the difference was not significant for

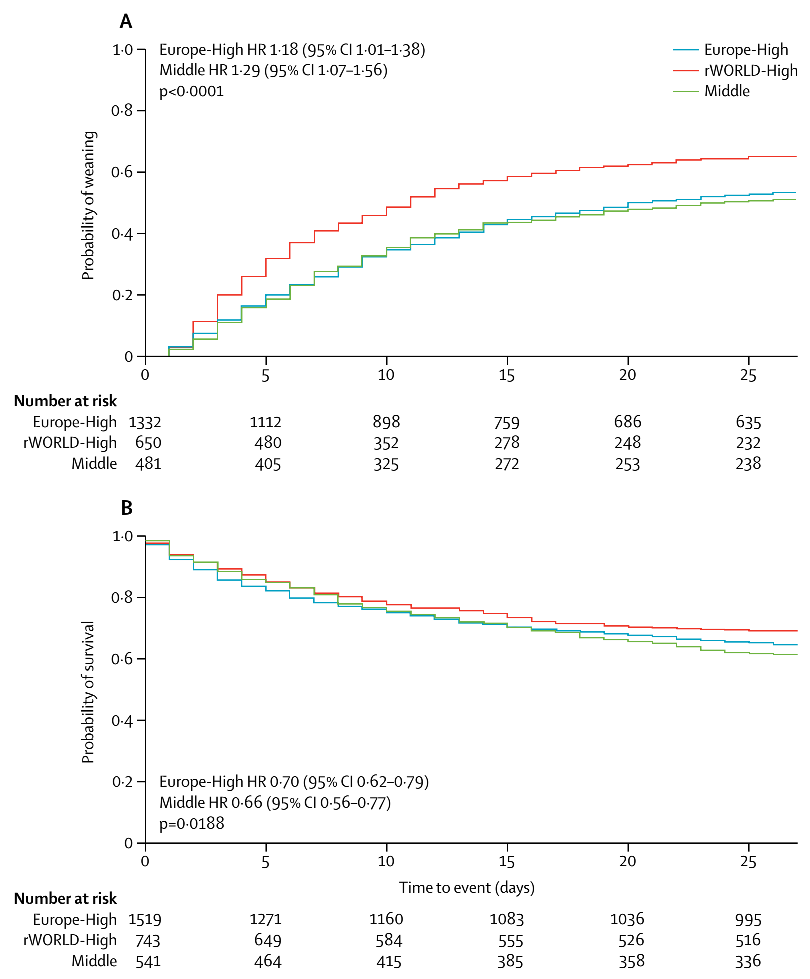

***Figure 3*: Kaplan-Meier curves of probability of weaning from mechanical ventilation (A) and hospital survival (B), by geo-economic region**

Patients discharged before day 28 were assumed to be alive and off invasive mechanical ventiation on that day. HRs were estimated with Cox proportional hazard models; we used rWORLD-High as the reference category. We used the log-rank test to assess the differences between curves. HR=hazard ratio. Europe-High=high-income European countries. rWORLD-High=high-income countries in the rest of the world. Middle=middle-income countries.

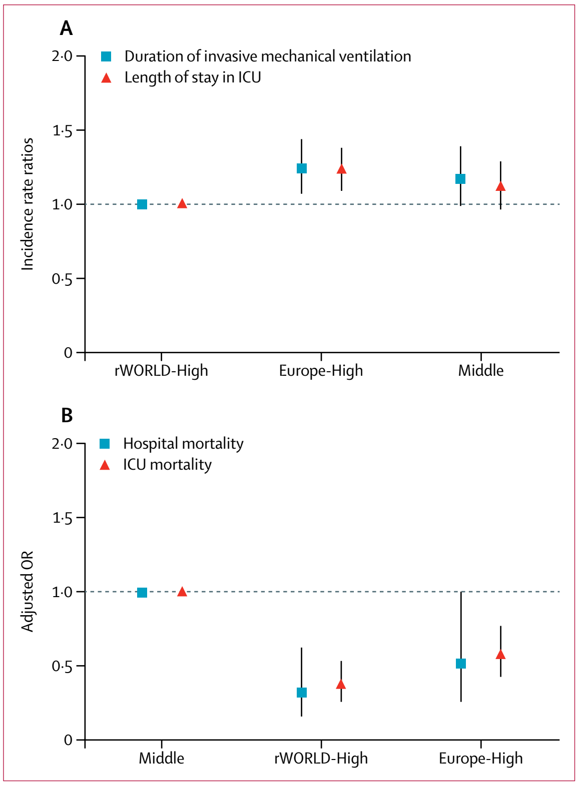

***Figure 4:* Adjusted incidence rate ratios for duration of mechanical ventilation and length of stay in ICU (A), and adjusted ORs of ICU and hospital mortality (B), by each geo-economic region**
rWORLD-High is the reference point for (A) and Middle for (B). Error bars represent 95% CIs. ICU=intensive-care unit. OR=odds ratio. Europe-High=high-income European countries. rWORLD-High=high-income countries in the rest of the world. Middle=middle-income countries.

	Parameter estimate (95% CI)	OR (95% CI)
Patient variables		
Age (years)	0·036 (0·026 to 0·046)	1·037 (1·026 to 1·047)
Active neoplasm*	0·749 (0·198 to 1·328)	2·115 (1·219 to 3·775)
Haematological neoplasm*	1·938 (1·222 to 2·802)	6·946 (3·395 to 16·473)
Chronic liver failure*	1·569 (0·815 to 2·504)	4·801 (2·260 to 12·228)
pH	–1·927 (–2·560 to –1·374)	0·146 (0·077 to 0·253)
PaO_2:F_IO_2 (mm Hg)	–0·002 (–0·005 to –0·0001)	0·998 (0·995 to 0·9999)
Non-pulmonary SOFA score (adjusted)	0·133 (0·094 to 0·174)	1·142 (1·099 to 1·190)
Respiratory rate (breaths per min)	0·047 (0·021 to 0·074)	1·048 (1·021 to 1·076)
Intensive-care unit variables		
Gross domestic product†	–0·017 (–0·028 to –0·007)	0·983 (0·973 to 0·993)
Number of beds	–0·005 (–0·023 to 0·012)	0·995 (0·977 to 1·012)
Proportion of beds in hospital	–0·001 (–0·005 to 0·005)	1·000 (0·995 to 1·005)
Beds per physician	0·009 (–0·029 to 0·053)	1·009 (0·972 to 1·054)
Beds per nurse	0·011 (–0·127 to 0·192)	1·011 (0·881 to 1·212)
Academic*	–0·098 (–0·496 to 0·307)	0·907 (0·609 to 1·360)

Patients discharged before day 90 were assumed to be alive at day 90. Inclusion criteria were onset of acute respiratory distress syndrome within 48 h from acute hypoxaemic respiratory failure. All patient variables were measured at disease onset. OR=odds ratio. PaO_2=partial pressure of arterial oxygen. F_IO_2=fraction of inspired oxygen. SOFA=sequential organ-failure assessment. *Yes versus no (reference). †In thousands of US$, 2014 (source: World Bank).

***Table 4:* Mixed-effects logistic regression model of factors associated with all-cause hospital mortality**

severe disease. Decision making about limitation of life-sustaining measures was similar in Europe-High and rWORLD-High countries, so it is unlikely to explain these differences in duration of mechanical ventilation and ICU stays. Better understanding of the reasons underlying differences in recognition of ARDS, the use of lower tidal volume ventilation, inspired oxygen concentrations, and adjuncts to ventilation could help to further improve these patient-relevant outcomes in ARDS.

Respiratory failure and cardiovascular failure were the most important factors leading to death in the ICU across all regions. This result contrasts to some degree with those of previous studies, which suggested that respiratory failure is less commonly the cause of death in ARDS.[25,26] However, in previous studies, respiratory failure was narrowly defined as severe gas-exchange failure, and deaths were attributed to syndromes such as sepsis as well as to organ failures. We limited the list of possible factors to organ systems, and did not ask for a cause of death per se. Possible additional explanations for our findings include improvement in outcomes from the shock phases of critical illness,[27] and the increasing role of decisions to limit life-sustaining measures when such measures are deemed futile.

The association of national-level indices of wealth with survival in ARDS is a novel and provocative finding. It might not reflect a different quality of care or resources in ICUs, but could be a result of a differing access to critical care services or preventive medicine.[28] Data show that residents from low-income areas have significantly higher rates of ICU admission[29] and more severe illness than do those from higher-income areas.[30] Our data add to a growing body of evidence showing that socioeconomic status affects survival from illnesses. Similar relations between income and patient survival have been reported in patients with sepsis,[31,32] underlining the effect of economic status on outcomes from critical illness. Studies have shown the disadvantages of low socio-economic status on outcomes from diverse major medical conditions such as diabetes,[7] asthma,[33] acute myocardial infarction,[34] and breast cancer.[35] These data collectively represent a substantial public health challenge, and future studies are needed to elucidate the mechanisms by which differences in socioeconomic status mediate differences in outcomes, so that targeted interventions can be designed and assessed.

Our study has several limitations. Our cohort is a convenience sample, and therefore might not be representative of actual clinical practice in ICUs worldwide. Thus, our results could be biased, particularly where specific types of ICUs (eg, academic ICUs) might be over-represented. Our study did not include any low-income countries, perhaps underlining the resource-dense nature of critical care. Our focus on winter months did not allow us to obtain annual incidence figures for ARDS, because previous studies have shown an increased incidence during winter. We did not have access to the source data for the patients in the enrolling ICUs, so all patients with ARDS in participating centres might not have been enrolled. However, enrolment of patients from participating ICUs met expectations based on recorded 2013 admission rates, and data from low-recruiting ICUs did not differ from those from high-enrolling ICUs (data not shown), suggesting the absence of reporting biases. We had a robust quality-control programme, in which all centres were asked to verify data that seemed inconsistent or erroneous. Although we have adjusted our analyses to account for known measured confounders, some of our findings might still have resulted from unmeasured or residual confounding. Finally, our assumptions that patients discharged from the hospital before day 28 were alive at that timepoint, and that inpatients at day 90 survived to discharge are further limitations.

In conclusion, this analysis of data from the LUNG SAFE study showed important geo-economic differences in severity, clinician recognition, and management of ARDS, and in patient outcomes. The finding that higher income is associated with better survival in the disorder is novel, and shows the effect of geo-economic factors in critically ill patients.

Contributors

JGL, GB, TP, and EF contributed to the search of published work; study design; data collection, analysis, and interpretation; drafting of figures; and Article writing and revisions. FM contributed to data analysis and interpretation, and figure design. LB, AE, DFM, FvH, MR, GR, HW, ASS, and AP contributed to study design, data collection and data interpretation, and Article writing and revisions. PA, YA, EKB, AB, VC, KC, LH, KK, JHL, JAL, LM, NN, JEP, LP, HQ, and JISJ contributed to data collection and interpretation, and Article writing and revisions.

Declaration of interests

We declare no competing interests.

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