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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1 **Title:** Geo-economic variations in epidemiology, patterns of care and outcome in

2 patients with Acute Respiratory Distress Syndrome: Insights from the LUNG SAFE

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105   **Word count:** 3,466.

106   **Take-home message**: Patients with ARDS from European high-income countries had higher

107   ARDS severity, received more adjunctive therapies and had a longer hospital length of stay than

108   patients from the rest of the world high-income countries. Lower country gross national income

109   was associated with poorer hospital survival in patients with ARDS.

110

111   **Tweet**: Geo-economic variations exist regarding ARDS severity, clinician recognition,

112   management approaches, and in patient outcomes from ARDS. [140-character limit]

Abstract

Background: There is limited information about the geo-economic variations in demographics, management and outcome of patients with acute respiratory distress syndrome (ARDS).

Methods: The Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) study was conducted during four consecutive weeks in the winter of 2014 in a convenience sample of 459 ICUs from 50 countries across 5 continents. A key secondary aim was to characterize variations in the demographics, management and outcome of patients with ARDS. We compared patients across three major geo-economic groupings, namely Europe high-income (Europe-High), Rest of World high-income (rWORLD-High), and Middle-income (Middle) countries.

Findings: 1,521 (54%) of the patients were recruited from Europe-High, 746 (27%) were from rWORLD-High, and 546 (19%) from Middle countries. Significant geographic variations were demonstrated regarding patient demographics, ARDS risk factors and comorbid diseases. The proportion of patients with-severe ARDS or with P/F ratio <150 was less in rWORLD-High compared to the two other regions. Use of prone position, neuromuscular blockade and ECMO were greatest in Europe-High. Adjusted duration of invasive mechanical ventilation and ICU length of stay were shorter in patients from rWORLD-High. Higher country per capita gross national income was associated with increased hospital survival in patients with ARDS, while the middle-income countries were associated with reduced hospital survival.

Interpretation: Important geo-economic differences exist regarding ARDS severity, clinician recognition of ARDS, ARDS management approaches, and in patient outcomes. An independent association exists between per capita income and outcomes in patients with ARDS.

135 **Trial Registration:** ClinicalTrials.gov NCT02010073

136   **Research in context**

137   ***Evidence before this study***

138   We searched PubMed in December, 2016, for articles published since Jan 1 Nov, 1990, with

139   search terms relating to 'acute respiratory distress syndrome' and 'geographic' or 'country'.

140   Specific search terms used were "respiratory distress syndrome, adult"[MeSH Terms] OR

141   ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields] AND "adult"[All

142   Fields]) OR "adult respiratory distress syndrome"[All Fields] OR ("acute"[All Fields] AND

143   "respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "acute

144   respiratory distress syndrome"[All Fields]) AND geographic[All Fields] OR country[All Fields].

145   Searches were not limited by language and were supplemented by review of reference lists. We

146   found some studies reporting findings from more limited regions, such as individual countries

147   or small groups of countries, but no study reporting data regarding acute respiratory distress

148   syndrome across major geo-economic groupings.

149

150   **Added value of this study**

151   Significant variations exist regarding patient demographics, ARDS risk factors and comorbid

152   diseases across the 3 major geo-economic groupings, namely Europe high income (Europe-

153   High), Rest of World high income (rWORLD-High), and Middle Income (Middle) countries. ARDS

154   severity was less overall in Rest of World high-income countries. In terms of patterns of care,

155   the use of prone positioning, neuromuscular blockade and recruitment maneuvers were

156   greatest in Europe-High countries. ICU length of stay was shorter, and the likelihood of

157   unassisted ventilation to day 28 was significantly ($P < 0.001$) higher, in rWORLD-High countries.

158   Lower country gross national product was associated with poorer hospital survival in patients

159   with ARDS. The middle-income country grouping was associated with worse ARDS outcomes

160   than either high-income country grouping.

161

162   **Implications of all the available evidence**

163   Important regional differences exist regarding the demographics, management and outcomes

164   of patients with ARDS. These data identify opportunities to enhance implementation of

165   evidence-based interventions that improve outcome from ARDS.

Introduction

Important geographic and economic variations in regard to the epidemiology, and patterns of care have been described for multiple diseases including diabetes [1], asthma [2], myocardial infarction [3,4], heart failure [5], atrial fibrillation [6], COPD [7], end-stage renal disease [8] and breast cancer [9]. Furthermore, the use of interventions such as blood transfusions [10], amputation [11], aneurysm repair [12] and carotid revascularization [13], and outcome following procedures such as coronary artery bypass grafting [14] also vary by region and/or socioeconomic status. Geo-economic variations in the epidemiology and management of patients with acute respiratory distress syndrome (ARDS) may have important implications for patient outcome. To date the extent and the impact of these variations have not been characterized.

The Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) study in 459 ICUs in 50 countries in 6 continents found a two-fold difference in the incidence of ARDS across the different continents [15]. ARDS was under-recognized by clinicians, while the use of evidence based ventilatory strategies and adjuncts was lower than expected. Of most concern, ARDS continues to confer a high mortality, with 40% of patients with ARDS dying in hospital.

A key secondary aim of the LUNG SAFE study was to characterize geo-economic variations in demographics, management and outcome of patients with ARDS. We compared patients across three major geo-economic groupings, namely Europe high income (Europe-High), Rest of World high income (rWORLD-High), and Middle Income (Middle) countries.

188   **Methods and Materials**

189   *Study Design*

190   The detailed methods has been published elsewhere [15]. In brief, LUNG SAFE was an

191   international, multicenter, prospective cohort study, with a 4 week enrollment window in the

192   winter season in each hemisphere [15]. The study, conceived by the Acute Respiratory Failure

193   Section of the European Society of Intensive Care Medicine (ESICM), was endorsed by multiple

194   national societies/networks (*Appendix 1*). All participating ICUs obtained ethics committee

195   approval, and either patient consent or ethics committee waiver of consent. National

196   coordinators (*Appendix 1*) and site investigators (*Appendix 2*) were responsible for obtaining

197   ethics committee approval and for ensuring data integrity and validity.

198

199   *Patients, Study Design and Data Collection*

200   Inclusion criteria were: admission to a participating ICU (including ICU transfers) within the 4-

201   week enrollment window; and receipt of invasive or noninvasive ventilation (NIV). Exclusion

202   criteria were: age<16 years or inability to obtain informed consent, where required. Patients

203   were classified as having ARDS based on the Berlin criteria [16]. To ensure a more homogenous

204   dataset, we restricted subsequent analyses to the large subset of patients (2,813 of 3,022

205   patients, 93.1%) fulfilling ARDS criteria on day 1 or day 2 (n=2,813) following the onset of acute

206   hypoxemic respiratory failure (AHRF) [*Figure 1*] that received invasive mechanical ventilation

207   (MV) or non-invasive ventilation (NIV). Data from the first day of fulfillment of ARDS criteria

208   were used in these analyses.

209

Data Definitions

211 We used the 2016 World Bank countries classification, which accounts for the gross national

212 income per capita (*http://databank.worldbank.org/data/home.aspx*) to define 3 major geo-

213 economic groupings: Europe high income (Europe-High), Rest of World high income (rWORLD-

214 High), and Middle Income (Middle) countries for this analysis (***Table 1***).

215

216 Duration of invasive ventilation was calculated as the number of days that the patient required

217 invasive mechanical ventilation up to day 28. Driving pressure was defined as plateau pressure

218 minus PEEP. Plateau and driving pressure analysis confined to patients (n=742) in whom plateau

219 pressure was measured and in whom there was no evidence of spontaneous ventilation (i.e.

220 when set and measured respiratory rates were equal). All modes other than volume and

221 pressure control modes were considered to permit spontaneous breathing. Mortality was

222 evaluated at 28-days, ICU and hospital discharge (or to day 90, whichever event occurred first).

223

224 *Data Management and Statistical Analyses*

225 Descriptive statistics included proportions for categorical and mean (standard deviation) for

226 continuous variables. The amount of missing data was low [15], and no assumptions were made

227 for missing data. Data were unadjusted unless specifically stated otherwise. Differences among

228 geo-economic groupings were evaluated using chi-square test (or Fisher exact tests) and

229 ANOVA or Kruskal–Wallis test as appropriate. The Shapiro-Wilk test was used to assess

230 normality in data distribution. Bonferroni correction was applied to determine significance in

231 the setting of multiple comparisons.

232

Kaplan-Meier analysis was used to estimate the likelihood of liberation from invasive

mechanical ventilation and of hospital mortality within 28 days of AHRF onset. We assumed

that patients discharged alive from hospital before 28 days were alive at day 28. The

comparison among geo-economic groupings was performed using the log-rank test.

We used mixed effect logistic regression to evaluate the association between mortality and

ICU-level predictors. We considered a two-level random intercept model for binary responses:

the first level was represented by individuals and the second level by the ICUs. Demographic,

risk, illness severity and management factors were considered at the first level; gross national

income (GNI) per capita, geographic area and ICU characteristics (number of beds, academic

ICU, beds per nurse, beds per physician, and percentage of ICU beds in hospital) were used as

predictors at the second level. Since some ICUs had few observations to support the normal

assumption of the model, we applied the bootstrap method (1,000 samples randomly

extracted) to estimate the model parameters, odds ratio (ORs) and the confidence intervals

(CIs). The individual predictors (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) applied to a logistic regression. These predictors were included in a mixed effect

logistic regression model and then, one by one, we evaluated the statistical significance of each

ICU variable (level two). Analogously, we applied the mixed effect Poisson regression to

evaluate the association between ICU-level predictors and ICU length of stay and duration of

invasive mechanical ventilation.

253   Statistical analyses were performed with R, version 3.0.2 (R Project for Statistical Computing,

254   (http://www.R-project.org) and SAS software, version 9.4 (SAS Institute, Cary, NC, USA). All p-

255   values were two-sided, with p-values <0.05 considered as statistically significant. The study

256   protocol, case report form and full statistical analysis plan are included in ***Appendix 3.***

257 **RESULTS**

258 Of the 12,906 patients screened for the LUNG SAFE study, 2,813 (22%) fulfilled ARDS criteria at

259 day 1 or day 2 following enrollment. Of these, 1,521 (54%) were recruited from Europe-High,

260 746 (27%) from rWORLD-High, and 546 (19%) from Middle countries [*Figure 1*]. ARDS

261 comprised 23% of screened patients in Europe-High, compared to 21% in both rWORLD-High

262 and in Middle countries [*Table 1*]. Overall, (298 of 459) 65% of participating ICUs were in

263 academic hospitals, with a median of 14 beds per ICU, and a median nurse to bed daytime ratio

264 of 0.6, and physician to bed ratio of 0.3. Table 1 details the number of ARDS patients enrolled by

265 country and geo-economic region, and data on the structure and organization of participating

266 ICUs.

267

268 **Patient Demographic Characteristics**

269 Patients from Europe-High countries were significantly older, and there was a stepwise increase

270 in body mass index in patients from Middle to Europe-High to rWORLD-High countries. Diabetes

271 mellitus, chronic renal failure and liver disease were significantly more frequent in rWORLD-

272 High countries, while congestive heart failure was highest in patients from Middle countries

273 [*Figure e1A*]. Pneumonia was the dominant risk factor for ARDS across each group [*Figure e1B*].

274 Extra-pulmonary sepsis was highest in Middle countries, while differences were also seen

275 regarding, trauma, inhalational injury, pancreatitis, and the absence of risk factors [*Figure e1B*].

276

277 **Patient Illness Severity**

278 ARDS severity varied by region, with mild ARDS significantly higher and severe ARDS

279 significantly lower in rWORLD-High compared to the Europe-High or Middle countries [**Table 2;**

280 **Figure e1C**]. rWORLD-High had a significantly lower proportion of patients with a P/F ratio <150

281 and a lower proportion of patients with persistent severe ARDS compared to both Europe-High

282 and Middle countries [**Table 2**]. Mean P/F ratios were significantly higher in rWORLD-High while

283 non-pulmonary SOFA scores were lower in Europe-High countries [**Table 2**].

284

285 **Clinician Recognition of ARDS**

286 Clinician recognition of mild and moderate, but not severe, ARDS was lower in rWORLD-High

287 compared to the Europe-High or Middle countries [**Table 3**].

288

289 **Ventilator Management of ARDS**

290 In rWORLD-High countries, more patients (66%) received lower tidal volumes (≤8 mL/kg PBW)

291 compared to 62% in Europe-High and Middle countries [**Figure 2A**]. Plateau pressure

292 measurement was highest in patients from Middle countries [**Table 3**]. The distribution of

293 plateau pressures and driving pressures were similar in Europe-High and the rWORLD-High, but

294 differed in Middle countries, with 18% of patients having a driving pressure <7.5 cmH$_2$O [**Figure**

295 **2B-C**]. Over 50% of patients in Middle countries had a PEEP <7.5 cmH$_2$O, compared to 44% in

296 Europe-High and 40% in rWORLD-High, respectively [**Figure 2D**]. The proportion of patients

297 receiving 'protective' ventilation, defined as a tidal volume ≤8 mL/kg PBW and plateau pressure

298 of ≤30 cmH$_2$O, was not different across the geo-economic groupings [**Table 3**].

299 Spontaneous ventilation in early ARDS was significantly more frequent in patients from

300 rWORLD-High countries compared to Europe-High [**Table 3**]. Inspired oxygen use differed by

301 region, with lower FiO$_2$ (FiO$_2 \leq 0.4$) greater in rWORLD-High countries, and higher FiO$_2$ more

302 frequent in Europe-High countries [*Figure 2E*]. Hypercapnia was more frequent in patients from

303 Europe-High countries, while hypocapnia was more frequent in patients in Middle countries

304 [*Figure e2A*]. Modes of ventilation differed, with least use of pressure support and greatest use

305 of SIMV in Middle countries. Use of volume and pressure control ventilation modes was similar

306 across the geo-economic groupings [*Figure e2B*].

307

308 **Use of adjunctive measures**

309 There was no significant variation in the use of NIV [*Figure 2F*]. The use of neuromuscular

310 blockade, and prone positioning in all patients and in the subgroup with a P/F ratio <150 [Table

311 e1] were significantly higher in patients from Europe-High countries. ECMO use in patients was

312 significantly lower in the Middle countries. Use of recruitment maneuvers was lower in

313 rWORLD-High countries. Adjustment for ARDS severity did not explain the regional differences

314 in the use of adjunctive measures.

315

316 **Outcome from ARDS**

317 Unadjusted duration of invasive ventilation and ICU length of stay were lower in rWORLD-High

318 countries [*Table e2*]. Kaplan-Meier analyses demonstrated significant differences in the

319 probability of weaning from invasive ventilation at each level of ARDS severity [*Figure 3 and e3*].

320 Probability of weaning was greater in patients from rWORLD-High countries compared to

321 Europe-high (P < 0.001, log rank test) and middle-income countries (P < 0.001, log rank test).

322 Multivariate analyses demonstrated that the adjusted incidence rate ratio for duration of

323   invasive mechanical ventilation, and ICU length of stay was significantly higher in Europe-High

324   countries, but not Middle countries, compared to rWORLD-High countries [*Figure 4; Tables e3-*

325   *4*].

326   Unadjusted ICU and hospital mortality were both lower in rWORLD-High countries [*Table e2*].

327   Kaplan-Meier analyses demonstrate that 28-day survival was highest in rWORLD-High countries,

328   and lowest in Middle countries [*Figure 3*]. Multivariate analyses demonstrated that the adjusted

329   incidence rate ratio for ICU and hospital survival significantly better in rWORLD-High and

330   Europe-High, countries, compared to Middle countries [*Figure 4; Tables e5-6*]. There was no

331   impact of differences in approaches to mechanical ventilation on ICU or hospital mortality by

332   geo-economic region [*Tables e5-6*]. Patient level variables associated with hospital mortality

333   included age, active or hematologic neoplasm, chronic liver failure, acidosis, P/F ratio, non-

334   pulmonary SOFA score, and respiratory rate. There was no independent association between

335   ICU level variables, including ICU size, beds per nurse/physician, and the percentage of

336   academic ICUs, and hospital mortality [*Tables e5-6*].

337

338   A separate multivariate analysis across all countries (i.e. without any grouping), and using per

339   capita GNI as a continuous variable, demonstrated that outcome from ARDS is independently

340   associated with GDI [*Table 4*]. Respiratory (42%) and cardiovascular failure (37%) were the most

341   common factors leading to ICU death, with no significant geographic variation seen [*Table e7*].

342   Decisions around limitation of life sustaining measures were less frequent in Middle (17%)

343   compared to Europe-High (27%) or rWORLD (26%) countries.

Discussion

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

While there were significant demographic differences among the patients from the 3 geo-economic regions, the impact on patient outcome appears limited. The older age of patients from Europe-High countries may partly explain the higher unadjusted mortality in this region, as age was independently associated with hospital mortality in this and in prior studies [17-19]. Of the pre-existing comorbidities associated with poor outcome, only chronic liver failure, was different, being higher in rWORLD-High countries. The pattern of critical illness seemed to differ, with patients from Europe-High countries having greater ARDS severity, and a higher proportion with persistent severe ARDS, while patients from rWORLD-High countries had more severe systemic illness. As has previously been demonstrated, both ARDS severity 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 P/F ratio <150, may reflect the fact that the evidence for these approaches was largely developed in Europe-High countries [20,21], and may have penetrated to a lesser extent in

366   the rest of the world. Other possible explanations include the unavailability of cisatracurium in

367   some countries, and lack of 'hands-on' experience with prone positioning. Even in Europe-High

368   countries, however, prone positioning was used in <10% of patients with P/F <150, the

369   population in which proning improves outcome [20]. A large clinical trial is being conducted in the

370   US by the PETAL network [ROSE trial, NCT02509078] to address any ongoing scientific

371   uncertainty regarding the efficacy of neuromuscular blockade in ARDS. These variations in the

372   use of adjunctive measures are not explained by differences in ARDS severity profile, by

373   economic differences (with the possible exception of ECMO, which was used less in middle-

374   income countries), or by differences in ARDS recognition. The lack of regional variation in the

375   use of NIV suggests that barriers to the use of adjuncts can be addressed [22]. Understanding and

376   addressing local barriers and facilitators to the implementation of simple and relatively

377   inexpensive adjunctive measures, such as prone positioning and neuromuscular blockade,

378   should be prioritized, given their potential to improve survival from ARDS.

379

380   Patients from Europe-High countries required longer durations of mechanical ventilation and

381   longer ICU stays compared to patients from countries of similar levels of wealth outside Europe.

382   These differences persisted after adjustment for ARDS severity and other covariates.

383   Importantly, we did not find any association between ICU level variables and outcome from

384   ARDS, suggesting that the differences in ICU organization and/or staffing do not explain the

385   effect of income. This suggests that differences in approaches to ARDS management may have

386   important implications for these highly patient-centered outcomes. Potential explanations

387   include the fact that the proportion of patients that received larger tidal volumes was lowest in

388   rWORLD-High countries and highest in Europe-High countries, a concern given that higher tidal

389   volume was associated with worse outcome in these patients[23]. The greater use of higher FiO_2

390   in patients from Europe-High countries is also a concern given the recent demonstration that

391   use of high FiO_2 in the critically ill may be harmful[24]. Other potential explanations include

392   differences in practices surrounding weaning from ventilation, but we do not have any data to

393   examine this issue. Interestingly, clinician recognition of ARDS was marginally lower in rWORLD

394   countries, although the difference was least marked for severe ARDS. Decision making around

395   limiting life sustaining measures was similar in Europe-High and rWORLD-High countries, so this

396   is unlikely to explain these differences. Better understanding of the reasons underlying

397   differences in the approach to the use of lower tidal volume ventilation, inspired oxygen

398   concentrations, and adjuncts to ventilation, may facilitate further improvement of these patient

399   relevant outcomes in patients with ARDS.

400

401   Respiratory failure and cardiovascular failure were the most important factors leading to death

402   in the ICU, across all regions. This contrasts to some degree with prior studies suggesting

403   respiratory failure is less commonly the cause of deaths from ARDS [25,26]. However, these studies

404   did define respiratory failure relatively narrowly, confining it to severe gas exchange failure.

405   They also attributed deaths to syndromes such as sepsis as well as to organ failures. We limited

406   the list of possible factors to the different organ systems, and did not ask for a 'cause of death'

407   per. Possible additional explanations for our findings include improvement in outcomes from

408   the shock phases of critical illness [27], and potentially the increasing role of decision making to

409   limit life sustaining measures where these are deemed futile.

410

411   The demonstration that national-level indices of wealth are associated patient survival from

412   ARDS is a novel and provocative finding. It does not appear to be explained by differences in

413   ICU organization or staffing. This association does not necessarily reflect a different quality of

414   care or resources in the ICU but may reflect a lower access to critical care services or

415   preventative medicine [28]. The latter is supported by data that residents from lower income

416   areas have significantly higher rates of ICU admission [29], and often with higher severity of illness

417   [30]. These data build on a growing body of evidence demonstrating the effect of socioeconomic

418   status on survival from illness. Similar effects of income on patient survival have been

419   demonstrated in patients with sepsis [31,32], underlining the impact of economic status on

420   outcomes from critical illness. In patients with diabetes, the percentage of deaths attributable

421   to high blood glucose or diabetes that occurs prior to age 70 is higher in low- and middle-

422   income countries than in high-income countries[1]. Socioeconomic differences contributed to

423   outcome in patients with COPD in China [7]. In an analysis of health administrative data from

424   Ontario, Canada, asthma-specific mortality rates were 60% higher among those in the lowest

425   compared with highest socioeconomic status [33]. In patients following acute myocardial

426   infarction in Italy, lower levels of education were associated with increased odds of 30-day

427   mortality[34]. Socioeconomic status also contribute to survival rates in patients with breast

428   cancer[35]. These data present a significant public health challenge, as they further highlight the

429   disadvantages of lower socioeconomic status on outcomes from diverse major medical

430   conditions. Future studies are needed to elucidate the mechanisms by which difference in

431 socioeconomic status mediate differences in outcome, so that targeted interventions can be

432 designed and evaluated.

433

434 ***Limitations:*** This study has a number of limitations. Our patient cohort is a convenience sample,

435 and therefore may not be representative of actual clinical practice in ICUs across the globe. This

436 could lead to bias in results, particularly where certain types of ICUs e.g. academic ICUs may be

437 over-represented. We did not have any low-income countries in our study, perhaps underlining

438 the resource dense nature of critical care. Our focus on winter months does not allow us to

439 obtain annual incidence figures for ARDS since previous studies have demonstrated an

440 increased incidence of ARDS in the winter months. We did not have access to the source data

441 for the patients in the enrolling ICUs, and it is possible that not all patients with ARDS in

442 participating centers were enrolled. However, enrollment of patients with ARDS from

443 participating ICUs met expectations based on their recorded 2013 admission rates, while data

444 from lower recruiting ICUs was not different from that from higher enrolling ICUs, suggesting

445 the absence of reporting biases. We instituted a robust data quality control program in which

446 all centers were requested to verify data that appeared inconsistent or erroneous. While we

447 have adjusted our analyses to account for known measured confounders, the possibility

448 remains that some of our findings may arise from unmeasured or residual confounding. Lastly,

449 our assumptions that patients discharged from the hospital before day 28 were alive at that

450 time point, and that inpatients at day 90 survived to hospital discharge are further limitations.

451

452 *Conclusions*: Important geo-economic differences exist regarding ARDS severity, clinician

453 recognition of ARDS, and the management of ARDS. An independent association exists between

454 per capita income and outcomes in patients with ARDS.

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Figure legends:

Figure 1: Flowchart of the study population

§ Patients could have more than one cause for AHRF

‡ This is the number of patients included in the primary analysis

Figure 2: Ventilator management of patients with ARDS by geo-economic region, including distribution of tidal volume (***Panel A***), plateau pressures (***Panel B***), driving pressures (***Panel C***), PEEP (***Panel D***), fractional inspired oxygen (***Panel E***), and adjunctive measures (***Panel F***).

* Indicates between region differences

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

Note: Patients discharged before Day 28 were assumed to be alive and off invasive MV on that day.

HR: Hazard ratio; HRs were estimated through Cox Proportional Hazard Models and we used rWORLD-HIGH as the reference category.

Figure 4: Plots of the adjusted IRRs and 95% confidence intervals for duration of mechanical ventilation and ICU length of stay (***Panel A***), and adjusted ORs and 95% confidence intervals of ICU and hospital mortality (***Panel B***) for each geo-economic area.

Note: rWORLD-High is the reference point for Panel A and Middle as reference for Panel B.

578　　Abbreviation: IRR, *incidence rate ratio; OR, odds ratio.*

579

580

581　　**ONLINE FIGURES**

582

583　　**Figure e1:** Patient demographics and ARDS severity profile by geo-economic region.

584　　*Panel A:* Frequency of pre-existing comorbidities.

585　　*Panel B:* Frequency of ARDS risk factors.

586　　*Panel C:* Frequency of ARDS severity categories.

587　　* Indicates between region differences

588

589　　**Figure e2:** Distribution of arterial PCO_2 tensions (*Panel A*) and modes of ventilation (*Panel B*)

590　　by geo-economic region.

591　　* Indicates between region differences

592

593　　*Figure e3:* Kaplan-Meier survival curves of probability of weaning from mechanical ventilation

594　　(*Panel A*), and of hospital survival (*Panel B*) in patients with mild, moderate and severe ARDS by

595　　geo-economic region

596　　Note: Patients discharged before Day 28 were assumed to be alive and off invasive MV on that

597　　day.

598　　HR: Hazard ratio; HRs were estimated through Cox Proportional Hazard Models and we used

599　　rWORLD-HIGH as the reference category.

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